Gastrointestinal Oncology

Basic and Clinical Aspects

edited by

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1987 **MARTINUS NIJHOFF PUBLISHERS**
a member of the KLUWER ACADEMIC PUBLISHERS GROUP
BOSTON / DORDRECHT / LANCASTER

Distributors

for the United States and Canada: Kluwer Academic Publishers, P.O. Box 358, Accord Station, Hingham, MA 02018-0358, USA
for the UK and Ireland: Kluwer Academic Publishers, MTP Press Limited, Falcon House, Queen Square, Lancaster LA1 1RN, UK
for all other countries: Kluwer Academic Publishers Group, Distribution Center, P.O. Box 322, 3300 AH Dordrecht, The Netherlands

Library of Congress Cataloging in Publication Data

Gastrointestinal oncology.

(Cancer treatment and research ; 33)
Includes index.
1. Gastrointestinal system--Cancer. I. Macdonald, John S. II. Series: Cancer treatment and research ; v. 33. [DNLM: 1. Gastrointestinal Neoplasms. W1 CA693 v.33 / WI 149 G2575]
RC280.D5G38 1986 616.99'433 86-18128

ISBN-13: 978-1-4612-9209-8 e-ISBN-13: 978-1-4613-2031-9
DOI: 10.1007/978-1-4613-2031-9

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Gastrointestinal Oncology

Cancer Treatment and Research

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Foreword to the series

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good indepth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes which aim to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion. First, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, pediatric oncology, etc. Second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each topic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging, markers, all forms of treatment modalities, basic biology, and more.

In *Cancer Treatment and Research,* we have an outstanding group of editors, each having made a major commitment to bring to this new series the very best literature in his or her field. Martinus Nijhoff Publishers has made an equally major commitment to the rapid publication of high quality books, and world-wide distribution.

Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that *Cancer Treatment and Research* provides an answer.

WILLIAM L. MCGUIRE
Series Editor

Preface

This is the third volume on gastrointestinal cancer of the Cancer Treatment and Research Series. The emphasis in this volume is to present a series of papers on areas of high clinical relevance in malignant diseases of the gut. As in the first and second volumes of this series, authors have been selected for their expertise and national and international prominence in their fields. This volume is organized so that papers explaining basic science prospectives proceed those dealing with clinical aspects of gastrointestinal cancer.

It is clear that in many instances advances gastrointestinal carcinoma cannot be effectively treated if 'cure' is the desired goal. When faced with poorly treatable diseases it is obviously important to look toward the causes and prevention of these illnesses. For this reason, there are several chapters in this volume that examine the issue of carcinogenesis of gastrointestinal cancer. Likewise, in diseases that are poorly treatable in advances stages, one is interested in early detection. Thus, early screening of populations becomes important and is dealt with in three papers in this volume. Chapters on treatment explore innovative approaches to therapy of gastrointestinal cancer. Second-look surgery with resection, arterial perfusion with chemotherapy, adjuvant therapy and neoadjuvant therapy are all addressed in various chapters in this volume. Finally, four chapters deal with unusual problems in gastrointestinal cancer. These papers include discussions of primary hepatobillary cancer, lymphoma of the gut, and gastrointestinal endocrine tumors.

In the area of carcinogenesis and natural history, there are four papers. Drs Longnecker and colleagues discuss the general principles of carcinogenesis in GI cancers. Dr DeWys discusses nutritional factors in the etiology of gastrointestinal cancer and Drs Larson and Melton from the Mayo Clinic present information on precursor lesions of upper gastrointestinal cancer. Finally, Dr Lynch and colleagues present a very careful and detailed analysis of the hereditary colon cancer syndromes including both polyposis and non-polyposis variants.

Two papers deal with the issue of screening and early diagnosis. Sugarbaker from the National Cancer Institute writes about the screening and early diagnosis of colorectal cancer. This paper emphasizes the issues of cost effectiveness of screening across large populations. Drs Antonow and McClain from the University of Kentucky have prepared an excellent chapter on endoscopy in the diagnostic and management of gastrointestinal cancer. The value of diagnostic and therapeutic endoscopy throughout the GI tract is carefully described.

Issues related to treatment are next discussed. Minton and Zahniser have prepared a well documented discussion of the role and effectiveness of second-look surgery in patients with colorectal cancer. This paper addresses the issue of carcinoembryonic antigen (CEA) monitoring. A discussion of the predictibility of elevated CEA as an indicator of recurrent colorectal cancer amenable to resection at second-look surgery is presented. Dr Kemeny from Memorial Sloan-Kettering next presents a review of both systemic and, more importantly, regional chemotherapy in advanced colorectal cancer. This paper is particularly topical because of the major interest now in hepatic artery infusion in patients with liver metastases secondary to colorectal cancer. Pazdur and Baker from Wayne State University address neoadjuvant therapy. They discuss specifically anal and esophageal carcinomas and present an excellent review of the evolving field of combined modality therapy as initial treatment for gastrointestinal cancer. Romond, Mendelsohn and Macdonald review the adjuvant therapy of gastrointestinal cancer. Adjuvant approaches to gastric, pancreatic, and colorectal cancers are included in this review.

Finally, several special problems in gastrointestinal oncology are discussed. Cady from Harvard University has written a clear and concise review of the etiology, diagnosis and treatment of primary hepatobiliary carcinomas. List and Hande from Vanderbilt University review the diagnosis and treatment of lymphomas of the gastrointestinal tract and Haller of the University of Pennsylvania reviews the diagnosis and treatment of carcinoid and islet cell tumors of the gut.

It is hoped that this third volume of Cancer Treatment and Research dealing with gastrointestinal cancer will serve to complement the first two volumes and be a highly useful update on important areas of gastrointestinal oncology for clinical scientists. The editor wishes to express his thanks to all the authors who labored so intensively to produce this volume.

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1. Carcinogenesis in gastrointestinal organs

DANIEL S. LONGNECKER, GEORGE K. MICHALOPOULOS and JAMES W. OSBORNE

Introduction

Concepts of carcinogenesis are evolving rapidly and have been refined into a multistep or multistage scheme during the past few decades. Longer reviews of progress in experimental carcinogenesis summarize the basis for these concepts which are derived from studies in many tissues and species, both *in vivo* and *in vitro*. The initiating event (initiation) of carcinogenesis is generally regarded as an early and probably irreversible effect of a carcinogen on a cell. It appears that alteration in the function of critical gene products and/or control of expression of cellular genes occur as a result of initiation. Such alterations start a series of changes in the initiated cell that may ultimately culminate in the development of a neoplastic phenotype, i.e. uncontrolled growth and perhaps the ability to invade and metastasize. These changes are commonly accompanied by some degree of loss of cell differentiation.

It appears that chemicals, radiation, and perhaps even spontaneous events within cells can cause DNA damage resulting in point mutations or more gross genetic changes such as chromosomal rearrangement. These mutations can trigger the activation of cellular genes called proto-oncogenes through structural changes in their coding regions which cause alterations in the function of their protein products, or by changes in their controlling regions, causing alterations in their levels of expression [1]. Alternately, the proto-oncogenes may become activated by integration into a virus so that initiation can be caused by infection of a cell by a virus that carries an oncogene – then designated as a viral oncogene. Activated proto-oncogenes, referred to as oncogenes, are associated with many types of cancer in humans as well as experimental animals [2, 3].

It appears that oncogene products are associated with critical pathways in the control of cellular proliferation and differentiation. For example, the sis

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

oncogene codes for a polypeptide growth factor that is normally found in platelets [3].

Many chemicals require metabolism to become active carcinogens capable of reacting with cellular macromolecules – including DNA. The liver is especially well endowed with the enzyme systems that are involved in such metabolic activation of procarcinogens. The critical enzymes are often members of the P450 cytochrome oxidase system and are inducible by exposure to xenobiotics that are substrates for the enzymes.

The probability that critical genetic changes will take place when a cell is exposed to a carcinogen is influenced by other factors such as the capacity of a cell to detoxify the carcinogen, the capacity of the cell to repair DNA damage, and the probability that a damaged cell will divide before DNA repair is completed. Agents that enhance initiation by modulating these factors are sometimes called cocarcinogens although this term has broad and imprecise usage [4].

The expression of the malignant phenotype after initiation seems to be limited or enhanced during later stages of carcinogenesis by physiologic or exogenous factors that influence cell proliferation and/or differentiation of genetically altered (initiated) cells. Factors that influence the development of neoplasms during later stages are called promoters or inhibitors of carcinogenesis.

Thus, in the consideration of carcinogenesis in any tissue we must try to identify agents that might serve as *initiators* or modulate initiation, and agents or physiologic factors that may serve as *promoters* or *inhibitors* of carcinogenesis after initiation has taken place.

Studies of carcinogenesis in the liver have contributed greatly to the formation of the concepts outlined above. The following section illustrates their basis in greater detail than is currently possible in other gastrointestinal organs.

Carcinogenesis in the liver

Liver carcinogenesis has been extensively studied in experimental animal models as well as in humans. Liver tumors have been a study of choice because of the unique properties of liver itself. As a soft organ, liver can be easily fractionated and a large data bank on the biochemistry of both liver and hepatocellular carcinoma is available from past studies. Liver is also endowed with a large capacity to regenerate. This feature, as we shall describe further, plays an important role in hepatic carcinogenesis. Study of liver regeneration has been done in the past in parallel with carcinogenesis, with the rationale that comparison of the two processes would yield information about the essential aberrations of normal cell growth control that are

responsible for neoplastic growth. Due to its large number of microsomal mixed function oxidases, the liver, more than any other organ of the mammalian body is capable of activating a wide spectrum of xenobiotics. Some of the xenobiotic chemical compounds are carcinogenic. As a result, liver is the organ where most tumors are seen in the chemical carcinogenesis bioassays conducted with rodents. In this section we will discuss the evidence from the epidemiological data and experimental models and seek common pathways.

Studies in humans

The epidemiology of hepatocellular carcinoma in humans has revealed striking differences in the incidence of this neoplasm between different countries. These differences have led to the identification of several factors whose carcinogenic potential for the liver has been well accepted and whose incidence correlated with the geographic distribution of the incidence of hepatocellular carcinomas. In Taiwan it is the leading malignant neoplasm whereas in the United States it ranks 22nd in incidence. In general, hepatocellular carcinoma is relatively rare in the developed countries and is seen mainly on the basis of preexisting micronodular cirrhosis for toxic (alcoholic) or other reasons. The incidence of this neoplasm is much higher in underdeveloped countries, especially in southern Africa and southeastern Asia. In those areas the neoplasm usually develops on a background of either normal hepatic histology or that of a macronodular (post-inflammatory) cirrhosis. In all places hepatocellular carcinoma is more common in males than females by a factor of 2 to 4. Studies of the pathogenesis of hepatocellular carcinoma in humans have shown that several factors may be implicated.

Hepatitis B virus

Strong epidemiological evidence suggests the association of hepatocellular carcinoma in humans with prior infection or presence of a carrier state of HBV. The evidence has been reviewed elsewhere [5] and only the salient features will be presented here. There is a close geographical correlation between the incidence of hepatocellular carcinoma and the incidence of a carrier state for the HBV. Case-control studies have also shown a good correlation between markers of previous infection with HBV and the presence of hepatocellular carcinoma. This was found to be true in studies of populations of New York as well as those of areas of high incidence. Other studies in Taiwan and elsewhere have shown that there is a higher incidence of HBV carrier status among the mothers as compared to the fathers of patients with hepatocellular carcinoma. The latter finding shows that a per-

inatal or early childhood infection is of importance for future hepatocellular carcinoma development. The maternal excess of HBsAg carriers in patients with hepatocellular carcinoma can only be interpreted as a proof that the infection with HBV precedes the formation of hepatocellular carcinoma rather than being a secondary consequence of an immune suppression of the patient induced after the tumor has already formed. Prospective studies with civil servants in Taiwan have also shown an association between the two entities. Out of 22,000 employees followed, 71 cases of hepatocellular carcinoma developed. Of these, 70 developed in persons that were HBV surface Antigen (HBsAg) carriers. The relative risk ratio between carriers and non-carriers was 390, an overwhelming evidence for the positive linkage between the carriers of HBsAG and the carcinoma. Also of interest was the fact that the carrier status for the HBsAg had a much stronger correlation compared to the presence of antibodies against the core antigen or any other viral marker. Other studies [6] have shown the presence of integrated HBV genomes into the DNA of hepatocellular carcinomas in all of twenty cases of alcoholics with hepatocellular carcinoma despite the fact that for some of these cases there were no markers of previous HBV infection. These findings demonstrate that prior infection with HBV is a strong determinant and may be a universal prerequisite for human hepatocellular carcinoma development.

Mycotoxins

A role for mycotoxins and especially aflatoxin B1 (AFB1) in the pathogenesis of human hepatocellular carcinoma has been argued from epidemiologic and laboratory data as well as from animal studies [7]. AFB1 is one of the most potent liver carcinogens for the rat and it has been found to be a liver carcinogen of variable potency in all of the experimental animals tested including primates. Aflatoxins are produced by the fungus *Aspergillus flavus* and they contaminate human food when conditions of humidity and heat during the storage of the grains favor production of these toxins by the fungus. The levels of contamination of food by aflatoxins correlate well with the incidence of hepatocellular carcinoma in mainland China and in Africa. In Thailand there are villages where children were estimated to be ingesting on a daily basis at the peak of the peanut harvest levels of AFB1 that were 20–30% of the dose that induces tumors in 100% of the rats. Aflatoxin metabolites have been measured in the urine of inhabitants of certain areas in People's Republic of China. An even more conclusive demonstration of the carcinogenic potential of these compounds was the demonstration in the urine of inhabitants of the Murang'a District in Kenya of the actual product of repair of DNA-aflatoxin adducts [8]. This proves that the active forms of this chemical are capable of interacting with the human genome. The carcinogenic potential of AFB1 was also shown in cultures of human hepato-

cytes in which addition of AFB1 induces DNA damage followed by repair. Though most of the studies have emphasized the role of aflatoxin, it should be emphasized that other mycotoxins which are known to be contaminants of human food (e.g. sterigmatocystin, luteoskyrin, etc.) have also been found in the food of inhabitants of areas of high incidence of hepatocellular carcinoma and they may contribute in the same way as AFB1 to its pathogenesis.

Alcohol

Alcoholic liver disease resulting in micronodular cirrhosis is the most common background for the development of hepatocellular carcinoma in the western world [9]. The association between micronodular cirrhosis and hepatocellular carcinoma is well documented by epidemiological studies. It is also well known however from *in vitro* genotoxicity assays that ethanol is not a genotoxic agent and as such it is unlikely that the role of ethanol in the pathogenesis of hepatocellular carcinoma is that of an initiator. A promoting role for ethanol has been invoked in carcinomas of the esophagus and oropharynx. In the case of the liver it is impossible to distinguish between the possible role of alcohol as a promoter and that of cirrhosis as an enhancing condition for hepatocarcinogenesis due to the high hepatocellular turnover rate. The role of hepatocyte replication in hepatocarcinogenesis has been emphasized in animal studies [10]. It is also of interest that a high incidence of hepatocellular carcinoma is seen in micronodular cirrhosis in general – regardless of the offending agent responsible for the induction of cirrhosis. A high incidence of hepatoma formation is seen in cirrhosis due to hemochromatosis. It should also be noted that the incidence of hepatoma is not increased in alcoholics who do not develop cirrhosis of the liver. These findings indicate that the critical factor for the high rate of hepatocellular carcinoma in cirrhosis is not ethanol but the high hepatocellular turnover rate of hepatocytes in cirrhotic livers. The interaction between the high cellular turnover and the expression of the HBV may also be of importance as shown from the previously mentioned studies with the presence of integrated genomes of HBV in the hepatomas seen in alcoholics in France [6].

Other factors

Several other factors have also been implicated in the pathogenesis of human hepatic neoplasia which cannot be extensively reviewed here. The use of oral steroid contraceptives has been associated with high incidence of benign hepatic neoplasms in women. To date there has not been any convincing association between these substances and hepatocellular carcinoma. Contraceptive steroids have been shown to be promoters of hepatic neoplasia in the rat [11] and are not considered to be genotoxic agents. Their role

for the benign neoplasms seen in human liver is very likely to be that of a promoter.

Tumors of bile ducts have been associated with infection by *Clonorchis sinensis*. The mechanism is not understood. The angiosarcoma of the liver is a rare tumor that appears in high frequency in the unusual circumstances of persons exposed to thorotrast or workers exposed occupationally to vinyl chloride.

Animal models

More than 100 chemical carcinogens have been identified that are capable of causing liver tumors in suitable doses. In typical protocols these chemicals are administered in the food or the drinking water. These carcinogens constitute complete carcinogens in the sense that they, by themselves, are capable of causing tumors when they are given at sufficient doses and for sufficient duration. The tumors are mainly hepatocellular carcinomas but also, less frequently, include tumors of the non-parenchymal cell types. In these chronic feeding regimens there is typically a spectrum of hepatic pathology that includes periportal fibrosis or even development of hepatic cirrhosis and formation of regenerative nodules [12]. Hepatic neoplasia appears in this background of hepatic pathology. The neoplasms are frank hepatocellular carcinomas and also benign neoplastic nodules. The regenerative nodules tend to regress after the discontinuation of the carcinogenic regimen. In parallel with the formation of regenerative nodules there is also appearance of a new hepatic subpopulation consisting of the so-called oval cells. These cells resemble bile duct epithelium in light microscopic observations but they have been shown to possess several markers characteristic of hepatocytes. They are considered by several investigators as a population of cells with differentiation that is intermediate between that of a hepatocyte and a bile duct cell. The role of regenerative nodules and oval cells in the formation of hepatocellular carcinomas has been widely argued. In view of the fact that in many instances oval cells have been shown to secrete alpha-fetoprotein and other parenchymal markers [13], and in view of the fact that alpha-fetoprotein secretion is low in some early neoplastic hepatocytic lesions, some investigators have argued that the oval cells, and not the early neoplastic lesions composed of parenchymal hepatocytes, are the forerunners of hepatocellular carcinomas. This argument, however, suffers from the fact that neoplasia has been shown in most instances to be of clonal origin. Clonal lesions composed of oval cells with altered growth properties have yet to be demonstrated.

The induction of hepatic neoplasia by chronic feeding of chemicals has led to the proof that specific chemicals can act as liver carcinogens. The

studies of hepatic carcinogenesis induced by chemicals, however, have been considerably advanced by the use of protocols of carcinogenesis with defined stages. These protocols have demonstrated that, in similarity to other tissues, liver neoplasia can be induced by the succession of two stages, i.e. initiation and promotion. Initiation should be considered as the accumulation of changes that result in the acquisition of relatively independent growth by a cell, the initiated cell. This relatively independent growth endows the initiated cell with the potential to form a true neoplasm (benign or malignant). Promotion should be viewed as a set of processes that enhance the probability that an initiated cell will form a visible tumor. At this point we should consider the nature of the hepatocytic changes that are believed to result in initiation. We shall follow this with a discussion of the chemicals or processes that enhance the incidence of hepatic neoplasia and thus affect promotion.

Initiation

Several studies have shown that the formation of initiated hepatocytes depends on the interaction of two essential factors. These are: (a) formation of DNA adducts (with two exceptions to be discussed below), and (b) hepatocyte proliferation at some stage after the administration of the carcinogen. The above two factors are of importance in development of hepatic neoplasia and need to be discussed in some detail.

Formation of DNA adducts

DNA adducts form between the DNA bases and reactive electrophiles that are produced after metabolic activation of the chemical carcinogens [14]. As mentioned above, liver has a large number of enzymes of the cytochrome P450 system, perhaps more than any other tissue. The reactions catalyzed by the cytochrome P450 system result in the formation of epoxidized or hydroxylated forms of the carcinogenic chemicals. These forms subsequently react with other cellular micromolecules in reactions catalyzed by specific enzymes and form conjugated derivatives such as glucuronides, sulfates, glutathione conjugates, etc. These reactions and the ones catalyzed by cytochrome P450 are reactions utilized by the cell in an effort to detoxify xenobiotic chemicals. In many instances during these reactions there is formation of electrophilic species (ultimate carcinogens) that are capable of reacting with DNA – given suitable conditions. The probability that a certain carcinogen will react with the nuclear DNA and form DNA adducts is dependent on the chemical properties of the carcinogen (highly reactive species may be inactivated by reacting with water, amino acids, etc.); the solubility properties (the reactive electrophile should be able to cross the nuclear membrane); and the concentration of the chemical. Of additional importance is the concentration of intracellular scavengers of electrophiles

such as glutathione. The role of the latter compound may be of importance in the determination of the final incidence of hepatocellular neoplasia. In experiments with vinyl chloride it was shown that after depletion of the hepatic glutathione, hepatocarcinomas were seen at much lower doses of the carcinogen. These doses were not carcinogenic in animals with normal levels of glutathione. The role of molecules that are capable of scavenging reactive electrophiles in enzyme catalyzed reactions or spontaneously should be seen as one of prevention of DNA adducts. In addition there are also systems that carry out the repair of already formed DNA adducts. The function of these DNA repair systems in the liver and other tissues has been extensively studied [15]. Despite the efficiency and high fidelity of the DNA repair systems, it has been shown that there are several DNA adducts that escape repair, particularly in instances of high rate of the hepatocyte turnover.

In general, the role of the formation of hepatic DNA adducts in the formation of hepatic neoplasia by chemical carcinogens is well accepted. There are however two instances of hepatocarcinogenesis in which there is no obvious formation of adducts between the administered chemicals and the DNA. One of these instances is the induction of hepatocellular neoplasms by peroxisome proliferators [16]. These compounds constitute a group of chemicals with diverse structure whose common denominator is the induction of large numbers of the organelles called peroxisomes. In addition to the induction of peroxisome proliferation these chemicals also induce hepatocyte proliferation by unknown mechanisms. The rodent liver appears to be more susceptible to these events than the liver of humans and primates although the phenomenon of peroxisome proliferation has also been demonstrated in primate species. After chronic feeding to rats and mice, these compounds induce hepatic neoplasia with both benign and malignant tumors. Despite extensive search, no adducts have been found between the hepatocyte DNA and the chemicals. It is postulated that the proliferation of peroxisomes results in the excessive formation of reactive oxygen species from beta-oxidation of fatty acids. These oxygen species are considered to reach concentrations which exceed the capacity of the detoxifying enzymes (catalase, superoxide dismutase, glutathione peroxidase, etc.) to remove them from the cytoplasm. In fact some of these chemicals result in lower levels of these enzymes for unknown reasons and apparently independent from the induced peroxisome proliferation. It is believed that the excess of these reactive oxygen species causes DNA damage. This damage plus the induced hepatic proliferation lead to neoplasia. The type of hepatic DNA damage induced is still under investigation.

Another example in which hepatic neoplasia induced by chemicals can proceed in the absence of apparent DNA adduct formation is the hepatocarcinogenesis induced by the choline deficient and methionine deficient

diet [17]. This diet results in fatty liver formation and hepatocellular toxicity. In chronic feeding with this diet, tumors are seen in the absence of the administration of any specific carcinogenic chemical. Though specific DNA adducts should not be expected by this protocol, it should be mentioned that the diet results in hypomethylation of the hepatic DNA. The role of hypomethylation in the formation of the neoplasia induced by this diet is not clear. Several studies have shown that hypomethylation is one of the modes of control of gene expression [18]. In the environment of chronic hepatocyte replication induced by the toxicity of this diet and the altered gene expression induced by the hypomethylation, it is possible that alteration of the control mechanisms of the hepatic genome may occur, resulting in altered oncogene expression or activation of oncogenic viruses.

Hepatocyte proliferation

Formation of a carcinogen – DNA adduct by itself is not sufficient for the formation of hepatic neoplasms. In fact this seems to be true for most tissues. In the liver, the formation of the adducts needs to be accompanied by hepatocyte proliferation to result in carcinogenesis [10]. In most instances of hepatic carcinogenesis by complete carcinogens, the chemicals are toxic to hepatocytes and cause hepatocellular death. The continuous feeding of tolerable levels of the chemical causes a continual wave of liver regeneration in which formation of new hepatocytes is attempting to keep pace with the loss of cells. The role of the induced hepatocellular proliferation has been shown to be crucial in the formation of hepatic neoplasia. Several chemicals are known which are capable of inducing hepatic DNA adducts, e.g. benzo(a)pyrene, etc. and yet are very weak inducers of hepatic neoplasia. The carcinogenicity of these same chemicals can be dramatically enhanced by performing a partial hepatectomy (followed by hepatocyte proliferation) or by administering the compound to neonate animals [19]. In rodents as well as in humans, there is significant hepatocyte proliferation in the first weeks after birth. Complete carcinogens that are capable of inducing hepatocellular carcinomas by themselves in chronic feeding are almost always toxic to the liver and induce hepatocyte death followed by compensatory regenerative activity. It is believed that the replication of the hepatocytes leads to 'fixation' of the promutagenic DNA adduct by formation of stable new base pairs consisting of normal DNA bases in the new strands that were replicated on the defective template that contained the DNA adducts. These new base pairs, present in the wrong location, constitute a point mutation. In addition to the formation of point mutations, numerous studies have shown that replication of chromatin that contains DNA adducts often results in structural chromatin changes due to DNA strand breaks, translocations, etc. The role of these chromatin changes as well as that of other more subtle functional changes in gene expression (e.g. enhanced gene expression due to

abnormal location or amplification) and their relationship to the formation of DNA adducts is currently under intensive investigation in the liver and in other tissues.

Not much is currently known about the nature of the genes whose alterations by chemicals would lead to neoplasia. The cellular genes c-Ha-ras and c-Ki-ras and c-myc have been shown to be expressed at specific times during liver regeneration and it is quite likely that these cellular genes are involved in the intracellular mediation of the signals that drive a hepatocyte towards replication. Increased expression of these oncogenes was seen in oval cells during hepatocarcinogenesis protocols [20]. In another study the c-Ha-ras gene was expressed at increased rates in all parts of the liver during carcinogenesis but the c-myc was found expressed only in tumors. The gene c-raf has been also found increased in pancreatic and hepatocellular tumors.

Promotion

The combination of genetic damaging agents followed by the fixation of the damage by hepatocyte proliferation results in the formation of initiated hepatocytes. These cells are considered to have the potential of forming hepatocellular neoplasms if they are given the proper environment. The studies from other tissues, especially the mouse skin, have demonstrated that the probability that the initiated cells will form tumors is influenced by the presence of substances known as promoters. These substances have restricted tissue specificities and they enhance the carcinogenic yield of low doses of carcinogenic chemicals. Several such substances have been identified as promoters of hepatic neoplasia. The first one discovered was *phenobarbital* [21]. This compound is a strong promoter of rat hepatic neoplasia but it has not been shown to be a promoter for neoplasia in the human liver. A typical protocol for the demonstration of promoting properties for hepatic neoplasia consists of the administration of a known initiating chemical (e.g. diethylnitrosamine) followed by partial hepatectomy. This combination of an initiating chemical coupled with the induction of regenerative proliferation results in formation of initiated cells. If phenobarbital is given in the drinking water continually after this treatment it results in the appearance of hepatic neoplasms, benign and malignant. By following this protocol, other compounds have also been shown to be promoters of hepatic neoplasia for the rat [22]. These include the compound tetrachlorodibenzodioxin (TCCD) as well as contraceptive steroids such as mestranol [11]. These compounds as well as others have been shown to enhance the yield of neoplasms after initiation. In addition to the use of specific compounds, enhancement of hepatic neoplasia after initiation also occurs with the use of specific nutritional protocols. The term 'promotion' also broadly applies to these protocols in the sense that they enhance hepatic neoplasia after initiation. It

should be realized however that these nutritional protocols bring about complex changes in the biology of the hepatocyte and that although the results of using these protocols are the same as the ones obtained by specific promoters, the mechanisms may be totally different.

One of these protocols is the 'resistant hepatocyte' protocol developed by Solt and Farber [23]. After giving a sufficient dose of an initiating chemical, e.g. diethylnitrosamine (DENA), the chemical N-2-acetylaminofluorene (AAF) is given to rats for a period of 2 weeks. In the midst of the AAF administration the rats are subjected to partial hepatectomy. AAF inhibits the replication of the normal (non-neoplastic) hepatocytes. The use of the initiating chemical results in the formation of clones of hepatocytes that soon acquire the size of visible nodules. These nodules are positive for the enzyme gamma glutamyl transpeptidase (GGT) and have similar histochemical markers as the foci described after the use of phenobarbital, above. These nodules are clones of cells that are resistant to the mitoinhibitory effect of AAF. The reasons for the resistance are decreased cytochrome P450 and/or increase in the enzymes and cofactors that aid in the detoxification of AAF. Though AAF itself is also an initiating carcinogen, its role in this protocol is totally different. It has been shown that if an initiating chemical (e.g. DENA) is not given at the early part of the protocol, formation of GGT-positive nodules does not occur. AAF is believed to act only as a mitoinhibitor that forces the brunt of the liver regeneration to be borne by the small numbers of cells that have become resistant to AAF due to the use of DENA at the early part of the protocol. The stimulus for liver regeneration is behind the rapid growth of the GGT-positive nodules. After the AAF is discontinued many of the nodules loose their histochemical markers and disappear in the regular hepatic parenchyma. A small subpopulation of nodules persists and at a later time frank hepatocellular carcinomas may also be seen. These findings demonstrate that despite the rapid growth of all the nodules at the initial stages of the protocol, the nodules are a mixed population of clones with different degrees of independence of growth. For most of them the growth will eventually cease as soon as the normal hepatic parenchyma is allowed to regenerate. Those that persist have a higher chance to progress to frank malignancy. This protocol also demonstrates that the rise of hepatic neoplasms may proceed through selective processes if a toxin is used that inhibits hepatic growth. The environment of mitoinhibitory toxic factors may set the stage where the strong stimulus for liver regeneration will force rapid growth of resistant cells. Further clonal variation (characterized as progression) may be enhanced in the environment of rapid growth of selective hepatic subpopulations and give rise to overt malignancy.

In addition to the above protocol, hepatic neoplasia has been shown to also be enhanced by choline-deficient (CD) diets. This protocol was devel-

oped by Shinozuka and Lombardi [24]. Again, initiation is induced prior to the CD diet. When rats are placed on a CD diet, clones of cells similar to the foci seen in the phenobarbital protocols and the nodules seen in the 'resistant hepatocyte protocol' emerge after several weeks. The use of CD diet does induce fatty liver and results in enhanced turnover of hepatocytes due to death of a percentage of hepatocytes on a daily basis as long as the CD diet is administered [25]. The mechanisms that result in increased numbers of foci are not clear. In this protocol there is also a combination of a stimulus for hepatic regeneration (due to the death of hepatocytes) and a toxic environment (CD diet) that may interfere with the regeneration of the normal hepatocytes. The result would again be the enhancement of the growth of clones that would be resistant to the toxic effects of the CD diet. Though this mechanism is the same as the one of the 'resistant hepatocyte' described above, the enhancement of the growth of the foci may also result from the specific effects of the CD diet on the biochemical phenotype of the hepatocyte. As mentioned above, hypomethylation of DNA is one of the mechanisms of control of gene expression and it is possible that the promoting effect of this diet may be due to genomic hypomethylation although other factors may also play a role.

A common finding from all of these three protocols is the formation of groups of hepatocytes with altered histochemical characteristics. These foci of hepatocytes have been called by different names (e.g. enzyme altered foci, putative preneoplastic foci, etc.) and the majority is positive for GGT. Other common histochemical characteristics are also shared but not all of the histochemical markers are demonstrable in all of the foci. Each focus has a combination of histochemical markers that characterize it as different from the adjacent liver. Several different foci may have similar or different combinations of the same histochemical alterations [22]. In addition to the foci, frank hepatocellular neoplasms (benign and/or malignant) are seen in these protocols. The neoplastic nature of these foci has been doubted in view of the fact that in many of the above protocols the foci regress after the protocol has been discontinued. This procedure, also called 're-modeling', has been well demonstrated in the resistant hepatocyte protocol by Farber and his collaborators. Regardless of the nature of these lesions it should be emphasized that these lesions are clonal (they are derived from single cells) and they have altered growth properties as compared to the normal hepatocyte. In some instances they have been shown to progress into hepatocellular carcinomas although usually the foci far outnumber the hepatocellular carcinomas. Although the growth rate of the foci appears limited compared to frank hepatocellular neoplasms, it should be emphasized that even in more defined models of neoplasia (e.g. transformation of cell cultures by oncogenic viruses) the resultant neoplastic cells usually have a wide spectrum of growth aberrations. In this context the enzyme altered foci should

best be considered as composed of transformed hepatocytes with minimal aberrations in growth control.

Liver regeneration and hepatic neoplasia

As mentioned above, proliferation of hepatocytes is an essential component of all protocols that result in hepatic neoplasia induced by chemicals. The role of enhanced hepatic proliferation is considered to be that of 'fixation' of the damage induced by the initiating chemical. In addition however, the regenerative stimulus of the liver after partial hepatectomy is the driving force in the growth stimulus for most of the nodules in some of the multistage protocols. The factors that control proliferation of hepatocytes are not well defined at this point. Four factors have been identified in the plasma. These are epidermal growth factor (EGF), norepinephrine and two substances called Hepatopoietin A and Hepatopoietin B [26]. The effect of any of these substances on hepatocellular carcinomas has not been yet studied. EGF stimulates hepatocyte proliferation directly through the EGF receptor whereas norepinephrine modulates the numbers of EGF receptors by heterologous regulation through the alpha-1 receptor. The receptor for EGF is at very low levels in hepatocellular carcinomas, suggesting that these tumors may be secreting factors that bind to the EGF receptor and cause internalization and degradation of the receptor. Such factors that are produced by hepatocellular carcinomas, bind to the EGF receptor and cause hepatocyte proliferation, have been recently identified and they may provide a conceptual link between the mechanisms that drive liver regeneration and those responsible for hepatic neoplasia.

Biochemical phenotype of hepatocellular carcinomas

This topic has been under extensive study by Potter *et al.* [27] and Weber *et al.* [28]. These studies have shown some common biochemical trends between the different hepatomas but also reveal some interesting aspects of their diversity. In general there is a tendency for hepatocellular carcinomas to contain isozymes and proteins found normally in fetal tissue. Of those alpha-fetoprotein is the one most recognized due to its clinical significance as a monitor of the tumor load of hepatomas that express it. The spectrum of fetal changes in hepatomas however is very broad and it affects many enzymes found in the normal hepatocyte. Many of these enzymes do not perform functions essential for cell growth and the whole phenomenon is considered to be one of altered differentiation. In general in hepatomas induced by chemicals, the levels of cytochrome P450 and other enzymes

involved in activation of carcinogenic chemicals and xenobiotics is very low. This is most compatible with the concept of the 'resistant hepatocyte' as being an essential element of the initiated cell [29]. Despite their similarities, however, hepatocellular carcinomas are also characterized by extreme diversity [27]. Studies with transplantable Morris hepatomas have shown that for each hepatoma there is a distinct isozymic profile. If the enzyme induction patterns and the isozymes that have been studied in each hepatoma are taken into account, no two hepatomas are biochemically alike. This individuality of biochemical phenotype is a stable characteristic for each and every hepatoma. This concept of diversity of the neoplasia has been discovered and best studied in hepatomas because of the large number of measurable enzymatic functions that are present in the normal and the neoplastic hepatocyte.

Induction of hepatocellular carcinomas by viruses

It has been shown in recent years that models of acute and chronic hepatitis virus infections with striking analogy to the human disease with hepatitis B virus exist in several animals, including woodchucks, ground squirrels and Chinese ducks [30]. The analogy with the human disease includes an acute and chronic hepatitis as well as association of hepatocellular carcinoma with high frequency in animals that have been infected or are carriers of the virus. Immunological studies have shown crossreactivity between the surface antigens and the core antigens of the human and the animal viruses. Infection with these viruses results in production of excess viral coat protein in the form of spherical and tubular particles. In both the human B virus and the animal viruses the virions are composed of a particle of 42 nm with a core containing a double stranded circular DNA and a DNA polymerase. The DNA also contains a large single stranded portion. The mode of replication of these viruses puts them in a separate taxonomic classification [30]. The replication of these DNA viruses proceeds through an RNA intermediate. The DNA of the viruses is synthesized within the viral particle by reverse transcription from RNA, in similarity with the reverse transcription seen in RNA tumor viruses. After the DNA is synthesized, the RNA is destroyed. Of interest for the purposes of this review is the evidence that chronic infection with these viruses is associated with high incidence of hepatocellular carcinoma in these animals as in the human. Studies with woodchucks have shown that the DNA of the woodchuck hepatitis virus is found incorporated in the genome of most of the hepatocellular carcinomas seen in this species. The development of the tumors proceeds through the formation of benign adenomatous nodules similar to those seen in other rodent models of carcinogenesis mentioned above [31].

Summary

The studies from both humans and animals clearly demonstrate that the initiation of hepatocarcinogenesis is associated with alteration of genomic information within the hepatocyte. This alteration may be induced by carcinogenic chemicals interacting with DNA or by inserting the new genetic information of the genome of the hepatitis B virus. The specific cellular genes whose alteration would lead to formation of oncogenes leading to hepatic neoplasia have not yet been identified. The nature of the specific alteration of the mechanisms for growth control in the neoplastic hepatocyte compared to the regenerating hepatocyte is also not clear. A better understanding of the role of normal hepatocyte genes and of the mechanisms that control the expression of the genome of HBV should help our understanding of the processes that lead to hepatocarcinogenesis.

Carcinogenesis in the esophagus

The incidence of carcinoma of the esophagus ranks below that of colon, stomach, and pancreas in the United States, but it varies greatly worldwide and ranks ahead of the other gastrointestinal sites in certain geographic areas. The carcinomas are predominantly non-keratinizing squamous type (about 70%) and occur in the middle and lower third of the esophagus. Adenocarcinomas comprise most of the remaining cancers and occur in the lower esophagus.

Human studies

Carcinoma of the esophagus occurs in more focal epidemics than any other human cancer. In Europe and North America the associated carcinogen has been tobacco - compounded by the coincident use of alcoholic beverages. No single explanation fits the high incidence that is seen in Curacao, the Transkei of South Afrika, Caspian Iran, and regions of mainland China. The people of these regions do not appear to smoke or drink heavily, but the intake of foods that contain vitamin C is low in Iran and central China [32].

Several abnormalities of esophageal mucosa have been found in the populations of high incidence areas. These include chronic esophagitis, focal atrophy of the squamous mucosa, squamous papillomas, epithelial dysplasia, and carcinoma *in situ* [33]. Esophagitis and atrophy appear first and may persist for years. These are regarded as predisposing lesions. Dysplasia occurs later and increases in frequency with age. Its presence suggests that

initiation has taken place. Correa has speculated that this series of changes may be present for 25 or more years during the development of a carcinoma [33].

Nutritional deficits, both general malnutrition and lack of specific vitamins, may alter the integrity of the esophageal mucosa and predispose to esophagitis. Deficiencies of vitamin A, riboflavin, niacin, iron (usually associated with the Plummer-Vinson syndrome), molybdenum, and zinc have all been implicated [33, 34].

Esophagitis may be caused by mucosal abrasion, and an atrophic mucosa is more vulnerable. Such abrasion may be caused by food when a dry, coarse diet is eaten as is characteristic of some high incidence areas such as the Transkei and Iran. Thermal injury may be another cause of esophageal injury that can predispose to cancer and the consumption of very hot beverages is characteristic of several population groups that are at high risk for esophageal cancer in Japan, Singapore, the Soviet Union, and Argentina [33]. Alcohol's role may be to damage the esophageal mucosa. Such injury implies the stimulation of mucosal cell proliferation during repair and regeneration.

The importance of multiple factors is emphasized by the data of Hirayama [35] which shows the interrelationship between cigarette smoking and alcohol drinking as risk factors for esophageal carcinoma. The standard mortality rate was 3–4 times higher among daily drinkers who smoked heavily compared with occasional or non-drinkers who did not smoke.

Adenocarcinomas have been associated with the presence of Barrett's esophagus which represents a significant risk for malignancy. Reflux esophagitis with glandular metaplasia (Barrett's esophagus) seems to predispose to dysplasia that sometimes progresses to carcinoma *in situ*, and then to adenocarcinoma. This seems to represent a second pathogenetic sequence with causes that are distinct from those outlined above for squamous carcinomas. Sjogren estimated that the incidence of carcinomas among patients with Barrett's esophagus is about 10% [36] although this association accounts for only a small fraction of esophageal cancers [33].

Heredity appears to play little or no role in the etiology of the majority of esophageal carcinomas, however, one association should be noted – that of esophageal carcinoma and tylosis which appears to be due to a single gene mutation [37]. A 95% risk of esophageal cancer by age 65 has been calculated for individuals with the mutant gene.

Animal models

Esophageal carcinoma can be experimentally induced in high yield in rodents with certain nitrosamines, e.g. methylbenzylnitrosourea, and the yield

of such tumors has been enhanced in zinc deficient rats [33]. Esophageal carcinomas have been induced in subhuman primates receiving methylnitrosourea (MNU). Each of the lesions that is characteristic of human populations at high risk for esophageal carcinoma, i.e. esophagitis, focal atrophy, papillomas, dysplasia and carcinoma *in situ* has been described in MNU-treated primates [33].

Conclusions

Exogenous nitrosamines have been suspected to be initiators of esophageal carcinomas in humans, but this is not proven. Potential sources include tobacco, alcoholic beverages, and certain foods such as pickled vegetables that are in the diet of high risk groups in China [33]. Foods may contain other mutagenic and genotoxic agents that could serve as initiators in the esophagus [34], as well as promoting agents. Phorbol esters and tannins are examples of promoters that are present in specific foods and beverages [33, 34]. The continued exposure of the esophageal mucosa to such agents seems to cause a sequence of changes that culminate in cellular dysplasia, *in situ* carcinoma, and ultimately carcinoma much as has been described in the cervix and in areas of squamous metaplasia within the lungs of smokers.

Carcinogenesis in the stomach

Adenocarcinomas of the stomach arise in mucosal epithelium and have two principal histologic patterns. Carcinomas with 'intestinal' type histology may grow as an exophytic mass or form an ulcer. The other histologic pattern is 'diffuse' or 'infiltrative' which also describes the growth pattern grossly – a thickened gastric wall (linitis plastica).

Gastric mucosal lesions that predispose to or precede the development of carcinoma have been studied by Correa [33, 38]. The most prevalent of these lesions are chronic atrophic gastritis with intestinal metaplasia which precedes intestinal type carcinomas. These mucosal abnormalities are also primary changes in pernicious anemia, gastric polyps and postgastrectomy states. Each of these is associated with an increased risk for gastric carcinoma although they are much less common than chronic atrophic gastritis. The increased risk of carcinoma postgastrectomy seems to be highest in patients that have had a Billroth II procedure.

Serial biopsies performed in individuals over a period of years have shown a progression from atrophic gastritis to carcinoma, and there has been a correlation of incidence of intestinal metaplasia and gastric carcinoma in high and low risk groups.

Correa has described sequential gastric mucosal changes that seem to be steps in the development of gastric carcinoma in the following order: superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, and epithelial dysplasia. His publications should be consulted for illustrations of these lesions. The presence of dysplastic cellular changes in the setting of intestinal metaplasia are believed to indicate an increased risk for progression to carcinoma, but a relatively small fraction of individuals with intestinal metaplasia seem to develop dysplasia [38]. The dysplasia may occur in either flat mucosa or polypoid growths, i.e. adenomatous or villous polyps [33].

Three types of chronic gastritis are described: autoimmune (pernicious anemia syndrome), environmental, and hypersecretory [38]. The distribution of mucosal involvement differs in the three types. Intestinal metaplasia occurs in both autoimmune, which involves the body, and environmental types, predominantly antral in location, and both are associated with an increased risk of carcinoma while hypersecretory gastritis is seldom associated with metaplasia or dysplasia and therefore is not regarded as predisposing to cancer. The considerations reviewed below suggest that the cause of chronic environmental gastritis and carcinoma of the stomach are the same.

Studies in humans

The incidence of gastric carcinoma has decreased over the last 60 years in the United States and now ranks well below that for carcinomas of the colon and pancreas. The incidence remains high in certain countries including Japan, Iceland, and portions of Central and South America. The recent incidence in Japan has been about 90/100,000 whereas in US whites it was about 10/100,000 [33]. These international differences have allowed studies of immigrant populations from high to low incidence areas and shown that an increased risk persists in the migrant groups. However, the risk for children of the immigrants is similar to that for natives of the new location. This suggests that critical exposures may have occurred prior to migration. The study of Japanese immigrants to Hawaii and the United States has been particularly informative.

The incidence of infiltrative carcinomas has remained relatively constant in the United States and is similar in most countries whereas the intestinal type has decreased selectively in the US and varies widely between populations.

The studies of immigrants suggested that dietary or environmental factors were more important than genetic influences. Dietary risk factors associated with gastric carcinoma include the high intake of salt and nitrates, and low

consumption of fresh vegetables and fruits [35, 39, 40]. Other characteristics include a low intake of animal fat and protein and a high intake of grains and tubers. In certain populations, increased risk is associated with intake of specific foods such as salted and smoked fish in Japan, pickled vegetables in China [34], and fava beans in Columbia [39]. Nitrosation of fava beans yields a potent mutagen. Cigarette smoking was a risk factor for stomach cancer in the study of Hirayama [35].

Certain clinical studies of individuals with chronic atrophic gastritis and intestinal metaplasia are important as background for understanding current views of gastric carcinogenesis. Such studies have shown that gastric pH was elevated, that bacteria were present in the stomach, and that high levels of nitrites may be present. Nitrite levels were also increased in the gastric contents of postgastrectomy (post-Billroth II) patients.

Although dietary influences seem to dominate considerations of etiology of carcinoma of the stomach, heredity plays a role in some cases [37]. Individuals with blood group A have about a 20% greater risk than those with other blood groups, and this risk is for development of the infiltrative form [38]. Heredity is important in pernicious anemia which in turn is associated with a strong predisposition to develop gastric cancer. Genetic factors are also important in the development of severe atrophic fundic gastritis which may be present in the absence of fully developed pernicious anemia – but still strongly associated with an increased risk of the cancer. Carcinoma of the stomach is one of the cancers that develops with increased incidence among patients with ataxia-telangiectasia which is inherited in an autosomal recessive pattern. There is some evidence that heterozygotes with this gene are also at some increased risk for gastric carcinoma [37].

Animal models

Several chemicals have induced carcinomas in the glandular stomach of rodents when they were given orally in the diet, drinking water, or by gavage. N-methyl-N′-nitro-nitrosoguanidine (MNNG) is one such agent and other nitrosamines and nitrosamides are also effective gastric carcinogens. The importance of this observation is linked to the independent finding that nitrosamides can be formed by reaction of nitrites and amines at low pH comparable to that found in the stomach. Nitrites are present in some foods, and nitrates in food may be reduced in the mouth by bacterial enzymes. Ascorbic acid has been reported to inhibit this reaction. These experimental observations provide the essential elements of a scenario by which potent initiating (genotoxic) carcinogens might be formed in the stomach from elements of the diet, and by which the consumption of foods that contain vitamin C such as green leafy vegetables might reduce the formation of such carcinogens [32].

Weisburger *et al.* recount an experiment in which a fish, Sanma hiraki, that is eaten in Japan was homogenized and exposed to nitrite at pH 3 yielding a mutagen or mutagens that induced carcinoma of the glandular stomach in rats [32]. It has been shown that gastric mucosa can perform nitrosation reactions to form mutagenic compounds [41].

The enhancing effects on gastric carcinogenesis of Billroth II gastrectomy and other anastomoses that allow biliary reflux into the stomach have been verified by studies in animals [39].

Conclusions

Correa and collaborators have proposed an etiologic model that is based on epidemiologic, experimental and pathologic observations. The model pertains specifically to the origin of intestinal type gastric carcinomas which are regarded as the result of a series of carcinogen-induced changes that begin early in life and evolve over the subsequent 20–50 years. The hypothesis that certain diets may predispose to the spontaneous nitrosation of amines in food providing endogenous nitrosamide or nitrosamine carcinogens, and that other genotoxic carcinogens may be formed in foods by cooking provides an explanation for the exposure of gastric mucosa to agents that may 'initiate' permanent genetic damage (mutation) in mucosal cells. This is regarded as the beginning of a transformation sequence which may progress through intestinal metaplasia to dysplasia and formation of a carcinoma. If this started early in life it would account for the persistent high risk of gastric carcinoma that has been noted in immigrant populations from high risk areas [34].

Physical characteristics of the diet such as abrasive hard grains may contribute to the initial mucosal injury and the mucosal barrier may be compromised by food with high salt content. Mucosal atrophy and intestinal metaplasia reduce the barrier function and increase gastric pH. As pH rises, bacteria can survive in the stomach. Some of these bacteria contain reductases that convert nitrates to nitrites. On the other hand, the formation of nitrosated products in foods may be inhibited by dietary vitamin C, vitamin E or other antioxidants.

The interplay between endogenous and exogenous risk factors is such that risk is low in some population groups such as white Americans. In the case of gastric cancer, current knowledge does not allow identification of separate initiators and promoters. However, the pathogenetic scheme outlined above provides for the continued, and probably increasing exposure of gastric mucosa to endogenous initiating carcinogens over the course of a lifetime. It is recognized that certain carcinogens are 'complete' in the sense that continued exposure to a single agent can both initiate and promote the development of a neoplasm. Such may be the case in the stomach.

Carcinogenesis in the small intestine

Smooth muscle, glandular epithelium, argentaffin cells, lymphoid tissue, fat, connective tissue, nerve sheath, and blood vessels are all capable of forming malignant (and benign) tumors in the small bowel. Benign tumors are found in 0.2–0.3% of autopsies. There is universal agreement that primary malignant tumors of the small bowel are rare and represent about 1% of all gastrointestinal malignancies. Only malignant tumors exclusive of lymphomas and carcinoids will be the focus of this section. Reviews typically state that the first reported malignant neoplasm of the small bowel was duodenal carcinoma described by Hamburger in 1746. They also commonly credit Leichtenstern with the first major review of malignant neoplasms in 1876. Several major reviews have been published in the last three decades and the general agreement among them is remarkable. The reader is referred to several relatively recent reviews which are representative of those available [42–45]. The most common primary malignant tumor is adenocarcinoma, constituting 40–50% of all small bowel malignancies. The incidence of adenocarcinoma is 1% or less than that of colorectal cancers or cancers of the stomach. The annular constricting 'napkin ring' carcinoma is characteristic of this tumor type and occurs most frequently in the duodenum, next most frequently in the jejunum, and least frequently in the ileum. The lesions are typically quite advanced when discovered and are sometimes only considered after other diagnoses are ruled out. The prognosis for 5-year survival is always poor. Obstruction caused by a malignant tumor is usually due to tumor infiltration in contrast to obstruction from a benign tumor due to intussusception. Clinical symptoms associated with duodenal carcinoma are more well-defined than those related to jejunal and ileal carcinoma.

Leiomyosarcomas arise almost exclusively from intestinal smooth muscle, were first described in 1883 by Wesener, and occur almost as frequently as lymphoma. They are found in the ratios of about 1:3:5 in the duodenum, jejunum, and ileum, respectively. However, on a per unit length basis, leiomyosarcomas are found most frequently in the duodenum and Meckel's diverticulum.

Rhabdomyosarcomas, fibrosarcomas, liposarcomas, malignant schwannomas, and angiosarcomas have been reported, but occur even more rarely than the other types and are not considered to be of great clinical significance [46].

The small intestine is not a common site for development of metastatic tumors. However, metastases may originate from extra-abdominal sites with primary tumors like cutaneous melanoma or adenocarcinoma of the breast or lung or from intra-abdominal sites such as cervix, ovaries, kidneys, stomach, and colon [45]. In a review of 3,584 cases of carcinoma, Wolther found an incidence of only 1.14% metastases to small intestine [47].

Studies in humans

Because of the extremely low incidence of small bowel tumors there are no epidemiologic studies of small bowel tumors except gastrointestinal lymphomas. No area of the world or population group has been associated with a particularly high or low incidence of small bowel cancer. There is general agreement that there is a peak incidence by age in the 6th or 7th decade. Some series show a slight male predominance. Adenocarcinoma arising in Crohn's disease usually occurs about 20 years earlier and shows a definite male predominance of about 3:1 [48]. All reported cases related to Crohn's disease have been adenocarcinomas. About 50–70% of adenocarcinomas arise in the duodenum and ileum except those associated with regional enteritis in which more than 70% of the lesions arise in the ileum.

The question has been asked for years, 'Why are small bowel tumors rare?'. This remains unanswered in spite of some attractive theories that are not readily amenable to testing. Several factors in small bowel have been compared with their counterparts in the large bowel and it has been suggested in a recent review [44] that rapid transit time with reduced exposure time to carcinogens in the lumen, liquid contents which are less traumatizing to the mucosa, relative sterility which may reduce endogenous formation of mutagens by bacteria, alkalinity of juices which should reduce spontaneous nitrosation, relative concentration of protective mucosal enzymes, and the capacity for high levels of IgA production relate to the relative resistance of the small bowel to tumor induction. These are the factors mentioned most frequently. However, the larger area of the small intestine, rapid elongation of the small bowel late in fetal life (with an attending freedom from fetal rests) and the more rapid cell turnover of the small intestinal mucosal cells are also occasionally mentioned.

Williamson *et al.* [49] point out that benzo(a)pyrene hydroxylase is more abundant in the proximal small bowel compared to distal small bowel. In agreement with other reports, he is supportive of the concept that high IgA levels in the small bowel may be very important in protecting the mucosa against viral infection which could include oncogenic viruses.

Adenomas occur in the small intestine and have the same general morphologic characteristics as those seen in the colon, i.e. tubular, tubulovillous, and villous [44]. Little is known about the malignant potential of tubular adenomas, but villous adenomas are regarded to have a significant potential for progression to adenocarcinoma – estimated to be in the range of 35–58% [44]. Villous adenomas occur most frequently in the duodenum. It seems likely that an adenoma-dysplasia-carcinoma sequence occurs in the small intestine although this is not so well documented as in the colon.

Studies in animals

Human studies have been retrospective. It has been necessary for the investigator to collect cases as they occur and make correlations when possible. In contrast, animal studies are prospective and allow for control of many variables such as diet, carcinogen dose, choice of examination times and other factors. Just as in humans, the baseline incidence of small bowel tumors in animals is extremely low. There are reports of autopsy series of thousands of animals without evidence of a single small bowel tumor [50].

These animal studies are considered especially useful when the characteristics of the tumors and their development closely resemble their counterparts in humans. Animals also provide the opportunity to study the effects of potential carcinogens in large numbers of animals. The animal models for small intestinal carcinogens which have been used generally involve mice or rats and occasionally other species such as hamsters. The agents employed include chemicals and radiation from external sources. Even though small bowel cancers are rare in humans, their poor prognosis makes it important to find a useful, readily available animal model which will permit studies of mechanism.

There are more studies of chemically-induced carcinogenesis in the large bowel than in the small bowel, possibly in approximate proportion to the natural frequency of occurrence of lesions in those sites. Chemical carcinogens may be fairly selective for inducing tumors in particular sites, such as adenocarcinoma in the duodenum and upper jejunum of rats after azoxymethane [49], but it is quite common for more than one site to be involved. For example, the compound 1,2-dimethylhydrazine is considered by some as the 'standard' for inducing large bowel adenocarcinomas since multiple injections over a period of weeks will always lead to 100% of animals with colonic tumors. However, at least in rats, lesions with different histologic types also appear in other gastrointestinal sites including the ileum, jejunum, and duodenum [51].

The variety of chemical agents tested for carcinogenicity in the small bowel is substantial and definitive data have been obtained. No pattern has evolved which associates particular compounds or a basic chemical structure with a particular tumor type or location in the gastrointestinal tract. The difference in carcinogenicity of two compounds may be due to a difference in one functional group. For example, N-ethyl-N-nitrosourethane induced duodenal lesions with a high frequency in rats, but N-amyl-N-nitrosourethane was ineffective [52]. With effective carcinogens, adenomas and adenocarcinomas have been the prevalent tumor types noted, and in azoxymethane-treated rats most carcinomas have occurred in the duodenum [49].

The following studies involving carcinogen and a modifying agent are illustrative of the many investigations of this general type. N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in the drinking water of rats [53] or hamsters [54] yielded duodenal adenocarcinomas in a few months. Pyloroplasty [53, 54] or truncal vagotomy [54] had an enhancing effect on tumor development. An association of increased duodenal proliferative cells at risk due to the effect of pyloroplasty and invasive tumors was made [53].

The role of hydrogen peroxide (H_2O_2) in duodenal tumor induction is of interest. When administered in drinking water alone [55] or in combination with methylazoxymethanol acetate (MAMA) [56], intestinal tumors developed. The results suggest that hyperplastic conditions caused by H_2O_2 alone can eventually lead to cancer, but that H_2O_2 and MAMA together are more effective than MAMA alone. It is likely that any mucosal injury followed by a hyperplastic cellular response serves to condition the small intestine to cancer induction by chemicals.

Quercetin occurs in many edible plant products including bracken fern (BF), a food delicacy. Quercetin may not be the only active agent in BF, but in common with BF, it caused intestinal carcinomas in rats with high frequency [57].

External radiation sources have been used under various conditions to induce small bowel adenocarcinoma in rodents. The conditions include: the whole body X-irradiation of rats pre-treated with p-amino-propriophenone or placed in parabiosis after X-ray treatment [58]; shielding of the femur during irradiation or injection of spleen homogenate prior to irradiation or neutron exposure of the total body of mice [59]; and local irradiation of the small bowel with deuterons [60]. A rat model for the study of small bowel tumors was discovered in 1963 and described in more detail in a later publication. Intestinal carcinomas were induced in over 50% of male adult Holtzman rats by X-irradiation of only the hypoxic, temporarily exteriorized ileum and jejunum [61]. This model was used for over 12 years, but is no longer available. Its demise may relate to the unfortunate known changes in the genetic constitution of the rats and the conditions under which they were housed.

Experimental chemoprevention involves the use of man-made and naturally-occurring chemicals to prevent gastrointestinal tumor induction in animals. As recently noted [62, 63], many different types of compounds and techniques have been utilized to inhibit chemical carcinogenesis, carcinogen metabolism, N-nitroso-compound formation, and tumor development. In only a few instances however, have the studies focused on small bowel carcinogenesis.

Selenium (Se) is known to inhibit the development of chemically induced, spontaneous, and transplanted tumors. However, Se has been shown to inhibit DMH-induced colon carcinogenesis while facilitating small bowel cancer in the same animals [64].

Wattenberg has formulated the concepts of inhibition of formation of carcinogens, the prevention of a carcinogen reaching or reacting with a critical target site ('blocking agents') and the later inhibition shown by such compounds as retinoids and protease inhibitors [65]. Under the influence of diet, induction of a high concentration of the enzyme benzo(a)pyrene hydroxylase in the small intestine is possible. Its presence as a detoxifying agent has often been cited as a possible reason for resistance of small bowel to cancer [66]. Although the data available relates mainly to fore-stomach and large bowel of rodents, the principles could likely be applied to the prevention of small bowel cancer.

Conclusions

The rarity of malignant small bowel lesions remains an engima. The paucity of tumors makes epidemiological studies very difficult. Even so, several reliable large series of cases have been reported and there is no correlative data to support an increased incidence related to race, religion, diet, or environment. There is increasing evidence that Crohn's disease predisposes the patient to small intestinal malignancy and modulates the course of the disease. Some new hypotheses and rigorous testing of them are needed. An animal model of intestinal carcinoma free from complications in other organs would stimulate future investigations directed to the delineation of causative factors in small bowel carcinogenesis.

Carcinogenesis in the colon

The majority of adenocarcinomas of the large bowel arise in the mucosal epithelial cells and are well differentiated or moderately differentiated carcinomas. Carcinomas in the colon and rectum are histologically similar [67]. Some secrete mucin but most do not. Poorly differentiated variants are less common. The considerations of etiology reviewed here pertain to garden-variety carcinoma of the large bowel and exclude carcinoid tumor, lymphoma, and sarcoma. Carcinoma of the rectum has a higher incidence among males than among females, but in the colon, the ratio of incidence in the sexes hovers around one [68, 69]. Because of the high rank of carcinomas of the colon and rectum as a cause of death for both sexes, their cause has been studied extensively. This topic has been the focus of reviews and symposia. Their published proceedings are referenced below and should be consulted for detailed review of epidemiologic and experimental work.

Studies in humans

Adenomas of the large bowel mucosa are considered to be preneoplastic lesions that are precursors to carcinoma. There are two histologic patterns, tubular and villous, although individual adenomas may have a mixture of these patterns. The concept of an 'adenoma-carcinoma' or 'adenoma-dysplasia-carcinoma' sequence is widely accepted. The presence of adenomas implies increased risk for cancer – either because of genetic predisposition or because there has been exposure to initiating and promoting agents that cause the development of both adenomas and carcinomas [68]. Most adenocarcinomas arise in adenomas but only a small percentage of adenomas progress to become carcinomas during the lifetime of the host individual [68]. A higher fraction of villous adenomas than of tubular adenomas give rise to carcinomas, and the risk of malignancy increases with size of the adenoma [69]. Data reviewed by Hill showed that the smallest adenomas (0.5 cm diameter) did not contain a malignant component whereas evidence of malignant change was present in 1% of adenomas < 1 cm in diameter, 10% of adenomas between 1 and 2 cm in diameter, and 46% of adenomas that were greater than 2 cm in diameter [69]. A malignant component was nearly ten times as frequent in villous adenomas as in tubular adenomas, and was intermediate in adenomas of mixed histologic type (tubulovillous).

Genetic factors play a clear role in the etiology of some carcinomas of the large bowel. Familial polyposis is transmitted as an autosomal dominant trait and leads to the formation of adenomas and a virtually absolute risk of carcinoma [67]. Other genetically determined syndromes that include the formation of adenomas of the large bowel and a high risk of large bowel carcinoma are Gardner's syndrome and Turcot's syndrome. Polyposis syndromes with an increased risk of carcinoma that is lower than that associated with familial polyposis are the formation of juvenile polyps and Peutz-Jegher's syndrome [67]. In addition to the genetically transmitted polyposis syndromes, a three-fold excess risk has been reported for relatives of patients with carcinomas of the large bowel in the absence of polyposis syndromes, but it is not clear whether this reflects a genetic factor or similarities of environment, diet and lifestyle [68]. In some such families, a genetic factor seems to be present and transmitted in an autosomal dominant pattern (Cancer Family Syndrome). Early age of onset, and in women, an association with an increased incidence of breast and endometrial adenocarcinoma is characteristic of such families [37].

A second etiologic substrate for the development of carcinoma is inflammatory bowel disease. The increased risk of carcinoma of the large bowel was first recognized in patients with ulcerative colitis of long duration (10 years or longer), and later established in patients with Crohn's disease

involving the large bowel although the risk appears to be lower in the latter than the former [37, 70, 71]. In both diseases, progression toward neoplasia is often associated with mucosal epithelial dysplasia – as assessed histologically in biopsies, providing the basis for an alternate concept of sequence in the development of colorectal cancer, i.e. 'inflammatory bowel disease-dysplasia-carcinoma'.

There is now a strong focus on diet in epidemiologic studies of the causes of large bowel carcinoma. Initially, geographic differences in the incidence of large bowel cancer attracted attention [72]. It appeared that dietary differences might be key as the basis was sought for the high incidence in affluent Western cultures and the low incidence in certain underdeveloped nations. The strongest positive correlations are with animal protein and total fat intake [68]. The strongest negative correlations are with increased intake of cereal grains, legumes and nuts, suggesting the importance of fiber [68] – specifically insoluble cereal fiber. Inverse correlations have also been reported for consumption of vitamins A and C with the incidence of carcinoma of the large bowel [69].

The unique biology of the large bowel appears to play a role in carcinogenesis in this organ. The fecal concentration of secondary bile acids have shown a positive correlation with the risk of large bowel cancer in international comparisons [68, 69] and in case control studies although the association has been less consistent in the latter [69]. The level of bile acid secretion is determined by the amount of dietary fat intake, and this relationship has been implicated as a possible basis for the increased risk associated with high fat diets. Secondary bile acids are formed by the action of specific bacterial enzymes in the lumen of the colon on bile acids secreted by the liver. The concentration of bile acids in the feces is also a function of fecal bulk and water content – both of which are increased by the consumption of a high fiber diet. The resulting dilution of bile acids is often cited as a mechanism for the protective effect of dietary fiber [73, 74].

Colonic epithelium has been cultured, allowing the study of cell kinetics of mucosal cells from a variety of precursor lesions under basal and special culture conditions [75, 76]. Both adenomas and mucosa from inflammatory bowel disease have been shown to have a common proliferative abnormality – an extreme degree of uncontrolled cell proliferation – which seems to confer an increased risk for malignant transformation [75]. Studies of the characteristics of cell division in preneoplastic colon lesions have shown both an increase in the labeling index and a shift in the location of dividing cells from the base of the crypt to the upper portion of the gland [76]. The classic tumor promoter, TPA, has been shown to stimulate mitogenesis in cultured cells of tubular adenomas from four patients, and the secondary bile acid, deoxycholic acid, produced a similar effect when added to culture medium [76].

Denis Burkitt has reviewed epidemiologic data that implicates a 'western' high fat-low fiber diet as a risk factor for carcinoma of the large bowel [73]. In commenting on the biologic plausibility of this association, he extends the hypothesis regarding mechanism to include an impact of the high fiber diet on the metabolic activity of the anaerobic fecal bacteria that convert primary bile acids to secondary bile acids, e.g. deoxycholic acid and lithocolic acid, by 7-dehydroxylation in the colon. The proposed link is acidification of the feces by fermentation which is fueled by breakdown of carbohydrate in the intestine. When fecal pH falls below 6.7, 7-dehydroxylation of primary bile acids is inhibited, thus reducing formation of putative promoting agents – the secondary bile acids.

One hypothesis that has been suggested by several epidemiologic studies of rectal carcinoma is that beer consumption is associated with an increased risk [77]. An equal number of studies have failed to identify beer as a risk factor for rectal cancer, and consumption of alcohol is not regarded as a risk factor for colon cancer. Other lifestyle factors that have been evaluated and failed to show an association with carcinoma of the large bowel include smoking, and use of drugs or laxatives [69].

Recent reports of an inverse relation between occupational exercise level and the risk of colon carcinoma [78] typifies the complexity of considerations of etiology and suggests the level of confounding that may cloud epidemiologic study of this disease.

Studies in animals

Animal models of colon carcinogenesis have been developed in rats and mice using the carcinogens 1,2-dimethylhydrazine, methylazoxymethanol acetate, and azoxymethane [79]. These indirect acting carcinogens can be given orally, or by injection subcutaneously or intraperitoneally. Direct acting carcinogens, methylnitrosourea and N-methyl-N′-nitro-N-nitrosoguanidine, may be used if they are instilled directly into the rectum or colon where they act locally. The same carcinogen can induce adenomas and carcinomas, and low doses have induced a larger fraction of benign than malignant neoplasms [79]. Ward has concluded that a larger fraction of experimentally induced invasive carcinomas in the rat arise *de novo* in flat superficial lesions than in humans where carcinomas seem typically to arise in polypoid adenomas [80]. The *de novo* pathway of histogenesis described in rats seems to be analogous to the way that carcinomas arise in humans with inflammatory bowel disease. Chang has described the genesis of adenomas and carcinomas from cells within a single crypt based on the study of mice treated with dimethylhydrazine [81]. He regards such tumors as likely to be monoclonal in origin.

Secondary bile acids have acted as cocarcinogens in an experimental model of carcinogenesis in the large bowel [68, 74, 79]. Many reports indicate that animals fed high fat diets develop more neoplasms than animals given the same dose of carcinogen that were fed low fat diets [74, 79], and this has been attributed to an increased level of bile acid secretion. Unsaturated fats have been generally more effective than saturated fats in promoting colon carcinogenesis in animal models [68], but in epidemiologic studies, a diet with high saturated fat has repeatedly been implicated [69].

Addition of insoluble fiber to the diets of carcinogen-treated animals has been effective in reducing the incidence of colon carcinomas while addition of soluble fiber such as pectin has been ineffective [68].

Conclusions

A simple model for colon carcinogenesis can be proposed. Initiation in sporadic cases seems likely to result from exposure to intraluminal carcinogens that were ingested or formed within the colon, while in fewer individuals a genetic trait may be inherited that plays an initiating role and leads to formation of adenomas. Ingested or endogenous intraluminal agents may also act as promoters – secondary bile acids are specifically implicated. Elevated levels of such promoters increase the risk of progression to malignancy of initiated cells in adenomas, or in flat dysplastic mucosal lesions.

As is the case in other organs, a knowledge of the mechanisms of carcinogenesis suggests several approaches to prevention of large bowel carcinoma. The first is to prevent ingestion of initiating agents so that all stages of carcinogenesis are prevented. Since some mutagens appear to be produced endogenously in the feces by bacterial action, and because mutagenic compounds appear to be formed during cooking of protein-containing foods [32], it is probably impossible to prevent completely the exposure to initiators.

A second approach is to remove or reduce cocarcinogenic and promoting agents in the diet. Bile acids seem to fall into this category, and reduction of dietary fat intake may offer an approach to reducing the concentration of primary and secondary bile acids in the feces. Increasing dietary carbohydrate and fiber provides another approach. The rationale for recommending a diet that is low in fat and high in cereal fiber is obvious from these considerations.

The addition of inhibitors of carcinogenesis to the diet is another attractive approach for prevention of large bowel carcinoma. The effectiveness and feasibility of adding enough vitamins, selenium or β-carotene to prevent large bowel carcinomas in humans is not fully established.

A final approach is to screen for precursor lesions, i.e. adenomas, and to

remove them. Recommendations for the latter have been formulated and will not be repeated here [82].

Carcinogenesis in the pancreas

Malignant neoplasms of the pancreas may be derived from the exocrine pancreas (acinar tissue and ducts) or the endocrine pancreas (islets). About 90% of primary pancreatic carcinomas arise in the exocrine component, and it is these tumors that are the focus of this section. Islet cell neoplasms are discussed in Chapter 12. About 75% of pancreatic adenocarcinomas are classed as being of ductal histologic type. Several other histologic types have been described, but only a small minority of these retain clear evidence of acinar cell differentiation in humans. Thus, ductal epithelium is commonly regarded as the origin of most human pancreatic carcinomas. The possibility that some carcinomas with a ductlike appearance may arise from acinar cells that undergo a metaplastic change receives support from experimental studies in animals. Therefore, the possibility that the acinar tissue may give rise to a significant portion of human carcinomas should remain an active consideration as the etiology of pancreatic carcinoma is considered.

Studies in humans

A series of epidemiologic studies have yielded few firm clues regarding the cause of pancreatic cancer, but there is a growing consensus that cigarette smoking is associated with increased risk by a factor of about two [83]. The incidence rate for pancreatic cancer has risen over the same time period as that for carcinoma of the lung, although the rise has been much less dramatic.

The recent emphasis on recognition of environmental chemical carcinogens has prompted several attempts to find occupational groups with increased incidence rates of pancreatic cancer. Isolated studies have implicated a few specific chemicals such as beta-napthylamine and benzidene as pancreatic carcinogens in relatively small populations with occupational exposure. Both of these are much better known as bladder carcinogens. However, no agent to which there is widespread population or occupational exposure has been identified as a cause of pancreatic cancer [84].

There are marked geographic differences in the incidence of pancreatic carcinoma with the highest incidence in Western and industrialized nations. As with other cancers, this has implicated dietary habits. The 'Western diet' and a high dietary fat content in particular has been implicated as a risk factor for pancreatic cancer [85]. Dietary fat intake and pancreatic cancer

incidence have shown a significant positive correlation in one international survey, and meat consumption has been identified as a risk factor for pancreatic cancer in a dietary survey done in Japan [35]. Meat consumption and fat consumption tend to be linked in such studies so that the high risk diet is sometimes defined as 'high-fat, high-protein'.

Alcohol consumption has been evaluated repeatedly as a risk factor for pancreatic cancer with a substantial disagreement among studies. No consensus exists and it appears that consumption of alcoholic beverages is at most a weak risk factor for carcinoma of the pancreas in spite of the established links with acute and chronic pancreatitis. Coffee consumption seems now to fall into a similar category as alcohol, although it has been evaluated in fewer studies – there is no consensus and the issue remains open [83].

Aside from environmental, dietary and lifestyle risk factors, there are also risk factors for pancreatic carcinoma that appear to be biologic or genetic. The incidence among males is higher than that in females by a factor of 1.5 to 2. The disease is rare in the young and rises in incidence through the seventh decade of life. Diabetes may be a risk factor although this has probably been overrated because diabetes may occur secondary to the presence of the carcinoma. The incidence rate among blacks exceeds the rate in the white population in the United States. A few pancreatic carcinomas have been examined for the presence of oncogenes, and k-ras has been identified.

Families with a high incidence of pancreatic cancer have been described, but the onset of the disease has been after the age of 60 rather than at an unusually early age as one might expect if there were an underlying genetic basis [37]. The only firm association of exocrine pancreatic cancer with a genetically determined condition is with hereditary pancreatitis which is inherited in an autosomal dominant pattern with incomplete penetrance [37]. Families with the disorder have been reported in France, England, and the United States. The incidence of cancers in these families has varied from 0 to 30% and some family members have developed carcinoma without clinical evidence of pancreatitis.

In summary, cigarette smoking is the only well established exogenous risk factor for human pancreatic cancer. Weaker evidence suggests that some occupational chemical exposures and the consumption of a high fat diet may also be risk factors.

Studies in animals

In the last decade, pancreatic cancer has been experimentally induced in rodents by more than 20 chemicals [86]. Most of these chemicals are known mutagens that seem to act as initiators of carcinogenesis. Several are nitro-

samines or closely related compounds. In many cases, it is clear that the carcinogen has reached the pancreas through the blood because the chemicals have been given by subcutaneous or intravenous injection. From these studies, we conclude that a variety of chemicals can initiate carcinogenesis in the pancreas of rats, hamsters, mice and Guinea pigs. Some of these same chemicals have induced carcinomas in cultured explants of human pancreas – demonstrating that agents identified as carcinogens in animals may also affect humans.

Some of the chemicals that are pancreatic carcinogens require metabolic conversion to the active carcinogenic form, and it has been shown that pancreatic cells can perform the necessary metabolic steps for some of these chemicals. An alternate possibility is that some of these chemicals may be metabolized in the liver, and then reach the pancreas in an activated form through the circulation.

Chemical carcinogens with a high degree of specificity for the pancreas have been used to establish 'animal models' for pancreatic carcinogenesis [86–88]. These animal models have been used in the study of factors that might affect either initiation of carcinogenesis, or inhibition or promotion of the development of cancers in carcinogen-treated animals. In most rat models, male rats have developed a higher incidence of pancreatic cancers than females by a factor of two or more [86]. This indicates that the sex difference is hormone- or sex-linked rather than due to environmental or lifestyle factors. Recent studies indicate that testosterone is required in male rats to achieve the expected response to pancreatic carcinogens [89].

Both rat and hamster models have been used to evaluate the effect of high fat diets on pancreatic carcinogenesis [85]. It appears that diets with a high content of polyunsaturated fat promote or enhance the later stage of carcinogenesis in the pancreas. The mechanism of this effect is unknown. In such studies the high fat diets usually contain 20% by weight of an unsaturated oil, e.g. corn oil, whereas the control diets usually have 5% oil. The 'western diet' eaten by most Americans typically contains about 20% fat. Recent studies in rats indicate that diets with 12–15% fat promote pancreatic carcinogenesis.

Another dietary factor has been shown to have a dramatic effect on pancreatic carcinogenesis in the rat – the feeding of raw soya flour (RSF) [85]. RSF contains a powerful trypsin inhibitor. It has been shown that the presence of active trypsin in the intestine inhibits the secretion of cholecystokinin (CCK) by the intestine. Inhibition of trypsin in the intestine interrupts a negative feedback mechanism and leads to the continued secretion of CCK. CCK is a trophic hormone for the pancreas, and sustained high serum levels cause pancreatic hyperplasia. The implication of these observations is that CCK can serve as a promoter of carcinogenesis by stimulating the growth of 'initiated' cells in the pancreas. The importance of this mecha-

nism in human pancreatic carcinogenesis is unknown – but it merits critical evaluation. Other pancreotrophic hormones may have a similar effect.

We know little as yet about factors that inhibit carcinogenesis in the pancreas, but initial studies have been done in animal models to see if the addition to the diet of large doses of vitamin A analogs, retinoids, will inhibit the development of cancers in carcinogen-treated rats and hamsters. Several retinoids have been effective and some have failed. In general, retinoids have been more effective in rats than in hamsters. It is known that vitamin A is needed to maintain normal differentiation of epithelial cells, but the mechanism of the effect on carcinogenesis is not specifically known. The retinoids have been effective when fed following exposure to the carcinogen so that the inhibitory effect seems to be during the later stages of carcinogenesis. There are isolated reports that certain synthetic retinoids have promoted the development of carcinomas in the pancreas and liver of rodents [85]. Thus, caution is required in regard to clinical trials.

Conclusions

It is possible to reevaluate risk factors in humans in view of recent findings in animals. The latter studies indicate that systemic exposure to a variety of chemical carcinogens can cause pancreatic cancer. It is quite likely that cigarette smoking introduces some chemical, e.g. a nitrosamine, that is capable of initiating carcinogenesis and that this chemical or its carcinogenic metabolite reaches the pancreas through the blood. We must accept the possibility that additional chemicals to which humans are exposed will be identified as pancreatic carcinogens. The observation that males are more susceptible than females among rats exposed to the same carcinogen, environment and diet suggests that some sex-linked factor, perhaps hormonal, promotes or inhibits pancreatic carcinogenesis.

The inaccessible internal location of the pancreas has limited the study in humans of early lesions that might be precursors to carcinoma. Analysis of surgical and autopsy specimens has shown an association of hyperplastic and dysplastic changes in ductal epithelium with the presence of pancreatic cancer [90]. Similar lesions have been reported in the ducts of hamsters that were treated with pancreatic carcinogens. Focal dysplastic changes in acinar tissue have been reported in human pancreas that are similar to focal acinar cell lesions characteristically found in carcinogen-treated rats [91]. More recently, focal replacement of lobular acinar tissue by ductular complexes was reported in human pancreas – similar to lesions that have been noted in both carcinogen-treated rats and hamsters [92]. In animals, each of these types of carcinogen-induced lesions seems to represent an early stage in the development of a neoplasm although only a small fraction of the lesions

progress. The lesions in humans may have similar significance, but studies to date have not indicated which type is most important as a precursor to carcinoma. None is detectable by currently available screening methods.

The striking influence of dietary factors in carcinogen-treated animals suggests that similar factors may be important in the human. The studies with RSF diets suggest that some of the effects of diet may be mediated by peptide hormones that affect pancreatic growth. The mechanism by which a high fat diet might enhance pancreatic carcinogenesis is less clear, but the consistency of this observation with the effect of high fat diets in experimental colon cancer reinforces the basis for a recommendation of decreasing dietary fat content in countries such as the United States where it is high.

Epilog

Epidemiologic studies often are in disagreement regarding the importance of specific risk factors for various cancers. This certainly pertains to diet which has been heavily implicated in the etiology of gastrointestinal cancers. In reviewing dietary risk factors for these cancers, we have reflected findings that have been consistent among several studies but have omitted reference to some studies that stand alone or in disagreement with the majority. These 'outliers' sometimes reflect studies of special populations in which multiple factors operate to yield a net result that is different from US-based studies. Two examples are notable.

Reddy's study of the population of Kuopio, Finland showed consumption of a high fat diet with a low risk of colon cancer relative to the US [74]. Further study indicated that the Finnish group consumed a high fiber diet, which is now regarded as offering protection by mechanisms that have been outlined earlier. Another example is provided by the data of Hirayama from a large prospective cohort study in Japan [35]. Dietary fat was not evaluated, but meat consumption was. Consumption of animal fat and meat is usually proportional so there is a tendency to regard meat intake as a surrogate index of fat intake. In this study, meat intake showed a significant correlation with risk of pancreatic cancer as we might expect if high fat intake is a risk factor for pancreatic cancer, but the daily intake of meat correlated with a lower than expected incidence of carcinoma of the colon. The explanation for this finding is not obvious.

Graham has commented on difficulties of dietary surveys [40, 93]. In such cases, data from animal studies has sometimes been helpful in clarifying the importance of findings in epidemiologic studies. Several reviews that focus on diet and cancer provide detailed discussion of these issues [34, 93, 94].

Acknowledgements

The authors thank several colleagues for assistance in preparation of this chapter: Thomas Colacchio, John Dunn and James D. Yager, Jr., for reviewing portions of the manuscript; Susan Barnett, Franco Milani, Loren Schutt, and Elna Kuhlmann for editorial assistance; and Matthew Longnecker for suggestions regarding content.

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2. Nutritional factors in gastrointestinal cancer

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Introduction

The relationships between diet, nutrition, and gastrointestinal cancer are multiple and complex. The diet may be the carrier for preformed carcinogens or may provide precursors for formation of carcinogens as reviewed in Chapter 1. Diet and nutritional status may modulate the risk of developing a cancer, and this will be discussed in this chapter, including the effects on cancer risk of body weight, dietary fat, dietary fiber, and the micronutrient content of the diet.

Nutritional status and diet are also important for the patient who has a cancer of the gastrointestinal tract. As noted in subsequent chapters, alterations in eating behavior and/or nutritional status may be presenting symptoms of gastrointestinal cancers. In this chapter I will summarize the current understanding of the prognostic effect of weight loss in cancer patients and will consider the nutritional needs of the cancer patient. Systemic factors contributing to weight loss will be reviewed (local mechanisms of weight loss are discussed in subsequent chapters), including mechanisms of decreased caloric intake and alterations in metabolism. Finally, guidelines for nutritional support will be considered.

Diet and nutritional factors which may modulate the risk of developing gastrointestinal cancer

An increasing body of evidence supports the conclusion that diet and nutritional factors influence the risk of developing cancer. Early studies in animals models [1–4] point to the effects of body weight, total calorie intake, and dietary fat on the incidence of spontaneous and carcinogen-induced cancers. Hundreds of subsequent studies supported and expanded these early observations so that by 1979 a series of dietary guidelines for cancer

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

Table 1. Statement on diet, nutrition and cancer, 1979 [a]

1. Excessive body weight should be avoided by maintaining a balance between caloric intake and proper exercise
2. A high intake of fat should be avoided
3. A generous intake of fiber would seem prudent
4. The diet should be well balanced, including ample fresh fruits and vegetables
5. Alcholic beverages should be consumed only in moderation

[a] See [5].

prevention could be proposed [5] (Table 1). An overview of research in this area and a somewhat expanded set of dietary guidelines were published in 1982 [6]. A further expansion of the dietary guidelines was published in 1984 [7].

With increased understanding of the process of carcinogenesis it has become possible to understand how diet and nutrition may modulate carcinogenesis. Metabolic activation or deactivation of carcinogens within the body may be influenced by diet. Carcinogens usually require metabolic activation in order to exert their cancer-inducing properties [8]. The metabolic fate of a compound is determined by a complex series of reactions including activation, deactivation, reactivation, and so forth. Scavenging and other defense systems may be altered by diet. Also, cells have the ability to repair damaged DNA and thus interrupt and reverse the carcinogenic process; this may be affected by diet. Certain dietary components may have promoting activity while other dietary components have anti-promoting activity.

Research in the area of diet, nutrition and cancer may be classified into several broad categories including epidemiologic studies, laboratory studies, biochemical epidemiologic studies (blending the technology of epidemiology with that of laboratory research), and clinical trials [9]. For each nutrient category discussed below a summary paragraph will be followed by a paragraph summarizing each of the above noted categories of research (epidemiologic, laboratory, etc.) where data are available. When adequate information permits, comments on the possible magnitude of effect and possible adverse effects if too large a change were to be implemented will be presented.

Total caloric intake and obesity

Epidemiologic studies in human populations and studies in animal models support the conclusion that total caloric intake affects the risk of cancer. Animal studies have involved restriction of total calories, stimulation of increased caloric intake, or comparisons between normal weight and obese

animals. In human studies it is difficult to measure total caloric intake accurately over long periods of time, but the cumulative balance between caloric expenditure and caloric intake is reflected in body weight. For human studies therefore we place most emphasis on relationships between body weight (including comparative data or a body weight index) and risk of cancer.

Human epidemiologic studies show that an increased risk of death from cancer correlates with increased body weight. This has been seen in multiple studies focusing on a single tumor type [10–13] and in cohort studies spanning a spectrum of tumor types [14]. In representative data, the lowest overall cancer risk for men was in those who were within 10% of the average weight for their age and height, while for women the lowest risk overall was seen in women who were 10–20% below the average weight for their age and height. When data from non-smokers were analyzed, the lowest risk for both men and women was in those weight was 10% or more below average weight. In men, being overweight increases the risk of cancer of the kidney, prostate and colon-rectum. In women, being overweight increases the risk for cancer of the gallbladder, uterus, breast, colon-rectum, ovary, cervix, and kidney [14].

Experimental animal model studies indicate that moderate restriction of caloric intake results in reduction in the incidence of many different cancers and an increase in life span [1, 2]. These experiments have been replicated recently using diets that incorporate current knowledge about nutritional requirements, and confirm that cancer incidence can be reduced by caloric restriction [15]. The greatest reduction of cancer incidence is associated with life-long restriction of calories. However, caloric restriction begun in adulthood may also have a protective effect [16]. Total calories and calories from fat both affect cancer risk. The relative importance of total calories or fat calories may be different for different tumor types. The interrelationships are discussed in more detail in the section on dietary fat.

Several possible mechanisms may underlie these effects of total calories on risk of cancer. Many of the chemicals which cause cancer are lipophilic and may be stored in body fat. They may be transported from body fat to target tissues where they cause cancer. Since one of the factors controlling cell growth is avalable energy supply [17, 18], it is likely that an excess of available energy permits increased cell division and thus affects the promotion phase of carcinogenesis. Excess available energy could also shorten the silent interval (the interval between development of a malignant cell and clinical detection of a cancer) by increasing the rate of growth from the initial cancer cell to a clinically detectable mass.

The possible magnitude of effect of excess body weight on risk of cancer may be estimated. In the largest available human study, when the effects of smoking were excluded, the risk of cancer increased with increasing body

weight over the entire range of weights studied. Compared to the risks of an average weight group, the risks of cancer for those 40% or more above average weight were increased 33% for men and 55% for women [14]. Thus the effect of excess weight is approximately a 1% increase in risk of dying from cancer for each 1% of excess weight with a greater effect in women than in men.

There is little risk from lowering body weight and/or reducing caloric intake. If weight is lost in moderation the only adverse effect is reduced resistance to the effects of famine which is not likely to be a problem in developed countries.

Dietary fats

A large body of epidemiologic evidence supports a direct relationship between dietary fat and incidence of cancer of the breast, colon, rectum, and prostate. Many important relationships between dietary fat and risk of cancer have been demonstrated in animal experiments including dose-response, phase of carcinogenesis, type of fat, and reversibility of effect. Early studies may be difficult to interpret because of uncertainties as to nutritional completeness of the study diets or differences of more than one factor between experimental and control groups. Recent experiments which have used nutritionally complete diets and have used experimental designs which isolate one factor for study have documented the role of dietary fat in cancer incidence.

Human epidemiologic studies show that the risk of cancer of the colon, breast, and prostate correlates with total fat consumption among countries [12, 19–22]. Studies which have not confirmed this correlation usually have had a limited range of variation in the fat intake in the population studied. People who migrate to a country with a high incidence of colon, breast, or prostate cancer acquire the dietary habits of their new country of residence and their cancer incidence increases proportionately to their dietary fat intake [23, 24]. Different dietary fats may have effects of different magnitude but the international correlations between risk of cancer and dietary fat are strongest for fats of animal origin. Several studies show correlations between breast or colon cancer and meat intake which are of the same magnitude as the correlation with fat intake. However, since animal studies show no consistent effect of protein intake on cancer incidence, it is generally felt that the correlations with meat intake are due to the fat content of the meat. The effect of dietary cholesterol per se on the indicence of cancer is difficult to determine because of its strong correlation with animal fat intake. In one study the correlation with colon cancer incidence was stronger for dietary cholesterol than for dietary fat [12], but other studies have shown a stronger correlation for total dietary fat.

Experimental animal model studies show a higher incidence of cancer of the breast, colon, and prostate in animals on a high fat diet compared to those fed a low fat diet. These observations have been confirmed with a variety of carcinogens including viruses and chemicals [25]. The effect of dietary fat differs with the type of fat, with polyunsaturated fat having the greatest tumor enhancing effect in experimental models [26]. This is in contrast to human studies that have suggested the greatest effect was from saturated fats [12, 19–22]. Animal experiments also show that dietary fat has its greatest effect during the promotion phase of carcinogenesis, but a lesser effect on initiation has been seen in some studies. The tumor enhancing effect is proportional to the fat content of the diet over a wide range of fat content. The effect is also proportional to the duration of administration of a high fat diet [27]. The effect of dietary fat is reversible within certain limits and reduction of dietary fat even late in carcinogenesis will reduce subsequent cancer incidence [28].

There are important interrelationships between dietary fat and other dietary factors. For example, in colon cancer part of the effect of dietary fat may be related to a higher intake of total calories during a high fat diet. Also, in colon cancer there is evidence for a complex interrelationship between dietary fat and dietary fiber in which fat may have an enhancing effect on carcinogenesis while fiber may have a protective effect [29].

Biochemical epidemiology studies have probed the relationship between serum cholesterol and colon cancer risk. Some studies show a direct correlation, others an inverse correlation, and still others no association [30]. Until more definitive evidence is obtained, one must conclude that there is no direct causal relationship between serum cholesterol and risk of colon cancer.

The magnitude of the reduction in cancer incidence that may be expected with changes in dietary fat can be estimated. The comparison among populations around the world indicates that the death rate from cancer of the breast, colorectum, and prostate is directly proportional to the estimated total dietary fat intake [31]. Thus, if the total dietary fat intake were cut in half one would expect a halving of the death rate from cancer of the breast, prostate and colorectum. Based on statistical estimation, reduction of rates of cancer of the colon and rectum by more than 50% may be achievable by a combination of reduction in fat intake, reduction in body weight, reduction in total caloric intake, and increase in the intake of foods rich in fiber such as vegetables, fruits, and cereal grain foods.

The interrelationships between dietary fat and total caloric intake are complex. The fat content of a diet may influence its hedonic characteristics and if a higher fat diet is more pleasurable, this may results in increased caloric intake. Fat has a higher caloric density than other nutrients and, to the extent that food volume influences food intake, high fat foods may

result in a higher caloric intake. Another determinant of the relationship between dietary fat and caloric intake is the net energy available for use. With intake of a low fat diet a significant fraction of the energy (up to 1/3) is lost as heat, the specific dynamic action of metabolism. With higher fat diets a smaller fraction is lost as heat, and more of the energy is available for use or storage. In an animal experiment using diets which differed in caloric value and fat content, Boutwell calculated that the increased tumor incidence observed with a higher fat diet could be explained on the basis of a higher net available energy from these high fat diets. He concluded that the major effect of dietary fat on certain types of carcinogenesis is indirect, mediated through an increase in the net energy available to the animal [32]. Additional research should focus on net available energy including studies in which the net available energy is manipulated by adjusting the level of exercise of the experimental animals.

Dietary carbohydrates and protein

The effects of dietary carbohydrates on cancer risk are generally explained on the basis of their contribution to total calories and their usually reciprocal relationship to dietary fat. To the extent that dietary carbohydrate contributes to increased caloric intake, an association with cancers related to total calories may be observed. However, when dietary carbohydrates are used for isocaloric substitution of dietary fat, increased carbohydrates have been associated with a decreased incidence of those cancers which are fat-related. Interpretation of these substitution studies is complicated by uncertainty as to what caloric value for carbohydrate should be used in the design and interpretation of these studies. Usually the caloric value determined from combustion in a bomb calorimeter is used. Perhaps the caloric value related to energy storage or efficiency of utilization should be used. When ingested fat is stored, its storage caloric value is nearly identical to its value by bomb calorimeter. When carbohydrate is stored as fat, energy value is lost in the biochemical conversion from carbohydrate to fat [3, 32]. As discussed above, these thermodynamic factors must be considered in evaluating the complex interrelationships between obesity, total caloric intake, calories from fat, calories from carbohydrate and risk of cancer.

Rats fed isocaloric diets containing different sugars have shown differences in the incidence of tumors which parallel the growth rates of the rats, i.e., the differences were attributable to differences in caloric intake probably related to palatability of the diets [33].

An association between intake of protein of animal origin and incidence of certain cancers has been observed in a number of human epidemiologic studies. This association is confounded by a parallel association between

intake of animal fat and the incidence of cancer. In animal model studies excess protein intake on an isocaloric substitution basis is generally not associated with an increased incidence of tumors, for most tumor sites. On the basis of these animal data the increased risk of cancer in human studies associated with animal protein is thought to be attributable to animal fat rather than to animal protein per se.

When animals are fed ad libitum diets with protein content over the range from 10 to 51% of calories, protein level did not affect total tumor incidence [4, 34], although the organ sites of involvement varied [34]. On a calorie restricted diet the group receiving the lowest protein content had fewer tumors [34] perhaps reflecting protein deficiencies in this setting. In other experiments the incidence of tumors was decreased by feeding a very low protein diet. However, these diets have suboptimal nutritional value so these observations cannot be considered relevant for recommendations for human diets.

Dietary fiber

An increasing body of evidence supports the conclusion that dietary fiber may have a protective effect against colorectal cancer, the second-most-common cancer in the US. However, a complex relationship exists between dietary fat and dietary fiber, including reciprocal relationships in terms of intake and interactive relationships on risk of colon cancer. Most human studies have focused on total dietary fiber or crude fiber, and little is known as to which components of dietary fiber may be most protective [35].

Human epidemiologic studies indicate that dietary fiber protects against the occurrence of colorectal cancer. Most of these studies either combined colon and rectum cases in their analysis or found a protective effect for both colon and rectum. One study which analyzed the two sites separately showed a protective effect for colon but not for rectum [36]. Studies which have failed to show a protective effect have, in general either studied populations having limited heterogeneity [37], or studied populations with associated conditions which could have resulted in a prescription for increased dietary fiber [38]. As an example of the latter point, the colon cancer patients studied by Martinez had an increased occurrence of diverticulosis, colitis, constipation and hemorrhoids prior to their cancer diagnosis, all of which could have led to a prescription to increase fiber intake, and this could explain the weak direct correlation between fiber intake and colon cancer noted [38].

The relationship between dietary fiber, dietary fat and risk of colon cancer may be formulated as shown in Table 2 [29]. Populations having a low fat, higher diet tend to have a low risk of colon cancer. Either a higher fat

Table 2. Colon cancer risk related to dietary fat and fiber

Dietary fiber (fecal bulk)	Dietary fat	
	High	Low
low	high (2.5)	intermediate (1.5)
high	intermediate (1.5)	low (1.0)

Modified from [29]. Numbers in parentheses express relative risks for different groups.

content or a lower fiber content will tend to increase the risk for colon cancer, and the highest risk will be seen in populations having a high fat, low fiber diet. An epidemiologic study may document the fiber relationship, the fat relationship, or both, depending on the heterogeneity of the study population. The fiber rich food sources which have been observed to be protective include vegetables [39], fruits [40], and cereal grains [29, 41, 42].

Experimental animal model studies show a protective effect of dietary fiber on colon cancer incidence using different carcinogens and different types of fiber [43]. Variability in the protective effect of fiber seen in different experiments may be explained by the complexity of dietary fiber, including its physical and chemical characteristics [35]. Animal studies suggest that certain fiber types (alfalfa) may be ineffective [44]. In some studies diet too high in fat may have overwhelmed a possible protective effect [43]. In another study a very potent carcinogenic stimulus may have overwhelmed a possible protective effect [45]. The fiber type used in this study was shown to be protective in other studies [46]. Thus, although a protective effect of dietary fiber is not a universal finding in animal experiments, the negative studies can be explained as illustrated above, and the overall impression is that of a protective effect of dietary fiber against carcinogenesis in the colon.

In biochemical epidemiologic studies, mutagens were found in feces from populations at high risk for colon cancer while populations at low risk did not contain detectable levels of mutagens [47]. Secondary bile acids are a class of mutagenic and carcinogenic chemicals found in feces and are formed by bacterial degradation of the primary bile acids [48]. The concentration of fecal bile acids correlates directly with incidence of colon cancer on a population basis [47].

Diet may influence colon carcinogenesis by several possible mechanisms as follows. Dietary fat may stimulate increased production of primary bile acids and may increase the conversion of these primary bile acids to secondary bile acids by effects on the metabolism of gut bacteria. Dietary fiber may dilute secondary bile acids and other carcinogens via its water holding properties, may adsorb mutagens or carcinogens, such as secondary bile

acids, or may alter metabolism of gut bacteria so as to decrease formation of secondary bile acids. Thus, the epidemiologic observations on dietary fat may translate into effects on bile acid production, while the epidemiologic observations on dietary fiber may relate to effects on fecal bulk. In addition, fermentation of fiber in the feces by gut bacteria results in the release of short-chain fatty acids. These may directly influence mucosal cells in the direction of differentiation, may have an indirect effect by changing fecal pH [35], or may affect metabolism of lipids. Studies of cell kinetics of colon mucosal cells show a correlation between proliferative state, diet and risk of colon cancer [49]. Populations with a low risk of colon cancer have less active proliferation of the cells in their colon mucosa than do high risk populations. This suggests that dietary fat and/or fiber may affect the promotional phase of carcinogenesis.

There is a theoretical concern that increased fiber intake may have adverse nutritional effects since dietary fiber may adsorb trace metals and thus interfere with their absorption from the intestine. This could result in suboptimal uptake of calcium and iron. These effects have primarily been observed in short-term studies and effects on a long-term basis are unknown. Safe upper limits of fiber intake which have been suggested for human consumption are 20–25 g/day of fiber measured by the neutral detergent method or 35–40 g of total dietary fiber [50].

Vitamin A and beta carotene

A large body of evidence supports the protective effect of beta carotene and/or vitamin A against a spectrum of epithelial cancers including cancer of the colorectum, lung, breast, bladder, stomach, cervix, larynx, and mouth. Epidemiologic studies have used food record data to analyze the intake of beta carotene (one molecule of beta carotene yields two molecules of vitamin A), vitamin A, or a combination of these two often referred to as a vitamin A index. Animal studies have focused on vitamin A and its synthetic analogues and have shown protective effects for a spectrum of sites and carcinogens. Inverse correlations between blood levels of carotene or vitamin A and risk of cancer have been shown in some, but not all, biochemical epidemiology studies. Preliminary reports from controlled clinical trials show a reduced incidence of cancers or precancerous lesions in treated groups.

Human epidemiologic studies show a protective effect of dietary beta carotene or dietary vitamin A index and cancer of the lung [51, 52], and a protective effect of vitamin A intake on cancer of the head and neck, larynx, breast, stomach, colon, and bladder [53]. Experimental animal model studies show a protective effect for vitamin A and/or synthetic retinoids for

cancer of the skin, lung, breast, bladder, esophagus, liver and oral cavity [53]. Synthetic analogues of vitamin A may have greater effects and less toxicity compared to natural vitamin A. Synthetic analogues may also have greater site specificity than natural vitamin A [54]. A protective effect has been seen in animals for beta carotene for skin cancer. A protective effect for retinoids is seen even when the retinoid is given after initiation, suggesting an anti-promoting or cell-differentiation mechanism of effect [55]. Biochemical epidemiologic studies show an increased risk of cancer with low levels of vitamin A in stored sera in some [56, 57] but not all [58] studies. The failure to find this effect in some studies has been attributed to homeostatic mechanisms which tend to maintain serum retinol within a narrow range over a wide range of dietary intake. Thus low dietary (and possibly tissue) levels of vitamin A could be present with normal serum levels. Studies of tissue levels may resolve this uncertainty.

Clinical trials show regression of precancerous lesions or biologic markers of neoplastic change of the oral mucosa using several different forms of

Table 3. Results of treatment of precancerous lesions of the oral mucosa with systemic administration of carotenoids and/or retinoids

Condition	Agent	No. persons treated	Result or effect	Reference
Leukoplakia	retinyl palmitate 30 M U/12 days	10	Cr 8 [a] PR 2	59
	all-trans retinoic acid 50–100 mg/day	10	CR 4 PR 2	60
	etretinate 75 mg/day	21	CR 5 PR 10	61
	13-cis-retinoic acid	16	CR 3 PR 6 NC 2	63
Micronucleus formation	beta carotene plus retinol	40	4.2% → 1.4% [b]	63
	beta carotene	25	3.4% → 1.2%	64
	vitamin A	26	4.0% → 1.7%	
	canthaxanthin	20	3.4% → 3.4%	
	Placebo	18	3.4% → 3.3%	

[a] Indicates number of patients in each category of response unless otherwise labeled. Abbreviations are: CR = complete regression; PR = partial regression (.50% reduction in area); NC = no change.

[b] Indicates percent of cells having micronucleus formation before and after the indicated treatment.

vitamin A or its precursor beta carotene. Wannemacher *et al.* studied ten patients with leukoplakia of the oral cavity (a precancerous lesion) treated with retinyl palmitate – 30 million units in 12 days. They observed eight complete regressions and two partial regressions among ten patients [59]. Toxicity sometimes required hospitalization, and included skin and liver toxicity. Subsequent trials employing vitamin A acid, etretinate, or 13 cis-retinoic acid have all given encouraging results (see Table 3 and [59–65]).

Stich and his colleagues have utilized a biologic marker of neoplastic change to evaluate beta carotene and vitamin A in oral cavity lesions. Persons who use betel quid receive carcinogenic exposure which results in abnormal cellular mitoses with the formation of micronuclei around the nucleus of the cell. The percentage of cells having micronuclei is proportionate to betel quid exposure. In an initial study Stich found that micronucleous formation was significantly reduced by the combination of beta carotene and vitamin A [63]. In a subsequent study they found that either vitamin A or beta carotene alone was effective, but that canthaxanthin, a carotene which has anti-oxidant properties but is not a precursor for vitamin A, was not effective [64].

Possible mechanisms of effect include the consideration that both beta carotene and vitamin A have antioxidant properties and could have a scavenging function to quench reactive intermediates before they can damage DNA. The studies of Stich *et al.* suggest that the effect of beta carotene may be related to its being a precursor of vitamin A, since no effect was seen for canthoxanthin a carotene which has antioxidant effects, but which is not a precursor of vitamin A [64]. An increasing body of evidence supports the hypothesis that vitamin A and retinoids (and beta carotene after conversion to vitamin A) may have anti-promotion or cell-differentiating properties [55].

Possible adverse effects of intake of pharmacologic amounts of beta carotene include yellowing of the skin, while pharmacologic amounts of vitamin A may cause adverse effects to skin, liver, and brain [66]. Increased intake via dietary selection is unlikely to have any adverse effects except that vitamin A toxicity may develop if large amounts of liver are consumed.

Vitamin C

A limited amount of information supports a possible protective effect of vitamin C for a limited number of sites of cancer, including cancer of the esophagus and stomach. The mechanism may be via interference with the formation of nitrosamines.

Human epidemiologic studies show a protective association between dietary vitamin C and cancer of the esophagus [67, 68], stomach [69–71] and cervix [72, 73]. However, the data in many of these studies do not permit a

clear distinction between vitamin C and some other food or food factor associated with total fruit intake [72].

Experimental animal model studies show reduced tumor formation in animals given vitamin C along with precursors of nitrosamines compared to animals given these precursors alone [74]. Administration of vitamin C reduced bladder tumors in conjunction with one carcinogen [75], but not in conjunction with another carcinogen [76].

A clinical trial which may be relevant for prevention of colon cancer has been reported and a successor study is currently in progress [77, 78], (Table 8). The background for this trial is that on a population basis the risk of colon cancer may be associated with the presence of mutagens in the feces. In the trial a combination of vitamin C and E was found to reduce the amount of mutagenic material in feces to 26% of pretreatment values [78]. A study currently in progress is focusing on subjects who have had colonic polyps removed and who thus are at increased risk of subsequent development of colonic polyps. In this study the combination of vitamin C and E is being compare to placebo using a randomized control study design [77].

Two clinical trials of vitamin C in patients with polyposis coli (multiple polyps of the colon) have been reported (Table 4). In an initial study, DeCosse observed regressions of these polyps after vitamin C administration [79]. In a subsequent randomized trial vitamin C was compared to placebo. At 9 months of follow-up the ascorbic acid group had a decrease in average polyp number (−0.5), while the placebo group had an average increase (+0.3). Also, at 9 months the measurement of polyp area showed a

Table 4. Clinical trials of ascorbic acid relevant to colon cancer

Condition	Agent	No. persons treated	Result or effect	Reference
Fecal mutagens	ascorbic acid 400 mg/day, α tocopherol 400 mg/day	20	to 26% of control	78
Polyposis coli (polyps remaining in rectum)	ascorbic acid 3 g/day	8	CR 2 [a] PR 3 NC 2 PROG 1	79
Polyposis coli	ascorbic acid 3 g/day vs. placebo	36	decreased polyp nos. & area scores, no. − 0.5 vs. +0.3 area − 1.9 vs. +2.1 $p < 0.02$	80

[a] Definitions as in footnote to Table 3, and PROG = progression or worsening of disease.

decrease in the ascorbic acid group ($-1.9\ cm^2$) compared to an increase in the placebo group ($+2.1\ cm^2$) [80].

Possible mechanisms of effect include the consideration that vitamin C may block the formation of carcinogenic nitrosamines from nitrates and nitrites within the digestive system [74, 81]. In addition, vitamin C may prevent oxidation of certain chemicals to an active carcinogenic form [75].

Possible adverse effects of intake of pharmacologic amounts of vitamin C include gastrointestinal disturbances (nausea, diarrhea), iron overload in susceptible individuals, altered metabolism of certain drugs, and interference with several laboratory tests [82].

Selenium

The trace element selenium may have a protective effect against certain types of cancer. Some epidemiologic studies suggest an effect across a range of intake levels while others suggest that prevention of deficiency is the major focus of effect. In animal studies protective effects often require near-toxic levels of selenium.

Human epidemiologic studies show an inverse correlation between average *per capita* dietary selenium intake and overall cancer mortality and mortality from cancer of the colon, rectum breast, ovary, lung; and mortality from leukemia for 27 countries [83].

Experimental animal model studies show a protective effect against cancer of the liver, breast, colon, and skin using selenite, selenate, or organic selenium [84]. However, the dose giving this protective effect in most experiments is at, or near the dose which may be toxic with long-term administration [84].

Biochemical epidemiology studies show an inverse relation between regional soil and crop levels of selenium and regional cancer incidence in the United States [85]. However, this study must be interpreted in light of the major use of non-regional food sources in this country, and the confounding with industrialization in the high risk, low selenium areas. Other biochemical epidemiologic studies show an inverse correlation between selenium in serum from blood banks in different regions and the incidence of cancer of the breast, colon, rectum, and lung in these regions [83]. Case control studies show an increased risk of cancer with low levels of selenium in previously stored sera, but no protective effect of high levels compared to moderate levels. In one study the risk was increased only in the subgroup having low values for both serum selenium and serum retinol [86]. Several case-control studies show lower blood selenium levels in known cancer cases than controls but these studies must be interpreted with caution since

the low levels may be a consequence of illness, rather than being a risk factor [84].

It is possible that several different mechanisms exist to explain a protective effect of selenium. At low intakes of selenium there may be increased risk because of subnormal levels of glutathione peroxidase, an enzyme which may be protective by scavenging carcinogens. At high levels selenium may have antioxidant properties and may decrease the formation of active carcinogenic metabolites [84].

Foods and food groups

An important question is whether the protective effects attributed to specific nutrients in the preceding sections are truly attributable to the nutrient or to some other factor(s) which may be present in the foods in association with the nutrient. To a certain extent this question has been addressed by the animal studies in which a specific nutrient in pure form has been added to a synthetic or semi-synthetic diet. However, until we know more about the relevance of these animal models to human cancer, the interpretation of these results is tentative. Another approach is the clinical trials which are currently in progress. Preliminary results support the concept of protective effects of specific nutrients and additional studies will mature over the next several years. A third approach is to evaluate the epidemiologic studies considering specific nutrients and specific food groups as independent variables. We can then apply the usual criteria applied to epidemiologic studies such as the magnitude of the risk estimate, the level of statistical significance, dose-response relationships, biologic plausibility, and so forth. Many studies have evaluated groups of foods in addition to specific individual foods. If the strength of association is greater for a food group than for an individual food, then it is likely that this grouping of foods has in common the factor(s) which increases or decreases the risk of cancer. Examples include larger relative risks for colon cancer related to 'meat, any type', or 'fat foods' than for specific foods such as 'beef' or 'pork', supporting conclusions as to the role of dietary fat as a risk enhancing factor. Also, a 'carotene index' or vitamin A index may show a stronger protective effect for lung cancer than is seen for any specific vegetable [51, 52]. In aggregate, these studies support the segregation of nutrient categories which have been emphasized in the preceding paragraphs.

A particular family of foods which has received specific research attention is the cruciferous vegetables (1). In a case-control study, Graham and his

1. Cruciferous vegetables are so named because of the cross-shaped pattern in the plant structure. The family includes cauliflower, cabbage, broccoli, brussels sprouts and several other less well known vegetables.

colleagues found evidence for a protective effect against colon cancer for this family of foods [39]. This family of foods contains high concentrations of indoles, and indoles have been found to protect against gastrointestinal cancers in animal models [87].

A few epidemiologic studies have evaluated intake of vitamin supplements, but these studies have limitations, including incomplete knowledge of dose, consumption of multiple vitamins and minerals rather than a single factor, and confounding of vitamin intake by other health oriented behavior. Overall, these studies are less convincing than studies based on analysis of food groups, providing partial support for recommending food choices rather than specific supplements.

Effects of food storage and preparation

Methods of storage and preparation of foods are quite different in different parts of the world, and these differences may contribute to differences in cancer incidence. Pickled foods have been associated with an increased risk of cancer of the nasopharynx, esophagus, and stomach. Pickled foods have a high content of nitrates and sodium chloride. Nitrates form carcinogenic nitrosamines in the mouth and stomach. Sodium chloride is co-carcinogenic for the stomach in animals [88].

Foods stored without refrigeration may become contaminated with fungal growth. These fungi may produce aflatoxin, a potent carcinogen for the stomach and liver in experimental animals. Epidemiologic studies support a role for aflatoxin in human liver carcinogenesis on a worldwide basis but the relevance of aflatoxin for stomach and liver carcinogenesis in the US is uncertain.

Foods which are cured by exposure to smoke contain carcinogenic polycyclic hydrocarbons. Foods which are flavored with 'articificial smoke' presumably are not so contaminated, since this preparation is made from smoke which has been chemically treated to remove the polycyclic hydrocarbons. Mutagens may be formed within foods during cooking and the rate of mutagen formation is related to the degree of temperature elevation and the duration of cooking at very high temperature [88–90]. Charcoal broiling is of theoretical concern since smoke from the coals may carry carcinogenic polycyclic hydrocarbons to the food and the high temperature of cooking may result in formation of mutagens in the food.

Dietary and nutritional factors in the prognosis and care of the patient with cancer

We turn our focus now from nutritional factors which may influence cancer risk to a discussion of dietary and nutritional factors in the prognosis and

care of the patient who has a diagnosed cancer. The major prognostic factors in cancer patients include tumor type, stage of disease, weight loss, and performance status [91]. Of these factors, weight loss is potentially the most amenable to therapeutic intervention and/or preventive intervention. This section will review data which delineate the prognostic effects of weight loss on survival and response to chemotherapy in cancer patients. The pathophysiology of weight loss in cancer patients will be discussed and this discussion will provide a background for understanding the nutritional needs of cancer patients. The final section will deal with nutritional intervention in support of the cancer patient.

Incidence of weight loss in cancer patients

In order to explore the extent of weight loss in cancer patients, data on pretreatment weight loss were collected from patients who were entering prospective clinical trials of cancer chemotherapy [91]. Patients were interviewed to determine the percentage of body weight they had lost during the 6 months prior to the chemotherapy trial. These patients could have had previous surgery or previous radiation therapy but had not received chemotherapy. Therefore, the weight loss was not chemotherapy-related, but rather, was due to the effects of cancer as well as the effects of prior therapy. As shown in Table 5, the frequency of weight loss ranged from 26% for patients with Duke's B and C colon cancer to nearly 90% of patients with gastric cancer [91]. Note that the tumor types (pancreas and gastric) most frequently associated with weight loss also led to the greatest degree (> 10%) of weight loss among patients studied.

Table 5. Frequency of weight loss in patients with gastrointestinal cancer

Tumor type	No. of patients	Weight loss in previous 6 months [a]			
		0%	0–5%	5–10%	> 10%
Rectal adjuvant [b]	152	74	12	9	6
Colon adjuvant	701	72	15	9	4
Colon, Duke's D, non-measurable	303	54	23	13	10
Colon, measurable advanced	307	46	26	14	14
Pancreas [c]	111	17	29	28	26
Stomach, non-measurable	179	17	21	32	30
Stomach, measurable	138	13	20	29	38

[a] Data shown are percentage of line total in each weight loss category.
[b] The rectal and colon adjuvant studies included Duke's B and C.
[c] Data for pancreatic cancer are weight loss in the previous 2 months.

Table 6. Effect of weight loss on survival

Tumor type	Median survival (weeks)		
	No weight loss	Weight loss [a]	P value [b]
Colon, measurable advanced	43	21	< 0.01
Pancreas	14	12	N.S.
Non-measurable gastric	41	27	< 0.05
Measurable gastric	18	16	N.S.

[a] All categories of weight loss (0–5%, 5–10%, > 10%) have been combined.

[b] The P values refer to a test of the hypothesis that the entire survival curves are identical, not merely a test of the medians. However, in all disease sites under study, the median is a representative indicator of the survival distribution, and consequently its use as a summary statistic is acceptable.

The differences in incidence and severity of weight loss from one tumor to another may reflect differences in the natural history of the different tumors. Patients with colon cancer which is associated with a low incidence of weight loss may receive medical attention relatively early in the course of their disease before weight loss has occurred because of symptoms such as bleeding and obstruction. In contrast, cancer arising in the pancreas and the stomach is deep inside the body and may not be as amenable to early detection.

Prognosis effect of weight loss

To evaluate the prognostic effect of prechemotherapy weight loss, the survival of patients who had lost weight was compared to that of patients with the same type of cancer who had not lost weight. A shown in Table 6, survival was shorter in patients who had experienced weight loss than in patients who had not [91]. For advanced colon cancer the median survival

Table 7. Effect of weight loss subcategories on median survival (weeks) in colon cancer

Weight loss category	Median survival [a]
None	43
0–5%	27
5–10%	15
> 10%	20

[a] $P < 0.01$ based on a simultaneous test of the null hypothesis that median survival is not affected by weight loss.

Table 8. Effect on median survival of weight loss and tumor extent for colon cancer

Tumor extent [a]	No weight loss		Weight loss		P value for survival difference
	Median survival (weeks)	Patients (no.)	Median survival (weeks)	Patients (no.)	
0	52	60	31	51	0.05
1	37	75	19	101	0.01
2 or more	25	6	14	14	NS

[a] Tumor involvement was coded as absent (0) or present (1) for three anatomic sites (liver, lung, bone) and the sum was taken as a representation of tumor extent.

was approximately twice as long in patients who had not lost weight as in the patients who had. When the data were analyzed by degree of weight loss, a greater shortening of survival was associated with greater degrees of weight loss (Table 7). For many tumors, the greatest difference was between the no weight loss group and the 0–5% weight loss category, as shown for colorectal cancer in Table 7 [91].

The interaction between tumor extent and survival is shown in Table 8 for patients with colon cancer. Tumor involvement was coded as absent or present for three anatomic sites (liver, lung, and bone), and this number was taken as an approximation of tumor extent. As shown in Table 8, for each tumor extent category, survival was nearly 50% shorter for patients with weight loss compared to those without weight loss.

Analysis of the effect of weight loss on response to chemotherapy showed that pretreatment weight loss was associated with a lower frequency of response to chemotherapy (complete remission plus partial remission) in four tumor categories (colon cancer, breast cancer, acute leukemia, and non-small cell lung cancer). However, only in breast cancer did this difference reach statistical significance [91, 92].

Pathophysiology of weight loss and the nutritional needs of the cancer patient

The pathophysiology of weight loss and the nutritional needs of the cancer patient reflect the combined effects of disease and treatment. Protein-calorie under nutrition is generally thought to be the most common nutritional problem of the cancer patient. Deficiencies of a number of specific micronutrients have been described but these rarely occur in the absence of protein-calorie undernutrition. If specific micronutrient deficiencies (vitamins

or minerals) have developed along with protein-calorie undernutrition, these deficiencies would be corrected by balanced nutritional supportive interventions.

The caloric needs of the cancer patient are frequently increased compared to controls matched by age, weight, height, activity level and caloric intake [93–95]. Since decreased activity level or decreased caloric intake should result in decreased caloric expenditure [96], the finding of even a normal level of energy expenditure in a cancer patient may be considered to reflect relative hyper-metabolism.

The metabolic needs of the cancer patient are increased because of the metabolism within the tumor as well as by changes in the host induced by the tumor. Metabolic needs within the tumor are due to the processes of active transport of small molecules across the cell membrane and active synthesis of new cellular structures especially synthesis of protein. Active transport of small molecules (sodium, potassium, amino acids, etc.) is needed to retain cell viability and to provide the building blocks for cell synthetic processes. Synthesis within tumor cells, especially protein synthesis, requires energy and this energy requirement is proportionate to the birth of new tumor cells rather than net tumor growth rate.

In most tumors there is a continuous turnover of cells with birth of new cells and death of tumor cells due to factors such as outgrowth of the tumor's blood supply. However, the sequence from synthesis for new cells to cell death results in net energy consumption since the energy required in protein synthesis is not recaptured at cell death. The synthesis of new cells also requires precursor amino acids, nucleic acids, and lipids but many of these may be recaptured after death of the tumor cells.

In addition to the energy consumed within the tumor, the tumor places other energy demands on host metabolism. Cancers induce formation of new blood vessels and frequently induce extensive formation of connective tissue. This neo-vascularity and desmoplastic reaction requires energy and substrate molecules for synthesis. Cancer frequently induces changes in protein synthesis also as a systemic effect of the cancer including altered synthesis of proteins within the liver [97].

The predominant pathway of carbohydrate metabolism within the tumor also affects host metabolism. As in exercising muscle and in red blood cells, a prominent pathway for glucose metabolism within tumor cells is anaerobic metabolism, the so-called Warburg effect. This results in release of lactate from tumor cells which is transported to the liver and kidney where the lactate is converted to glucose in an energy requiring process via the Cori cycle. In the normal person 75 g of lactate passes through this cycle per day, while in the cancer patient lactate production frequently is in the range of 200–300 g per day and its production is correlated with weight loss [98, 99].

In addition to the nutritional needs related to the tumor, anti-cancer treatment may impose extra nutritional needs on the cancer patient. The needs associated with surgery include those related to uncomplicated surgery and those related to surgical complications. Patients who have an uncomplicated course have moderately increased nutritional requirements related to the stress of surgery and the requirements for wound healing [100]. These requirements can usually be fulfilled from body stores of energy, amino acids, etc. and no specific nutritional support may be required other than the usual fluids and electrolytes.

In cancer patients who have lost weight prior to surgery there is an increased incidence of post-operative complications including an increase in wound-related and respiratory complications. Wound complications may be explained by delayed wound healing in the nutritionally depleted patient as well as by decreased reactivity of host defenses (see below). Respitatory complications can be attributed in part to decreased muscle function and thus decreased ability to clear pulmonary secretions. If such complications develop, the nutritional requirements will be further increased over the usual post-operative requirement [100]. In the cancer patient who has lost weight prior to surgery one should recognize the nutritional deficit and anticipate that this deficit may be accentuated if surgical complications develop. One should begin replenishing the nutritional deficit prior to surgery in an effort to decrease complications and speed post-operative recovery.

The nutritional impact of radiation therapy includes the requirements for repair of normal tissues damaged by radiation, decreased caloric intake due to a variety of mechanisms depending on the site of radiation, and specific food aversions as a conditioned response. The magnitude of the nutritional requirement for repair of damaged tissue is not known but will vary with field size, radiation dose and anatomic site of radiation. Radiation may interfere with swallowing or digestion due to its effects on mucosal surfaces. Radiation to the stomach can halt stomach emptying and thus cause nausea and anorexia with major effects on caloric intake. The taste of foods eaten in temporal proximity to radiation may be subconsciously associated with the nausea caused by irradiation and thus a conditioned aversion to these foods may develop [101], which may also contribute to decreased eating of specific foods.

The nutritional impact of chemotherapy includes the same three categories discussed above for radiation. The nutritional requirements for repair of normal tissues damaged by chemotherapy will vary with the agents used, but for most agents will include the need for repair of bone marrow and mucous membranes. The time course of this nutritional requirement in relation to cyclic chemotherapy is important. Although repopulation of bone marrow stem cells begins shortly after chemotherapy, maximum proliferation of recovering normal cell populations does not occur until midway

between doses of chemotherapy [102]. Repair of mucosal damage follows a similar time course. Increased proliferation of mucosal cells is noted several days after chemotherapy, reaches a peak mid-way between chemotherapy cycles, and returns to baseline prior to the next dose of chemotherapy. Decreased caloric intake is an acute side effect of most chemotherapy but fortunately this acute effect will usually have subsided prior to the time of maximum nutritional requirements for repair of normal tissues described above. Damage to mucous membranes often becomes symptomatic about a week after chemotherapy, coinciding with the period of maximum requirement for repair of normal tissues. A decreased caloric intake due to damage to mucous membranes may delay repair of normal tissues resulting in subsequent delays of chemotherapy. Therefore damage to mucous membranes merits specific nutritional intervention as discussed below. Conditioned aversions for foods eaten in temporal proximity to chemotherapy may result in decreased intake of specific foods. These aversions are especially likely to develop in children and young adults [103].

Mechanisms of decreased eating in cancer patients

Symptoms that might interfere with eating have been studied through questionnaire interviews of cancer patients [104]. Alterations in taste and smell were the most frequently reported symptoms. Objective measurement of taste sensation has been reported in cancer patients and abnormalities have been correlated with symptoms [105, 106]. A frequent abnormality is an elevated threshold for sweet taste, observed in approximately one-fourth of patients studied. Patients with this abnormality reported a general loss of taste for foods. Other abnormalities include an increased sensitivity to bitter taste, and an elevated threshold for salty taste. The abnormality of bitter taste was correlated with meat aversion. The frequency of taste abnormalities increased with increasing tumor extent, but did not correlate with tumor cell type. The abnormalities were reversible with regression of the tumor, and correlated with reduced caloric intake.

The most common symptom related to the gastrointestinal system was a report of a sense of filling up quickly, which might be expected to interfere with the size of a meal [104]. This symptom may reflect alterations in gastrointestinal sensing or delays in gastric emptying (discussed below in relation to blood glucose). Appetite is also influenced by blood levels of several metabolites and hormones, and the alterations in blood insulin and glucose discussed below may contribute to decreased eating. It is of note that eating requires energy expenditure. A cancer patient who is in negative energy balance may have less energy for eating, leading to a vicious cycle of decreased energy for eating, decreased eating, and so forth.

Learned aversions as an effect of cancer may also contribute to decreased eating [103]. The Cori cycle or some other metabolic sequence might be involved in the development of learned food aversions in cancer patients. A learned aversion to food could develop if ingestion of food were followed by an unpleasant sensation. In cancer patients, intake of carbohydrate leads to increased production of lactate accompanied by an increase in plasma lactate [99]. It is known from studies in normal volunteers that infusion of lactate produces a symptom complex that includes anorexia, nausea, and anxiety. Thus, it is possible that carbohydrate intake by a cancer patient would result in increased blood lactate levels and lead to the unpleasant symptoms of anorexia, nausea, and anxiety, which would serve as the stimulus for a conditioned aversion to intake of carbohydrate foods.

Cancer patients have glucose intolerance as a systemic effect of cancer, and this may have an effect on appetite via several mechanisms. Blood glucose is one of the factors that influences the appetite center in the brain, and an elevated blood glucose may depress appetite. Because cancer patients may have abnormally long-lasting elevations in blood glucose following the ingestion of glucose-rich substances, they may show a correspondingly prolonged suppression of appetite after intake of carbohydrate. An elevated blood glucose level also may delay stomach emptying, resulting in a prolonged sense of fullness and further suppression of appetite. These two effects of an elevated blood glucose may provide a partial explanation for reduced appetite for meals, other than breakfast, often reported by cancer patients. The patient may be able to eat breakfast because the blood sugar has returned to normal overnight, but lacks appetite later in the day due to the prolonged elevation of blood glucose following breakfast.

It is possible that in some patients caloric intake is reduced as a homeostatic mechanism to reduce the body's metabolic rate. As discussed above, metabolism within the tumor tends to result in an increase in metabolic rate in the cancer patient. In normal person if caloric intake is restricted on a chronic basis, resting metabolic rate will decrease [107]. The cancer patient may decrease his caloric intake to decrease his body metabolism so as to offset the increased metabolism attributable to the tumor. Such a reduction in caloric intake could be viewed as adaptive in terms of normalization of metabolic rate but maladaptive in terms of meeting host nutritional requirements.

Systemic effects of malnutrition

Alterations of the functions (and in some cases structure) of many organ systems occur in the cancer patient and some may be associated with a nutritional basis. However, the association between altered function of an

ortan and an altered nutritional state does not prove causality. Evidence of mechanism of effect and/or reversal of the altered function with correction of the nutritional status will be required to prove causality. In some instances other factors such as serum inhibitory factors produced by the tumor or produced by the host in response to the tumor contribute to the observed alterations in function.

Muscle function, both strength and endurance, is diminished in the debilitated cancer patient [108]. Detailed studies of muscle function have shown that measurement of the response of muscle to nerve stimulation may provide a sensitive index of nutritional status and of response to nutritional repletion [109]. Studies of body composition in cancer patients show considerable loss of muscle mass. Approximately half of the weight loss in the cancer patient can be explained on the basis of loss of muscle mass [110]. In contrast, when a normal person loses weight the majority of this loss is drawn from adipose tissue [96]. In the muscle of a healthy person, the normal process of cell renewal results in breakdown of old proteins and the synthesis of new proteins. The breakdown of old proteins yields amino acids, some of which are released into the circulation. New proteins are synthesized from amino acids, in part drawn from the breakdown of old proteins, and, in part derived from dietary sources. In the healthy person the process of breakdown of old proteins (catabolism) and the synthesis of new proteins (anabolism) is precisely balanced so that muscle mass is preserved.

In the cancer patient there is an increased breakdown of proteins in muscle, with a corresponding increase in release of amino acids into the circulation [111]. In addition, there is an overall decrease in synthesis of protein within the muscle of cancer patients [112]. Other alterations in protein synthesis are beyond the scope of this paper [113, 114]. Synthesis of protein in muscle tissue can be measured by following the incorporation of labeled amino acid into protein. Lundholm and his colleagues studied synthesis of muscle protein by taking muscle biopsy specimens from cancer patients and controls and observed reduced protein synthesis in the muscle tissue from cancer patients [115]. Based on the evidence for decreased insulin production in the cancer patient, they studied protein synthesis in muscle in the presence of increased insulin. Although added insulin did increase protein synthesis, the increase occurred in both the cancer patients and the controls with persistent differences between the cancer patients and the controls [116]. They also studied the effect of supplemental amino acids. Adding excess amino acids to muscle tissue *in vitro* increased protein synthesis in both the cancer patients and in the controls. Again the difference between normal subjects and cancer patient persisted. Therefore, the decreased protein synthesis in muscle in cancer patients appears not to be caused by either insufficient insulin or insufficient amino acids.

Muscle in cancer patients may aso be broken down to provide glucose for tumor cells. Tumor cells derive their energy requirements from anaerobic metabolism via the Cori cycle and thus use glucose rather than lipids as their main energy source. A major source of glucose is food and if the amount of glucose ingested is insufficient to meet energy needs, stored glycogen is broken down to supply glucose to the tumor. However, the body has a limited store of glycogen, and as this becomes exhausted, glucose is derived from metabolic conversion of amino acids. The largest reservoir of amino acids in the body is the skeletal muscle, and amino acids will be drawn from muscle to supply the glucose needs of the tumor. In addition, amino acids are drawn from the muscle to provide precursors for protein synthesis within the tumor. Thus, there are several mechanisms for loss of amino acids from muscle in cancer patients. The result is muscle weakness and wasting.

This wasting of muscle involves not only skeletal muscle, but also cardiac muscle. The latter may contribute to the symptoms of easy fatigue and exertional dyspnea noted by many cancer patients. This loss of cardiac muscle mass must also be kept in mind when administering a fluid load to a cancer patient such as during parenteral nutrition. In a recent study of parenteral nutrition in patients with small cell lung cancer, 50% developed the complication of fluid overload, including 9% with congestive heart failure [117].

Immune reactivity is frequently diminished in the malnourished cancer patient. Testing for delayed hypersensitivity reactions is often included in a battery of tests for the assessment of nutritional status on the basis that this is a measure of the impact of nutritional status on cellular function. The degree of abnormality correlates with other parameters of malnutrition such as weight loss and serum albumen level. In addition, nutritional intervention is often associated with improvements in immunologic reactivity [118].

Anemia is a common finding in malnourished cancer patients. The degree of anemia may be related to tumor mass and nutritional status [119]. The pathophysiology of anemia is likely multifactorial. Decreased availability of nutrients may be a significant factor. The red cells precursors in the bone marrow from cancer patients demonstrates a lower rate of hemoglobin synthesis in response to erythropoietin compated to normal red cell precursors [119]. Serum inhibiting factors may also play a role in that hematopoietic cell proliferation *in vitro* is partially inhibited by sera from anemic cancer patients [120].

Granulocyte reserve, as measured by the increment in peripheral blood granulocyte count in response to hydocortisone, is diminished in malnourished cancer patients compared to cancer patients with normal nutritional status [121]. In this study, the granulocyte reserved did not correlate with

baseline neutrophil counts, but was inversely correlated with degree of weight loss. Baseline granulocyte counts were similar for malnourished and well-nourished cancer patients. Impairment of granulocytopoiesis as measured by granulocyte reserve may result in decreased ability to resist infection in the malnourished cancer patient.

This overview of the systemic effects of malnutrition in the cancer patient is incomplete but demonstrates the wide spectrum of effects which may be related to nutritional effects of cancer. These systemic effects in turn partially explain some of the complications observed during the treatment of cancer patients.

Nutritional support in the care of the cancer patient

The goals of nutritional support for the cancer patient include prevention or reversal of the adverse effects of the disease, prevention or amelioration of the side effects of therapy, improvement in the overall results of therapy, and improvement in the quality of life. Concerning prevention and reversal of the adverse nutritional effects of cancer and improvement of the patient's quality of life, an important first step is an understanding of the problem by the clinician and the patient. Together they should discuss the problems and priorities and tailor an intervention program for the individual [122]. The results should be evaluated periodically recognizing that not all approaches will be suitable for all patients and that different approaches will be required at different stages of illness.

For the cancer patient who requires surgery and has had previous weight loss, this prior weight loss is an important predictor of surgical complications [123]. In addition, several contraolled clinical trials have demonstrated that pre-operative parenteral nutrition in patients with cancer can reduce post-operative complications [124, 125]. Complications which were reduced include problems in wound healing and the incidence of and/or severity of pneumonia [125]. The severity of pneumonia may be reduced because nutritional support improves muscle function and thus the ability to clear pulmonary secretions [109]. Overall post-operative mortality was also reduced by parenteral nutrition begun pre-operatively [125]. A discussion of the details of administration of parenteral nutrition is beyond the scope of this chapter and the reader is referred to several recent publications [126, 127]. In the cancer patient who has not lost weight, parenteral nutrition may not be needed unless complications develop in which case vigorous attention to nutrition may speed recovery.

For the cancer patient receiving radiation therapy or chemotherapy, the increased nutritional requirements for repair of normal tissue can usually be met by suggesting nutritional supplements such as dessert foods having high

caloric density. To minimize the development of conditioned aversion, novel or infrequently eaten foods should be avoided for 4–6 h before and after radiation. Since conditioned aversion is less likely to develop for very familiar foods, these may be eaten in closer temporal relation to radiation therapy. A similar strategy of avoiding novel or infrequently eaten foods before and after chemotherapy should be considered to minimize conditioned aversions related to chemotherapy.

Management of mucous membrane toxicity from either radiation therapy or chemotherapy requires specific strategies depending on the location of the mucosal toxicity. For oral and esophageal involvement a mild anaesthetic such as phenol/sodium phenolate in dilute solution or lozenge form is often useful. Foods should be moist, soft, bland and lukewarm. Fruit juices should be avoided because their acid character may be irritating while creamy soups should be encouraged. Mucous membrane toxicity involving the small or large intestine if mild or moderate may be managed using elemental diets to minimize the burden on the digestive processes. Since elemental diets have poor patient acceptance because of their taste, tube feeding may be needed. Severe mucous membrane toxicity of the small or large intestine may require putting the intestine at rest until the damage has been repaired. Parenteral nutrition is useful in this setting to maintain or improve nutritional status until the mucosa recovers.

When chemotherapy is given on a cyclic schedule, nutritional advice should be given based on the anticipated characteristics of the cycle. For the initial post-chemotherapy nausea, the emphasis should be on avoidance of dehydration. This should include instruction in hyperhydration over the day prior to chemotherapy. After chemotherapy, tea and weakly carbonated beverages may be useful. No effort should be made to force caloric intake and the patient should be advised that weight loss of a few pounds may be acceptable. When nausea has subsided, increased caloric intake should be emphasized in order to replace the caloric deficit sustained during the period of nausea and to meet the needs for repair of normal tissues. Emphasis should be placed on tasty foods of high caloric density.

As noted above, the nutritional requirements for repair of normal tissues may reach a peak midway between doses of chemotherapy. Patients should be advised of this time course and advised to increase their intake accordingly. Mucous membrane toxicity may develop during this period of increased requirement and should be managed as discussed in relation to radiation therapy. Tube feeding or parenteral nutrition may be quite useful in meeting the increased requirement during a period of mucosal toxicity.

Changes in food selection or seasoning may be of value in dealing with the changes in taste sensation which may occur with advanced cancer. Patients who note a general decrease in the flavor of foods may be able to eat more if they increase the seasoning of foods. Patients noting a distaste

for red meats may be able to eat fish, poultry, eggs and cheese as nutritious sources of protein. Aversions to specific foods are best handled by avoidance of those foods and selection of foods having clearly different patterns of flavoring, such a change to the cuisine of another country or region. Several reports on small series strongly support the value of nutritional support in the care of the cancer patient [128].

Additional studies are needed to further define the role of augmented nutritional intake in the cancer patient who has lost weight and is receiving radiation or chemotherapy. Such studies must take into account many complex interactions between nutrition and therapy including the negative impact of radiation and several chemotherapy drugs on host protein synthesis [129], and the apparently increased sensitivity of a tumor to certain drugs when they are given shortly after initiation of parenteral nutrition [130, 131].

Finally, it may be noted that attention to nutritional aspects of patient care will give the patient a sense of control over his own destiny, and may keep him from turning to unorthodox therapies [132]. Understanding nutritional problems and providing nutritional support may contribute to an improved quality of life of the cancer patient.

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3. Precursors for upper gastrointestinal cancer: the need for screening

DAVID E. LARSON and L. JOSEPH MELTON III

Introduction

Over the past two decades, an increasing number of reports in the literature have suggested that cancer of the esophagus and stomach may develop in association with certain underlying disorders or following previous surgery for benign disease. These reports have prompted recommendations for periodic surveillance, particularly endoscopic surveillance, of patients with achalasia, columnar epithelium-lined (Barrett's) esophagus, pernicious anemia, gastric polyps, and those who have had a previous operation for benign peptic ulcer disease, the presumption being that these conditions are associated with an increased risk of malignant disease. The actual benefit of disease screening programs of this sort is not necessarily obvious, however, and the utility of periodic surveillance for these conditions remains controversial. In this chapter, we describe the general conditions under which periodic screening constitutes optimal clinical practice. We then assess present knowledge about the relative benefits of screening patients with these specific precursor lesions.

General principles

Disease screening is a complex activity with the possibility of great benefit to some individuals but potential hazard to others. Likewise, screening may result in substantial savings for society at large, but it is possible for these savings to be outweighed by the expenses of the screening program. Consequently, the decision to implement a screening program cannot be made lightly but requires consideration of many factors (Table 1), some of which are somewhat removed from the usual concerns of clinical practice.

There is no question that esophageal and gastric cancers are serious conditions with grim prognosis. There is also little debate that treatment of

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

Table 1. Principles for disease screening programs

1 The disease to be screened for must be one with serious consequences
2. Effective treatment for the disease must be available
3. Treatment must be more effective when the disease is detected earlier (i.e. in the asymptomatic stage)
4. An acceptable test must exist which can detect the disease early in its course
5. The benefits of screening must outweigh its costs

such patients would be improved by early detection. It is less clear, however, that sufficiently early detection is likely in the context of a program of periodic surveillance. In many of the reports to be presented, patient outcomes were little affected. Despite the availability of safe, if expensive, endoscopic screening procedures, the clinician is faced with a dilemma. He now has the tools (endoscopy with brushing and biopsy) to screen patients, but is unsure whether or not endoscopic surveillance will benefit his patients. The yield may be negligible.

In an analysis of screening programs for postgastrectomy cancer, which can be applied to all endoscopic surveillance programs, Logan and Langman point out that all screening programs cannot simply be assumed to be useful: 'For screening to be worthwhile, the disease under consideration should be a serious health problem in the population to be examined, and account must be taken of the risk in the rest of the population' [1]. As will be illustrated below, case reports and studies of clinical series of patients attended at referral centers may seriously overstate the risk of cancer. Some reports contain a mixture of patients with precursor lesions who are followed prospectively until a malignancy develops and others whose lesions were detected as a result of a symptomatic malignancy. Adding these incidence and prevalence cancers together to arrive at an overall 'risk' of malignancy cannot be expected to reflect the actual risk among unselected patients in the community. Moreover, case reports and patients series do not demonstrate a casual relationship, nor do they prove that such events occur more frequently than might be expected on the basis of chance alone. The naturally occurring risk of esophageal or gastric cancer in the general population must be known in order to decide whether or not the excess cancer risk in those with precursor lesions justifies a routine surveillance program.

In addition, it needs to be pointed out that surveillance programs for presumed premalignant disorders imply that screening is being carried out on asymptomatic individuals. The literature on which endoscopic surveillance recommendations are based contains a mixture of patients populations. Often times, these studies are from retrospective or autopsy reviews and/or are generated from referral centers in which patient selection bias is

inherent. They often include patients who are symptomatic or patients in whom the discovery of the underlying disorder occurs simultaneously with the diagnosis of its associated upper gastrointestinal cancer. Surveillance recommendations from this type of data are virtually meaningless.

Even if the relative risk of esophageal or gastric cancer were increased among asymptomatic individuals who would be candidates for a surveillance program, one must take the absolute level of risk into account. These malignancies are relatively uncommon even among patients with precursor lesions. Consequently, the hazards and expense of performing hundreds of endoscopies with biopsy for each malignancy found might result in more harm than benefit.

As Logan and Langman correctly point out, '... screening for any disease is useful only when early therapy, at the screened stage, is more effective than treatment given at a later stage' [1]. It is not at all clear that this is generally true for the esophageal and gastric cancers discovered as a result of periodic screening of patients with precusor lesions. Routine screening of a high-risk group (even if the relative risk is three or higher) may do little to influence life expectancy for the group as a whole. When effectiveness of screening is presented in terms of patients who have been found to have cancer, it may be dramatic; however, when viewed prospectively in terms of the yield of the entire program, the impact may be very small [2]. Thus the results of cancer surveillance programs must be critically analyzed. At the present time, the only cancer surveillance programs on asymptomatic individuals that have withstood critical evaluation are those for breast and cervical cancers [3, 4].

Factors other than the 'medical question' also need to be considered. One must be cognizant of benefit: cost ratios, particularly in a society emphasizing cost restraint, when the number of patients to be surveyed is large and the long-term benefits of finding a cancer through surveillance are unknown.

Population-based studies, which involve the natural or spontaneous incidence of upper gastrointestinal tract cancer, are needed to adequately determine whether extensive surveillance programs on mainly asymptomatic individuals are mandated. We would agree with Dr Hans Popper who stated that, '... evidence is emerging that epidemiologic study of population groups by meticulous statistical analysis makes an imput on the health of the whole population' [5]. In an editorial, Relman [6] also called attention to the need for population-based data on which to base decisions regarding optimal medical care. Much more definitive data, especially population-based data from North American, is needed [7].

With these thoughts on the appropriate use of surveillance in mind, let us turn to the question of whether endoscopic surveillance should be performed in those conditions which have been presumed to be premalignant conditions of the upper gastrointestinal tract.

Achalasia

Achalasia is a motor disorder of the esophagus of unknown etiology. In this condition, absent or ineffective peristalsis of the lower two-thirds of the esophagus, coupled with incomplete lower esophageal sphincter relaxation and increased lower esophageal sphincter pressure, prevents the movement of solid and liquid food into the stomach. Case reports as early as 1872 [8] and literature reviews since then have suggested an association of achalasia with subsequent squamous cell carcinoma of the esophagus [6–17]. It has been hypothesized that these cancers develop as a consequence of chronic irritation of the esophageal mucosa by retained foods and saliva [13, 16]. Although this seems reasonable, no conclusive proof exists that this is the etiology of cancer in patients with achalasia. Indeed, the fact that achalasia is equally or more common in women than men [18] while squamous cell carcinoma of the esophagus occurs most frequently in men [17, 18] suggests that other important risk factors must be involved.

Estimates of the risk of subsequent esophageal carcinoma vary from 1.7 to 20% [8–16]. However, these studies must be interpreted cautiously because none reflect the actual natural history of achalasia among unselected patients in an entire community. Rather, because of the rarity of the primary disorder [18], most studies are from referral centers. Consequently, it is likely that selection bias (the disproportionate referral of patients with both achalasia and esophageal cancer) could potentially inflate risk estimates.

Several studies have assessed the risk of esophageal cancer in achalasia prospectively. In one recent investigation of 100 patients with well-defined achalasia from 1974–1981, 91 patients were followed for a mean of 77.6 months (6–276 months) after the diagnosis of achalasia. No cases of esophageal cancer were noted in 589 person-years of follow-up [19]. However, the period of follow-up may have been insufficient since these cancers rarely occur before 15 years of symptomatic disease [8–16].

For those patients adequately treated with good esophageal drainage early in the course of achalasia, the risk of the subsequent development of an esophageal cancer was found to be minimal in a large series from the Mayo Clinic [17]. In this study, 1,318 patients were treated either with balloon dilatation (1,019 patients) or esophagomyotomy (269 patients) and followed for 17,098 patient-years with the average follow-up 13 years. Seven patients developed a subsequent esophageal cancer for an incidence rate of 41 cases of esophageal cancer per 100,000 person-years of observation. The incidence of esophageal cancer in these patients was said to be seven- to eight-fold increased over that in the general population, although the estimate was not standardized by age and sex and no comparison rates from the general Mayo Clinic population were presented [17].

It is important to note, however, that the absolute risk of esophageal car

cinoma is small, 0 of 91 patients and 7 of 1,318 patients, respectively, in the two studied quoted above [17, 19]. Moreover, when the charts of all patients with esophageal cancer from 1971–1981 were reviewed, no cases of achalasia preceding the onset of esophageal cancer were found [19].

The latter data suggest that hundreds if not thousands of annual endoscopies would have to be performed for each case of esophageal cancer detected. The sensitivity of esophagoscopy may be reduced in patients with achalasia unless preceded by thorough esophageal lavage [15], and the risks of the procedure may not be negligible in this group. Moreover, there is no good evidence that annual esophagoscopy actually improves patient outcomes. Despite these uncertainties, it seems reasonable to recommend that there is no need for endoscopic surveillance if effective dilatation or esophagomyotomy has been performed *early* in the course of symptomatic disease. However, for the rare patient who remains untreated, periodic endoscopic surveillance after 15 years may be justified. There are no data to determine whether or not patients who are treated later in the course of achalasia are at significant risk for the subsequent development of esophageal cancer and thus the role of endoscopic surveillance in this subset of patients has not been adequately determined.

Caution is clearly needed in defining endoscopic surveillance recommendation in patients with achalasia due to lack of population-based data, referral center bias in the studies that have been published, the difficulty in defining 'early' versus 'late' in the natural history of achalasia, and the question of whether or not the length of disease necessarily correlates with the duration of symptoms. Better data, preferably population-based data, are needed to accurately define the risk of esophageal cancer in patients with achalasia and to rule out other factors, such as alcohol and smoking, as significant contributing causes.

Barrett's esophagus (columnar epithelium-lined esophagus)

Barrett's esophagus is a disorder in which the distal esophagus is lined by columnar epithelium instead of the usual stratified squamous epithelium. Barrett originally thought the columnar-lined esophagus consisted of a congenitally short esophagus with cephalad displacement of the stomach [20]. However, most evidence at present supports an acquired etiology [21–23]. Clinical observation and serial endoscopic studies show migration of the squamo-columnar mucosal junction proximally in the esophagus as much as 3 cm per year, and experimental studies in the dog show that re-epithelialization of the distal esophagus by columnar epithelium follows surgical removal of squamous epithelium when this area is maintained in an acid environment. Thus, the current concept is that Barrett's esophagus repre-

sents the histologic sequalae of the healing process that follows destruction of squamous mucosa by refluc of noxious fluid into the distal esophagus.

Associated symptoms are related either to gastroesophageal reflux or to a complication of Barrett's esophagus: esophagitis, ulceration or perforation, stricture, bleeding, and/or the development of an adenocarcinoma of the esophagus. The frequency of Barret's esophagus in patients with symptoms of reflux esophagitis is unknown. Published reports of 11% of patients with esophageal reflux [24] and 44% of patients with chronic peptic esophageal strictures [25] undoubtedly reflect the bias of patients referred to medical centers because of symptoms unresponsive to conventional medical therapy. The true incidence of Barrett's esophagus in a defined population is unknown and would be difficult to determine, as only some of those who are symptomatic are investigated endoscopically and there are asymptomatic patients in whom the diagnosis is never made.

Barrett's esophagus has been associated with adenocarcinoma of the esophagus, with retrospective reviews suggesting a risk of development of esophageal cancer varying from 2.5 to 46% [24, 27–31]. The higher figures probably include patients with the simultaneous discovery of adenocarcinoma of the esophagus and Barrett's esophagus and thus cannot be used to provide surveillance guidelines in the asymptomatic patient with Barrett's esophagus. Two comprehensive recent reviews suggest that the overall incidence is approximately 10% [32, 33]. The cancers can be noninvasive and multifocal [34–36]. Most authors agree that medical therapy or an adequately performed antireflux operation, while healing inflammation, ulceration and/or strictures, does not reverse the malignant protential of the esophagus [24, 27, 37]. A recent study challenges this position but needs confirmation [38]. These reports have prompted recommendations for endoscopic surveillance with biopsies and brushings on a periodic basis [28, 32, 33, 39].

A recent study from the Mayo Clinic was designed to determine the incidence of adenocarcinoma in a population of patients with Barrett's esophagus who did not have a carcinoma when the diagnosis of Barrett's esophagus was first made [40]. Patients with a diagnosis of Barrett's esophagus from 1961–1979 were included if the endoscopist or pathologist found the junction between squamous and columnar mucosa to be 7 cm or more above the stomach, above the lower one-third of the esophagus, or 32 cm or less from the incisor teeth. Esophageal biopsy proof of columnar mucosa was also required. One-hundred and twenty cases met these criteria. Eighteen (15%) had adenocarcinoma at the time of the initial Barrett's diagnosis. Ninety-eight percent of the remaining 104 patients were traced in 1982–1983. Twenty-five had died at a mean age of 73 years. One died from metastatic adenocarcinoma of the esophagus, two from complications after diaphragmatic hernia repair and two after esophageal hemorrhage. The other 20

patients died of unrelated causes. Seventy-seven patients were alive with mean follow-up of 8.5 years. One had a multicentric esophageal adenocarcinoma resected and is well 5 years later. The two patients had developed an adenocarcinoma 6 and 10 years after the initial Barrett's diagnosis.

The authors concluded that patients with a Barrett's esophagus may have an adenocarcinoma at the time of initial presentation, but, if they do not, the risk of the subsequent development of a malignancy was only one per 441 patient-years of follow-up [40]. In Olmsted County, Minnesota, the annual incidence of esophageal cancer is 8.5 per 100,000 for males and 2.3 per 100,000 for females, only 22% of these having adenocarcinoma instead of the more common squamous cell type [41]. In the Mayo Clinic study, the yearly incidence of adenocarcinoma of the esophagus in patients with Barrett's esophagus was 227 per 100,000 – about 30 times the expected rate. A similar study from Boston followed 105 patients, with Barrett's esophagus not found to have an esophageal cancer initially, for a total of 350 person-years. Only two patients developed an adenocarcinoma during that follow-up period for an incidence of one case per 175 person-years [42].

Although better data are needed, these studies do suggest that the risk of esophageal carcinoma is increased and, unlike the case with achalasia, a substantial proportion of esophageal cancer cases appear to have had Barrett's esophagus [27]. Again, however, the absolute risk of esophageal carcinoma was low and the yield of one formal screening program questionable [42]. Moreover, improved outcomes for patients have not been clearly established [42]. These observations suggest that the risk of developing an esophageal cancer is insufficient to warrant endoscopic surveillance, but more long-term studies are needed to define the role of surveillance for this group of patients. At the present time it may be reasonable to recommend periodic endoscopic examination with multiple brushings and biopsies of the columnar portion of the esophagus for patients with histological confirmation of Barrett's esophagus without concurrent adenocarcinoma.

Pernicious anemia

Patients with pernicious anemia may be clinically asymptomatic, present with symptoms related to anemia or complications of long-standing B_{12} deficiency, or have non-specific symptoms attributed to the upper gastrointestinal tract. These patients have been said to be at increased risk for the subsequent developed of a gastric carcinoma. Early reports in the literature, primarily retrospective reviews and autopsy studies, have suggested that the risk of developing gastric cancer is 3 to 18 times greater than that expected, and because of this, have advised either radiographic or endoscopic surveillance [43–50]. These reports do not demonstrate a casual relationship, nor

do they even show that such events occur more frequently than might be expected on the basis of chance alone. Futhermore, these studies are flawed by the disproportionate inclusion of patients with upper gastrointestinal symptoms, incomplete follow-up of asymptomatic patients, and the inclusion of patients whose gastric cancer preceded pernicious anemia or where both conditions were discovered simultaneously. Most of the studies were reported in the 1950s when gastric cancer rates were apparently greater than they are now, and life-table methods were not used to adjust for differences in duration of follow-up. Moreover, most investigations have been based on selected series of referral patients.

Two recent population-based studies from Scandinavia suggest that the incidence of gastric cancer in patients with pernicious anemia is only slightly increased over that of the general population. Using the Danish Cancer Registry, Elsborg *et al.* estimated the incidence of gastric cancer among pernicious anemia patients ≥ 70 years old to be 3.7 per 1,000 per year. This was about three times greater than the incidence of gastric cancer in the general population of Denmark which was 1.3 per 1,000 in 1972 [51]. Eriksson *et al.* in a population-based autopsy study from Malmo, Sweden, noted that 2% of all gastric cancers occurred in patients with a previous diagnosis of pernicious anemia [52]. Both investigators felt that surveillance of patients with pernicious anemia was unjustified.

Because of the lack of any population-based studies from the United States, we undertook a population-based study in Rochester, Minnesota, using a system of medical-records-linkage which allows the details of essentially all care provided to the residents of Rochester to be available for study. The potential value of this data system (The Rochester/Olmsted County Epidemiology Project) for population-based studies has been previously described [53]. Using this unique data base, we identified all 152 patients who were residents of Rochester when first diagnosed as having pernicious anemia in the 30-year period 1950–1979 and who did not already have gastric cancer at the time of diagnosis of pernicious anemia. One hundred and ten members of the entire study cohort (72%) have been followed until death, and 41% of these were examined at autopsy. The median duration of follow-up prior to death was 8.3 years in this group of 110. Of the survivors, 48% have been followed through 1983. The median duration of follow-up for all survivors was 12.5 years. In about 1,555 person-years of follow-up overall, we encountered only one primary gastric carcinoma. On the basis of age- and sex-specific incidence rates of gastric cancer for the local population [55], 1.02 new cases of stomach cancer would have been expected in the study cohort. Thus, the relative risk was slightly less than 1.0 (95% confidence interval 0.02 to 5.5) [54].

Thus, our data indicate that gastric cancer is no more common among patients with pernicious anemia than among members of the population at

large; and, in any event, the absolute risk of gastric carcinoma was very small. In the patient with symptoms suggestive of upper gastrointestinal disease, a complete investigation should be carried out; but we find no evidence to support extensive radiographic or endoscopic surveillance programs in asymptomatic patients simply because they have the diagnosis of pernicious anemia.

Gastric polyps

Gastric polyps may be discovered endoscopically or radiologically during the evaluation of symptoms such as obstruction or bleeding or may be incidental findings in patients with specific gastrointestinal conditions. Most polyps are associated with achlorhydria, and there appears to be an increased frequency of these in patients with atrophic gastritis, pernicious anemia and gastric cancer [56]. Nonetheless, gastric polyps are uncommon; the prevalence of adenomatous polyps in autopsy series is approximately 0.4% and is only slightly higher in radiological series [57, 58].

There is very little data on the natural history of gastric polyps. A longitudinal study from Japan suggests that the majority of gastric polyps do not seem to change in size with time [59]. Histologically, however, gastric polyps can be adenomatous, hyperplastic, hamartomatus, retention or heterotrophic in nature; only the adenomatous polyps are associated with malignancy. Size, distribution or number of polyps do not adequately differentiate adenomatous from non-neoplastic polyps [60, 61]. The risk of cancer apparently rises with increasing size of adenomatous polyps in an analogous situation with adenomatous polyps of the colon [58, 60–63]. Retrospective studies suggest that the risk of development of gastric cancer in adenomatous polyps increases in those polyps greater than 2 cm [62, 64]. It also should be pointed out that gastric cancer can develop in the intervening mucosa in patients with adenomatous or hyperplastic polyps, often in the setting of atrophic gastritis [60, 61]. Consequently, gastric polyps may serve as marker for an increased susceptibility to gastric cancer generally, as well as constitute a potentially premalignant lesion in some instances. A recent long-term endoscopic follow-up study from Finland noted gastric cancer developing in 12% of patients with polyps, with the gastric cancer actually occurring in the intervening gastric mucosa and not in the polyps themselves [65]. However, it should be noted that endoscopic biopsies may miss areas of focal cancer in adenomatous polyps [66].

It should be obvious from the above discussion that we have very little current, prospective, population-based data on which to base recommendations for long-term surveillance of patients with the finding of a gastric polyp. In the absence of adequate data, it may be reasonable, however, to

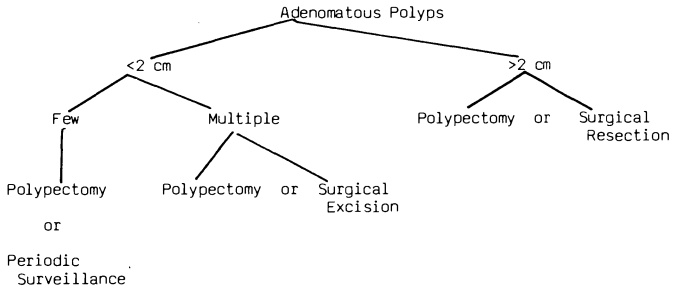

Figure 1. Adenomatous polyps.

suggest the following provisional recommendations for patients with gastric polyps:

1. all patients with polypoid defects of any size detected radiographically should be initially endoscoped with biopsy and/or polypectomy;
2. polyps causing symptoms, such as obstruction and bleeding, should be removed;
3. asymptomatic pedunculated polyps should be removed endoscopically when feasible;
4. asymptomatic sessile polyps should be initially biopsied or excised;
   a. if non-neoplastic, no further surveillance is indicated;
   b. if adenomatous, the following flow chart applies (Fig. 1).

A special situation exists in those patients with familial polyposis coli or Gardner's syndrome. Adenomatous polyps of the stomach in association with familial polyposis coli was initially described in the Japanese literature [67]. More recent reports suggest that more than 50% of such patients will have gastric polyps if studied endoscopically [68, 69]. A case of gastric adenocarcinoma in a patient with gastric polyps and Gardner's syndrome has also recently been described [70]. Although data again are lacking, it seems reasonable to perform a gastroscopy on all patients with either familiar polyposis coli or Gardner's syndrome. If initially negative, we would elect to repeat this at 2- to 3-year intervals. If adenomatous polyps are found, we would then follow the recommendations as noted on the flow diagram above.

Study of colorectal polyps has indicated little malignant potential of small, mostly hyperplastic lesions [71]. The rate of subsequent carcinoma in larger polyps is increased, but the distinction between histologic types was not so clear as previously reported [72]. With both large and small colorectal polyps, however, subsequent malignancies usually appeared some distance away from the initial lesion. Comparably detailed long-term follow-up

data on patients with gastric polyps would help suggest management approaches that were most efficient as well as optimally effective.

Post gastric surgey

Chronic changes in the gastric mucosa are invariably present following gastric surgery, often just proximal to the gastrointestinal anastomosis. The relationship of these changes to upper gastrointestinal symptoms is, however, unclear. There has been speculation that these changes may somehow lead to the development of a subsequent gastric carcinoma.

Carcinoma of the stomach occurring after an operation for benign peptic ulcer disease was first described by Balfour in 1922 [73]. Although it was initially considered rare, by 1972 more than a thousand cases of gastric cancer after surgery for peptic ulcer disease had been reported in the medical literature [74]. In the vast majority of these cases, at least 5 years had elapsed after the original surgery, effectively ruling out the presence at the time of surgery of an unsuspected carcinoma. Autopsy, retrospective reviews and prospective endoscopic studies, primarily from Europe, have suggested an apparent increased risk of gastric carcinoma in the range of 2–8.7% with the risk being independent of type of ulcer surgery, location of initial benign ulcer and sex [74–86]. Other investigators have not found any increased risk [87–93]. Nonetheless, many authors currently recommend periodic endoscopic surveillance beginning 10–15 years after the initial ulcer surgery [81, 86, 94, 95].

The impact of this recommendation for surveillance on predominantly asymptomatic individuals becomes apparent when one considers that in 1966 approximately 136,000 partial gastrectomies and vagotomies were done for peptic ulcer disease [96]. Although improved medical treatment may have played a role in decreasing the incidence of peptic ulcer surgery, as many as 56,000 to 97,000 operations were still being performed annually as late as 1977 [96, 97]. We have estimated, using actuarial tables, that if all living individuals with previous operation for benign peptic ulcer disease were endoscopically surveyed, we would be screening 1,500,000 patients per year if screening began 10 years after the initial operation and 1,100,000 per year if surveillance started 15 years after the initial operation. We further estimate the cost of a surveillance program such as this (using Mayo Clinic costs) to range from $ 542–878 million/year at 10 years to $ 400–647 million/year at 15 years [98]. Thus, endoscopic surveillance on a periodic basis on primarily asymptomatic individuals could represent an enormous expense.

Our concern has been that there have not been enough data, particularly population-based data, to justify the recommendation for endoscopic sur-

veillance at an enormous cost among asymptomatic patients who have no risk factor other than a previous operation for benign peptic ulcer disease.

Using the unique capabilities available to us to do population-based studies (discussed in the Pernicious Anemia section), we identified 338 Olmsted County residents (233 males and 105 females) who underwent surgery for benign peptic ulcer disease in the 25-year period 1935-1959 and who did not have evidence of gastric cancer for 5 years following their operations [99]. These patients were followed subsequently for over 5,600 person-years of observation (male 3,743 years and female 1,892 years). Based on age- and sex-specific gastric carcinoma rates for the local population, 2.6 new cases of stomach cancer would have been expected in the study cohort [55]. In fact, two new cases were found for a relative risk of 0.8 (95% confidence interval 0.1–2.7). In addition, an actuarial analysis demonstrated that up to 15% of patients surviving 40 years after an operation for benign ulcer disease could develop gastric cancer in the gastric remnant without invoking any increased risk above that experienced by the general population. Thus, it was our recommendation that in the asymptomatic patient with a previous operation for benign peptic ulcer disease, there is no indication for periodic endoscopic surveillance. Obviously in those patients with symptoms suggestive of upper gastrointestinal disease or unexplained anemia, a full investigation should be performed.

Several recent publications have supported these recommendations. A case-control study of all patients with adenocarcinoma of the stomach in the North Caroline Memorial Hospital Tumor Registry from 1952–1982 failed to demonstrate an overall increased risk for gastric cancer after surgery for benign peptic ulcer disease [100]. In addition, a cost-effectiveness analysis suggested that the benefit of endoscopic screening would be too low to justify screening in the American population [101].

We certainly need a better understanding of the changes that take place in the gastric mucosa both in the aging patient with atrophic gastritis and in the patient who has undergone surgery for benign peptic ulcer disease. Studies are also needed that expand our knowledge of the significance of dysplasia and its potential importance as a percursor to gastric carcinoma. In addition, the role of cytoprotection and local prostaglandin activity needs to be further evaluated. Perhaps then a subset of patients can be identified who do, in fact, carry a higher risk for the development of gastric cancer. This would provide a more cost-effective basis for surveillance.

Conclusion

The most striking conclusion from this review is the small amount of definitive data available to guide surveillance recommendations for these precursor lesions. It often seems self-evident to the clinician that subsequent carcinoma in these patients would be managed more effectively with earlier detection. However, it must be clear that hundreds if not thousands of annual endoscopies must be done to find each subsequent carcinoma, and it does not follow that the overall benefits of such screening outweigh the costs eigher to individual patients or to society at large. It seems ironic that more definitive data are required to question a surveillance program than are needed to initiate one on the basis of clinical judgement. However, with the coming challenges to clinical practice, it would behove investigators to conduct the large, especially population-based, studies needed to put these surveillance programs on a firmer foundation.

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4. Hereditary colon cancer syndromes: polyposis and nonpolyposis (Lynch syndromes I & II) variants

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Introduction

Colorectal cancer is second in incidence only to lung cancer in many of the western industrialized nations [1]. Its incidence has shown a steady increase since the turn of the century, a trend which has been attributed by some to changes in dietary patterns [2]. While environmental factors are of unquestionable significance in the etiology of colorectal cancer, the role of genetic factors, as in all forms of human diseases, must be considered. Unfortunately, in the case of colorectal cancer, with the exception of familial multiple adenomatous polyposis coli (FPC), the importance of genetics has been severely neglected. Recently, this entire subject has been extensively reviewed [3–5].

Colon cancer survival has not improved in the last two decades [6]. A major problem is its early detection. Surveillance programs that focus on high risk groups would logically show a higher cancer yield and thereby become more cost effective. Identification of high risk groups should therefore become a high priority to our national cancer effort [3, 6].

The purposes of this chapter is several-fold: (1) to update the literature on the genetics of colorectal cancer, including a historial sketch of Aldred Scott Warthin's contributions; (2) to focus attention upon new facets of the natural history of colorectal cancer, including new data on an increasing tumor spectrum in the several putatively distinct hereditary colorectal cancer hereditary syndromes; (3) to provide findings from a consecutive series of cancer patients, including those with colorectal cancer from Creighton's Oncology Clinic. Particular attention will be given to findings of heterogeneity in cancer of the colorectum; (4) to provide new leads to biomarker determination in all forms of hereditary colorectal cancer; (5) to discuss surveillance/management programs for cancer of the colorectum; and finally, (6) we shall provide an etiologic hypothesis for hereditary colon cancer

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

which integrates oncogenes, primary genetic factors, and environmental interaction.

History of colon cancer genetics: tribute to Aldred Scott Warthin, M.D. (1866–1931) (1).

We consider Aldred Scott Warthin, an esteemed pathologist whose lifetime career in this discipline was exercised at the University of Michigan, Ann Arbor, to have been the 'father' of cancer genetics.

Dr Warthin's accomplishments are many and great. While he is celebrated most popularly for his work in pathology, a most distinguished portion of his work, the true value not yet sufficiently appreciated, was in the relationship between cancer and genetics.

Warthin's insights into hereditary cancer, given the temper of the times, were truly phenomenal. The first notion that cancer may be genetic appeared in the Roman medical literature of 100 A.D. when physicians were intrigued by familial clustering of breast cancer [7]. However, the intellectual soil in familial cancer remained sterile until Broca documented an association between carcinoma of the breast and gastrointestinal tract and its transmission through several generations in his wife's family [8].

A major milestone in the history of cancer genetics occurred when, in 1895, Dr Warthin's seamstress appeared rather depressed and he queried her about her grief. She told him that everybody in her family '... had and would die of cancer ...' and she was fearful that she, too, would ultimately succumb to this disease. She died some years later of endometrial carcinoma, one of the integral tumors in her family, now known as Warthin's Family G [9].

Evidence of Warthin's profound creativity was seen by his meticulous studies of Family 'G' (and others as well) several years *prior* to the rediscovery of Mendel's principles at the turn of the century. All of Dr Warthin's original materials on Family G, which comprise meticulously documented pedigree charts, with genealogy and pathology, on countless relatives, were made available to my colleague Anne Krush and me in the mid-1960s, and ultimately, updated by us spanning more than 75 years of research [10].

It is only fitting that Wartin, the 'father of cancer genetics', was a pathologist with constant demands for detailed pathology descriptions. Unfortunately, too many of his followers in cancers genetics were less driven to accuracy, and relied on information from death certificates, a problem that

1. This is reproduced from Lynch, H.T. in Ca: A Cancer Journal for Clinicians, by permission.

impeded progress and still remains the bane to this rapidly developing discipline.

The impetus of Warthin's initial observations have now led to studies of countless cancer-prone families similar to Family 'G' in the United States, and subsequently in virtually all areas of the world [3, 11]. The tumor pattern of hereditary nonpolyposis colorectal cancer which he first described has now been refined, with specific criteria of pathology and natural history, and has been delineated into at least two clinical variants: (1) Lynch syndrome I, characterized by autosomal dominant predisposition to site-specific colonic cancer with early age at onset, predominance of cancer in the proximal colon, and multiple primary colonic cancers; and (2) Lynch syndrome II, characterized by these same features, but in addition, showing an excess of other adenocarcinomas, particularly involving the endometrium and ovary [4]. These disorders will be addressed in greater detail later in this chapter.

Warthin's last paper, published in the year of his death [12], reflected on his investigations over the years and noted that in ordinary case histories seen from surgical clinics, less than 1% of patients operated upon for cancer gave any family history of cancer. However, when such patients were subjected to detailed scrutiny, including letters and personal communications with the family of the patient, the family history of cancer was raised to over 50%! In extensive data from our own oncologic clinic, we find that about 50% of cancer patients have a first degree relative with cancer and that about 6% will have *three* or more first degree relatives with cancer (Lynch, H.T.: unpublished data, 1985). Warthin went on to admonish the average practitioner, as well as medical teachers, for *not* recognizing the significance of hereditary susceptibility to cancer, as reflected by their inadequate case histories as well as the imperfections of history taking which tended to *ignore* the family history of cancer. Unfortunately, the family history of cancer is all too often given short shrift by physicians even in 1986.

Dr Warthin's professional philosophy is described in a quotation [13] from only a month before his death: 'Pathology is not to my mind a separate subject to be taught academically, but one underlying and intimately connected with all the clinical subjects of the curriculum; the correlation of pathology with the living clinical picture represents to my mind the highest function of medical teaching, and were I starting my career again today, I should follow the same ideals and practice initiated in 1895'. It is clear that this catholic approach to medicine enabled Warthin to begin mapping the uncharted waters of cancer genetics and, true to his discipline, he was able to play a major role in steering a course which now holds promose for ultimately solving many mysteries of carcinogenesis through the new biology and pathology of DNA, including of course, the role of oncogenes.

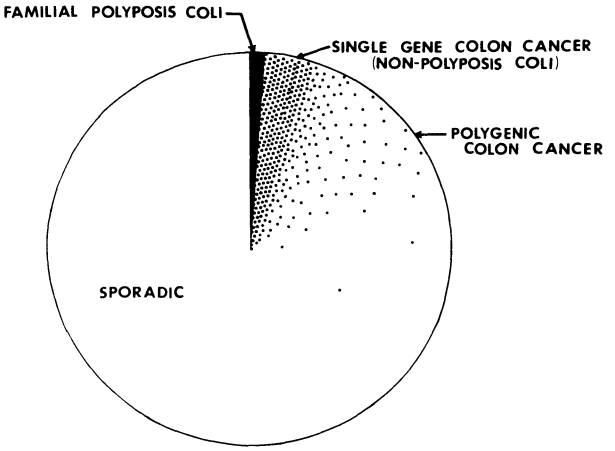


Figure 1. Distribution of hereditary colon cancer and heterogeneity (from HT Lynch *et al.* [4]).

Classification of hereditary colorectal cancer

We have operationally classified hereditary colonic cancer into four major categories:

1- multiple polyposis coli syndromes (FPC);
2. hereditary *non*polyposis colorectal cancer syndromes (HNPCC);
3. familial inflammatory bowel disease syndromes (IBD); and
4. miscellaneous hereditary cancer aggregations and/or syndromes.

Hereditary polyposis colorectal cancer syndromes

Table 1 provides a listing of the cardinal characteristics of the several hereditary multiple adenomatous, as well as nonadenomatous and/or mixed polyp disorders which predispose to colorectal carcinoma. Figure 1 provides a schematic depiction of the relative frequency of the hereditary varieties of colorectal cancer (polyposis vs. nonpolyposis forms) vs. their sporadic colorectal cancer counterparts. Based on our experience, hereditary polyposis syndromes account for approximately 1% of colon cancer cases seen [3, 14].

Familial multiple adenomatous polyposis coli: a systemic disease(s)

FPC is a well-characterized autosomal dominant disease with an estimated incidence of 1:8,000 [15]. Affected kindred members will have onset of

Table 1. Biomarkers associated with hereditary colon cancer syndromes (reprinted by permission of Lynch, H.T. *et al.* [4].)

Conditions *with* premalignant polyp expression	Mode of inheritance	Biomarker(s) and/or clinical precursors (phenotype)	Associated cancers
Familial polyposis coli (FPC)	AD	Polyp expression and Gardner's syndrome stigmata [148] Abnormal tritiated thymidine uptake of colonic mucosa [58] Increased tetraploidy in colonic mucosa [57] Abnormal skin fibroblast cytoskeleton [86], and *in vitro* growth and response to transforming agents [87] Abnormal glycoprotein synthesis by colon cells (increased proportion of sialomucins) [80] Increased transformation of *in vitro* skin fibroblasts of family subjects with chemical carcinogens [92] Increased *in vitro* sensitivity of skin fibroblasts to mitomycin C [81]	Colon, thyroid, and brain tumors
Gardner's syndrome	AD	Soft tissue and bone lesions [150] Increased *in vitro* tetraploidy in colonic mucosa and skin [57] Defective cellular immunity in two patients [4] Abnormal skin fibroblast growth in presence of tumor promotor [88] Increased *in vitro* skin fibroblast radiation sensitivity in some families [85] Hypertrophy of retinal pigment epithelium in one family [152]	Colon tumors, malignant degeneration of colon, adenomatous polyps, sarcomas, thyroid cancer, periampullary cancer, and adrenal cortical carcinoma
Turcot's syndrome (possible Gardner's variant)	AD	Adenomatous polyps of colon and central nervous system tumors [147, 149, 154–157]	Colon tumors and malignant gliomas
Generalized GI colon tumors juvenile polyposis	?	Polyp presence [155]	
Peutz-Jegher's syndrome	AD	Melanin spots (oral, vaginal, fingers) [157] Generalized gastrointestinal hamartomatous polyps Increased skin fibroblast sensitivity to viral transformation [91]	Colon tumors, adenocarcinoma of small bowel, theca cell granulosatype tumor of ovaries, and possibly breast cancer

Table 1. (continued)

Conditions *with* premalignant polyp expression	Mode of inheritance	Biomarker(s) and/or clinical precursors (phenotype)	Associated cancers
Oldfield syndrome	AD	Colonic polyps and sebaceous cysts [158]	Colon tumors
Multiple hamartoma syndrome (Cowden's disease)	AD	Multiple ectodermal, mesodermal, and endodermal nevoid neoplastic abnormalities [159], and colonic polyps Cutaneous lesions (multiple trichilemmomas) Gingival and palatal papules Thyroid, breast, gastrointestinal, and central nervous system abnormalities may also coexist	Colon, breast, thyroid, and benign visceral tumors
Solitary polyps	AD	Polyps [119, 160]	Colon tumors
Conditions *without* premalignant polyp expression			
Cancer Family Syndrome (CFS, Lynch syndrome II)	AD	Features of Torre's in small subsets of patients [42] Abnormal tritiated thymidine labelling of colonic crypts [58] Increased *in vitro* skin fibroblast tetraploidy [161] Elevated CEA levels in high risk individuals and spouses [162] Possible linkage with Jk blood group [161] Linkage with HLA [163, 164] Abnormal fibroblast growth with exposure to tumor promotor [165] Suppressor cells for mixed leukocyte culture responses in some affected and high risk family members [151] Low serum IgA and serum factors inhibiting ADCC and/or NK effector cells [166] Continuing investigation of possible usefulness of monoclonal antibodies [167]	Colon, endometrium, breast, ovary, and multiple other visceral malignancies

Table 1. (continued)

Conditions *without* premalignant polyp expression	Mode of inheritance	Biomarker(s) and/or clinical precursors (phenotype)	Associated cancers
Hereditary site-specific colon cancer exclusive of multiple polyposis coli (HSSCC, Lynch syndrome I)	AD	Possible correlation between low mitogen (PHA) responses and/or HLA antigens [84] Abnormal tritiated thymidine uptake may predict cancer risk [58] Abnormal *in vitro* tetraploidy may be a marker [119] Brachydactyly in one family [90] Decreased conversion of cholesterol to its degradation products [127]	Colon tumors
Dyskeratosis congenita	Sex-linked, AD	Altered skin pigmentation [64] Nail dystrophy Atresia of lacrimal ducts Thrombocytopenia and anemia Testicular atrophy in most cases	Colon tumors, squamous cell carcinoma of oral cavity, esophagus, nasopharynx, skin, anus, and cervix
Bloom's syndrome	AR	Telangiectatic erythema [168, 169] Photosensitivity Dwarfism with dolichocephaly Increased sister chromatid exchanges (SCE), low culture temperature greatly reduces SCE in BS cells [95], skin fibroblasts secrete factor increasing rate of SCE in normal fibroblasts [79], increased mitotic chiasmata in endoreduplicated BS lymphocytes [89], ultraviolet induction of abnormally high levels of unscheduled DNA synthesis [83] Decreased immunoglobulin production by B-lymphocytes and impaired mitogen responsiveness [94]	Colon tumors, leukemia, lymphoma, and squamous cell cancer of esophagus
Torre's syndrome	AD – may be sporadic forms	Multiple sebaceous adenoma, carcinoma, and keratoacanthoma	Colon tumors, sebaceous neoplasia, squamous and basal cell lesions, multiple visceral cancers

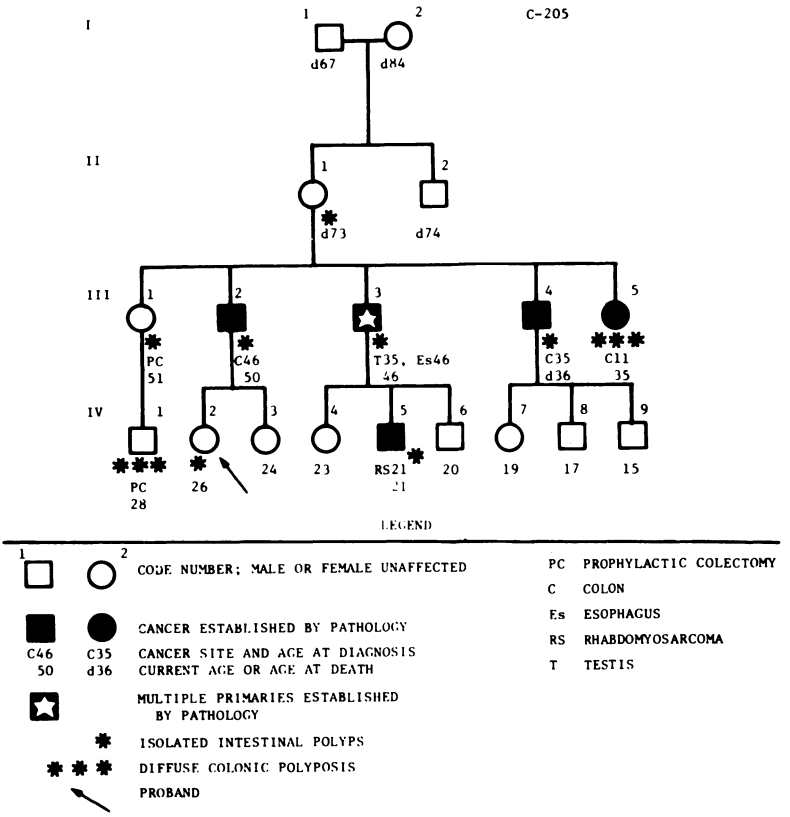


Figure 2. Pedigree of a family with familial polyposis coli that shows various polyp expression (this pedigree has been updated since it was first reported by HT Lynch *et al.* [119]).

adenomatous polyps beginning around puberty, that occur throughout the colon, but almost invariably involve the rectum. Over the years, hundreds to thousands of polyps can form, with symptoms of bleeding or mucous discharge. Virtually all affected members will develop cancer of the colon 10–15 years after the onset of polyps and these most often occur in the distal colon [16]. When accompanied by extracolonic manifestations of desmoid tumors, osteomas, and epidermal cysts, the disease has been called Gardner's syndrome. This no longer warrants a separate classification since most poplyposis patients have multiple mandibular osteomas at X-ray [17, 18].

Figure 2 shows a family with FPC and variable manifestations of the polyposis phenotype. This concept of variable number of polyps is exceedingly important for diagnosis and ultimate management of this disease(s) [19]. For example, certain individuals in the pedigree had only isolated polyps, but yet manifested early onset adenocarcinoma of the colon, while others had florid manifestations as evidenced by carpeting of the entire colonic mucosal surface with adenomatous polyps and early onset

colorectal carcinoma. One individual in the pedigree is highly instructive (Figure 2, III-1) in that this woman, who during middle age had a prophylactic colectomy because of *isolated* colonic polyps, transmitted the syndrome to her son (Figure 2, IV-1) who also underwent prophylactic colectomy because of *florid* manifestation of adenomatous polyps of the colonic mucosa.

Evidence is rapidly accruing in support of the systematic nature of FPC. Hisatomi *et al.* [20] describe an FPC kindred with embryonal carcinoma of the testis. The authors also suggest that findings in their patient may support the hypothesis that FPC is a systemic or generalized disorder with tumorigenicity that is not restricted to the colon and rectum. Hence, a total colectomy with ileostomy may not prevent all phenotypic expression of hereditary cancer propensity.

We have long considered FPC to be a disease which predisposes to a variety of cancers, as evidenced in the family seen in Figure 2. The total tumor spectrum, which may be integral to this hereditary disorder, is as yet unknown [19]. For example, Butson [21] described a patient which, as they state, '... combines almost every recorded manifestation of the syndrome of associated tumors; namely, carcinomatous changes in the polyps, osteomas of facial and other bones, periampullary carcinoma, transitional-cell carcinoma of the bladder, adrenal adenoma, intra-abdominal fibrous tumors with bowel obstruction, and a remarkable tendency to contain and survive the malignancies'. This 45-year-old patient with putative Gardner's syndrome had a remarkable pedigree consistent with facts known about this disorder.

More recently, Painter and Jagelman [22] described two unrelated patients with FPC, one of whom had adrenal adenoma, while the second had an adrenocortical carcinoma. These authors reviewed the literature with respect to extracolonic manifestations in FPC. Table 2 is a modification of their findings dealing with extracolonic manifestations in this disease.

Jarvinen *et al.* [23] provide further support for the view that FPC is a systemic disease which is not restricted to the colorectum. They describe a 63-year-old male with polypoid masses identified as adenocarcinoma in the common and hepatic ducts, and a 38-year-old female who, while undergoing surgery for duodenal adenomas, was found to have a solitary benign adenoma of the distal common duct in addition to duodenal adenocarcinoma.

Weinberger *et al.* [24] described a 20-year-old white female with FPC and epidermoid cysts. At $3\frac{1}{2}$ years of age, the patient presented with a 3-month history of an enlarging epigastric mass which extended into the right upper quadrant. At laparotomy, a multinodular tumor was histologically diagnosed as malignant hepatoma. This lesion was later updated to hepatocellular carcinoma. It was of interest that her maternal grandfather had 'genito-urinary' tumor, a brain tumor was present in the maternal grandmother,

Table 2. Extracolonic manifestations of hereditary adenomatosis of the colon and rectum. (Modified and reproduced by permission from Painter and Jagelman [22])

Manifestation	Study
Osteomas	Gardner and Richards [150] Collins [170]
Epidermoid cysts	Leppard and Bussey [171]
Gastric polyposis	Halsted *et al.* [172] Hoffman and Goligher [173] Coffey *et al.* [28]
Gastric carcinoma	Ushio *et al.* [174] Murphy *et al.* [175]
Duodenal polyposis	Ranzi *et al.* [176]
Periampullary malignancy	Jones and Nance [177] MacDonald *et al.* [178]
Desmoid tumors	McAdam and Goligher [179]
Papillary thyroid carcinoma	Crail [180] Camiel *et al.* [181]
Thyroid adenoma	Coffey *et al.* [28]
Brain tumors	Sayed *et al.* [149]
Embryonal cell cancer of testes	Hisatomi *et al.* [20]
Transitional cell cancer of the bladder	Butson [21]
Medulloblastoma	Turcot *et al.* [153]
Glioblastoma	Turcot *et al.* [153]
Glioma	Baughman *et al.* [154]
Meningioma	Dowton [182]
Pancreatic carcinoma	Parks *et al.* [183]
Adrenal adenoma	Naylor *et al.* [184] Devec and Bussey [185]
Adrenal carcinoma	Marshall *et al.* [186]
Cholangiocarcinoma	Lees and Hermann [187]
Lipomas	Gardner and Richards [150]
Dental abnormalities	Coli *et al.* [188]
Skin pigmentation	Weston and Wiener [189]
Retinal pigmentation	Blaire and Trempe [152]
Pararectal rhabdomyosarcoma	Lynch *et al.* [19]
Seminoma	Lynch *et al.* [19]
Duodenal carcinoma	Jarvinen *et al.* [23]
Hepatocellular carcinoma	Weinberger *et al.* [24]
Hepatoblastoma	Kingston *et al.* [27]
Ileal adenomas	Hamilton *et al.* [34]
Adenocarcinoma, mid-jejunum	Phillips [33]
A single patient with FPC and: IgA deficiency, lymphocytic lymphoma, malignant thymona, choroid tumor of eye, malignant astrocytoma of cerebrum, squamous cell cancer of scalp, and adenocarcinoma of colon	Hamoudi *et al.* [48]

and a colonic tumor was reported in one of her maternal aunts. Interestingly, no other members of the family had been diagnosed as having FPC. Zeze *et al.* [25] described a 33-year-old man with hepatocellular carcinoma in association with FPC. These investigators called attention to the rare association of hepatocellular carcinoma with FPC. They noted only two other documented cases, namely, the one by Weinberger and a second by Veale [26]. Furthermore, Kingston *et al.* [27] have described five cases of hepatoblastoma in children of FPC kindreds.

Coffey *et al.* [28] reported a 37-year-old woman with FPC and the Gardner's type manifestations who had diffuse gastric polyps and gastric carcinoma. In addition, she had mesenteric and retroperitoneal fibromatosis, thyroid adenomas, chest wall hemangiomas, and fibrocystic disease of the breasts. Thompson *et al.* [29] described a 22-year-old white female with multicentric papillary carcinoma of the thyroid. Two years following this diagnosis, she underwent a prophylactic colectomy because of FPC. These investigators called attention to additional reports of papillary carcinoma of the thyroid in FPC and stressed the importance of searching for malignancies of differing anatomic sites of the lifetime of FPC patients.

Though gastroduodenal polyps and duodenal carcinomas are not infrequent [30–32], Phillips [33] noted that polyposis of the more distal small bowel occurs uncommonly. Nevertheless, Hamilton *et al.* have collected nine patients with ileal adenomas following colectomy [34]. Multiple polyposis of the small bowel in context with primary cancer of the small bowel is even more unusual. Phillips [33] described a 34-year-old white male with multiple polypoosis of the small bowel and primary adenocarcinoma of the mid-jejunum, in concert with FPC. Continuing experience with FPC shows that it is indeed a systemic disease and lifetime follow-up is required in spite of what has previously been considered a 'curative' colectomy.

Familial juvenile and mixed juvenile/adenomatous colonic polyps

Juvenile or retention polyps are sometimes classified with hamartomatous polyp syndromes [15], but are easily differentiated histologically by thickened lamina propria separating mucous cysts. Though solitary retention polyps are not uncommon in children, the juvenile polyposis syndromes (colonic, disseminated, and Chronkite Canada syndrome) are less frequent than adenomatous polyp syndromes.

Juvenile colonic polyps present at an average age of six [15], younger than FPC. There may be tens to hundreds of polyps present, and as with FPC, the rectum is always involved, thereby making sigmoidoscopy effective in screening. Occasionally, retention polyps can occur throughout the GI tract. Called disseminated juvenile polyposis and thought to be a different entity

from juvenile polyposis coli [35], the mode of transmission for both syndromes is consistent with an autosomal dominant factor [3].

Jarvinen and Franssila [36] reviewed pathologic colon specimens from a patient with diffuse juvenile polyposis (unaffected family members) and from six members of one family affected with the syndrome. Of interest was the fact that histologic findings in the colonic polyps showed a spectrum ranging from juvenile polyps through focal and extensive adenomatous change, dysplasia, and ultimately to adenocarcinomas in two patients. The authors reviewed other case reports and stressed that, contrary to previous opinion, neoplastic change is frequent in juvenile polyposis coli and requires surgical treatment.

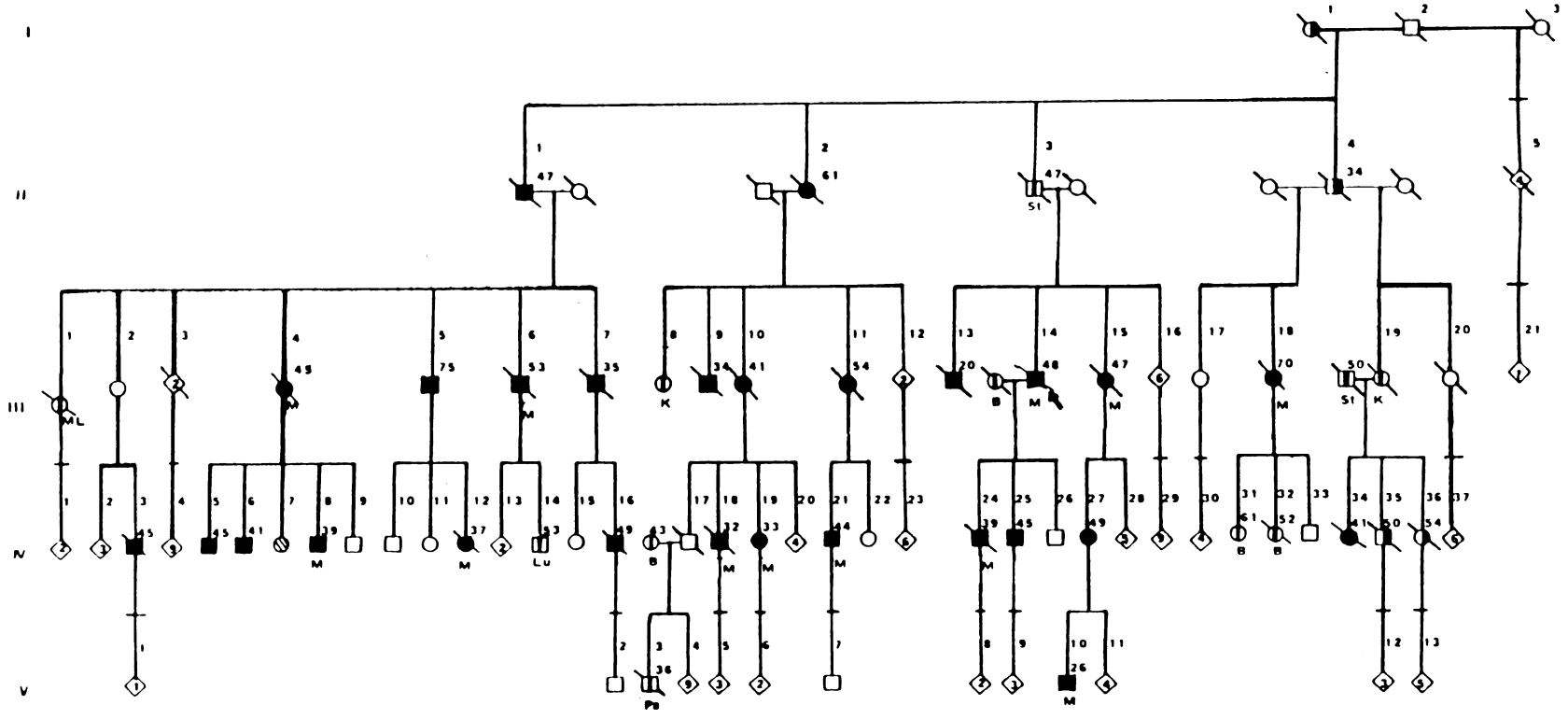
Ramaswamy *et al.* [37] also discussed the malignant potential of juvenile polyposis and described a 19-year-old boy with diffise juvenile polyposis with mucosal dysplastic changes which ranged from mild dysplasia to carcinoma in situ. They discussed the pathogenesis and malignant potential in juvenile polyposis coli.

Hereditary nonpolyposis colorectal cancer syndromes (HNPCC) (Lynch syndromes I and II) [38]

As seen in Figure 1, HNPCC constitutes at least 5–6% of all occurrences of colorectal cancer, as opposed to approximately 1% or less in the case of FPC.

The HNPCC syndromes may be further divided into two subcategories: (a) Lynch syndrome I – hereditary site-specific nonpolyposis colonic cancer (HSSCC); and (b) Lynch syndrome II – HNPCC in association with *other* forms of cancer, particularly endometrial and ovarian carcinoma. This has also been termed the cancer family syndrome (CFS). In both of the hereditary nonpolyposis colorectal cancer syndromes, there is *proximal* predominance of nonpolyposis colonic cancer (making sigmoidoscopy an ineffective screening tool), vertical transmission, early age at cancer onset, an excess of multiple primary cancer, and significantly improved survival when compared stage for stage with the American College of Surgeons Audit Series [39]. In Lynch syndrome I, the multiple primary cancers are restricted to colonic mucosa, and herein, about one-third will involved the distal colon inclusive of the rectum. In Lynch syndrome II, cancers will involve the entire colon, including the rectum, as in the former category, but *other* anatomic sites can be involved, including the endometrium and ovaries [3, 39].

Figure 3. Pedigree of family R showing colon cancer occurring in five generations (pedigree has been slightly altered since it was originally published by HT Lynch *et al.*, Arch Surg 112: 170–174, 1977). →



LEGEND

Lu	Lung
ML	Malignant Lymphoma
St	Stomach
B	Breast
K	Kidney
Pa	Pancreas
M	Multiple Primary Colon Cancer

Female, Male Unaffected
Deceased
Age of Onset
Male and Female Progeny
Colon Cancer, Verified
Colon Cancer by History
Prophylactic Colectomy
Cancer of Other Sites
Proband

C 198

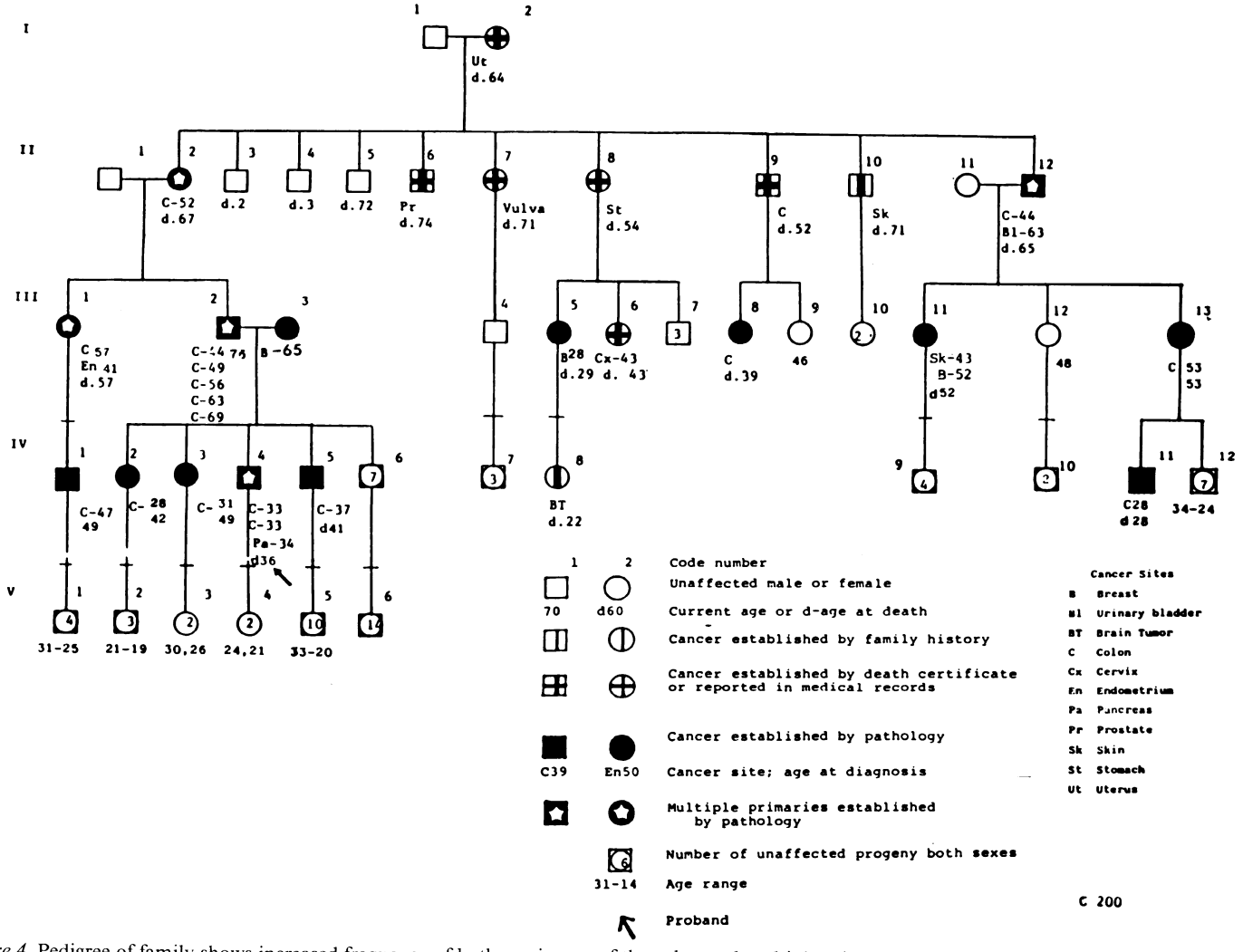


Figure 4. Pedigree of family shows increased frequency of both carcinoma of the colon and multiple primary malignant neoplasms (this pedigree has been updated since it was first reported by HT Lynch *et al.*, Surg Gyn Obstet 134:781–786, 1972).

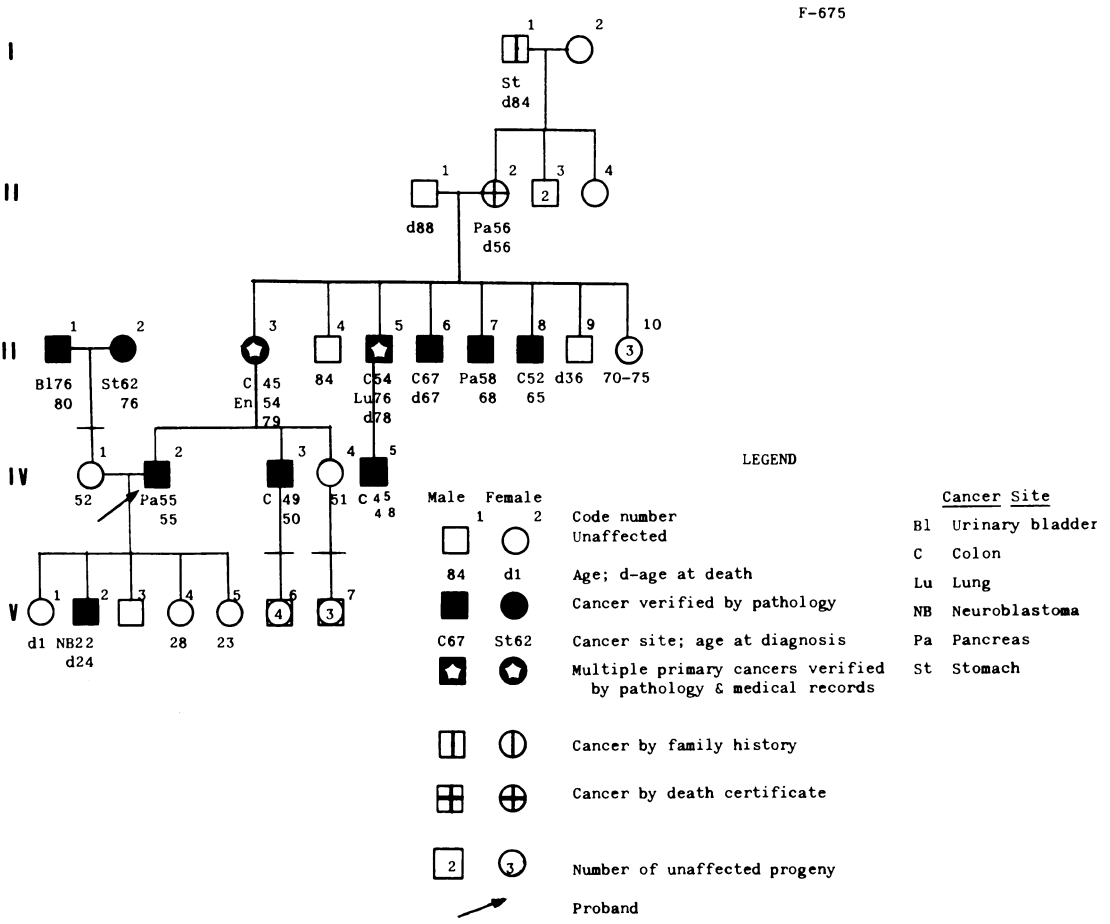


Figure 5. A Kindred showing clinico-pathologic features of hereditary nonpolyposis colorectal cancer in association with carcinoma of the pancreas (from HT Lynch *et al.* [40]).

Figure 3 depicts an example of an HSSCC pedigree (Lynch syndrome I), while Figure 4 shows a pedigree with CFS findings (Lynch syndrome II).

We have recently described a kindred (Fig. 5, F-675) with vertical transmission of cancer through five generations which showed features of Lynch syndrome II in concert with pancreatic cancer [40]. The proband was a 55-year-old white male with verified pancreatic cancer. Interestingly, as seen in the figure, all of the family members manifesting colon cancer showed proximal location in the colon, and none had evidence of multiple adenomatous polyposis coli by history or pathological verification (Figure 5, III-3, III-5, III-6, III-8, IV-3, IV-5). There was early age of onset of colorectal cancer (mean 52 years, n = 6), although the number of affected individuals was not large enough for assessment of statistical significance. Adenocarcinoma of the pancreas was identified in three genetically informative relatives (Figure

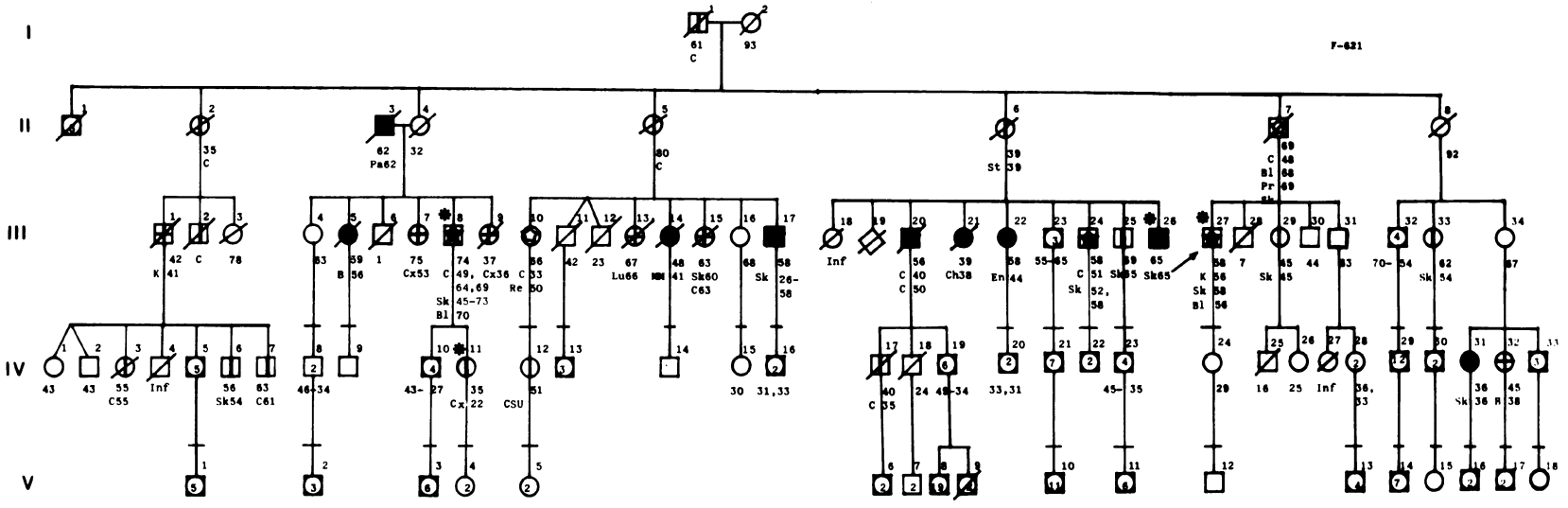
5, II-2, III-7, IV-2). Multiple primary cancers occurred in the proband's mother and in the proband's maternal uncle (Fig. 5, III-3, III-5) in this remarkable kindred.

Genetic heterogeneity with respect to variation in tumor spectrum has become increasingly more evident in Lynch syndrome II [11]. The etiologic significance of pancreatic carcinoma in Lynch syndrome II kindreds remains enigmatic. There are several possible explanations: (1) its occurrence in this particular family may be fortuitous; (2) pancreatic carcinoma may be integral to the Lynch syndrome II genotype, but heretofore, it may have been underreported because of incomplete pathology documentation of patients with intra-abdominal cancer; (3) due to extant heterogeneity, Lynch syndrome II may be attributable to a different allele at the same locus in a manner consonant with other hereditary colon cancer syndromes which also may be associated with pancreatic carcinoma, such as FPC and Gardner's syndrome; and (4) pancreatic cancer may be a pleiotropic manifestation of Lynch syndrome II's cancer-prone genotype which is being expressed as a result of temporal changes in environmental exposures which are perturbing this deleterious genotype.

An interesting finding in this kindred was that of neuroblastoma (Fig. 5, V-2) in a patient at age 22. This lesion is more characteristic of childhood and its occurrence in this patient is puzzling. While this could be fortuitous, it is also possible that it represents a pleiotropic manifestation of the Lynch syndrome II genotype. For example, Sorensen *et al.* [41] reported a familial aggregation of adult onset gastrointestinal tract tumors, including carcinoma of the colon. Four members of that particular family manifested childhood cancer; two were neuroblastomas, one was bilateral retinoblastoma, and one was an unconfirmed brain tumor.

Muir-Torre syndrome (M-T) is characterized by the occurrence of sebaceous hyperplasia, adenoma, and carcinoma, basal cell carcinoma with sebaceous differentiation, and /or keratoacanthoma in association with visceral cancer (often multiple), and improved survival. Family studies of M-T have been either wholly lacking or too incomplete to elucidate hereditary etiology. We initially proposed that M-T was integral to Lynch syndrome II [42]. More recently, we described the cutaneous phenotype of M-T in an extended kindred with a possible variant of Lynch syndrome II (Fig. 6, Table 3) [43]. We emphasize the need for more thorough documentation of family histories and cancer association in this cancer-associated genodermatosis in order to clarify hereditary syndrome identification, and to improve cancer control through employment of cutaneous signs as a beacon for highly targeted forms of visceral cancer.

Figure 6. Pedigree of family with tumor spectrum consonant with Muir-Torre cutaneous phenotype in association with Lynch syndrome II Variant (From HT Lynch *et al.* [43]). ⟶



LEGEND

Male	Female	
		Code number
		Unaffected
43	68	Age at time of study
		Died
61	93	Age at death
		Cancer by pathology
Pa62	MM41	Cancer site; age at diagnosis
		Cancer by family history
		Cancer by death certificate or medical records
		Multiple primary cancers by pathology
		Multiple primary cancers by family history

Twins

Number of unaffected progeny (both sexes)

Stillborn

Cutaneous phenotype (sebaceous hyperplasia, adenoma, carcinoma; keratoacanthoma(s)

Proband

Cancer Sites

B	Breast
Bl	Urinary bladder
C	Colon
Ch	Choriocarcinoma
CSU	Cancer site unknown
Cx	Uterine cervix
K	Kidney
Lu	Lung
MM	Malignant melanoma
Pa	Pancreas
Pr	Prostate
Re	Rectum
Sk	Skin
St	Stomach
En	Endometrium

Table 3. Family tumor registry, Muir-Torre syndrome (reprinted by permission of Lynch, H.T. *et al.* [43])

Pedigree number	Tumor diagnosis	
	Visceral	Cutaneous
I-1	Colon Ca (H-61)*	
II-2	Colon Ca (H-?)	
II-5	Colon Ca (H-?)	
II-6	Stomach Ca (H-39)	
II-7	Colon Ca (H-48)	
	Papillary Ca of bladder (P-68)	
	Prostate Ca (H-69)	
		Skin Ca (H-?)
III-1	Kidney Ca (C-41)	
III-2	Colon Ca (H-?)	
III-5	Breast Ca, duct cell (P-56)	
III-7	Uterine cervical Ca (R-53)	
III-8		Skin, squamous cell Ca × 2 (P-45)
		Skin, squamous cell epithelioma (P-49)
	Colon Ca (sigmoid) (P-49)	
		Basal cell epithelioma (P-49)
		Sebaceous gland hyperplasia (P-49)
		Basal cell epithelioma involving a sebaceous gland (P-49)
		Skin, squamous cell epithelioma × 2 (P-54)
	Colon Ca (transverse) (P-64)	
		Sebaceous gland hyperplasia (P-64)
		Keratoacanthoma (P-67)
		Sebaceous adenoma × 2 (P-67)
		Skin, squamous cell carcinoma (P-68)
		Keratoacanthoma (P-69)
	Colon Ca (P-69)	
	Adnexal tumor (most consistent with eccrine acrospiroma) (P-70)	
	Papillary transitonal cell Ca of bladder (P-70)	
		Basal cell Ca (P-71)
		Keratoacanthoma (P-72)
		Sebaceous hyperplasia (P-73)
		Sebaceous epithelioma (P-73)
		Keratoacantoma (P-73)
III-9	Uterine cervical Ca (C-36)	
III-10	Colon Ca (H-33)	
	Rectal Ca (H-50)	
III-13	Lung Ca (R-66)	
III-14		Malignant melanoma (P-41)
III-15	Colon Ca (R-63)	

Table 3. (continued)

Pedigree number	Tumor diagnosis	
	Visceral	Cutaneous
		Basal cell Ca (R-60)
III-17		Basal cell Ca (P-26)
		Basal cell Ca (P-39)
		Basal cell Ca (P-40)
		Basal cell Ca (P-44)
		Basal cell Ca (P-45)
		Basal cell Ca (P-56)
		Basal cell Ca (P-58)
III-20	Colon Ca (R-40)	
	Colon Ca (hepatic flexure) (P-50)	
III-21	Choriocarcinoma of uterus (P-38)	
III-22	Papillary adenocarcinoma of endometrium (P-44)	
III-24	Colon Ca (ascending) (P-51)	
		Skin, squamous cell carcinoma (P-52)
		Skin, squamous cell carcinoma (P-58)
III-25		Skin Ca (H-65)
III-26		Sebaceous epithelioma (P-65)
III-27		Keratoacanthoma × 2 (P-55)
		Keratoacanthoma with sebaceous gland hyperplasia (P-55)
	Papillary transitional cell Ca of renal pelvis (P-56)	
	Transitional cell Ca of bladder (R-56)	
		Sebaceous adenoma × 3 (P-56)
		Keratoacanthoma (P-58)
		Skin, squamous cell Ca (P-58)
		Sebacaous hyperplasia (P-58)
		Sebaceous adenoma × 2 (P-59)
III-29		Skin Ca (H-45)
III-33		Skin Ca (H-54)
IV-3	Colon Ca (H-55)	
IV-6		Skin Ca (H-54)
IV-7	Colon Ca (H-61)	
IV-11	Uterine cervical Ca (H-22)	
		Keratoacanthoma (P-33)
IV-12	Cancer, site unknown (H-?)	
IV-17	Colon Ca (H-35)	
IV-31		Basal cell Ca (P-36)
IV-32	Intraducal Ca of right breast (R-38)	

* (H-61) = basis of diagnosis - age at diagnosis.
Abbreviations: H = family history; P = pathology; C = death certificate; R = medical record.

Love [44] has described a kindred with features of Lynch syndrome II but which showed certain rare cancers which have not ordinarily been associated with this syndrome. Specifically, in addition to the typical tumor presentations of Lynch syndrome II, patients in the direct genetic lineage also manifested small bowel cancers and B-cell lymphatic leukemia. One patient in this family manifested six primary cancers; the first, a cystadenocarcinoma of the ovary, was diagnosed at age 32 years. She was subsequently diagnosed with adenocarcinoma of the colon (splenic flexure) at age 35, mucinous adenocarcinoma of the colon (hepatic flexure) at age 45, two primary adenocarcinomas of the rectum at age 54, and an infiltrating ductal carcinoma of the breast at age 63. She had evidence of metastases, namely, an hepatic nodule found to be an adenocarcinoma, over the years, yet at the time of Love's publication, she was 64 years of age, in good health, and without clinical evidence of cancer.

Budd and Fink [45] described a black American kindred with features consistent with Lynch syndrome II. Of particular interest was the finding of mucoid colon adenocarcinoma in seven of 14 patients with colonic cancer.

We have reported a unique Navajo Indian kindred (Fig. 7) that manifested a tumor pattern which was at some variance with Lynch syndromes I and II. Pathologic study was unable to determined whether the proband's initial cancer originated in the ovary or in the endometrium. Longitudinal study of this family will be required for classification of this hereditary cancer syndrome (should it exist) [46]. So far as we have been able to determine, this represents the first description of the syndrome among American Indians. Although nonpolyposis colorectal cancer is relatively rare in this American Indian population, its occurrence in this family is consonant with a significant cancer-prone genotype that may be expressed in an otherwise low environmental carcinogenic milieu.

Miscellaneous examples of colon cancer-prone patients/families

Mir-Madjlessi *et al.* [47] published a case report of a 14-year-old male who had IgA deficiency and coexisting adenocarcinoma, an adenomatous polyp of the rectosigmoid, and a primary lymphoma of the cecum (large cell histiocytic type). It was of interest that the boy's 14-year-old sister died of gastric carcinoma, but unfortunately, her serum immunoglobulins were not measured. In their literature review, these authors noted that the occurrence of multiple neoplasias with IgA deficiency is rare. They cite a report by Hamoudi *et al.* [48] of a 20-year-old IgA deficient girl who developed six primary neoplasms, including multiple adenomatous polyps of the colon (one of which underwent malignant transformation), malignant thymoma,

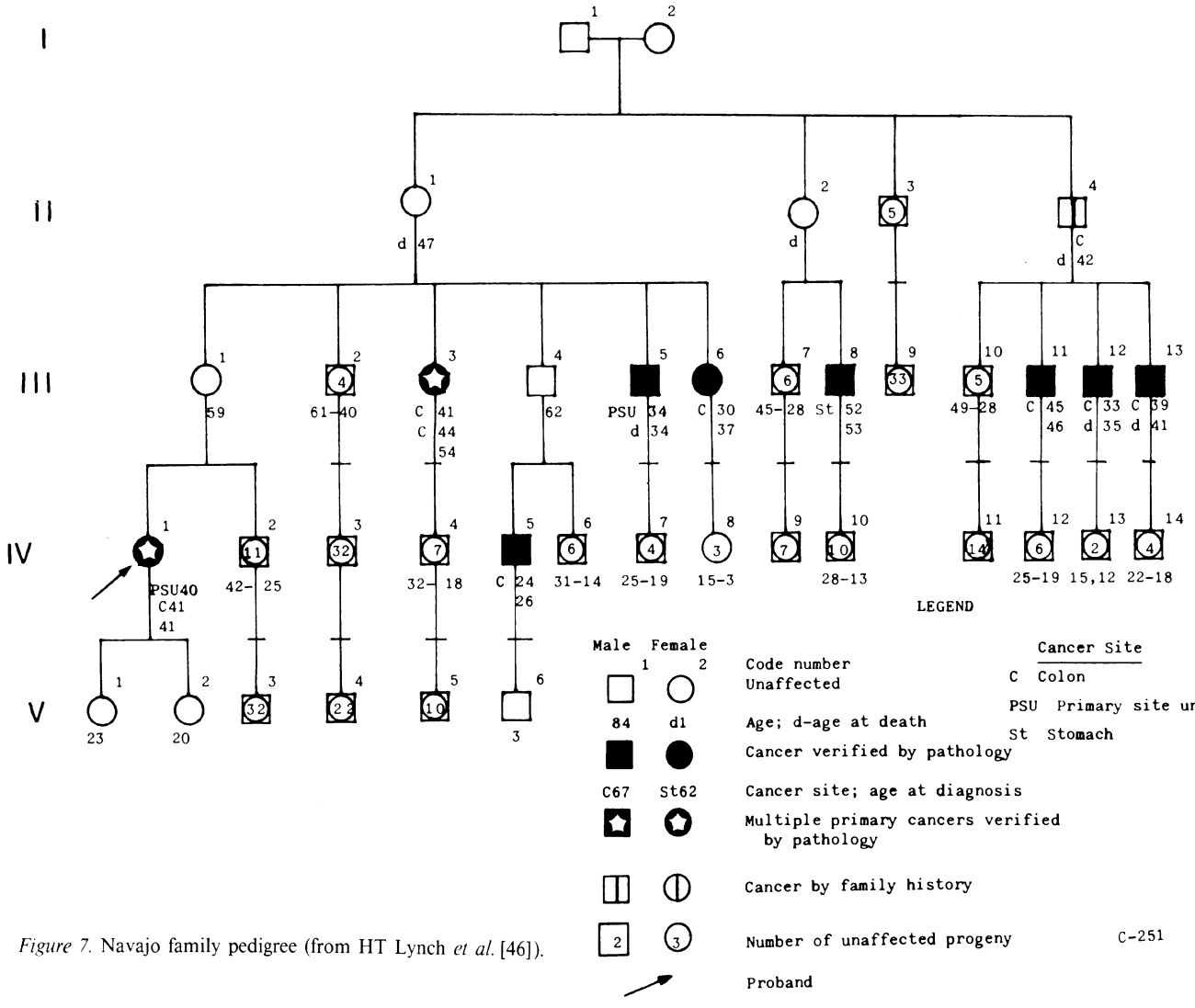


Figure 7. Navajo family pedigree (from HT Lynch *et al.* [46]).

squamous cell carcinoma of the scalp, adenocarcinoma of the colon, choroid tumor of the eye, and malignant astrocytoma of the cerebrum. It was of interest that her brother had a total absence of IgA and died at age 16 of lymphocytic lymphoma. Mir-Madjlessi *et al.* [47] discuss other examples of IgA deficient patients who developed differing forms of cancer and they conclude that IgA deficiency might be found to be a more common predisposing factor to the development of multiple primary cancer.

Pines *et al.* [49] have called attention to an association between acromegaly and tumors of the gastrointestinal tract, particularly colonic cancer. They noted that more than 30 years ago, an association between growth hormone and certain tumors had been established at the infrahuman level. This was in contrast to the failure to demonstrate a link in clinical studies of acromegalic patients and cancer association. Recently however, an association between acromegaly and colon cancer, as well as other tumors has been reaffirmed [50, 51]. These investigators therefore performed a retrospective study of 48 acromegalic patients in the search for association of gastrointestinal tract cancer. Five individuals with cancer were identified; two involved carcinoma of the stomach, two of the colon, and one of the rectum. One of the patients with stomach cancer and one with sigmoid carcinoma had recurrent colonic polyps. The observed vs. expected findings of gastrointestinal carcinoma and acromegaly for this Israeli population were statistically significant. These investigators postulated that there may exist an as yet unidentified pathogenetic mechanism which might explain the association between gastrointestinal tract cancer and acromegaly.

Occasionally, certain curious, anecdotal cases invite interesting speculation of genetic cancer mechanisms. One such example is a report by Winkler *et al.* [52] which involved identical, 57-year-old twin men who presented simultaneously with colonic cancer. In one of the twins, adenocarcinoma was found in the sigmoid colon, with two benign adenomatous polyps located in the transverse colon. This patient's identical twin brother had adenocarcinoma of the transverse colon and two additional polyps, one in the descending colon and another in the transverse colon. It was of interest that the father of these patients died of colonic cancer in his 60s. Unfortunately, no additional family history was provided. Finally, the authors indicate that so far as they could determine, this was the first case of site-specific colonic cancer developing simultaneously in monozygotic twins.

Heterogeneity of colorectal cancer in an oncology clinic series

We have assembled detailed family histories of cancer on 857 consecutively ascertained cancer probands from a single oncology clinic, of whom 180 manifested colorectal carcinoma [53]. The method of analysis employed

was one which has been termed the permutation test. The permutation test is totally self-contained in that only the sample itself is required, and hence, avoids some of the problems in the selection of and comparison with a control group. The proband is excluded from analysis. A list of all individuals in the families is made and subdivided according to year of birth, age (for our purposes, age is defined as age at last examination or, if affected, age of onset of cancer or, if decreased, age at death), and sex. Each family is then randomly reconstructed out of this list. Reconstruction of the families is constrained by the three variables mentioned (viz. age, year of birth, and sex) and the structure of each family in the sample, but the selection of affected vs. unaffected is left to freely vary. In this way, the sample of families can be reconstructed such that it reflects what would have been expected had the distribution of cancers been random. This reconstruction or permutation is done multiple times. For each permutation, a Z score is estimated for each family in the sample. The Z score for the ith family is defined as

$$Z' = (a_i' - e_i)/e_i$$

where a_i' is the number of affected as obtained from the permutation and e_i is the expected number of affected. The prime notation (′) denotes a value calculated from a permutation and not from the actual data. The expected number of affected, e_i, is calculated based upon the frequencies derived from the total sample

$$e_i = n_{ijkl} * f_{jkl}$$

where n is the number of individuals in the ith family belonging to the j, k, l categories and f is the frequency of affected in the j, k, l categories as estimated from the total sample. The variance of Z′ is then calculated for the permutation. By repeating the permutation several times, a likelihood distribution of the variance of Z′ can be directly estimated and compared with the variance of Z in the actual sample (calculated using the true value of a). In practice, the permutation test was repeated 99 times so that if the variance of the sample was greater than the highest variance obtained in the 99 permutations, then the actual variance can be said to be significantly increased with $p < 0.01$.

The permutation test is not a genetic test per se. When the variance of Z in the actual sample is significantly greater than expected, it indicates only that some families in the sample have a higher than expected risk. These may legitimately be called the familial cases. The test, however, does not make any statement with regard to the nature of this familial concentration; i.e., it could be due to either genetic or common environmental factors and/or their interaction. However, the distribution of Z scores identifies probable high risk families which can be more intensively investigated.

The reference population used in the permutations consisted of all prima-

ry relatives, excluding probands, of the 857 families. They were divided according to age, decade of birth, and sex. Division by age and year of birth were both into 10-year classes as indicated in Table 4 and 5. Entry into the reference population did not depend on family size. The families used in the test population were a part of the reference population, but did not comprise the total reference population. The total sample served as the basis for the permutations of the smaller sample of test families. The larger sample thus provided a better means for discrimination of risk than would have been otherwise possible.

Family size is a factor which influenced the variation of Z scores in the permuted sample. Small families would be expected to have a reduced variance. In order to determine the critical family size, permutations were done on the total sample relative to colorectal cancer in the family members. An analysis of homogeneity of variances showed significant differences with regard to family size. It was noted that the variances in family groups with two or less members was significantly reduced. Removal of all families with less than three members resulted in a test sample whose variances were not dependent upon family size. Nine colorectal families were too small to be

Table 4. Year of birth of primary relatives (by cancer cite in proband)

Year of Birth		Colon	Rectum	Lung	Breast	Other	Pooled
Before 1890	N	123	76	180	116	225	720
	%	16.1	17.9	11.9	12.0	14.5	13.8
1890–1899	N	88	52	154	115	161	570
	%	11.5	12.3	10.1	11.9	10.4	10.9
1900–1909	N	107	70	248	159	272	856
	%	14.0	16.5	16.3	16.4	17.5	16.4
1910–1919	N	165	93	289	162	288	997
	%	21.6	21.9	19.0	16.7	18.5	19.1
1920–1929	N	121	54	253	129	250	807
	%	15.8	12.7	16.6	13.3	16.1	15.4
1930–1939	N	52	48	178	102	159	539
	%	6.8	11.3	11.7	10.5	10.2	10.3
1940–1949	N	55	12	115	95	107	384
	%	7.2	2.8	7.6	9.8	6.9	7.3
1950-1959	N	37	16	68	55	62	238
	%	4.8	3.8	4.5	5.7	4.0	4.6
1960–1969	N	11	3	29	27	23	93
	%	1.4	.7	1.9	2.8	1.5	1.8
After 1970	N	6	0	5	8	6	25
	%	0.8	0.0	0.3	0.8	0.4	0.5

Table 5. Age of primary relatives at time of study (by cancer site in proband)

Age		Colon	Rectum	Lung	Breast	Other	Pooled
< 10	N	8	14	18	14	18	72
	%	1.1	3.5	1.2	1.5	1.2	1.4
10–19	N	9	6	19	24	19	77
	%	1.2	1.5	1.3	2.6	1.2	1.5
20–29	N	39	20	71	50	55	235
	%	5.3	5.0	4.7	5.3	3.6	4.6
30–39	N	58	19	125	88	134	424
	%	7.8	4.8	8.2	9.3	8.7	8.2
40–49	N	49	39	192	122	164	566
	%	6.6	9.8	12.7	13.0	10.6	11.0
50–59	N	128	74	265	142	267	876
	%	17.3	18.6	17.5	15.1	17.3	17.0
60–69	N	169	77	362	181	362	1151
	%	22.8	19.4	23.9	19.2	23.4	22.4
70–79	N	138	80	288	143	301	950
	%	18.6	20.1	19.0	15.2	19.5	18.5
80–89	N	89	54	152	140	164	599
	%	12.0	13.6	10.0	14.9	10.7	11.6
> 89	N	55	15	25	38	61	194
	%	7.4	3.8	1.7	4.0	4.0	3.8

used in this analysis, leaving 171 families to make up the test sample for this group.

Variance for the colon cancer group was significantly increased, while heterogeneity of risk was not observed for any of the other groups. 10.6% of the colon group and 5.56% of the rectal cancer families fell into the high risk category, but only 3.95% of the other groups combined were at high risk. Anatomic sites with the highest Z scores and variances were sigmoid and transverse colon, while the lowest variances were seen for cecum and descending colon. Risk status may therefore be partially dependent upon exact anatomic sites within the colon. The effect of *age* of diagnosis was not signigicant, but did show the possibility of an effect on risk for both the younger and older groups. Our findings of colon cancer heterogeneity warrant intensive genetic-laboratory epidemiologic investigations to determine why certain families express high vs. low risk for colorectal cancer.

Presently unclassifiable familial coloreactal cancer aggregations

We studied a familial aggregation of colorectal cancer which encompassed many of the pitfalls in classification of *hereditary* vs. *familial* status, a diag-

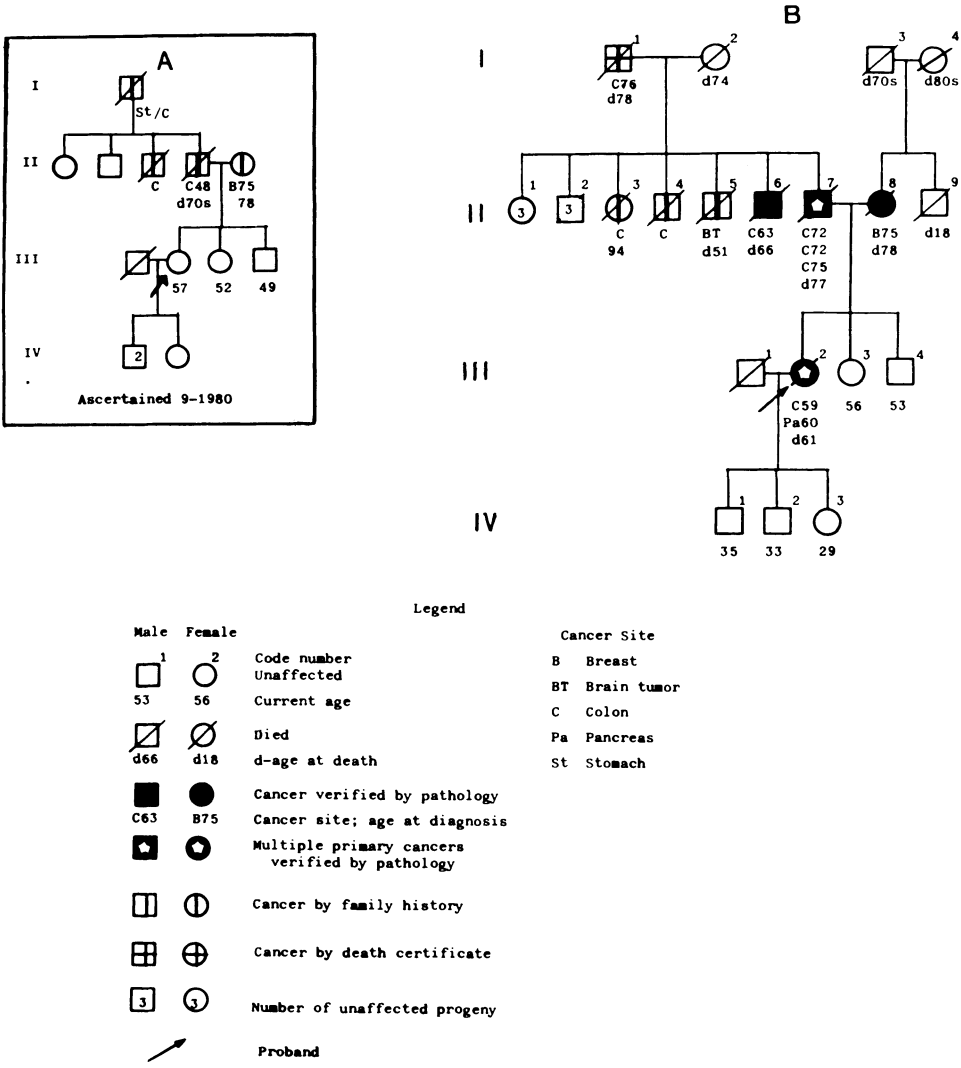


Figure 8. (A) Pedigree of the family showing the family cancer history as originally related by the proband. (B) Updated pedigree of same family 4 years later (from HT Lynch *et al.* [54]).

nostic dilemma which, as we have emphasized, may be encountered frequently in clinical practice, but where its ultimate resolution may determine the strategy for lifetime surveillance/management [54].

The proband in this kindred (Fig. 8A) was initially evaluated by us in 1980 when she was 57 years old. She was concerned about her personal increased familal cancer risk. Although she was a poor historian, a limited working pedigree was compiled. Additional information was obtained by

interviewing family members, although unfortunately, signed permission forms for only a limited number of affected persons were obtained, thereby restricting the receipt of primary medical and pathologic documents. Figure 8B depicts the updated pedigree and Table 6 shows the respective cancers, colonic polyps (when known to be present), and their mode of identification.

The family discussed here is an excellent example of the difficulties occasionally encountered in clinical practice in differentiating a chance familial cancer cluster from hereditary cancer syndrome identification. The proband (Fig. 8B, III-2) developed adenocarcinoma of the sigmoid colon (Duke's B1) and later developed a second primary cancer, namely, an adenocarcinoma of the head of the pancreas, from which she expired. Detailed inspection of the proband's colonic mucosal surface failed to reveal any adenomatous

Table 6. Tumor registry and colonic polyp which correspond to data contained in Figure 8 (from Lynch, H.T. *et al.* [54])

Patient number	Age at diagnosis	Cancer site	Cancer and polyp verification	Number of colonic polyps
I-1	76	Colon	Death certificate	
II-3	?	Colon	Family history	
II-4	?	Colon	Family history	
II-5	?	Brain tumor	Family history	
II-6	63	Malignant changes in polyp	Medical records	14 (13 benign)
	65	Large bowel with metastasis to omentum	Pathology	3 (benign)
II-7	51		Pathology	2 ('not frankly malignant')
	58			3 (benign)
	72	5 cm lesion, splenic flexure – adenocarcinoma,	Pathology	
		malignant change in polyp	Pathology	10 (9 benign)
	72		Pathology	2 (benign)
	73		Pathology	5 (benign)
	75	Malignant changes of superficial cells of polyp	Pathology	'multiple small benign'
	77	Metastatic adenocarcinoma to liver	Pathology	
II-8	75	Adenocarcinoma of breast	Pathology	
III-2	59	Adenocarcinoma of sigmoid colon	Pathology	None
	60	Adenocarcinoma of head of pancreas	Pathology	

polyps. She had mandibular osteomas (Figs. 9A, B), a finding known to be linked to FPC [17]. There was, however, no evidence of epidermoid cysts which, in the presence of osteomas and colonic polyposis, form the triad of so-called Gardner's syndrome [3]. Osteomas may possibly occur in HNPCC [55], although this supposition is preliminary and will require more investigation. The two lesions in our patient were 5×11 mm in size and met the criteria of Bulow *et al.* [17] for osteomas.

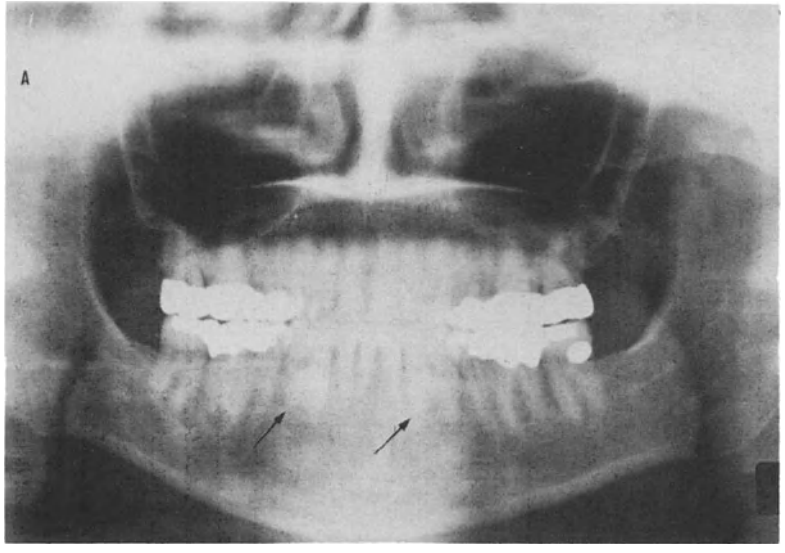
The differential diagnosis of radiopaque lesions in the mandible includes a group of bony, odontogenic and inflammatory conditions. There is considerable variation in terminology among different authors in describing these lesions of the mandible. Bulow *et al.* [17] used a radiologic definition of an osteoma as a definite homogeneous radiopaque area of at least 2 mm in diameter without a surrounding radiolucent zone. Lesions with a surrounding radiolucent zone are most likely inflammatory in nature. Odontogenic lesions, such as cementomas, usually involve the roots of the teeth and are easy to distinguish radiographically.

Bulow *et al.* [17] discovered one or more osteomas in 35 of 46 FPC patients (76.1%) and one osteoma in two of 46 control patients (4%). Utsunomiya and Nakamura [18] noted radiopaque lesions in the mandibles of 27 of 29 FPC patients (93%). They reported finding radiopaque bone lesions in the mandibles of 26 of 438 patients (6%) who had panoramic X-ray films at the Department of Dental Radiology in Tokyo. Their observation is similar to the 4% incidence of osteosclerotic lesions of the mandible reported by Boyne [56] in a series of 927 roentgenograms of male patients between the ages of 22 and 56 years.

In spite of the two primary cancers and the presence of osteomas in the proband (Fig. 8, III-2), the presence of three primary cancers of the colon in her father (Fig. 8, II-7) (with adenomatous polyps), adenocarcinoma of the colon in his brother (Fig. 8, II-6) (with occasional colonic polyps), plus the remaining historical knowledge (Fig. 8, I-1, II-3, II-4, Table 6), it was not possible to clearly delineate this familial cancer aggregation into any of the known hereditary colonic cancer syndromes [3].

Further clarification of this issue might have been possible had we been able to obtain pathologic confirmation of the cancers reported (Fig. 8, I-1, II-3, II-4, II-5) and to determine whether any of these patients might have manifested multiple adenomatous polyps of the colon. However, after intensive effort to secure these details, we remain at an impasse with findings limited to those reported above. The discovery of carcinoma of the breast in the patient's mother may have confounded the cancer risk to the proband and possibly to the proband's children. However, more explicit definition of this risk is not possible.

Further elucidation of genotypic status in this family would be aided significantly by the disclosure of one or more biomarkers, such as increased *in*



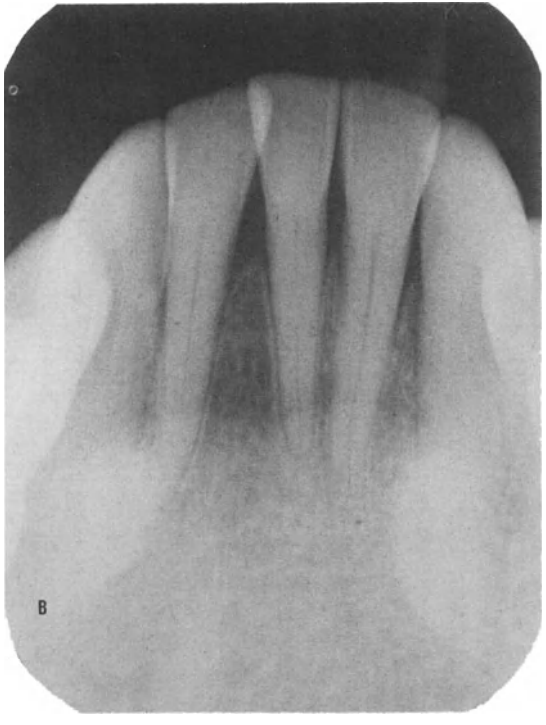


Figure 9. (A) Osteomas in the mandible of the proband (arrow). (B) Enlarged view (from HT Lynch *et al.*, Dis Colon Rect, in press, 1985).

vitro tetraploidy in cultured skin fibroblasts [57] or abnormal tritiated thymidine labeling pattern of colonic mucosal cells [58, 59], which putatively correlate with several forms of hereditary colonic cancer [3, 60, 61]. Unfortunately, such markers could not be obtained on our patient or her relatives.

Inflammatory bowel disease (IBD)

An additional group of disorders not classically included among discussions of hereditary syndromes predisposing to colorectal cancer are the inflammatory bowel diseases, namely, ulcerative colitis (UC) and Crohn's disease (CD). Substantial evidence exists for a genetic basis for at least a fraction of the occurrences of these two diseases [62–75]. Among this evidence are concordant occurrences in monozygotic twins and increased frequency of these two diseases among bloodline relatives of patients.

Korelitz has reviewed the epidemiology and genetics of IBD [76]. He observed that 20% of patients with Crohn's disease in New York City had one or more blood relatives who suffered from IBD. This was usually Crohn's disease, but occasionally UC was also observed. He concluded that the most likely type of inheritance was polygenic. In this setting, those at greatest risk share the most genes in common with the affected patient. A further observation was the fact that patients with Crohn's disease are more likely to have relatives with UC. Those with UC, on the other hand, are more likely to have relatives with UC. Finally, there was an increased frequency of IBD among Jewish individuals. Additional evidence comes from a primate model (Tamarins) wherein both UC and the associated colon cancer susceptibility are clearly genetically transmitted [77].

According to Sachar's review [73], UC may be present for 8–10 years before any statistically increased risk of colorectal cancer occurs when compared to the general population. Colorectal cancer risk is highest for patients with pancolitis, although patients with left-sided disease, extending up the descending colon or as far as the midtransverse colon, have a time curve of cancer development which is parallel to that of patients with universal disease. The difference is that it requires about 10 years longer for patients with left-sided disease to develop their cancer. Another classical concept has been that patients who develop UC in childhood or in their teens harbor an intrinsically higher cancer risk than patients who develop the disease later in life. However, the total duration of disease is the major cancer risk determinant as opposed to the age of onset. An additional classic concept in UC is that the associated cancer has a worse prognosis. This may be due to the fact that colorectal cancer in UC is more often multiple than in patients lacking UC (12% of UC patients show multiple colonic cancers as compared

to 3% of the noncolitis population). Finally, the cancers in UC are more often extensive and harder to detect, not only due to the fact that the patients are young and manifesting UC symptoms, but because the cancers are more evenly distributed and shifted to the right in their anatomic distribution than are colorectal cancers in the general population.

In the case of CD, it is traditionally taught that there may be some increased cancer risk, but the magnitude of this risk is nowhere near that for UC. When viewing the observed to expected ratio, the risk for cancer of the colon in patients with Crohn's ileitis, or ileocolitis, is overall about seven times greater than in the age and sex-matched population. This incidence is less than the 26-fold ratio that one derives from similar calculations in patients with universal UC. However, as Shorter points out [78], the subset of patients with extensive colonic Crohn's disease of long duration (> 7 years) have an approximate 20-fold increased risk of colon cancer. There is an important difference between the gastrointestinal cancers that occur in CD and those that occur in UC. In patients with UC, 96% of the colorectal cancers develop in the areas of disease. In contrast to these findings, only 2/3 of the gastrointestinal cancers in CD occurred in a site of recognized gross disease; the others occurred elsewhere in the gastrointestinal tract [73].

Biomarkers

Table 1 provides a summary of biomarker findings in hereditary colon cancer predisposing syndromes. The table demonstrates that within the FPC syndromes abnormalities of putative biomerkers exist in uninvolved colonic epithelial cells and even skin fibroblasts [38, 57, 58, 79–96]. This suggests that the putative biomarkers associating with predisposition to colonic cancer are expressed by diverse cell types throughout the body and that mechanisms must exist whereby the colon (or other target tissues) are predisposed as specific sites of cancer development. Similar biomarkers suggest the possibility of a common biological basis for eventual colorectal cancer in the different classes of colorectal cancer susceptibility. Common immunological phenomena in both the classified and unclassified case reports (Table 1) further suggest the possibility of common, genetically-determined biological etiologies.

Assessment of biomarkers

When clinical stigmata are lacking, as in the HNPCC disorders, one must rely heavily upon the pedigree for assessment of cancer risk status. Howev-

er, this has a major limitation for clinical application. Specifically, progeny or siblings of cancer syndrome affecteds can only be assigned a maximum cancer predictability risk of 50% in autosomal dominantly inherited cancer syndromes. Therefore, the discovery of a biomarker(s) associating with the cancer-prone genotype would prove invaluable for the elucidation of genotypic status, thereby enabling the clinician to predict with greater confidence those patients who *will* (and contrariwise, those who *will not*) manifest the phenotype (syndrome cancer). This knowledge would then harbor cancer control implications which could become legion. It could also be useful for studies of environmental interaction with a cancer-prone genotype, thereby enabling a more critical assessment of cancer etiology.

We have operationally broadened the term 'precursors' to encompass clinical stigmata and those markers of cellular kinetics, cellular metabolism, cytogenetics, immunity, or enzymatic activity which may provide the potential for the identification of genotypic status of cancer risk. These markers will hereafter be referred to as biomarkers of genotypic status.

In addition to these literature reports, our group's collaborative research on Lynch syndromes I and II has recently obtained evidence that biomarkers in these disorders may be soon confirmed. Two families with HSSCC (Lynch syndrome I) and nine families with CFS (Lynch syndrome II) were investigated [60, 61]. Syndrome cancers were restricted to direct line relatives, as opposed to non-bloodline relatives, thus arguing against involvement of shared environmental factors. Other clinical features of these syndromes which were documented include: (1) predominance of proximal colonic involvement, although rectal cancer does occur; (2) an earlier age of onset for proximal vs. distal cancer; and (3) penetrance of the cancer-prone genotype(s) was found to be 95% complete during the 6th decade of life. Biomarker studies on these families revealed: (1) positive lod scores for linkage to Jk (Kidd blood group) in Lynch syndrome II (lod score of 3.0), and for increased *in vitro* tetraploidy in cultured skin fibroblasts in both Lynch syndromes I and II (lod score of 3.5); (2) association between cancer risk status and tritiated thymidine uptake by cells in the distal crypt compartments of colonic mucosal biopsy specimens; (3) a high incidence of polymorphisms in peripheral leucocytes of centromeric heterochromatin in three Lynch syndrome II kindreds and chromosomal translocations in one of these families; and (4) low serum IgA levels in significant excess in 1 CFS kindred. It therefore seems probable that further biomarker studies will prove their utility in HNPCC and provide insight into specific genetic heterogeneity with HNPCC syndromes. In addition, the linkage of Lynch Syndrome II to Jk suggests that the deleterious CFS gene is located on chromosome 2.

Segregation analysis in HNPCC kindreds

Segregation analyses were performed on a set of 11 extended families with HNPCC to elucidate the role of a major gene in colorectal cancer susceptibility [97]. There was no significant departure at the 0.05 significance level from Mendelian autosomal dominant transmission (chi-square = 2.62, 2–3 d.f., $p > 0.20$), but there was significant departure from the hypothesis of Mendelian autosomal recessive transmission (chi-square = 32.88, 2 d.f., $p < 0.0005$), and from the hypothesis of no intergenerational transmission (chi-square = 60.27, 1–2 d.f., $p < 0.0005$).

The estimate of the gene frequency of the putative susceptibility allele was 0.0155. We signify 'A' as the autosomal dominant cancer predisposing allele and 'a' as the recessive normal allele. The estimates of the mean of the age of onset distribution was 46.82 for individuals of genotype AA and Aa, and 100.78 for individuals of genotype aa. The common variance for these age of onset distributions is 101.385.

Most patients will not survive to age 100, which implies that only the lower tail of the distribution with mean of 100.78 and variance of 101.385 is relevant to human data. The findings therefore show that sporadic cases of HNPCC can exist under this mode, but the age of onset for such sporadic cases is substantially greater than that of the genetic cases. The estimate of the susceptibility was 0.785. More detailed findings on our HNPCC resource, including clinical description and biomarkers, have been published [60, 61].

Surveillance/management strategies

It will be important for the clinician to appreciate that a meticulous study of each patient/family will be essential for determination of hereditary cancer syndrome identification. The natural history of each disease must be understood. Patient/family education and genetic counselling must be employed, preferably by the mid-teens. The physician must provide an empathetic 'listening ear', since patients at high cancer risk may employ strong defense mechanisms of *denial* as a result of fear. They may become fatalistic. This psychological setting may then lead to poor compliance with the cancer prevention and control program [98–103].

The HNPCC disorders, in particular, pose a profoundly vexing problem to the cancer geneticist, oncologist, and primary care physician. However, as already emphasized, the primary site of colonic cancer expression is in the *proximal* colon in these particular disorders. Hence, surveillance strategies targeted at the proximal colon must be implemented. Fecal occult blood testing (FOBT) has become a standard screening tool for colon cancer in the

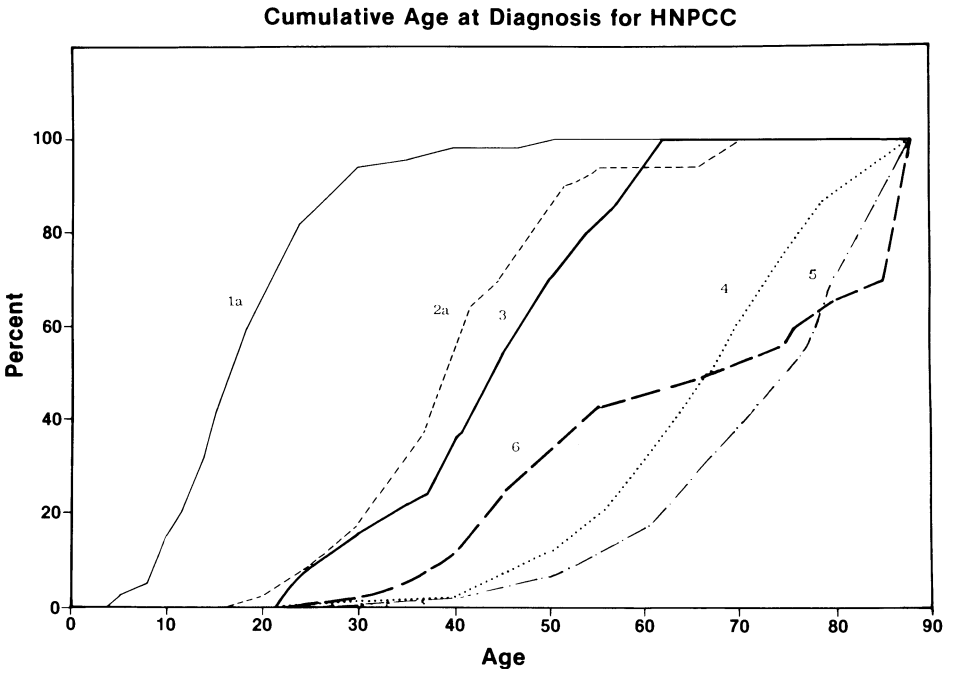


Figure 10. Cumulative percent of incident cases at various ages having familial polyposis, compared to cumulative age incidence of colon cancer in other population groups. Curve 1A shows the onset of nonmalignant polyposis and curve 2A the onset of cancer in familial polyposis, derived from data of 38 cases seen at Memorial Hospital. Curve 3 shows early age at onset of cancer in 28 individuals from Memorial Hospital series who have familial colon cancer-prone disease without polyposis, Curve 4 illustrates the age at onset of colon and rectal cancer in the general population of the United States, from the Third National Cancer Survey, NCI, and includes white and black males and females combined. Curve 5 illustrates the onset of colon and rectal cancer in males and females in Japan from data supplied by Dr T. Hirayama (from LCM Lipkin, *et al.* [105] reproduced by permission). Finally, curve 6 has been added to this figure with assistance from William Kimberling, PhD, who also provided the table which further characterizes this curve. This curve illustrates the age at diagnosis as calculated from a segregation analysis of 11 HNPCC families (the current Creighton resource series; Bailey-Wilson *et al.* [97].

general population. However, reports of high false-negative rates, especially for right-sided colonic neoplasms, have led to interest in refinements in stool assessment for blood products [104]. We feel that the role of FOBT has yet to be defined for the general population, and that it has little utility in the management of the high risk syndromes discussed in this chapter. We propose the following strategies, based on premises proposed by Lynch and Lynch [3] and by Lipkin [105].

Age at onset of colonic cancer is an important consideration for the development of surveillance/management programs. Lipkin *et al.* [105] have provided data dealing with the cumulative age at colorectal cancer diagnosis in

a variety of clinical settings (Fig. 10). Bailey-Wilson *et al.* [97] computed curve 6 which has been superimposed on this figure, and which shows the cumulative age of onset of colorectal cancer as estimated from a segregation analysis of 11 large HNPCC families. This should be compared with curve 3 which was based upon a cohort of 28 patients with hereditary nonpolyposis colorectal cancer investigated by Lipkin *et al.* [105]. The major differences between the two curves occur at both early and late ages, and reflect the anticipated yield of affected individuals.

The yield of expected individuals was calculated by assuming an autosomal dominant pattern of inheritance. Based on the cumulative age distribution, the fraction of known gene carriers who have presented with clinical disease prior to evaluation (colonoscopy) can be estimated (Fig. 10). Probability estimates can then be used to calculate what fraction of unaffected individuals are gene carriers and liable to develop cancer during a given time period of colonoscopy surveillance. The yield was calculated under three different conditions. The results are shown in Table 7.

We first assumed that the age of diagnosis would not change. In other words, there would be no leftward shift in the age of onset curve. These results are shown in the first Z columns of this table. Assuming that there are equal numbers of individuals in each of the six 5-year age groups selected, we would anticipate that approximately 2.82 to 3.43% of the sample will become clinically affected during the five-year duration. Given a 2-year shift to the left of the age of onset distribution, we would anticipate 3.67 to 5.47% individuals to be diagnosed by colonoscopy. If the age of diagnosis curve shifts 5 years to the left, then the anticipated yield would be between 9.03 and 6.37% of the sample.

Table 7. Anticipated yield of positive persons during a 5-year period

	No shift [a]		2-year shift		5-year shift	
Age group	Curve 3	Curve 6	Curve 3	Curve 6	Curve 3	Curve 6
25–29	3.19	0.89	4.27	1.74	5.92	3.48
30–34	2.52	2.54	4.37	2.93	7.14	4.39
35–40	4.29	1.76	7.57	2.49	12.48	7.62
40–45	7.37	5.63	8.91	6.42	11.39	10.32
45–50	3.22	4.03	4.42	4.94	6.21	7.41
50–55	2.08	2.90	3.30	3.49	5.12	5.02
Average [b]	3.43	2.82	5.47	3.67	9.03	6.37

[a] Clinical colon cancer.

[b] Assuming equal numbers of individuals in each age category.

Based on these data, we conclude that given a sample size of 100, one would need at least a 5-year shift in the age at diagnosis in order to obtain numbers of adequate size in order to insure a significant statistical test.

Surveillance, ideally, should also contain a research component on these high risk patients in the search for premorbid pathology. A number of human cancers have been associated with or preceded by aberrant histology that has been considered to be 'premalignant'. In the gastrointestinal tract, leukoplakia (mouth and pharynx) and dysplasia (esophagus, stomach, colon) are considered strong evidence for development of carcinoma [106]. In laboratory-induced cancers, tissues go through neodifferentiation into preneoplastic, then premalignant, stages prior to identifiable cancer formation [107, 108].

Though these studies lend insight into the natural history of carcinogenesis, in the specific issue of colon cancer, the progression from normal to malignant tissue is poorly understood. Questions remain whether cancer arises de novo or from adenomatous polyps. Circumstantial evidence is strong for a polyp to undergo cancer transition [109], but this is not wholly accepted [110, 111] and the incidence of this occurrence is unknown. It has been suggested that a significant proportion of colonic cancers in the general population arise *de novo* from flat mucosa [3, 14]. This appears to be the case in colon cancer complicating ulcerative colitis, where the premalignant condition appears to be dysplasia as first described by Morson and Pang [12]. Adenomatous polyp formation does not seem to play a role [113, 114].

Lynch syndromes I and II are diseases of hereditary colon cancer, unassociated with adenomatous polyps [38]. In these disorders, colonic epithelium would be expected to undergo change from a precancerous to cancer state similar to that seen in other malignancies. Furthermore, it would be expected that in these disorders, cancer arises de novo in flat colonic mucosa and not from polyps. Though we postulate its existence, our extensive experience with this disease(s) has failed to identify a transitional or premalignant mucosa [3]. We have discussed the issue of searching for natural history changes in colonic mucosa, including premorbid pathology, since screening of high risk patients provides such a profound potential for elucidation of this enigmatic issue.

The cumulative age at onset data (Fig. 10, Table 7) provides, in part, a rationale for age stratification in our surveillance/management strategy. In addition, it should be appreciated that when such drastic measures as colectomy are indicated, this procedure may be less psychologically damaging to the young adults than to teenagers. We therefore provide the following surveillance/management suggestions.

Cancer education and genetic counseling

One of the most important components of any cancer surveillance/management program for hereditary cancer pertains to a well-concerted educational program for the patient and his or her close relatives. Focus should be given to the natural history of hereditary cancer since, as noted throughout this chapter, there are certain nuances of these diseases which command surveillance/management programs which differ strikingly from that of its particular sporadic counterpart. Thus, in HNPCC, focus must be given to the proximal colon and, should colon cancer present, subtotal colectomy as opposed to more limited resection is mandatory because of the propensity for extraprimary colonic cancers in the remaining segment of the colon. Differentiation must be made between Lynch syndrome I where, as noted, the concern is focused exclusively upon the colon, as opposed to Lynch syndrome II wherein adenocarcinomas of other anatomic sites, particularly of the endometrium and ovary, must receive primary attention. Genetic counseling using an empathetic listening ear is essential for this educational process. A very close liaison with a physician who is knowledgeable about the particular hereditary form of cancer of concern is also essential and this, then, must become a lifetime process. We begin education of our patients in their early teens, and reinforce this during each cancer surveillance session. This is one of the primary missions of Creighton's Hereditary Cancer Institute.

FPC inclusive of so-called Gardner's Syndrome

1. Yearly sigmoidoscopy (procto) beginning at age 15 and continuing to age 40; if negative, then as per recommendation of the American Cancer Society for the general population;
2. begin earlier age screening if the patient is symptomatic or his family history suggests onset before age 15;
3. during screening, if polyps develop go to yearly colonoscopy with polypectomies;
4. elective colectomy with ileoanal anastomosis if:
   a. too many polyps to remove through endoscope;
   b. nonmalignant symptoms become intolerable;
   c. carcinoma in polyps;
   d. prophylactic colectomy in early 20s, or within 7 years of onset of polyps.

At present, thorough yearly physical and awareness of natural history and diagnostic features of hereditary syndromes is the most cost effective way to screen for extraintestinal neoplasms.

Juvenile polyposis
1. Flexible sigmoidoscopy every 2–3 years beginning at age 10;
2. elective colectomy after age 20 in affected individuals;
3. double contrast barium swallow or upper endoscopy every 3 years; if polyps noted, yearly upper endoscopy.

HNPCC
1. HemoQuant [104] every 2 years beginning at age 25 and alternating with every other year colonoscopy;
2. colonoscopy every 2 years and when HemoQuant positive.

When cancer of the colon is detected, a subtotal colectomy, as opposed to a more limited resection is mandatory. Attention must be given to surveillance/management of extracolonic sites (particularly endometrium and ovary) in Lynch syndrome II. When biomarkers available to identify kindred at risk, proceed with colectomy.

CUC
1. Pancolitis: dysplasia screening at 7 years with yearly colonoscopy and biopsy;
2. left-sided: dysplasia screening at 15 years.

Crohn's
Severe Crohn's colitis for 7 years: dysplasia screening with yearly colonoscopy and biopsy.

Discussion

Advances in medicine are of such magnitude as to require physicians to remain constantly abreast of knowledge which can significantly influence patient management. In context with cost consciousness and the ever increasing pace of our knowledge-intensive patient care system, a well-orchestrated family history, in certain circumstances, may prove to be one of the most cost-effective instruments in the physician's entire medical armamentarium. Compiling the family cancer history through selected second degree relatives (paternal and maternal grandparents, aunts, and uncles) could, in certain circumstances, show at a glance that one may be dealing with a cancer aggregation consonant with hereditary cancer.

Hereditary nonpolyposis colorectal cancer (HNPCC) occurs about five times more frequently than its autosomal dominantly inherited counterpart, familial multiple polyposis coli (FPC), a fact which has contributed to the recent increased interest in this disease [3]. There have been rare reports of HNPCC with cutaneous signs (sebaceous adenoma, sebaceous carcinoma,

sebaceous hyperplasia, and/or multiple keratoacanthoma) of Torre's syndrome [42]. With this exception, however, there is a uniform lack of premonitory signs in HNPCC when compared, for example, to multiple adenomatous polyps in FPC and/or extracolonic stigmata (osseous and cutaneous) in Gardner's syndrome, respectively. One must therefore rely heavily upon pedigree evaluation for the diagnosis of HNPCC.

Estimates of the frequency of familial and hereditary colorectal cancer show significant variability, which is dependent in a major way upon the intensity of family history collection and cancer verification (all sites). For example, preliminary findings of family history on 134 consecutively ascertained patients with histologically verified colorectal cancer from our oncologic clinic (1978 to 1983) showed the following: (a) 21% of our colonic cancer probands showed *familial* colorectal cancer (two of more first-degree relatives with colorectal cancer); and (b) approximately 6–7% of the total sample (134 patients) showed findingfs consonant with *hereditary* etiology. Similar findings have been reported in the literature [3, 115, 116].

These observations clearly indicate that familial proneness to colorectal cancer is very high. However, knowledge relative to any individual family member's risk status is necessarily crude when based solely upon familial cancer aggregation. Empirical risk estimates in these circumstances show about a threefold excess risk for colonic cancer to first-degree relatives of a colonic cancer-affected proband when compared to expectations for the general population [3, 115, 116]. In contrast to these relatively crude cancer risk estimates, more precision in cancer risk assessment is possible, based upon Mendelian genetic principles, when dealing with a *hereditary* colorectal cancer syndrome [3, 19, 38, 60, 61, 116–118]. However, it may be exceedingly difficult, if not impossible, in certain circumstances, to establish hereditary cancer confirmation [3].

We [19] have stressed the importance of meticulous evaluation of all facets of the phenotype in colon cancer-prone families, including variation in polyp expression in FPC, as well as tumor expression (cancer of all anatomic sites) in this disease, and in the hereditary nonpolyposis colorectal cancer variants (Lynch syndrome I, Lynch syndrome II). Thus, in the previously mentioned kindred [119] with FPC, there was extant variation in polyp phenotype ranging from isolated polyps to myriad polyposis with associated colorectal cancer (Fig. 2). In addition to early onset colonic cancer, a patient with isolated polyps had a seminoma and subsequently developed gastroesophageal cancer (Fig. 2, III-3). His son, (Fig. 2, IV-5), also with isolated colonic polyps, manifested a pararectal rhabdomyosarcoma. Thus, cancer susceptibility in FPC is systemic, and *not* restricted to the colorectum. We concluded that the significance of these variations can only be assessed fully through the study of cancer of *all* anatomic sites in many additional families.

Our studies of colorectal cancer genetics clearly document its extant heterogeneity and hence, the need to search meticulously for all forms of cancer when considering its genetic etiology. For example, Bremond *et al.* [120] performed a case/control study involving 145 patients with carcinoma of the breast and 144 controls. Proctosigmoidoscopy was performed on each case as well as its matched control. The investigators observed an odds ratio for adenomatous polyps to be 2.65 (confidence limits 1.56 and 3.74), thus providing new evidence for a close relationship between carcinoma of the breast and colon, given the known association between colonic polyps and colorectal cancer. The authors therefore recommend the importance of performing pansigmoidoscopy in all patients with breast cancer and, when positive, they suggested that polyps be removed through the colonoscope.

The very high incidence of colorectal cancer in the population is a factor which obviously contributes to familial aggregations of this disease, a fraction of which must, therefore, necessarily be due to chance. This poses difficulties in the differentiation between etiologies which contribute to familial clustering, inclusive of those which may be due to primary genetic factors. This problem may therefore prove vexing to the practicing physician as well as to the cancer epidemiologist and geneticist.

Hypothesis regarding colorectal cancer etiology: oncogenes, environment (particularly diet), and genetic interaction

We provide a complex hypothesis involving genetics and oncogenes, in concert with environmental perturbation to explain colorectal carcinogenesis. We postulate that colorectal cancer does not occur *randomly* in the general population. Expression of colorectal cancer stems from several primary genetic components which interact with variable environmental factors, including the activation of one or more ubiqutious oncogenes, and predispose to at least three general disease categories: (1) multiple colonic polyps; (2) inflammatory bowel disease (IBD); or (3) *de novo* cancer expression in flat mucosa. Our hypothesis will focus upon colonic cancer occurring in flat colonic mucosa in hereditary *non*polyposis colorectal cancer (HNPCC).

Adenoma-polyp-cancer sequence hypothesis

While our main focus of attention will be given to *non*polyposis colorectal cancer, it is essential that the issue of adenomatous polyps be placed in proper perspective. The polyposis-adenoma-cancer sequence hypothesis [3] has been the leading etiologic explanation for colorectal cancer. Perhaps the best known model concerns patients with any of the several varieties of

familial multiple adenomatous polyposis coli (FPC) syndromes [15]. Recent evidence has also implicated patients with so-called benign harmatomatous polyps, as found in familial juvenile polyposis coli [36] and Peutz-Jegher's syndrome [121].

The adenoma-carcinoma model obviously does not cover all cases. Maskens [122], in addressing this issue concludes that a preexisting large polyp is *not* mandatory for the development of a carcinoma. Carcinomas may arise wherever epithelial cells are present, including occcurrence in small adenomas, in hyperplastic polyps, in normal flat mucosa, and in inflammatory states. In addition, studies of experimental carcinogenesis have clearly shown that most carcinomas arise *de novo* in flat mucosa where preexisting benign neoplasms were not present [123, 124].

Adenomas and *de novo* carcinomas may both have a genetic origin [3]. Though evidence for adenoma to carcinoma progression is strong, their simultaneous presence in any one population could also result from exposure to a common etiologic agent or group of agents [122] in concert with an underlying colon cancer-prone genotype(s) [3]. For example, susceptibility of benign polyps to malignant transformation would, in part, represent a consequence of some of the tissue properties that distinguish them from normal mucosa, such as increased proliferative activity [59]. At the infrahuman level, this phenomenon has been shown to be influenced by specific carcinogens [125].

Metabolic factors may be important. Specifically, in FPC, the inability to degrade fecal cholesterol and bile acids to secondary products has been hypothesized as a phenotypic marker in this disease [126]. Interestingly, approximately 25% of the general population shows a failure to degrade cholesterol, a factor also identified in high risk groups [127]. These observations suggest the importance of environmental interaction in concert with host factors in colon carcinogenesis and are in accord with our hypothesis.

Dietary factors in colon cancer based upon international studies

McKeown-Eyssen and Bright-See [128] studied the relationship between dietary factors and mortality from colon cancer through an analysis of the correlation between age-adjusted colon cancer mortality rates for men in 38 countries wherein it was possible to assess a number of pertinent dietary components. It was of interest that cereal was the only source of fiber found to be negatively associated with cancer mortality once adjustment was assessed for the availability of total or animal fats, or total or red meats (foods which heretofore have been positively associated with colorectal cancer mortality). A finding of interest was that dietary fiber from cereal was

more closely associated with mortality when compared to that of crude fiber. The previously postulated protective effects of vitamins C and A, as well as cruciferous vegetables, were not supported by these international data. Finally, the previously reported association between colon cancer and beer consumption disappeared once adjustment for animal fat had been performed. Ideally, primary genetic risk should be assessed for colon cancer in concert with dietary interaction. This would be exceedingly difficult, although some researchers have attempted to study this problem in differing ways.

Lipkin *et al.* [129] studied the proliferation of epithelial cells utilizing tritiated thymidine labeling pattern in cells from colonic mucosa among individuals whose risk for colon cancer showed marked variability. Focus was given to the Seventh-Day Adventists, who are vegetarians and who have been known to show significantly lower mortality rates from colon cancer when compared to those found in the general United States population. It was therefore of interest that this group had the most quiescent proliferative activity of colonic mucosal epithelial cells. In contrast, increased replication and expansion of the proliferative compartment was accompanied by increased colonic cancer risk in the several groups investigated who were known to have variable hereditary susceptibilities to colon cancer. These investigators suggested that '... the analytical methods of this study may be useful in assessing the influence of dietary components involved in the initiation, promotion, or inhibition of colon cancer, and in developing strategies for nutritional intervention'.

The already mentioned work of Nair and Turjman [126] dealing with the role of bile acids and neutral sterols in familial colorectal cancer syndromes is pertinent to this discussion. This work focused upon the fact that there exists many structural similarities between carcinogenic aromatic hydrocarbons and bile acids, a factor which has aroused suspicion over the years that bile acids might play an important etiologic role in colorectal carcinogenesis. Cholecystectomy with increase in secondary bile acids has been reported to be a risk factor for colon cancer [130, 131]. These investigators studied fecal sterols and bile acids in patients with and at risk for FPC. There has been evidence of failure to degrade fecal cholesterol and bile acids to secondary products and this had been postulated as being a biomarker indicative of genetic predisposition to FPC. These observations were in contrast to large scale epidemiologic studies of groups at high risk for colonic cancer who were consuming diets high in animal fats, protein, and refined carcbohydrates. Such individuals showed positive correlation with high fecal concentrations of bile acids and their metabolites. Lithocholic acid is a secondary bile acid which is unique in that it has been shown to be comutagenic and has acted as a promotor of self-transformation and has the capability for inducing DNA strand breakage *in vitro*. These investigators concluded

that '... there is sufficient evidence to warrant further investigation into the interactions between inherited premalignant syndromes and the role of diet and metabolic products, such as neutral sterols and bile acids, in the etiology of colonic neoplasia'.

Those readers interested in pursuing the matter of diet, nutrition, and metabolism in high and low risk colorectal cancer populations are referred to a supplement to the American Journal of Clinical Nutrition, which has been edited by Nair [132].

The role of oncogenes in our hypothesis

Cancer liability is variably dependent upon perturbation by environmental carcinogens in concert with primary genetic factors. The latter may include expressor and suppressor genes which activate or deactivate an oncogene(s) [133, 134]. Cellular sequences related to the transforming genes of Kirsten (Ki) and Harvey (Ha) murine retroviruses have been shown to be actively transcribed in human tissues. Spandidos and Kerr [135] observed Ki-*ras* and Ha-*ras* related transcripts to be elevated in premalignant (adenomatous polyps) and malignant tissues (colonic cancer), but absent in normal colonic mucosa. None of these tissues came from patients known to be members of cancer-prone families. However, information was not provided about criteria used for assessment of family history. These findings indicate that Ki-*ras* and Ha-*ras* expression is linked to the transformed state of the cells and thereby is crucial to carcinogenesis. It is significant that only a small fraction of premalignant polyps undergo malignant transformation in the face of elevated oncogene expression in *all* of the polyps. Hence, the elevation *per se* is not sufficient for carcinogenesis. This is cogent to our hypothesis, since of the relatively enormous amount of colonic mucosal surface at cancer risk, only a miniscule fraction of this tissue undergoes malignant transformation. The fact that Ki-*ras* and Ha-*ras* related transcripts were elevated in the premalignant and malignant states as opposed to *normal* colorectal mucosa indicated that expression of these *onc* genes is associated with the *transformed* state of the cells.

We hypothesize that the apparent ubiquitous nature of the *ras*-related oncogenes, relevant to premalignant and malignant tissues of the colorectum, and the absence of their elevated expression in the normal colonic mucosal counterpart of this organ in those subjects investigated [135], is compatible with the necessity for a primary genetic initiating event as one component of this stated multistep process of carcinogenesis. On the other hand, the so-called 'normal' colorectal mucosa in HNPCC may be the harbinger of *ras*-related oncogenes in those patients with prior colorectal cancer and/or increased tritiated thymidine labelling patterns of their distal colonic

mucosal crypts (obligate gene carriers of HNPCC). Our rationale for this hypothesis is based in part upon the presumption that the *apparently* normal colorectal mucosa in genotypically positive carriers of HNPCC is in a similar premorbid category to those premalignant polyps which showed expression of *ras*-related oncogenes.

The *ras*-related oncogene expression may have been the result of a somatic mutation. Evidence for this assumption has emerged in other tumor systems. Feig *et al.* [136] have described a patient with serous cystadenocarcinoma of the ovary which contained an activated K-*ras* oncogene which was detected by transfection of NIH/3T3 cells. Normal cells from the same patient lacked transforming activity. It was inferred that activation of this transforming gene was the consequence of somatic mutation in the neoplastic cells. Similarly, Santos *et al.* [137] described a patient with squamous cell carcinoma of the lung who had malignant activation of a K-*ras* oncogene in his tumor, but it was absent in normal bronchial and parenchymal tissue, and in his lymphocytes. These investigators concluded that the malignant activation of a *ras* oncogene appeared to be specifically associated with development of a neoplasm.

Given the preneoplastic proclivity of the so-called normal colonic mucosal cells in HNPCC, we postulate that these cells may harbor an activated *ras*-related oncogene and that its activation could be due to a somatic mutation. In accord with Knudson's two mutation (hit) carcinogenesis hypothesis [138], we speculate that a germinal 'hit' has already occurred in *all* of the colorectal mucosal cells of HNPCC genotype positive patients. Therefore, should the *ras*-related oncogene be associated with this 'normal' tissue, then a lesser amount of environmental perturbation; i.e. diety, other unknown factor (second hit), would be required for oncogene activation and malignant transformation in these HNPCC subjects (as compared to patients from the general population).

This hypothesis merits testing in HNPCC. However, we are not aware of any such studies to date. If elevated *ras*-related oncogene activity were observed in colonic mucosal cells from HNPCC obligate gene carriers, there would then be additional reason to negate the adenoma-polyp-cancer sequence as a prerequisite for *all* colonic cancer expression. We would also have a valuable model for studies in colonic carcinogenesis and its control [139].

Summary and concluding comment

Is hereditary colonic cancer far more common that most investigators have been estimating? This is a cogent question which was recently addressed by Burt *et al.* [140]. They studied an extremely large (approximately 5000

patients) Utah pedigree which had multiple cases of colorectal cancer. The interesting facet of the study is that there had been no recognizable inheritance pattern of colorectal cancer in this family. It was only after systematic screening for colonic polyps, using flexible rectosigmoidoscopy, on pedigree members and spouse controls that the inheritance pattern was able to be clarified. There was a statistical difference ($p < 0.005$) of adenomatous polyps observed in family members (21%) vs. controls (9%). In addition, the polyps in the family members appeared to be larger than those in the controls. Likelihood methods were employed for pedigree analysis which compared the random occurrence of cancer in polyps with autosomal recessive and autosomal dominant modes of inheritance. The observed excess of discrete adenomatous polyps, as well as colorectal cancers, was found to be consistent with an autosomal dominant gene as predisposing to susceptibility, as opposed to either an inherited recessive gene or chance occurrence.

An interesting aspect of Burt *et al.* [140] study was the lack of early age of onset of colorectal cancer as opposed to other familial colon cancer syndromes. The fact of the matter was that the ages of onset of family members and the ages of onset in the Utah Cancer Registry were virtually the same.

The authors emphasized that familial occurrence of colon cancer is common, but specific inheritance patterns are often not readily apparent. When intensively investigated, additional support for hereditary etiology, as in the Burt *et al.* [140] study, may be demonstrated.

These investigators justified the use of flexible proctosigmoidoscopy as opposed to colonoscopy in that there was no evidence for proximal colonic cancer predominance in the family. While this may well be an accurate assessment, it is our belief that colonoscopy (in spite of its problems of increased time, expense, and morbidity) would nevertheless be highly preferred in such kindreds in that one could be easily misled by the finding of an 'apparent' excess of *distal* colonic cancer due to a limited number of individuals affected and/or at risk when, in fact, closer scrutiny of the family might well yield the predominance of proximal colonic cancer. In addition, the yield for polyps would be increased through colonoscopy.

Burt *et al.* [140] stressed the importance of environmental factors as possible causes for familial aggregations of neoplastic lesions. As they emphasized, such common environmental exposures would provide a more likely explanation in small pedigrees, but it would become a more remote issue when studying families of the magnitude which they investigated. Still, it is mandatory that environmental factors be considered in the study of polyps as well as cancer within kindreds.

Ideally, one should attempt to map the colorectal cancer susceptibility locus to one of the many restriction-fragment-length polymorphisms which have presently been identified [141, 142]. Such genetic mapping for the

colonic cancer susceptibility locus would allow precise identification of individuals who are genetically predisposed. Intensive investigation of their environmental exposures and those in the family who lack the colonic cancer susceptibility locus would enable a powerful study of the effect of environment on the cancer-prone genotype. This would lead to better understanding of environmental modulation on phenotype, including polyp and/or cancer age at onset as well as location within differing segments of the colon.

Mulvihill [143], in an editorial based upon the study by Burt *et al.* [140], raises some very cogent questions about what, in fact, is a 'cancer family'? He emphasizes the fact that cancer is common (one in four Americans will be affected during their lifetime, should they live long enough), thereby making it likely that most inviduals in the population will have one or more relatives with cancer. Hence, by chance, there will be significant occurrences of familial aggregation of cancer. For example, Lynch *et al.* [144] observed that half of 200 consecutively ascertained patients from Creighton's Oncology Clinic had at least one first degree relative with cancer. This trend still prevails with almost 2000 patients in our current series (Lynch, H.T., unpublished data, 1985).

Mulvihill stresses the difficulties in delineating a 'cancer family'. Such delineation must depend upon the type and site of cancer as well as age at diagnosis, sex, multiple primary cancers, and the absolute number of affected relatives, given the total number of relatives existing in the particular family. One of the major advantages of delineating a 'cancer family syndrome' which Mulvihill appropriately emphasizes, is that one might then identify a specific cause so that pathogenesis might be better understood and this information could then be utilized for improving cancer control.

The methods employed by Burt *et al.* [140] for determining mode of inheritance utilized both colon cancer and polyps as part of the phenotype. Mulvihill [143] suggests that a mathematical model would be more informative if it allowed for ecogenetics as well [145] and included the extracolonic cancers which occurred in the family.

Lynch *et al.* [3] has repeatedly stressed for more than two decades the value to be found from the standpoint of diagnosis and clinical management through better use of family history, particularly when this extends through informative second degree relatives; i.e. grandparents, aunts, and uncles. These, of course, acquire more meaning when medical and/or more preferably, histologic documentation is obtained. However, Mulvihill's experience, as well as our own, is that such measures, just as in Warthin's day, are rarely exercised in clinical practice. Finally, Mulvihill very succinctly makes a plea for greater attention to cancer genetics as follows: 'Cancer families deserve more research and clinical attention than they have received in the

past. For researchers, advanced techniques in statistical methods, clinical evaluation, and molecular genetics (either singly of combined in an interdisciplinary approach) could be applied with profit to these unusual clusters of cancer [146]. Clinicians can contribute to the national goal of reducing mortality from cancer by 50 per cent by the year 2000 by asking each patient with or without cancer about his or her family history of cancer'. This statement provides a major challenge to all of us who are concerned with strategies for best effecting cancer control.

Acknowledgements

We gratefully acknowledge William Kimberling, Ph.D., for his genetic and statistical assistance in our section dealing with heterogeneity of colorectal cancer in our Oncology Clinic Series.

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5. Screening and early diagnosis of colorectal cancer

PAUL H. SUGARBAKER

Why screen for large bowel cancer?

Screening devices, if accepted by a large segment of the population, can profoundly decrease the incidence of a disease process. Institution of wide spread use of the pelvic examination and Papanicolaou's smear have been accompanied by a profound decrease in the incidence of cervical cancer. In this disease process, a premalignant lesion known as carcinoma *in situ*, is present. This is detected by the Papanicolaou smear and leads to cauterization of the cervical epithelium in order to interrupt the transition of *in situ* cancer to invasive malignancy [1]. In Japan, flexible fiberoptic upper gastrointestinal endoscopy has led to marked improvement in survival of patients undergoing surgery for gastric cancer [2]. In Japan the survival following surgery for gastric cancer approaches 50%. In the United States where the disease is usually diagnosed only after severe symptoms occur, it is accompanied by a less than 20% 5-year survival. In this instance, patient and physician awareness of the disease process plus a fiberoptic endoscope to detect early cancer has led to a marked improvement in the survival of patients with this disease.

Unfortunately a majority of patients with colon or rectal cancer present with symptoms to their physician late in the natural history of this disease. After symptoms occur, a full 15% of patients are determined inoperable for cure because of hepatic metastases or unresectable intra-abdominal spread of cancer [3]. Those remaining may have a poor prognosis because large bowel obstruction (15%) involvement of adjacent organs or structures (10%) or metastases to local regional lymph nodes (50%) has occurred [4].

Several facts suggest that survival from colorectal cancer could be improved significantly if adequate screening tests were to be generally employed. First, this is an extremely common malignancy, with approximately 140,000 new cases in the United States each year. Every man and women in

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

the United States has approximately one chance in 25 of developing color or rectal cancer in his or her lifetime.

Second, as reviewed in Reference 4, much data has accumulated suggesting that large bowel cancer often originates in a precancerous lesion known as an adenoma [5–12]. It is thought that large bowel polyps are a premalignant precursor of colorectal cancer. With the passage of time they undergo neoplastic degeneration and evolve into a large bowel malignancy. This suggests that patients who are kept free of polyps may not be at risk for developing large bowel cancer. Gilbertsen showed through repeated proctosigmoidoscopy that patients kept polyp free will also be kept cancer free in the rectum.

In this study, 21,250 individuals underwent proctosigmoidoscopic examination on an annual basis. Polyps found were removed. Twenty-five adenocarcinomas were detected on the initial examination. However, over the subsequent 92,650 patient-years of follow-up, only 13 additional cancers were detected by sigmoidoscopy. Epidemiologic data predicted one cancer per thousand patient-years, or about 90 cancers. Only 13 of 90 (15%) of the expected cancers appeared. Also, the cancers detected were at an early stage of development and all had excellent chance for cure [10, 11]. Shinya made a similar observation in a high risk population of patients with treated carcinoma of the large bowel [12]. One group of patients with previous adenocarcinoma of the large bowel underwent six monthly colonoscopy. In this group 64% were shown to develop subsequent polyps in a 6-month to an 11-year follow-up. Histologic evaluation of these polyps revealed that 85% were benign, 8% had severe dysplasia and 7% had carcinoma *in situ*. Invasive carcinoma did not develop in any patient in this group. In a control group of patients who did not have regular follow-up colonoscopy, 9% of patients developed invasive adenocarcinoma.

A third feature of colorectal cancer that suggests that screening may be possible is the long latency period of the primary tumor. Clinical incidence suggests that the colon or rectal cancer may be present many years before it becomes symptomatic. Tumors within the colon or rectal epithelium have been shown to be remarkably slow growing so that there is ample time for detection. The first quantitation of the rate of growth of a primary cancer of the large bowel was recorded by Spratt and Ackerman [13]. They reported the slowly progressive growth of a transverse colon cancer that was studied nine times by double-contrast barium enema over 7 and 1/2 years. The cancer finally was removed from the patient and was shown to be a not unusual constricting adenocarcinoma of the transverse colon. Spratt and Ackerman calculated that the cancer grew with a doubling time of 636 days. It was first thought that this particular tumor was exhibiting abnormally slow growth. Welin, Youker, and Spratt, however, reported the doubling time for 20 additional carcinomas serially studied in Malmo, Sweden, to be

620 days [14]. These authors conclude that large bowel tumors must have very long periods of silent growth before they become large enough to produce symptoms. Even the fastest-growing cancer they observed would have required 6 years to 8 years to grow from glandular size to a diameter of 60 mm.

The growth rate of pulmonary metastasis and hepatic metastasis from large bowel cancer is much more rapid than that of the primary tumor within the bowel wall. Collins reported that the average doubling time for 25 separate patients with pulmonary metastasis was 116 days [15]. Confirming this, Welin, Youker, and Spratt reported the median doubling time of 43 pulmonary metastases in 36 patients to be 109 days [14]. Havelaar and colleagues used a liver contrast agent to determine the doubling time of hepatic metastases. In untreated patients it varied between 50 and 95 days [16, 17]. Apparently, the mean growth rates of metastases in the lung from colonic and rectal cancers are five-fold to ten-fold faster than those of the primary cancers growing in the colon or rectum. It may be that ulceration of tumor and exfoliation of tumor cells into the colonic lumen account for the slower growth of the primary.

The fourth feature known about the natural history of this disease that suggests a possible role for screening is the surgeon's capability to cure this tumor. Large bowel cancer (not only the adenoma but invasive cancer itself) is nearly 100% curable by simple surgical resection of the tumor and adjacent colon if detected early in an asymptomatic state. Unfortunately, at present, 15% of the patients who are diagnosed with large bowel cancer have disseminated disease and are incurable by surgery at the time of presentation. The remaining patients who have potentially curative surgery have a survival rate of 50% [1]. Diagnosis in the asymptomatic state places the patient in a favorable diagnostic group. Sanfellippo and Beahrs [18] reported on 391 patients treated for colorectal cancer at the Mayo Clinic. When the patient was asymptomatic at the time of diagnosis, 5-year survival was 71% compared to 49% when symptoms were present.

At present the most efficient approach to colorectal cancer screening seems to be (a) the identification of high-risk groups, (b) the use of currently available screening tests in these groups, and (c) a thorough work-up of patients with positive screening tests to find or exclude colorectal pathology.

High-risk groups for colorectal cancer

Age greater than 40 years

The risk for men and women is quite similar and begins to rise significantly between ages 40 and 45 (Table 1). There is approximately a two-fold

Table 1. High-risk groups for colorectal cancer

Age
Over 40 years in asymptomatic men and women
Associated disease
Ulcerative colitis
Granulomatous colitis
Past history
Colorectal adenomas
Colorectal cancer
Female genital cancer
Female breast cancer
Family history
Familial polyposis
Gardner's syndrome
Turcot's syndrome (CNS tumors)
Oldfield's syndrome (extensive sebaceous cysts)
Colorectal cancer in the general population
Colorectal polyps in the general population
Cancer family syndrome
Generalized gastrointestinal juvenile polyposis

Modified from Sugarbaker PH *et al.* [4].

increase in each decade, reaching a peak at age 75 [19]. It is important to remember that cancer of the colon does occur before the age of 40 years, and when it does the survival may be reduced.

Associated disease and colorectal cancer

Ulcerative colitis

In patients with ulcerative colitis the risk of malignant change is greater when ulcerative colitis begins in childhood, has continuous rather than intermittent symptoms, and was of severe onset. The incidence of cancer is twice as high if colitis began before the age of 25 [20]. In all patients with ulcerative colitis compared to a normal population, the colorectal cancer risk is five to 11 times higher [21–24].

Granulomatous colitis

Weedon and co-workers showed that patients with granulomatous bowel disease (Crohn's disease) with disease onset before age 21 had a 20 times greater risk of developing colorectal cancer [25]. Involved areas of both the small and large bowel are at increased risk. Cancer occurs at an earlier age than in a normal population and frequently was found in bypassed segments of intestine as well as in fistulous tracts.

History

Colorectal adenomas

Prager and co-workers at the Lahey Clinic followed 305 patients who by proctosigmoidoscopy were shown to have adenomas. After a follow-up period of 15 years the incidence of cancer in this population was twice that expected in a normal population; this was a statistically significant ($p < 0.05$) increased incidence [26]. Rider and co-workers reviewed their experience with carcinoma of the colorectum in patients with and without polyps [27]. In 7086 patients without polyps the incidence of carcinoma was 2.1%. The incidence of invasive malignancy in 401 polyp patients was 10.7%. In 14 of the 43 polyp patients (33%), the polyp itself was the site of invasive malignancy. In the other 29 patients the carcinoma developed before (nine patients), at the same time (13 patients), or after (seven patients) the polyp, and in a different area of the large bowel. Rider and associates also showed that patients with multiple polyps are twice as likely to develop carcinoma as are patients with a single polyp. They found 33 carcinomas in 352 patients with a single polyp (9.4%) and ten carcinomas in 49 patients with multiple polyps (20.4%).

Copeland, Miller, and Jones presented additional data to support the concept that a colon that develops an adenoma is also prone to undergo malignant degeneration at some time; 23% of patients with a single colon cancer had associated polyps [28]. The incidence of polyps in the general population is only 5.4% [27]. In patients who had second primary large bowel cancer, 50% of synchronous lesions and 60% of metachronous lesions had associated polyps. Also, in patients with multiple polyps in the primary cancer specimen the incidence of second primary large bowel cancer was 2.5 times greater than in patients with single polyps.

Colorectal cancer

There can be no doubt that patients with previous colorectal cancer must be considered at increased risk for subsequent large bowel cancer, even though a substantial part of this organ may be resected with the first cancer. Schottenfeld, Berg, and Vitsky reported the annual incidence of subsequent primary cancer of the large bowel to be 3.51 per 1000 patients at risk, which represents a threefold excess over that expected in the general population [29]. Similar increased risk for a second primary large bowel cancer has been reported [30].

Female genital cancer or breast cancer

Women with female genital tract or breast cancer have an increased large bowel cancer risk [31]. It is not clear whether this association exists only

within the 'cancer family syndrome' or whether these combinations of multiple primary cancer can occur as isolated cases.

Radiation therapy for cervical cancer

MacMahon and Rowe as well as Castro and colleagues have suggested that prior radiation therapy for cervical or uterine cancer was related etiologically to the development of sigmoid colon cancer [32, 33]. No data on the overall incidence of rectosigmoid cancer in patients receiving pelvic radiation were available in these studies, and more study of this problem needs to be done before a definite correlation of rectosigmoid cancer and prior pelvic irradiation can be made.

Family syndromes and heredity

Familial polyposis syndromes

Familial polyposis is a disease in which the colon of affected persons becomes covered by innumerable adenomatous polyps by age 15 to 25. The disease is inherited as an autosomal dominant trait with 90% penetrance. Unless colectomy is performed in early adulthood, death from colon cancer approaches 100% by age 55. By age 37, over 50% of patients will develop adenocarcinoma; patients often manifest multiple colon and rectal cancers [34]. After age 50, persons with a polyposis family who have not yet developed polyps are unlikely ever to manifest the disease [35].

Familial polyposis may arise *de novo* in a population as a genetic mutation. More commonly, a family history with autosomal dominant inheritance is discovered. It becomes extremely important to identify these persons so that family members can be examined frequently to determine whether they are among the unlucky 50% to develop polyposis. In the past, two-thirds of patients when first seen with polyposis also had evidence of cancer. In carefully followed family groups this has been reduced to 9% [36]. Only a very small number of all patients with colorectal cancer occur in polyposis families. In Michigan, Reed and Neel found the incidence to be 1 in 8300; in Kentucky, Pierce found it to be 1 in 6850 [37, 38]. In this clinical situation early diagnosis and treatment can eliminate the risk of cancer.

Gardner's syndrome is a second polyposis syndrome [39]. About one in seven families with a polyposis syndrome has one or several of the associated features of Gardner's syndrome. These are sebaceous cysts, desmoid tumors, fibromas, facial bone osteomas, and abnormal dentition. Turcot described a variant polyposis syndrome in which malignant tumors of the central nervous system (CNS) were associated with familial polyposis [40]. Oldfield also described a syndrome in which multiple sebaceous cysts were

found in patients with polyposis coli and colorectal adenocarcinoma [41]. In the Peutz-Jeghers syndrome, multiple polyps throughout the gastrointestinal tract are association with melanin pigmentation of the buccal mucosa, lips, face, fingers, toes, vagina and anus [42]. However, in this syndrome the intestinal polyps are not adenomas but hamartomas, and there is no good evidence for an increased risk of intestinal cancer.

There is increasing evidence that the genetic defect in the polyposis syndromes is not limited to the adenomas that develop [43]. The colonic epithelial cells throughout the colon lose their ability to repress DNA synthesis. Cutaneous epidermal cells also are apparently abnormal. If these cells are grown in culture, cutaneous fibroblasts grown with crisscross orientation and multilayers rather than in the usual growth pattern of monolayers. Fibroblasts in culture from patients with polyposis coli also are comparatively more susceptible to viral transformation by murine sarcoma virus [44]. Metabolic abnormalities are suggested by higher amounts of undegraded cholesterol in the stool of familial polyposis patients [45]. These systemic variations seen in associations with familial polyposis syndromes offer great promise in screening families and perhaps even the fetus for disease.

Family history of colorectal cancer

Independent of polyposis syndromes and cancer families, colon cancer shows a 'modest familial aggregation' [46]. This familial susceptibility is not synonymous with genetic causation but may be caused by environmental factors. Whatever the cause, family members who have a relative with large bowel cancer have three to four times the risk of this disease. Lovette obtained detailed family histories on 209 patients treated at St. Mark's Hospital in London for cancer of the large bowel [36]. Forty-two cancers of the large bowel were found in mothers, fathers, brothers, or sisters of colorectal cancer patients. Only 11.65 such cancers would be expected in a general population. This was not just an increase in all cancers for those families but seemed to be largely specific for colon and rectal malignancy. In male relatives, carcinoma of the large bowel was recorded more than twice as frequently as cancer of the bronchus. Among females, colorectal cancer was recorded more than twice as frequently as breast cancer. In addition, large bowel malignancy occurs at an earlier age in relatives of patients with large bowel cancer [47].

Hereditary colorectal cancer

Lynch and co-workers have reviewed the multiple reports of hereditary colon cancer occurring without a polyposis syndrome [48]. The syndrome is characterized by autosomal dominant inheritance, a low mean age (41 years) for the occurrence of colon cancer, and a marked increase proportion of

tumors in the proximal colon. Sixty-five percent of large bowel cancers in this syndrome occur in the proximal colon (above the sigmoid), whereas only 35% occur in this portion of the colon in a general population [49]. In this syndrome solitary adenomatous polyps may occur in a large proportion of family members in either the presence or absence of colorectal cancer [50].

Cancer family syndrome
In some families there is an increased risk of adenocarcinomas of all varieties, with a particular predominance of carcinoma of the colon and endometrium [51, 52]. Cancers occur at an early mean age, and multiple primary malignant neoplasms in one family member frequently occur. The inheritance is autosomal dominant. Williams has emphasized the need for serial diagnostic tests and education in cancer families [53].

Familial juvenile polyposis
Haggitt and Pitcock described two patients with juvenile polyposis of the colon accompanied by a family history of colonic cancer at a young age [54]. The patients did not have a typical familial polyposis syndrome because the polyps were not numerous enough (30 in one patient, 80 in the other) and were typical juvenile polyps rather than adenomas. Stemper, Kent, and Summers emphasized that the juvenile polyps could occur throughout the gastrointestinal tract and that malignancy in the family occurred unusually frequently in the stomach and right colon [55]. No cases of primary rectal or sigmoid cancer were seen. Haggitt and Pitcock suggest that persons with a gene for juvenile polyps may express this gene in more than a single fashion; malignant foci within the gastrointestinal tract would be an alternate mode of gene expression.

Screening techniques for colorectal cancer

After one identifies the groups at high risk for colorectal cancer, the appropriate screening test must be identified.

Stool test for blood: Hemoccult

Success with the Hemoccult test to screen a general population for cancer must be attributed in a large part to the persistent efforts of Greegor [56, 57]. He developed a test that used guaiac-impregnated paper on which a small quantity of stool could be smeared. This slide of paper was contained in a cardboard envelope; by this method the testing of stool for occult blood is esthetically tolerable for most people. By adjusting the sen-

sitivity of the test, the number of false-positive and false-negative tests has been minimized. Christensen, Anker, and Mondrup compared the sensitivity and reproducibility of five different methods of testing the stool for occult blood and concluded that the Hemoccult method was the best available [58].

To help decrease false-positive tests, patients are asked to refrain from eating meat, fish, and chicken for at least 24 h before stool specimens are collected. In addition, large quantities of vegetables, fruit, and cereal are to be consumed for a high-residue diet. This roughage in the diet is designed to cause an ulcerated or necrotic area of tumor to bleed slightly and, in so doing help eliminate false-negative examinations. Deyhle and co-workers presented data suggesting that a high roughage diet did decrease false-negative tests [59]. To help eliminate false-negative examinations further, two samples of stool from different areas of a fecal mass were to be collected on three consecutive days (total of six specimens). Winawer and co-workers called attention to the fact that a single positive slide was as likely to reveal neoplasia as multiple positive slides [60]. Therefore, careful follow-up studies were required if only one slide was positive, the same as if all slides were positive.

In the experience in using the Hemoccult test to date, several problems have been identified. Miller pointed out that responses to mass screening were from 'cancer-oriented' populations [61]. In five different mass screening projects, just under 10,000 people returned slides. Twenty-two cancers were found; however, only three to five cancers would be expected in a general population. It seems likely that not all patients participating were actually asymptomatic. It is not suprising, therefore, that the stage of disease in the early Hemoccult studies was not much different from that which would be found in a group of symptomatic patients. A second consistent finding is the low proportion of a population participating in a mass screening projet. Only 1 to 3% of all people in a study population participate [62–65]. In contrast to the low proportion of participants, the compliance of people who do enroll is 85%.

Undoubtedly, the greatest problem with the Hemoccult method as used today is false-negative results. Even with the most cautious interpretation of the results, a negative test for cancer implies that malignancy has been ruled out – especially to the patient. Unfortunately, nearly as many adenomas are missed as are found, and some cancers (about 20%) are not detected when people completing the Hemoccult test undergo sigmoidoscopy or fiberoptic sigmoidoscopy [65–67]. The various causes of false-positive and false-negative Hemoccult tests are shown in Table 2. Many of these undesirable results can be avoided by careful patient instruction.

In an ongoing study at the Strang Clinic in New York City, data on the usefulness of the Hemoccult method in large numbers of truly asymptomat-

Table 2. Causes of false-positive and false-negative tests using the Hemoccult method

False-positive tests	False-negative tests
Meat in diet	
Diverticulosis	Failure to employ high-residue diet
Minor anorectal problems	Vitamic C in diet
Hemorrhoids	Time lag between specimen collection and specimen examination
Fissures	
Proctitis	Failure to prepare slides properly or complete all six slides
Peroxidases in skins of vegetables and fruits (tomatoes and cherries)	Follow-up examinations which failed top detect lesion
Upper gastrointestinal pathology	Lesion not bleeding at the time of stool collection
Gastritis from ASA ingestion	Outdated Hemoccult slides or reagent
Ulcer disease	
Hiatus hernia	

Modified from Sugarbaker PH *et al.* [4].

ic persons are being accumulated [67]. In 9709 Hemoccult tests in men and women aged 40 years or older, 1% of patients had a least one positive slide. Half of the Hemoccult-positive patients had, on workup, neoplastic lesions. Neoplastic lesions were defined as polyps greater than 5 mm in diameter (38%) and cancers (12%). The other 50% of Hemoccult-positive patients had diverticulosis only, polyps less than 5 mm, or no abnormalities were found. This meant that the Hemoccult method had a very respectable predictive value of 50%. The false-positive ratio was 0.5%; this probably is a tolerable number of negative follow-up studies that must be completed.

Gilbertsen and co-workers have emphasized that proper follow-up examination of Hemoccult-positive patient populations is required so that early potentially curable carcinomas are detected [68]. At the time of Gilbertsen's report, 72 primary carcinomas had been detected through Hemoccult screening. Sixteen were in the rectum and found by endoscopy. Fifty-six of the carcinomas were in the colon, 33 were suspected by barium enema. No evidence for the presence of cancer in the remaining 19 was found by careful roentgenographic examinations. These cancers were detected by subsequent colonoscopic examination. Roentgenographic examination missed on one of 11 Dukes' C and D carcinomas but missed 19 of 45 more likely curable Dukes' A and B carcinomas. Gilbertsen and colleagues conclude that colonoscopy was superior to barium enema in the diagnostic evaluation of Hemoccult-positive patients. Their routine at this point in time is to recommend barium enema only if colonoscopy is not complete.

The most encouraging results from studies using the Hemoccult method are those showing patients with an early stage of disease when cancer is detected by Hemoccult screening [69]. Seventy-seven percent were Dukes'

Table 3. Credits and debits of fecal occult blood testing

Credits
Good patient compliance (85%)
Manageable percentage of positive slides (approximately 1%)
High percentage of neoplastic lesions in patients with positive slides (approximately 50%)
Favorable pathologic staging of detected cancers in asymptomatic screened patients (86% localized)
Debits
Low participation by general population
False-positive rate for both colorectal cancers and adenomas (approximately 0.5%)
Demonstrated false-negativity for neoplastic lesions by total colonoscopy, especially with adenomas
Conversion of positive slides to negative with drying

Modified from Winawer SJ *et al.* [67].

A or B lesions, 16% were Dukes' C, and only 7% Dukes'D. The improved prognosis one expects from cancer diagnosis in the asymptomatic state apparently is true for the Hemoccult method of testing.

Winawer and co-workers have itemized the 'debits and credits' of the Hemoccult method of testing for fecal occult blood to detect colorectal cancer [67]. A modified list is given in Table 3.

Digital rectal examination

Although digital examination of the rectum is a standard part of every physical examination and proctosigmoidoscopic examination, few studies have singled out the usefulness of rectal examination for screening. Miller and Knight provided rectal examination as an optional part of their Hemoccult screening project [64]. Patients with a 'rectal mass' were studied subsequently by sigmoidoscopy and barium enema. Of 2332 patients, 28 rectal masses were noted; two carcinomas and four adenomatous polyps were among these 28. False-positive examinations included hemorrhoids, hypertrophic papillae, postoperative tear, fissure, and normal examination. Digital rectal examination does detect significant numbers of neoplasms and should be a part of a screening program if logistically possible.

Sigmoidoscopy

There seems little doubt that sigmoidoscopy used as a screening test can detect significant number of rectal and rectosigmoid cancers. The real question is whether the expenditures of time and money are best spent on sigmoidoscopy or on other health care programs. Between two and five cancers

will be found by sigmoidoscopy in each 1000 asymptomatic men and women over the age of 40 [70, 71]. The tumors identified in asymptomatic patients also will result in a markedly improved prognosis (see section on prognosis).

There is a second benefit to the patients from sigmoidoscopic examination. Adenomas are seen and removed, and this apparently interrupts the polyp to cancer sequence. This led Gilbertsen to postulate that large bowel cancer was a 'preventable disease' [72].

Bolt questioned if 'routine sigmoidoscopy was the final answer to cancer of the rectosigmoid' [73]. His reasoning was as follows: for each 10,000 examinations, about 20 cancers would be detected in an asymptomatic state. From the data of Hertz, Deddish, and Day, 88% 5-year survival would be expected in these patients; with symptoms, 50% survival would be expected [71]. Therefore, 17 of 20 rather than ten of 20 of these patients would survive their malignancy. If the cost of each sigmoidoscopy examination is $ 50, the screening program for the 10,000 patients would cost $ 500,000. Each life spared a cancer death would cost about $ 70,000.

Because of the expense of routine sigmoidoscopic examination, Corman, Coller, and Veidenheimer suggested that screening should not begin until age 50 [74]. Because of the growth rate of adenomas and carcinomas, repeat examinations could be done every 2 years rather than annually. In 2500 sigmoidoscopic examinations at the Lahey Clinic in asymptomatic patients 50 years of age or under, no cancers were found.

Flexible fiberoptic sigmoidoscopy

Recently, interest in a flexible fiberoptic instrument to examine the entire rectum and sigmoid colon has been renewed. This instrument, about 60 cm in length, can be navigated from anus to junction of sigmoid and descending colon; biopsy channels allow biopsy and polyp removal on an outpatient basis.

Several groups have shown, as was predicted, that with visualization of about three times the length of bowel, about three times the number of adenomas and carcinomas are detected [65, 66, 75, 76].

Credits for flexible sigmoidoscopy as a screening device include the following points. First, a greater number of lesions are detected as compared to rigid sigmoidoscopy. Recent epidemiologic data suggest that there has been a proximal migration of carcinoma of the colon [77–79]. Second, patient tolerance of the examination with the flexible instrument is the same or better than with the rigid instrument [66, 75]. Finally, photographic recording of lesions is possible, and biopsy and polypectomy are safer and speedier with the fiberoptic instrument than with the rigid sigmoidoscope; this is especially true if polyps are above the peritoneal reflection.

Debits of the flexible fiberoptic instrument include (a) greater time requirement for the procedure; (b) more involved patient preparation; (c) a requirement for more highly trained personnel; (d) greater cost for the instrumentation; and (e) still about one third of colonic lesions (those above junction of sigmoid and descending colon) not detected.

Further trials with the flexible fiberoptic sigmoidoscope are needed to assess fully its usefulness.

Colonoscopy

One might ask why total colonoscopy is not currently used as a method for screening the large bowel for cancer and polyps. Reasons given in the past are that this screening is not cost effective. It has been too expensive in terms of physician time and instrument cost to offset the number of carcinomas found in a general population. Colonoscopy as practiced at the present time requires a highly trained physician for insertion of the scope and proper visual interpretation of the endoscopic findings. A second reason that colonoscopy is not currently employed as a screening tool is that there is insufficient personnel and an inadequate number og endoscopes to use colonoscopy in a large population. At the present time it requires a highly trained person to navigate the instrument to the cecum. A third reason for not widely employing colonoscopy as a screening tool is that it is not accepted as necessary by the general public. The inconvenience, discomfort, and cost that a patient must experience during this examination is not thought by the public to be commensurate with the gains from large bowel cancer screening.

However, there are flexible sigmoidoscopes that have been used for screening in the general population [65, 75, 76]. Also, total colonoscopy has been used with good results in high risk groups [80]. Patients with ulcerative colitis are examined at regular intervals in order to look for dysplastic changes. It is undoubtedly true that the preparation required for a complete colonoscopic examination is a handicap to the greater utilization of this procedure to date.

Future prospects

Endoscopy for screening for adenomas or cancer in the large bowel has great possibilities. Endoscopes can visualize the entire mucosal surface of the bowel but their use is currently unpleasant, time consuming, expensive and requires a vigorous preparation of the bowel. A self advancing colonic endoscope (SACE) would overcome many of these obstacles to effective screening [81].

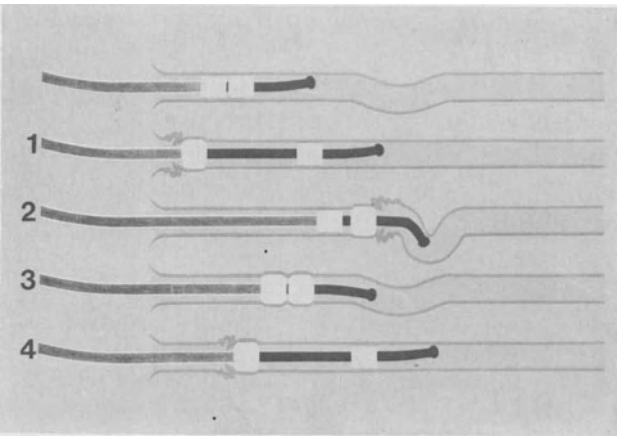

Figure 1. Mode of action of a self advancing colonic endoscope (SACE). Introduction of the colonoscope into the anus is accomplished manually with both cuffs deflated and placed together in a closed position. Repetitive advancement starts (step 1) when the rear cuff is inflated and gentle retrograde traction is placed on the sleeve. This straightens the colon and permits the endoscope to be pushed through the sleeve to advance the endoscope tip and the forward cuff. At this point, (step 2) the forward cuff is inflated until it grips the colon wall and the rear cuff is deflated and brought forward by manual advance of the sleeve. Having reached a closed position the rear cuff is inflated (step 3). With both cuffs gripping the colon wall, and with gentle retrograde pressure, the colon is straightened for several centimeters. Endoscope advancement is accomplished in step 4, a repeat of step 1. This sequence of maneuvers is repeated under direct vision until the cecum is reached. When the cecum is entered light appears at McBurny's point and the control unit is shut off. Modified from Sugarbaker PH *et al.* [81].

The principle of SACE advancement is illustrated in the steps of Figure 1. Introduction of the colonoscope into the anus is accomplished manually with both cuffs deflated and placed together in a closed position (step 0). Repetitive advancement starts as shown in step 1 when the rear cuff is inflated and gentle retrograde traction is placed on the sleeve. This straightens the colon and permits the endoscope to be pushed through the sleeve to advance the endoscope tip and the forward cuff. At this point, in step 2, the forward cuff is inflated until it grips the colon wall and the rear cuff is deflated and brought forward by manual advance of the sleeve. Having reached a closed position the rear cuff is inflated, as shown in step 3. With both cuffs gripping the colon wall and with gentle retrograde pressure, the colon is straightened for several centimeters. Advancement occurs in step 4, a repeat of step 1. This sequence of maneuvers is repeated until the cecum is reached. When the cecum is entered light appears at McBurney's point and the control unit is shut off.

Visualization is performed while the endoscope is being withdrawn. The front cuff can be alternatively inflated and deflated to facilitate visualization.

A major problem with SACE could be proper preparation of the large bowel so that feces did not obscure complete visualization. If water is used to fill the colon as the automated endoscope moves from anus to cecum this device may participate in bowel preparation as well as enable adequate visualization. After removal of formed stool from the sigmoid and rectum, the large bowel can be gently filled with water, the control device then turned on and the endoscope find its own way to the cecum. In this manner complete preparation of the bowel would be accomplished at the same time that the automated endoscope is navigating through the large bowel. It is our hope that with continued efforts a painless endoscopy of a completely prepared bowel can be accomplished within several minutes. If this can be accomplished screening of large segments of the population at risk for developing large bowel malignancy can be performed.

With present colonoscopic techniques the major limitation in the procedure is still getting to the site of colon pathology. Navigation from anus to cecum can be time consuming sometimes taking as long as 2 h to complete. With this apparatus routine colonic endoscopy would be greatly facilitated. Perhaps, also, there would be increased acceptance of the procedure by the general public.

A second prospect for screening may be monoclonal antibody. Several colon cancer specific antibodies have been described. These reagents combine with the tumor cell glyco calyx; rarely do they combine with intracellular components of the tissue. The mucins that surround the tumor are usually strongly reactive with the monoclonal antibody. Even mucins produced by polyps may be recognized by antibody. The intrarectal and intracolonic administration of labeled monoclonal antibody into a prepared colon may allow recognition of adenomas or ademocarcinomas. The most efficient label for the antibody and its subsequent detection remain to be determined.

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6. Endoscopy in the diagnosis and management of gastrointestinal cancer

DAVID R. ANTONOW and CRAIG McCLAIN

Introduction

Advances in instrumentation over the past two decades have made complete endoscopic examination of the upper gastrointestinal tract and colon a routine procedure in most medical centers. As a result, there has been a growing reliance on endoscopy as a primary tool for the diagnosis of gastrointestinal conditions, including cancer and its complications. Together with the increasing diagnostic use of endoscopy, there has been a remarkable growth in therapeutic applications of these procedures. However, endoscopic technology has often advanced ahead of controlled critical evaluation of these sophisticated modalities in the clinical setting. In many situations, clear proof of the efficacy and cost effectiveness of endoscopy is lacking. Close collaboration among specialists in endoscopy, radiology, pathology and surgery will be necessary if improvements in patient management are to follow from our technical progress. For the present, few rigid recommendations can be made, and the choice and sequence of specific tests needs to be tailored to fit the individual patient.

The aims of this review will be to present a balanced view of the role of endoscopy in patients with cancer, to discuss endoscopic therapy for cancer (or precursor lesions), and to point out areas of controversy. The chapter will be organized into segments, each dealing with a specific anatomic region: esophagus, stomach, duodenum, and colon. As a preliminary, the technical aspects of the various endoscopic procedures will be briefly reviewed.

Upper gastrointestinal endoscopy

Modern upper gastrointestinal fiberoptic endoscopes allow the examiner to completely inspect the mucosa of the esophagus, stomach and proximal

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

duodenum. The trend in instrument development has been toward decreasing caliber (less than 10 mm) with increasing biopsy channel size (2.8–3.5 mm). In most situations, an end-viewing endoscope, able to achieve approximately 180° of tip deflection, is used. Patient preparation for endoscopy involves only a 12 h fast. In most cases the procedure is done after premedication with topical pharyngeal anesthesia and intravenous diazepam or meperidine. The endoscope is advanced under direct vision, and a complete examination of the esophagus, stomach and duodenum can be done in less than 5–10 min. A side-viewing endoscope may give a slightly improved view of the medial duodenal wall, but this instrument is employed mainly for cannulation of the duodenal papilla and injection of radiocontrast medium into the biliary and pancreatic ducts. To provide medical documentation, a photographic and/or videotape record of the endoscopic procedure may be obtained for later review.

Tissue specimens obtained during the procedure are an important diagnostic adjunct to endoscopy. The main technique is the use of biopsy forceps for targeted sampling of suspicious lesions under direct vision. Since the specimen obtained is quite small, diagnostic adequacy depends on both careful selection of the area to be sampled, and the collection of a large number of samples. In selected cases, a larger particle biopsy can be obtained by the 'lift-and-cut' technique, where the lesion is enclosed within a wire snare and removed by monopolar electrocautery [1]. This technique is only applicable to discrete, polypoid lesions or infiltrated folds. Targeted brushing of lesions for cytology specimens may be done during endoscopy. In addition, cytologic specimens may be obtained by direct, transendoscopic needle aspiration [2], or by 'salvage' of material aspirated from the biopsy channel during and after forceps biopsy [3].

Upper gastrointestinal endoscopy has proven to be quite safe in the hands of trained examiners. In a retrospective survey of 211,400 upper gastrointestinal endoscopic examinations in the US during 1972-1973, the overall complication rate was 1.3/1,000 [4]. Complications which were reported include: 70 performations, 63 episodes of bleeding, 129 episodes of cardiopulmonary failure, 17 infections, and 228 miscellaneous medication reactions.

Colonoscopy

Fiberoptic colonoscopy is a great deal more demanding technically than upper GI endoscopy. The success rate for insertion of the colonoscope to the cecum is approximately 85–95% for experienced endoscopists; unsurprisingly, this is substantially lower for the less well trained [5, 6]. A thorough preparation of the colon is necessary for a safe, complete examination. Recently, the use of whole gut lavage with a polyethylene glycol-electrolyte

solution has simplified bowel cleansing [7, 8]. Complete examination may be done as an outpatient procedure after sedation with diazepam or meperidine, usually in 30 min or less. In addition to forceps biopsy and cytology, colonoscopic polypectomy using a wire electrocautery snare is routinely performed. The incidence of complications during colonoscopy varies depending on whether polypectomy is done [6–12]. For diagnostic colonoscopy alone, perforation occurs in 0.2–0.4% with mortality rates of roughly 0.02%. When polypectomy is done, bleeding occurs in 0.7–2.5%, perforation in 0.3–1.0% and mortality in 0.01%. Shortened versions of the fiberoptic colonoscope, measuring 35–60 cm, have been introduced as an alternative to rigid proctosigmoidoscopy. These are being used by growing numbers of primary care physicians for screening purposes.

It is important to emphasize that for all endoscopic procedures, the diagnostic accuracy and safety depend greatly upon the skill and experience of the examiner, which may vary considerably among endoscopists. Also, it should be obvious that ability to perform one endoscopic procedure, does not automatically assure competence in the performance of different or new techniques.

Cancer of the esophagus

Clinical features

Progressive dysphagia is the cardinal symptom of esophageal cancer; this symptom is often accompanied by chest pain, odynophagia or weight loss. Unfortunately, esophageal cancer is rarely diagnosed at an early stage in this country. By the time of onset of symptoms, local spread is usually present. The majority of esophageal carcinomas are squamous - between 60 and 90%, depending upon whether or not adenocarcinomas of the esophagocardiac junction are included. Alcoholism and smoking are the major predisposing factors for squamous carcinoma of the esophagus in the US. Most primary adenocarcinomas of the esophagus (not involving the stomach) arise in Barrett's epithelium, related to chronic gastroesophageal reflux. A number of predisposing conditions or premalignant lesions associated with esophageal cancer have been identified; the role of endoscopy for surveillance of patients with these conditions will be discussed elsewhere in this volume.

Diagnosis

In patients with swallowing difficulty, a conventional barium swallow is the usual first test. The diagnosis of cancer is often strongly suggested by the

clinical appearance on X-ray; however, patients with progressive dysphagia or other suggestive symptoms should undergo endoscopy whether or not a lesion is seen. The aim for endoscopy in esophageal cancer is to define the nature and extent of the lesion and to make a tissue diagnosis of malignancy. The endoscopic appearance of squamous carcinoma of the esophagus takes one of three main forms: polypoid mass, ulcerated mass, or malignant stricture. Adenocarcinoma of the esophagus usually occurs in the distal third, associated with Barrett's metaplasia. This lesion is characteristically located 2–3 cm below the endoscopically identified squamocolumnar junction. Such cancers tend to have a mixed exophytic and infiltrative growth pattern, usually presenting as a malignant stricture.

In the presence of an irregular, friable or superficially ulcerated lesion projecting into the esophageal lumen, the main diagnostic problem is in differentiating squamous carcinoma from other primary esophageal malignancy (adenocarcinoma, lymphoma) or extrinsic, invading malignancy

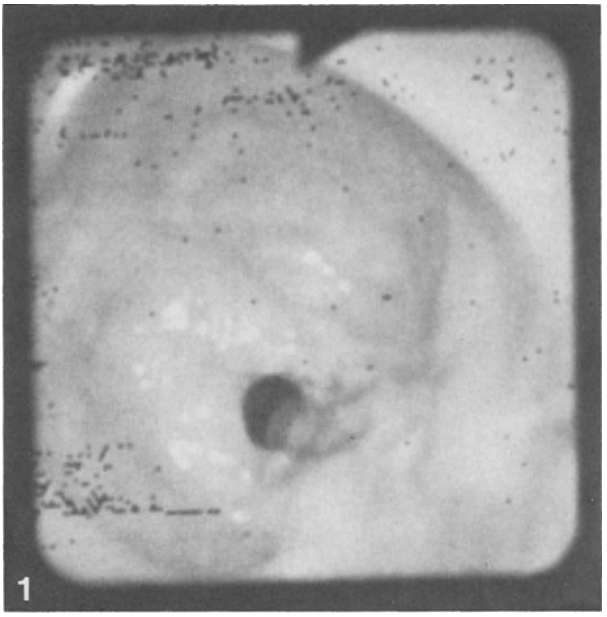


Figure 1. Benign peptic stricture; note the symmetric and relatively smooth appearance of the stenotic area.

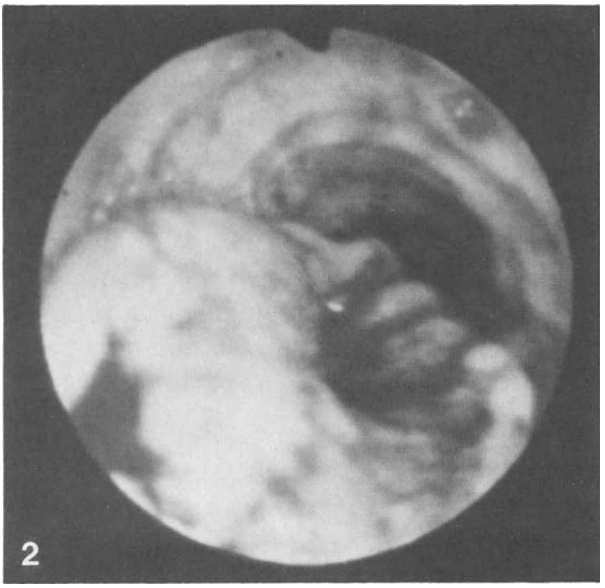


Figure 2. Squamous carcinoma of the esophagus; involvement of the wall with a large ulcerated mass.

(lung, stomach, mediastinal nodes). Similarly, the appearance of an ulcerated mass with irregular, heaped-up edges should strongly suggest malignancy; although, this appearance may occasionally be produced by severe peptic esophagitis with ulceration and pseudomembrane formation (Figs. 1, 2). Differentiating benign from malignant strictures based on appearance can often be difficult. Severe esophagitis can produce marked deformity and mucosal abnormality which may mimic malignancy. Location plays an important role in differential diagnosis. Most strictures in the distal esophagus are peptic; however, the absence of an associated hiatus hernia or location of the stricture below the squamocolumnar junction are features suggestive of malignancy. A stricture of the proximal two-thirds of the esophagus, with no evidence of Barrett's epithelium, is highly suspicious for malignancy. Regarding the endoscopic appearance of the stricture itself, an asymmetrical appearance, coarse nodularity or a pinpoint lumen all suggest cancer.

In general, the combined use of endoscopic biopsy and cytology allows a correct histological diagnosis to be made in over 90% of esophageal cancers [13–18]. The optimal type and number of specimens obtained is determined by the macroscopic appearance of the lesion. In addition, it should be noted that the value of cytology depends largely on the local availability of a skilled, interested cytologist.

With multiple, directed biopsies, there is usually no difficulty in making a histologic diagnosis of polypoid or ulcerated lesions. Biopsies should be taken from points where the cancer is visibly breaking through the mucosa. In ulcerated lesions care should be taken to avoid inflammatory debris in the ulcer base. If six to ten biopsy specimens can be obtained, the addition of cytology should not add greatly to the diagnostic yield. In contrast, stenotic lesions are quite often problematic. If the proximal tumor margin is visible within the stricture, six or more biopsies should be obtained. When the stricture cannot be passed and no evidence of tumor is seen, brushing cytology is the most useful technique. On occasion, it may be necessary to perform repeat biopsy after the lesion has been dilated.

Therapeutic endoscopy and palliation of esophageal cancer

The ideal therapy for esophageal cancer has not been determined. In a recent extensive review, only 39% of squamous carcinomas were resectable at diagnosis, with 1- and 5-year survival rates of 18 and 5%, respectively [19]. In view of this poor prognosis, palliation of dysphagia is of major importance in the management of this disease. Currently, the trend in treatment is toward aggressive use of multiple modalities, including palliative resection, for those not resectable for cure. There are a number of supportive endoscopic techniques directed toward the establishment of an adequate esophageal lumen, so allowing adequate nutrition and preventing pulmonary aspiration. These are summarized in Figure 3.

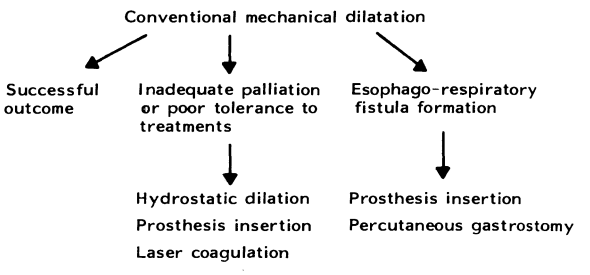


Figure 3. Nonoperative management of malignant dysphagia.

Chronic peroral dilation of malignant esophageal strictures

Several studies have shown mechanical dilation to be safe and effective in the management of dysphagia secondary to esophageal cancer [20–22]. Mercury-weighted rubber dilators are widely used; however, for narrow (less than 12 French) or irregular lesions, metal olive dilators can be passed along an endoscopically-inserted, spring-tipped guidewire. Fluoroscopic monitoring is recommended to facilitate safe passage of the dilators through the tumor. In a study by Heit *et al.*, 26 patients with cancer of the esophagus underwent 616 dilations with only one closed perforation [20]. Twenty-four of these 26 patients were able to resume oral feedings until shortly before their death. No morbidity was seen in the 222 dilations done while patients were receiving radiation treatments. In a larger series of over 1,300 dilations in 154 patients with esophageal cancer, Cassidy *et al.* noted only three serious complications [21]. In this group, 15% failed to achieve adequate palliation from dilation alone. The morbidity for dilation of malignant strictures does not appear to differ greatly from reported complication rates for dilations in general, either with mercury-weighted rubber dilators (0.1%) or Eder-Peustow metal olives (0.3%) [23].

Balloon dilation of esophageal strictures is a recently available technique [24–26]. The principle advantage of the use of balloons is that the force applied to the stricture is stationary and radially directed, rather than longitudinally shearing as with conventional techniques. This may reduce the risk of perforation during the dilation procedure. In most cases, a guidewire is placed throught the stricture under direct endoscopic visualization. Then the balloon catheter is placed through the stricture over the guidewire and slowly inflated with radiocontrast medium, under fluoroscopic monitoring. In most instances a luminal diameter of 15 mm can be achieved at the initial procedure, accompanied by symptomatic improvement in over 90%. Although reported experience is limited, it appears that balloon dilation of malignant strictures of the esophagus is easy and safe. Graham *et al.* reported no complications with this procedure in 12 malignant strictures [25]. Lindor *et al.* dilated 19 malignant strictures of the esophagus with an 89% success rate [26]. These authors noted further procedures were required in 73% with no complications requiring hospitalization.

While it is clear that many patients can be managed successfully with dilation alone, there comes a point where the dilation procedures become progressively more difficult and need to be done at steadily decreasing intervals. In some cases, dysphagia is not relieved despite 'adequate' dilation because the tumor masses are only pushed aside and recollapse promptly after dilation. In these patients, the morbidity and discomfort associated with dilation become excessive and other forms of therapy are often needed.

Peroral prosthesis placement for esophageal cancer

There has been widespread use of perorally inserted prostheses for treatment of dysphagia secondary to esophageal cancer in inoperable patients [27–32]. Intubation, however, is associated with substantial complications such as perforation, pressure necrosis, bleeding, obstruction and tube migration. This procedure should not be a substitute for conventional mechanical dilatation except for refractory dysphagia or to minimize esophageal wall contact with food or secretions when there is an esophagorespiratory fistula. Although there is great methodologic diversity among reported series, the basic procedure involves placement of an individually constructed plastic tube to stent the cancer after initial dilatation. Den Hartog Jager *et al.* achieved generally good palliation in 200 patients with obstructing esophagogastric malignancy [29]. They performed dilatation and intubation under local anesthesia, using the endoscope as the lumen guide-obturator. A large number of complications were reported including 16 perforations (one fatal) and four procedure-related deaths. Obstruction or migration of the prosthesis requiring replacement was seen in 39.5% of patients. Olgivie *et al.* reported satisfactory palliation with prothesis insertion in 112/118 patients [30]. Most intubations by this group were done under general anesthesia with a complication rate similar to that of den Hartog Jager, including 15 perforations (five fatal). Using a more gradual program of preintubation dilatation, Palmer reported his experience with prosthesis insertion in 75 patients without procedure-related mortality [31].

Most authors feel intubation is not suitable for lesions situated near the cricopharyngeus muscle; otherwise, patients with dysphagia refractory to conventional dilatation or symptomatic esophagorespiratory fistulas are potential candidates. Unfortunately, there have been no controlled comparisons in unselected patients of oral prosthesis insertion with other treatment modalities: mechanical dilatation, surgical prosthesis insertion or radiation. Therefore, comparison between the results obtained with different treatment methods can only be made with difficulty [32].

Laser therapy for esophageal cancer

In a few centers, endoscopic laser therapy has been used to palliate obstructing esophageal cancer [33–35]. This sophisticated technique involves photocoagulation and photodestruction of tumor under direct endoscopic visualization. Patient tolerance of the procedure is similar to that for routine endoscopy. In most cases, laser therapy can be initiated during a short initial hospitalization and continued on an outpatient basis. Treatment-related morbidity has been slight; although, complications such as perforation or fistula formation may occur. The number of treatment sessions necessary to establish an effective lumen varies, depending on the size and complexity of the tumor. Previous irradiation or surgery do not interfere with laser treat-

ments, there is no maximal tolerated dose, and retreatment for recurrent tumor after an initial course of therapy is possible.

In the initial report by Fleischer, 14 patients with obstructing esophageal cancer received a mean of 5.3 laser treatments (2–13) over a mean period of 11.6 days (5–28) with clinical, radiologic and endoscopic improvement in all [33]. All patients were able to eat solid food after laser therapy. Two major complications were noted: a tracheoesophageal fistula which developed after completion of therapy and a perforation which occurred during insertion of a 34 French Edlich tube. Mellow *et al.* noted improvement in performance status in 8/11 and relief of dysphagia in 11/11 patients after laser therapy [34]. In this series, five patients with tumor reocclusion were retreated with laser therapy at a mean of 10 weeks after initial treatment. Cello *et al.* noted substantial immediate palliation with continued symptomatic relief from dysphagia in 12 patients who received a mean of 3.3 laser treatments over a mean of 18.5 days [35]. Laser therapy has also been used for palliative management of advanced adenocarcinoma of the gastric cardia, with similar encouraging results [36]. While the reported experience is small, there is great interest in the use of laser therapy for obstructing carcinoma throughout the gastrointestinal tract. The clinical application of laser therapy will be limited by the cost and availability of the necessary equipment as well as by the number of skilled examiners. However, over 200 medical lasers are now in use in the US, and this procedure should soon be regionally available to nearly all patients.

Percutaneous endoscopic gastrostomy

Patients with obstructing esophagogastric cancer are often nutritionally depleted and suffer continued inability to maintain adequate dietary intake due to dysphagia and the side-effects of therapy. Since distal gut function is generally intact, these patients are conventionally managed with intermediate to long-term enteral feedings via gastrostomy. Recently, an endoscopic technique for placement of a permanent gastrostomy has been described, which avoids the need for laparotomy or general anesthesia [37–39]. Briefly, a silk suture is introduced percutaneously into the stomach lumen (through an intravenous catheter) under endoscopic visualization. The suture is then withdrawn through the mouth by the endoscope, attached to a modified mushroom feeding catheter and pulled back through the mouth, esophagus, stomach and anterior abdominal wall. An advantage of this procedure is that it can be done at the bedside or in the endoscopy suite, under local anesthesia. Furthermore, feedings can be instituted within hours of insertion. In patients who become able to take adequate oral nutrition, the gastrostomy tube can be removed without formation of a gastrocutaneous fistula. In the reported experience, complications have been few. Ponsky *et al.*, who first described this technique, reported no mortality with percutaneous

endoscopic gastrotomy insertion in 30 patients and only two major complications – a leak into the peritoneal cavity and a gastrocolic fistula [38]. Larson *et al.* described two immediate complications in 23 patients – a wound infection and a minor stomal leak [39]. Thus, the rate of complication compares favorably with that reported for the insertion of a conventional feeding gastrostomy. For example, in a recent series of 147 patients undergoing surgical gastrostomy the complication rate was 16% and mortality was 6.1% [40]. Because of its safety, efficacy and low cost, this endoscopic technique should become the procedure of choice for longterm enteral nutrition in patients who require tube feeding and have an intact small intestine. However, patients with esophageal obstruction also require establishment of a patent esophageal lumen to allow drainage of salivary secretions.

Cancer of the stomach

Clinical features

As in the esophagus, malignancy dominates the tumor pathology of the stomach, and 90–95% of gastric malignancies are adenocarcinoma. Despite epidemiologic evidence of a decline in incidence of gastric adenocarcinoma in the US, this is still the most common malignancy encountered during upper gastrointestinal endoscopy. Although most patients present with advanced disease, increased awareness of the early presentation of this disease should increase the number of cases diagnosed at the prognostically favorable, early stage.

The clinical presentation of gastric cancer varies according to the location and pathologic type. Early, patients often have nonspecific dyspepsia which may simulate chronic peptic ulcer disease, or be described as vague abdominal discomfort, fullness or belching. The new onset of dyspepsia in patients over the age of 40 should always be investigated, often with endoscopy, to avoid overlooking early gastric cancer. Later in the course, patients with gastric cancer may develop epigastric pain, weight loss, bleeding, symptoms of anemia, dysphagia or symptoms of gastric outlet obstruction. Of course, a normal physical exam does not exclude gastric malignancy; however, in advanced cases an epigastric mass, lymphadenopathy, or hepatomegaly may be found. A number of premalignant conditions have been associated with an increased risk for developing gastric cancer. The role of endoscopic surveillance for patients with these conditions will be considered separately in this volume.

Diagnosis

In general, it is important for the endoscopist to characterize the appearance

of gastric lesions as completely as possible. The endoscopic appearance often suggests the diagnosis of malignancy and accurately reflects the extent of disease. It is important, both conceptually and clinically, to consider advanced gastric cancer separately from early gastric cancer. It should be noted that radiology and endoscopy are complementary techniques in the diagnosis of gastric carcinoma, and most patients will have both studies performed.

Advanced gastric cancer

This diagnosis implies invasion beyond the submucosa and is the usual stage at the time of diagnosis in the US. Although endoscopy does not improve outcome in these patients, it does provide descriptive information and allows tissue to be obtained for definitive diagnosis. The macroscopic appearance of the lesion during endoscopy is an accurate predictor of advanced disease. Such lesions are usually classified into three main groups:

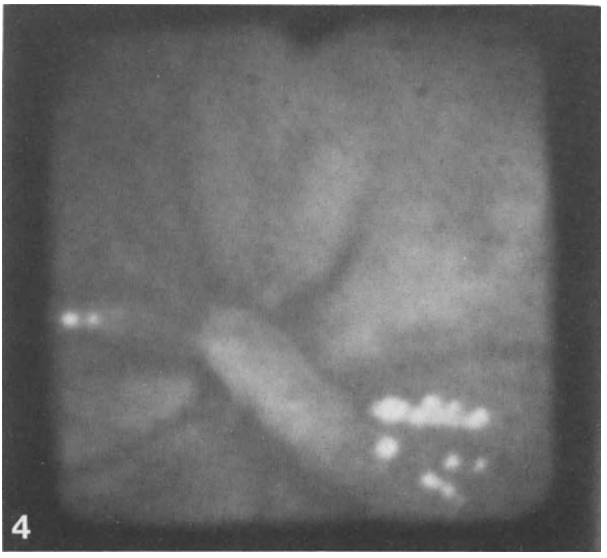


Figure 4. Benign gastric ulcer; margin is sharply demarcated, base is smooth and flat, mucosal folds radiate to the crater's edge.

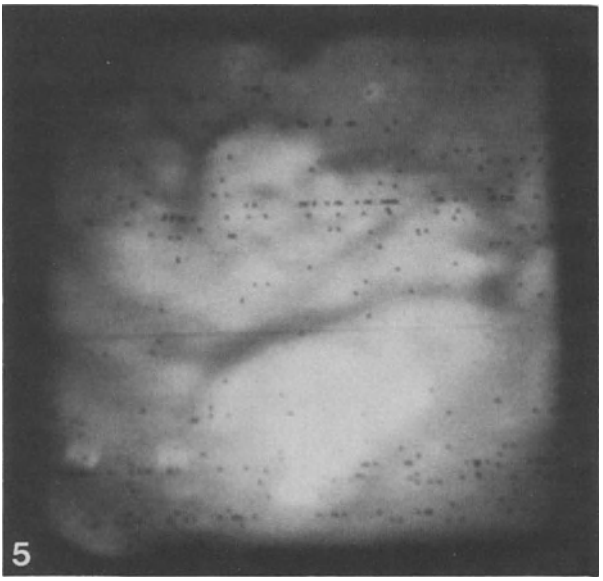


Figure 5. Adenocarcinoma of the stomach; changes are typical of an irregular, nodular, infiltrating mass.

polypoid, infiltrative, and ulcerative. Either of the first two may also involve ulceration, but this is not the dominant appearance. The proportion in each group varies somewhat in different reports; in a large retrospective series, Dupont *et al.* found the macroscopic appearance to be polypoid in 54%, ulcerative in 17.5% and infiltrative in 7% [41].

The diagnosis of cancer is strongly suggested by the presence of an exophytic mass, with or without ulceration (Figs. 4, 5). Adenocarcinoma must be distinguished from other malignant involvement including metastatic carcinoma, extrinsic invasive cancer (e.g. pancreas) and lymphoma. The differential diagnosis also includes benign diseases such as peptic ulcer disease, gastric polyps, Crohn's disease, pseudolymphoma, eosinophilic gastritis and tuberculosis. The appearance of linitis plastica – which presents as a stomach decreased in size, lacking in peristalsis, with a normal rugal pattern – may be caused by adenocarcinoma, lymphoma, pseudolymphoma,

Crohn's disease, tubercolosis, eosinophilic gastritis or corrosive ingestion. Primary gastric lymphoma may mimic any of the forms of advanced gastric adenocarcinoma, but commonly presents as an infiltrating lesion, associated with hyperrugosity and nodularity involving large areas of the stomach [42, 43].

There is general agreement that the addition of endoscopic biopsy and cytology will improve diagnostic accuracy over endoscopic or radiologic appearance alone. The most appropriate means for obtaining tissue specimens in suspected gastric cancer has been the subject of numerous reports [14–18, 44, 45]. Winawer *et al.* studied the diagnostic yield of endoscopic biopsy in 50 patients with advanced gastric cancer in whom four biopsy specimens were obtained from each lesion [44]. In this study there were 26 exophytic and 24 infiltrative cancers. For the exophytic lesions, a diagnostic yield of 65% was obtained with biopsy compared with 85% for brush cytology, for an overall yield of 92%. Not surprisingly, for infiltrating lesions the diagnostic yield was less; the yield with biopsy alone was 33%, while that for brush cytology was 50%, for an overall diagnostic yield of 50%. These authors also noted that the anatomic distribution of the lesion correlated with the diagnostic yield, with location in relatively inaccessible sites such as the cardia or in the antrum behind the incisura presenting the greatest difficulty. A number of studies have indicated that the accuracy of biopsy diagnosis increases with the number of specimens obtained. In a series of 174 gastric cancers, Sancho-Poch *et al.* found the probability of a positive biopsy diagnosis of malignancy, regardless of the endoscopic appearance of the lesion, to be more than 99% when eight biopsy specimens were obtained [45]. Dekker and Tytgat correctly diagnosed 140/142 gastric malignancies (99.8% overall accuracy) when ten or more specimens were obtained from the lesions [16]. These studies show that for polypoid or ulcerating lesions, the diagnostic accuracy for biopsy is high, provided a minimum of eight specimens can be obtained from the inner margins. Careful inspection of the entire lesion for subtle abnormalities of coloration and texture will maximize the yield of biopsy. In such cases, the adjunctive value of cytology is limited and applies mainly to situations where the location of the lesion precludes adequate visualization and sampling. In contrast to the high diagnostic yield for polypoid or ulcerating lesions, in the case of diffuse infiltrating carcinoma, biopsy and brushing will confirm malignancy in only 50–60%, even in the presence of strong clinical suspicion [14, 44]. Careful inspection within abnormal rugal folds may sometimes reveal areas of mucosal breakthrough by the tumor which can be selectively sampled with high diagnostic yield. Techniques such as needle aspiration cytology or 'lift-and-cut' diathermy biopsy have been proposed to increase diagnostic yield in such situations, but these methods are not in general use [1–2]. It is important to note that endoscopy is often less sensitive than X-ray (espe-

cially computed tomography) in establishing the extent of submucosal involvement with advanced or infiltrating gastric cancer.

Early gastric cancer

Early gastric cancer has been defined as carcinoma that is limited to the mucosa and the submucosa [46]. As expected, 5-year survival rates of 80–90% have been reported [46–48], in comparison with 5-year survival rates of 10–20% for advanced gastric adenocarcinoma [41, 49, 50]. There is controversy over whether early gastric cancer and advanced gastric carcinoma are part of the spectrum of the same disease process; however, several lines of evidence suggest this may not be so. While there have been unquestioned cases of progression from early to advanced cancer, in a prospective study from Japan the endoscopic appearance of early gastric cancer remained unchanged for an average of 33 months (15–64 months) [51]. The mean age of patients with early gastric cancer is not less than that for advanced cancer; this is inconsistent with what would be expected if early gastric cancer develops into advanced gastric cancer. Also, quite unlike the case for advanced gastric carcinoma, the 5-year survival of patients with early gastric cancer following surgery does not seem to be greatly affected by the presence or absence of lymph node involvement at the time of diagnosis [52, 53].

Early gastric cancer was described initially in Japan, but has since been recognized world-wide. In a report from this country, early gastric cancer was found in 28 of 213 patients (13.1%) undergoing resection for gastric carcinoma over a 10 year period, with an overall 5-year survival rate of 68% [54]. The classification system developed by the Japanese Society for Gastroenterological Endoscopy should be familiar to all endoscopists [46]. Type I lesions are polypoid and must be distinguished from benign polyps. Features suspicious for malignancy include irregular contour, superficial bleeding and size greater than 2 cm. Type II is subdivided into three subtypes. A type IIa lesion is a focal elevation of less than the thickness of the surrounding gastric mucosa. Type IIb is recognized by focal discoloration of the mucosa with neither elevation or excavation. Type IIc is a slightly depressed lesion with disruption and clubbing of the surrounding mucosal folds. The margins of the depressed area are irregular and the base of the lesion often contains adherent mucous or exudate. Type III is an excavated lesion similar in appearance to a benign gastric ulcer. The commonest endoscopic appearance of early gastric cancer is that of a benign-appearing ulceration whose margin shows focal depression and discoloration (type IIc+III). It is important to be aware that a cycle of healing and reulceration has been described in early gastric cancer, which may add to the difficulty in differentiating such lesions from benign gastric ulcers [55]. While endoscopic biopsy of these lesions provides an extremely accurate histologic diagno-

sis, considerable experience and attention to endoscopic details are necessary for the endoscopic recognition of early gastric cancer.

Role of endoscopy in gastric ulcer patients

In many studies, endoscopy has been found to be more effective in the detection of gastric ulcers than radiology. Furthermore, endoscopy allows biopsy and cytology specimens to be obtained. However, availability and cost often make barium X-rays the initial diagnostic studies obtained in patients with upper gastrointestinal symptoms. There has been considerable debate over the indications for endoscopy once a gastric ulcer has been found by X-ray. While some recommend endoscopy with biopsy for all patients with gastric ulcers, regardless of radiological appearance, this would greatly increase the cost of medical care. The radiologic differentiation of benign and malignant gastric ulcer has been extensively studied and has proved generally reliable. Nevertheless, approximately 5% of radiographically benign ulcers will ultimately prove to be malignant – not an inconsequential figure [56, 57]. Because of the large number of patients which would be required, it is not likely that a controlled clinical trial will be done to provide a scientific basis for clinical practice on this issue [58]. However, adequate information is available to make a rational decision in individual patients.

When a ulcer is first diagnosed endoscopically, careful inspection of the ulcer and surrounding mucosa will sometimes identify features suggesting carcinoma, as described above. Indeed, in a study evaluating biopsy number in the tissue diagnosis of upper gastrointestinal malignancy, experienced endoscopists were able to achieve 70% accuracy with the first biopsy specimen in malignant gastric ulcers, by selective biopsy based on subtle endoscopic features [18]. However, depending on the level of experience, the endoscopist will be unable to clearly differentiate benign from malignant ulceration in 20–50% of cases. For example, in a study of 265 gastric ulcers, 37 of which were malignant, visual inspection at endoscopy revealed a tendency to overdiagnose malignancy [56]. Of the benign ulcers in this group, 56% were termed indeterminate and 18% malignant. Of the malignancies, 19% were felt to be indeterminate and only 3% benign. However, even when the endoscopic impression is benign, a minimum of four biopsies from the ulcer margin, together with brush cytology, are recommended to avoid overlooking early gastric cancer.

If the ulcer is first found by X-ray and judged to be radiographically benign, endoscopy can be delayed until the first follow-up examination in 6–8 weeks (fig. 6). This will allow time to assess for healing – an important indication for benign disease. It is important to recognize that if the radiographic appearance is indeterminate, or if the ulcer is large (over 2 cm), endoscopy should be done at the time of diagnosis. In the Veterans Admin-

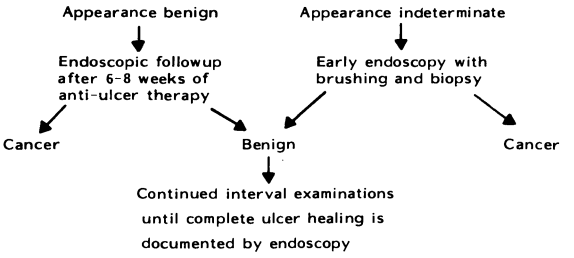


Figure 6. Management of radiologically diagnosed gastric ulceration.

istration Cooperative Study on gastric ulcers, 19/574 radiographically-benign ulcers proved to be malignant (3.3%) [57]. Certain features were found to be associated with an increased likelihood of malignancy, including size over 2 cm (10.4% having cancer), absence of associated duodenal ulceration (6% with cancer) and a radiographically-indeterminate appearance. Even when initial biopsy and cytology specimens are benign, gastric ulcers should be followed until complete healing is demonstrated.

Gastric polyps and endoscopic polypectomy

Gastric polyps are relatively rare lesions; for example, an incidence of 50/7,000 autopsies was reported in one series [59]. The term 'polyp' has been used somewhat indiscriminately to describe a wide variety of lesions. Benign epithelial tumors of the stomach are divided into neoplastic (adenomatous) and non-neoplastic (inflammatory or hyperplastic) types. Adenomatous polyps are usually large, single and occur predominately in the antrum. Hyperplastic polyps are smaller, frequently multiple and are located throughout the stomach. Other lesions which may present as polypoid tumors include mesenchymal tumors, carcinoids, hamartomas, heterotopic pancreatic tissue, polypoid adenocarcinoma, lymphoma or metastatic cancer. The primary interest in gastric polyps relates to their malignant potential. An early report by Stewart found associated carcinoma in 28% of gastric polyps and associated polyps in 5% of gastric carcinomas [60]. Others have reported incidences of malignancy arising in gastric polyps ranging from 0–51% [61, 62]. Hyperplastic polyps are relatively more common than adenomatous polyps with a relative incidence of up to 8:1. Although hyperplastic polyps have rarely been found to contain malignancy, they may appear together with gastric carcinoma [63]. On the other hand, there appears to be a definite association between adenomatous polyps and gastric carcinoma. In adenomas greater than 2 cm in diameter, *in situ* or invasive carcinoma was found in 59% in one series [64]. Although polypoid lesions should be biopsied, it has been shown that endoscopic biopsy is an unreli-

able means of screening polyps for malignant potential. In one series, the initial histologic diagnosis was changed in 75% of cases after the entire polyp was removed for study [65].

Endoscopic gastric polypectomy has been proposed as the definitive therapy for gastric polyps. This technique involves the standard endoscopic procedure followed by loop snaring of the lesion with a polypectomy catheter and application of cutting and electrocoagulation current. Although experience with gastric polypectomy is rather limited, this procedure appears to be associated with slightly higher incidence of complications than colonic polypectomy. Potential complications include bleeding, perforation and the formation of a gastric ulcer. Routine use of ulcer therapy for 2–4 weeks after polypectomy has been advised. In a review of 48 consecutive endoscopic polypectomies, ReMine *et al.* reported two bleeding episodes requiring surgical ligation of the site [66]. No deaths or other adverse consequences occurred. Gastric polypectomy should be considered for polyps greater than 1 cm, those which are enlarging on serial examinations, those which contain severe atypia on biopsy, or those which occur in association with conditions such as prior gastric resection or pernicious anemia. Complete endoscopic polypectomy appears to be adequate therapy for benign adenomatous polyps. Surgical resection is recommended for very large or sessile lesions or whenever there is a question of whether endoscopic removal was complete. The presence of symptoms or multiple polyps are only relative indications for surgery. The appropriate management for polyps containing cancer is somewhat controversial. Many recommend gastric wedge resection in good risk patients, but endoscopic removal appears to be adequate therapy for polyps with carcinoma *in situ.*

Cancer of the duodenum and pancreatic-biliary system

The effective limit for upper gastrointestinal endoscopy is through the third portion of the duodenum. In addition to direct endoscopic inspection, duodenoscopy has been combined with cannulation of the duodenal papilla to carry out radiographic studies of the pancreatic and biliary systems. As an extension of endoscopic retrograde cholangiopancreatography (ERCP), methods have been developed to simultaneously diagnose and palliate malignant biliary obstruction.

Duodenal malignancy

Primary duodenal carcinoma is quite rare, accounting for less than 1% of cancers of the upper gastrointestinal tract [67]. The typical endoscopic

appearance is that of an exophytic mass, and the diagnostic yield with endoscopic biopsy and cytology is high. Lymphoma accounts for about 20% of duodenal malignancies, associated with gastric lymphoma in the majority of cases [68]. The commonest source of duodenal malignancy is from another primary site. The majority of cases represent duodenal extension from contiguous carcinoma in the head of the pancreas, producing an endoscopic appearance of an irregular, friable, nodular mass. Such a carcinomatous mass must be distinguished from extrinsic compression without direct malignant involvement. The latter appearance may also be produced by benign inflammatory disease of the pancreas, such as chronic pancreatitis or pseudocyst.

Primary carcinoma of the ampulla accounts for roughly 2% of upper gastrointestinal malignancies and less than 10% of all ampullary malignancies [69]. The clinical importance of such lesions rests not on their prevalence, but rather on their high rate of resectability (over 60%) and 5-year survival (34%) relative to other upper gastrointestinal cancers [69, 70]. The classic presentation of painless, fluctuating jaundice is found in a minority of cases. The diagnosis is usually made by endoscopy (often during ERCP) where the papilla is seen to be enlarged, with central excavation or associated ulcers and nodularity. Forceps biopsy combined with cytology will have a high diagnostic yield in this condition.

In patients with obstructing ampullary carcinoma who are felt to be inoperable, endoscopic sphincterotomy, with or without introduction of a biliary stent, has been used as a palliative measure. In a series of 88 cases in which palliative endoscopic sphincterotomy was performed for inoperable ampullary cancer, the average symptom-free survival was 5 months with an overall average survival of 8 months [71]. These results compare favorably with other palliative measures in this condition.

ERCP in the diagnosis of pancreatic and biliary cancer

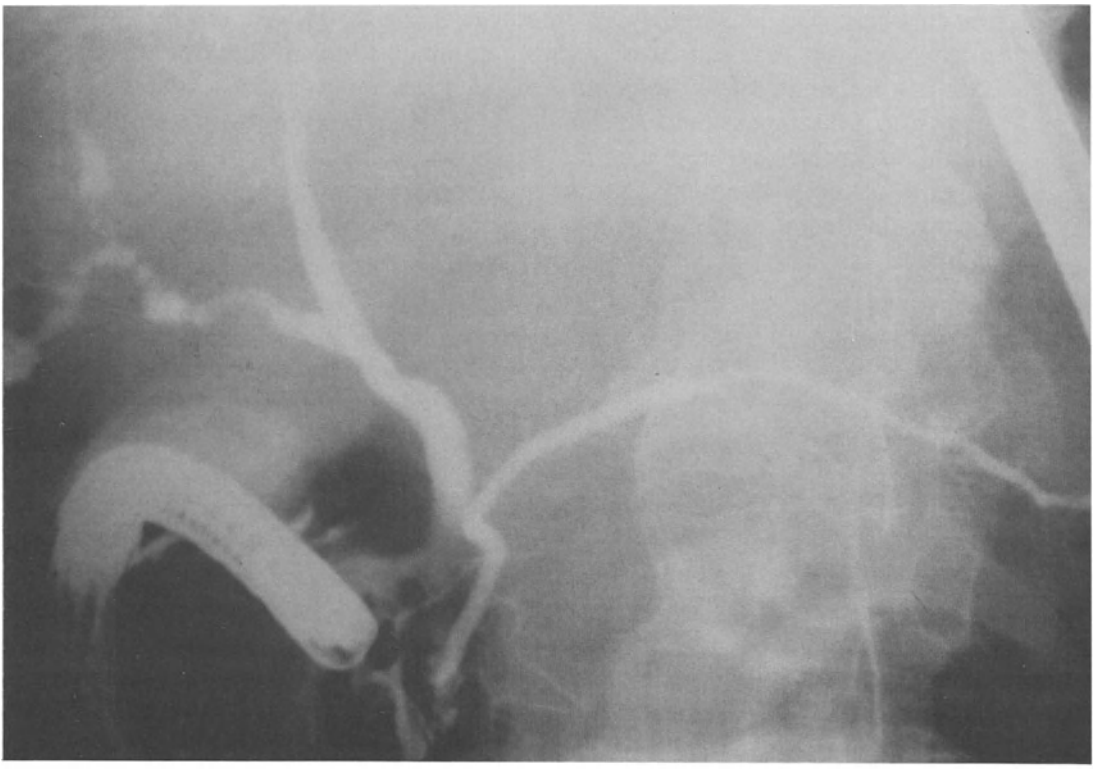
Over the past 10 years ERCP has become an established method for the diagnosis of pancreatic and biliary malignancy. The diagnostic hallmarks of malignancy are stenosis and obstruction of the ductal tracts; however, even in the presence of gross ductal abnormalities, differentiation of cancer from chronic pancreatitis may be difficult. Silvis *et al.* evaluated 84 cases of pancreatic and biliary malignancy with ERCP; the study was successful in 73 patients with a diagnosis of tumor made in 67 patients (92%) [72]. ERCP was successful in 40 of 43 patients with pancreatic carcinoma, and a correct diagnosis was made on the basis of stenosis or obstruction in 37 patients. It is of interest that the diagnosis of pancreatic carcinoma was based on cholangiographic abnormalities in seven patients, five of whom had normal

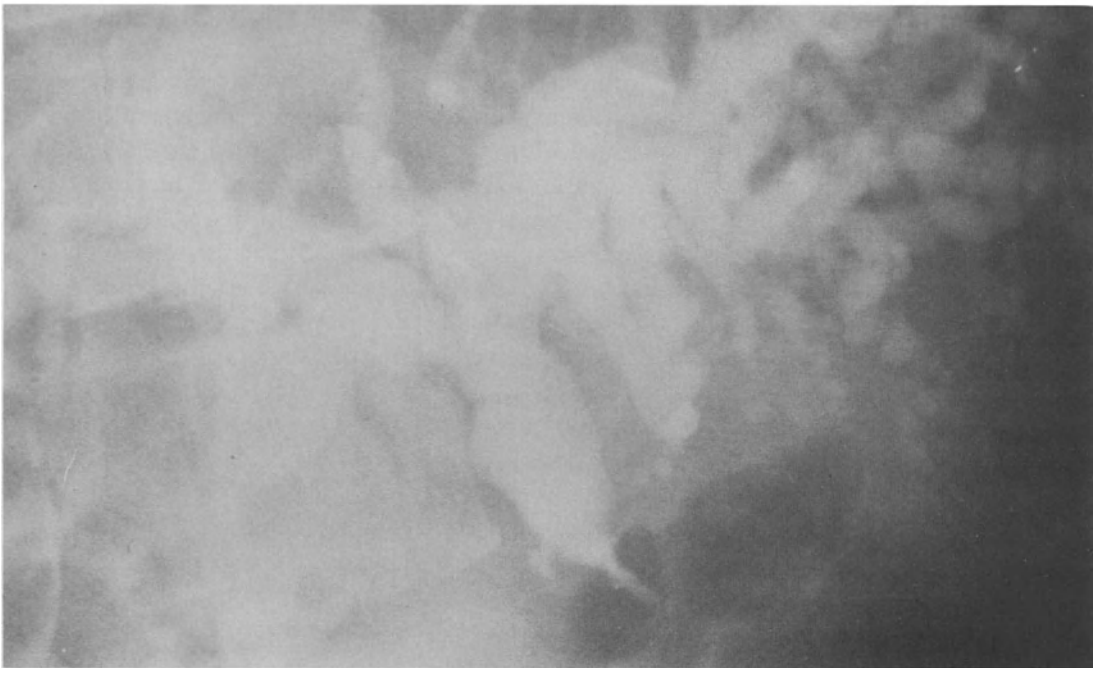
pancreatography. The remaining three patients had abnormal pancreatic ducts; however, the findings were misinterpreted as indicating chronic pancreatitis. Other studies have confirmed the accuracy of ERCP in the diagnosis of pancreatic or biliary malignancy [73–75]. When radiograms of diagnostic quality are obtained, a correct diagnosis can be made in over 90% of cases. More importantly, a negative study is strong presumptive evidence against the diagnosis of malignancy (if both ductal systems are visualized), although false-negative studies have rarely occurred (Fig. 7).

Some investigators have attempted to improve the accuracy of ERCP by obtaining fluid for cytology during pancreatic duct cannulation. Blackstone *et al.* reported positive cytologic results in 8/11 (73%) of patients in whom pancreatography revealed a malignant-appearing obstruction [86]. Osnes *et al.* combined direct, transendoscopic brushing of the pancreatic duct with pancreatography in 69 cases of pancreatic cancer [77]. Ductal abnormalities were found on pancreatography in all, with 11 cases showing suspicious but not diagnostic results. Brush cytology was positive in three, suspicious in two and normal in six of these equivocal cases. It appears that in most circumstances, collection of pancreatic fluid for cytologic studies (or determination of tumor marker concentration) adds to the technical difficulty of the examination without providing clinically important information.

It is important to bear in mind that ERCP is a costly and time-consuming procedure in which the safety and chance of success are directly related to the experience and expertise of the examiner. In a survey of over 10,000 ERCP procedures (done by a large number of physicians) Bilboa *et al.* found the overall success rate for visualization of the biliary three was 70% [78]. However, the success rate improved significantly for those with greater experience (200 or more examinations) compared with inexperienced endoscopists (25 or less examinations) – the success rates being 85 and 38% respectively. In most cases, it is easier to cannulate the pancreatic duct than the common bile duct and success rates rise accordingly. In this study, the complication rate was 3% – including pancreatitis (1%), cholangitis or sepsis (0.8%), and medication reactions(0.6%). It is noteworthy that for experienced endoscopists the complication rate was 3%; for the inexperienced, complications occurred in 7% of unsuccessful studies and in 15% if the ducts were successfully cannulated. Since ERCP is both more difficult and less often indicated than other endoscopic procedures, the availability of an experienced endoscopist is often the limiting factor in the utilization of this procedure.

In addition to ERCP, a number of other diagnostic methods are now available for the evaluation of suspected pancreatic or biliary cancer – notably ultrasonography (US), computed tomography (CT) and percutaneous transhepatic cholangiography (PTC) (Fig. 8). There have been a number of reports which compare diagnostic information obtained by a battery of





these procedures in patients with suspected pancreatic malignancy. Most are retrospective studies which compare the results of a highly skilled proponent of a particular technique to several other methods. All these results are confusing, and none provides a simple diagnostic algorithm which is readily applicable to the 'average' medical setting, where local expertise and available methods may vary greatly. While a comprehensive discussion of the relative merits of these various diagnostic techniques is beyond the scope of this discussion, it is fair to say that in most clinical circumstances where pancreatic or biliary malignancy is suspected, either US or CT has become the initial diagnostic procedure of choice. Indeed, in a recent study the introduction of CT resulted in a 68% decrease in the use of ERCP for the evaluation of pancreatic disease [79]. US and CT are both highly accurate in separating patients with jaundice into obstructive and nonobstructive categories. In addition, these tests frequently provide useful information through direct imaging of the pancreas, liver and other abdominal structures. The diagnostic accuracy for malignancy can be enhanced through the use of fine needle aspiration cytology or biopsy under US or CT guidance [80]. Results of noninvasive imaging tests may indicate that further invasive studies are unnecessary, or may suggest which direct cholangiographic method is most likely to benefit the patient. Compared with ERCP, PTC does not evaluate the duodenum, papilla or pancreatic duct. It is less expensive and technically easier to perform than ERCP. The success rate for visualization of the biliary system is higher for PTC when the intrahepatic biliary ducts are dilated, while ERCP is more likely to be successful in the absence of biliary dilatation. Overall, the complication rate is similar, both in frequency and kind, for both studies. Both can be combined with techniques for biliary decompression, either temporary or permanent. It must be emphasized that local expertise is the overriding determinant in choosing one technique over the other. It should also be remembered that the sensitivity and specificity of both ultrasound and CT are less than 100%; in a certain percentage of cases, the clinical impression will strongly indicate that cholangiography be performed, even when the results of CT or US do not.

Endoscopic decompression of the biliary tree

The majority of patients with malignant obstructive jaundice are unresectable at the time of presentation, and the mean survival regardless of therapy

Figure 7. Normal ERCP; both the pancreatic and biliary systems have been opacified.
Figure 8. Adenocarcinoma of the head of the pancreas; PTC demonstrates marked biliary dilation with an irregular stricture of the distal common bile duct.
←

is 5–7 months [81, 82]. Palliative surgical bypass procedures have a high mortality, ranging from 33% for obstruction from cancer of the pancreas [81] to 20% with nonpancreatic malignancy [83]. Because of the high cost and morbidity associated with palliative operation, a number of nonsurgical alternatives to formal surgical bypass procedures have been developed.

Percutaneous biliary drainage with combined external/internal catheter decompression has proven effective in the palliation of patients with malignant biliary obstruction [84–86]. Success rates of up to 90% have been reported; although, the procedure has been associated with appreciable hazards. Acute, severe complications occur in 5–10% of cases, including hemorrhage, cholangitis, and bile peritonitis. In addition, delayed complications related to catheter malfunction occur in nearly half the patients, and long-term follow-up for catheter care is required. Permanent indwelling stent endoprostheses have been developed which effectively relieve malignant biliary obstruction while avoiding the necessity of an external catheter device [85, 87, 88]. Transhepatic stent placement is successful in about 75% of cases and carries a complication rate of 5–10% with a mortality rate of 2–3%. A disadvantage of the internal device is that the long-term patency has not been established, and access to the biliary tract for correction of occlusion or migration of the endoprosthesis is often difficult.

Analogous to these radiologic procedures, endoscopists also have extended their diagnostic skills with ERCP to provide therapeutic decompression of the biliary tree. These newly evolving techniques include endoscopic sphincterotomy (as previously discussed in the management of patients with ampullary obstruction), nasobiliary drainage and transpapillary insertion of large-caliber endoprostheses.

Nasobiliary cathethers are not difficult to place even without prior sphincterotomy [89, 90]. They provide adequate initial decompression of biliary obstruction and allow access to the biliary tree for repeat cholangiography. However, because of the inconvenience to the patient and their small caliber, nasobiliary drains are not suitable for long-term management in most patients.

Since 1979, endoscopic techniques for the placement of biliary endoprostheses have been developed [91–95]. During endoscopic retrograde cholangiography, a guidewire is advanced through the area of obstruction into the proximal biliary tree. A succession of dilating catheters (5–10 French) are then passed over the guidewire to enlarge the lumen in preparation for insertion of the biliary stent. The endoprosthesis is positioned across the stricture with a pushing catheter under direct endoscopic and fluoroscopic guidance. If necessary, further manipulation or exchange of the prosthesis can be readily accomplished. In some cases more than one stent may be placed in order to achieve maximum palliation. Sphincterotomy is not

necessary when small or medium-sized stents (5–8 French) are used, but greatly facilitates the insertion of larger endoprostheses (10–12 French). Huibregtse and Tytgat have reported their experience with endoscopic insertion of large-bore biliary endoprostheses in 300 consecutive patients [94]. The procedure was technically successful in 89% of patients with a procedure-mortality of 2%. Overall, jaundice was relieved in 78% of patients; although, the success rate was substantially lower and the incidence of complications higher for lesions involving the mid common duct or hilus. Among 151 patients with a distal malignant common duct obstruction, endoprosthesis insertion resulted in a decline in bilirubin level in 143 patients (94.7%). Early cholangitis occurred in 12 patients (7.9%) and there were two deaths due to a complication of the procedure. The main late complication of endoprosthesis insertion was clogging with recurrent cholestasis, usually accompanied by signs of cholangitis. Improvement in catheter design and the use of larger caliber prostheses appeared to lessen this problem. In another large series, Siegel and Snady treated 277 cases of malignant biliary obstruction with endoscopically placed prostheses (7–12 French) [95]. The rate of successful drainage exceeded 90%. The overall complication rate was 20%, with major complications in 3% of patients and no procedure-related mortality. The hospital stay required for the procedure was 3–4 days, and the endoprosthesis patency rate was 70% at 3 months.

It should be remembered that these excellent results have been obtained by very experienced endoscopists, devoted to the advancement of this technique. It is not clear that the transduodenal approach offers a significant reduction in morbidity or improved quality of life for patients with malignant biliary obstruction, compared with percutaneous biliary drainage or surgical bypass procedures. Controlled clinical studies are clearly indicated, but in the meanwhile, either endoscopic or percutaneous biliary decompression should be considered as the first step in the management of patients with unresectable malignant biliary obstruction. The nonoperative approach to palliation is outlined in Figure 9.

I. Intervention: external/internal drainage or endoprosthesis insertion

II. Approach: endoscopic vs. percutaneous

	Site of obstruction	
	Distal CBD	Hilus or proximal CBD
A. When local expertise with both techniques is high:	Endoscopic	Percutaneous
B. When local factors favor a single approach:	Endoscopic	Percutaneous

Figure 9. Nonoperative palliation of malignant biliary obstruction.

Colorectal neoplasia

Lower gastrointestinal endoscopy has come to play a central role in the diagnosis and treatment of both benign and malignant neoplasms of the colon. Despite the acknowledged usefulness of colonoscopy, there is persistent debate over the relative value of colonoscopy and barium X-rays in the diagnosis of large bowel neoplasms. While endoscopic polypectomy has revolutionalized the treatment of benign adenomas of the colon, there is controversy over the appropriate management of polyps containing invasive cancer. Finally, delineation of the role of lower gastrointestinal endoscopy in screening various populations 'at risk' for colorectal cancer is a pressing concern. Adenomas and adenocarcinoma will be focused upon in this review; other, rarely encountered, tumors are not considered further. Familial polyposis syndromes are covered elsewhere in this volume and will not be reviewed here.

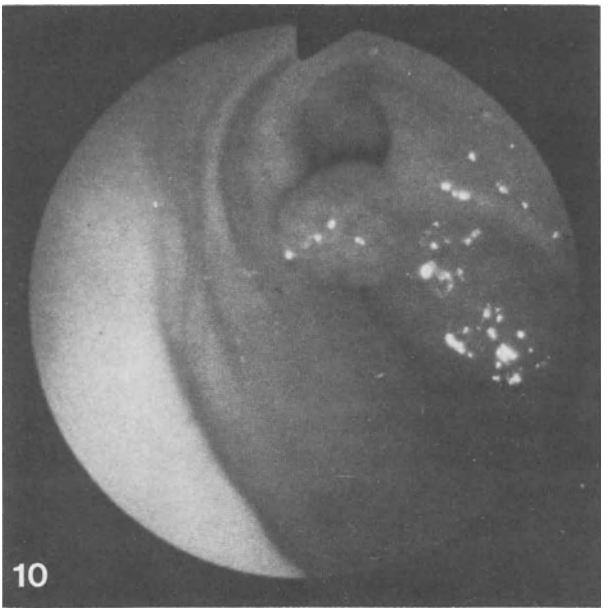


Figure 10. Tubular adenoma; 10 mm pedunculated polyp in the sigmoid colon.

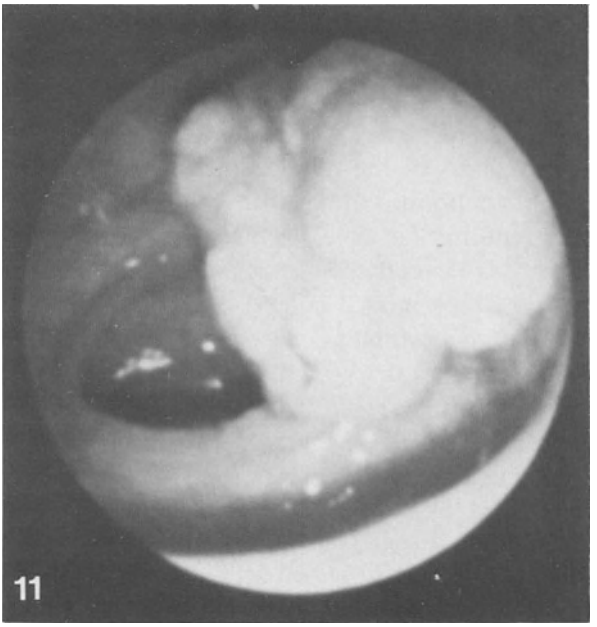


Figure 11. Villous adenoma with invasive carcinoma; 30 mm broad based, irregular, sessile polyp in the transverse colon.

Polyps of the colon

Polyps are the most common pathologic abnormality found during lower gastrointestinal endoscopy. They are found during proctoscopy in about 5–10% of healthy individuals over the age of 40 years, and in over 50% of cases in autopsy series [96]. While they may occasionally produce symptoms (principally bleeding), the main clinical importance of colorectal polyps lies in their potential for malignant transformation. Much of our knowledge about the natural history, distribution and morphology of polyps comes from study of surgical and necropsy specimens; however, the introduction of colonoscopy and polypectomy have made it possible to accurately localize and determine the histology of large bowel polyps at all stages of development.

Classification

From the endoscopic point of view, a polyp is seen as an outgrowth of epithelial tissue which is described according to size, location, number and whether sessile or pedunculated (Figs. 10, 11). Histologically, polyps are broadly classified into non-neoplastic (hyperplastic) and neoplastic (adenoma) types. Only neoplastic polyps have a potential for malignant transformation, and hyperplastic polyps will not be considered in the following discussion. Adenomas are further divided into tubular, villous and tubulovillous types on the basis of the relationship of the neoplastic glands to the polyp surface. It is important to note that removal of the entire polyp, rather than biopsy, is required for accurate histologic classification.

The majority of colorectal adenomas have a tubular growth pattern. In a series of 7,000 polyps removed colonoscopically, Shinya and Wolff found 64% of adenomas to be tubular, 27% tubulovillous and 8% villous [97]. The distribution of histologic growth types found in this study is in agreement with other reported series. In this survey, the majority of adenomas were located in the left side of the colon – with 6% located in the rectum, 46% in the sigmoid, 24% in the descending colon and 24% located proximal to the splenic flexure. In a similar large series, Gillespie *et al.* found 77% of 1,049 adenomas to be located in the left colon, although only 3.3% were found in the rectum [98]. There are two important clinical consequences of these findings. First, a sizeable percentage of adenomas will be located in the proximal colon, making examination of the whole colon necessary whenever polyps are suspected. Similarly, only a very small percentage of adenomas are located in the rectum, within the diagnostic range of the digital rectal examination or rigid proctoscope. Thus, these studies are of limited usefulness in polyp detection, either for screening or in the evaluation of symptoms.

The majority of large bowel adenomas are small; for example, Gillespie *et al.* found that 48% of adenomas were less than 10 mm in diameter, with 83% less than 20 mm [98]. In general, the larger adenomas (and carcinomas) are predominately located in the left colon, while relatively more small adenomas (less than 10 mm) are located proximal to the splenic flexure. Although the majority of adenomas are single, the incidence of finding synchronous adenomas has been almost 50% in some series [99, 100], further emphasizing the need for whole colon evaluation whenever an adenoma is found during proctosigmoid examination.

Malignant potential of polyps

Considerable evidence strongly supports the concept that large bowel adenomas may progress to become malignant [101, 102]. Conversely, it is felt that most colorectal carcinomas arise from benign adenomas. However, given the great preponderance in incidence of adenomas compared to adeno-

carcinoma of the large bowel, this must be a relatively rare occurrence. Three interrelated factors have been found to affect the malignant potential of adenomas: size, histologic growth pattern and degree of epithelial atypia. In the St. Mark's Hospital experience, the prevalence of cancer in adenomas increased progressively with size, ranging from 1.3% in adenomas less than 1 cm, to 9.5% for those measuring 1–2 cm, up to a malignancy rate of 46% for adenomas measuring greater than 2 cm in diameter [103]. These percentages, from the pre-colonoscopy era, can be compared with those from the colonoscopic survey of Shinya and Wolff, where the prevalence of malignancy in adenomas less than 1 cm was 0.5%, rising to 4.6% in lesions measuring 1–1.9 cm, up to 10.8% for adenomas over 2 cm in diameter [97]. There is evidence that the frequency of malignancy in adenomas rises with the amount of villous growth pattern. In turn, the frequency of finding villous growth also rises with the size of the tumor. Referring again to the St. Mark's Hospital series, in tubular adenomas the prevalence of cancer was 4.8% while in villous adenomas the figure rose to 40.7% [103]. Also, regardless of the histologic growth pattern, the malignant potential of adenomas increases progressively with increasing degress of epithelial atypia.

Given the above, several points pertinent to clinical management can be made. While the malignant potential is greater with large polyps, invasive cancer definitely occurs even in polyps less than 1 cm. Also, small adenomas may grow, and as they grow may develop an increasing risk of malignant transformation. At present, there is no way to know which individual lesion is 'at risk' to grow or to become malignant, nor is there anyway to predict the rate at which this might occur. Until the results of controlled clinical studies demonstrate otherwise, a policy of vigorous detection and eradication of all colorectal adenomas seems justified.

Diagnosis

The obvious first step in management of colorectal adenomas is their identification. Historically, barium enemas has been utilized for evaluation of polyps located beyond the reach of the sigmoidoscope. Recently, a number of retrospective studies have documented that colonoscopy is superior to barium enema in the detection of large bowel adenomas, particularly for lesions less than 1 cm in diameter. This appears to be especially true for conventional, single-contrast barium enemas. For example, in a series of patients undergoing colonoscopic polypectomy, double-contrast barium enema found 98% of lesions larger than 1 cm in diameter but only 78% of those 1 cm or less [104]. In comparison, the detection rate for single-contrast barium enema was 77% for lesions over 1 cm and only 18% for those 1 cm or smaller. In another study, the false-negative rate for diagnosis of colonic polyps was 45.2% for single-contrast enemas compared to 11.7% with a double-contrast technique [105]. In this study, colonoscopy failed to

identify 12.3% of polyps. Seventy-eight percent of these 'misses' were because of failure to reach the area in question with the colonoscope. Obviously, incomplete examination accounts for the failure to identify lesions by endoscopy in a number of cases. In addition, areas of sharp angulation or large mucosal folds may create endoscopic 'blind' spots. In a series of 72 polyps diagnosed by double-contrast barium enema, the false-negative rate for colonoscopy was 9% (and the false-positive rate for radiology was 10%) [106]. Of the six adenomas missed initially by endoscopy, five were identified by a second colonoscopy after review of the X-rays. This study emphasizes the concept that colonoscopy and barium enema are diagnostically complementary. Even for examiners of equal ability, certain areas of the colon are seen better on endoscopy and other areas on barium enema. As in all procedures, the relative level of expertise of the examiner is an important variable influencing the diagnostic yield.

Barium enema has the advantage of being quick, almost without risk, and less expensive than colonoscopy. The entire colon can be studied in nearly all patients, with an accuracy approaching that of colonoscopy, especially for lesions over 1 cm. Where optimal radiologic examination of the large bowel is available, this is usually the first test done for patients suspected of colonic disease. The principle advantage of colonoscopy over barium enema is that it allows the options of biopsy or immediate polypectomy, with minimal added time or discomfort. It is important to note that discovery of a lesion on barium enema generally leads to colonoscopy for histologic verification or endoscopic therapy. In clinical settings where the probability of finding neoplasms is high – for example, in patients over age 40 years with positive fecal occult blood tests – it may be reasonable to proceed directly to colonoscopy, sparing the patient the additional time, expense and discomfort of the radiologic study. In such cases, if total colonoscopy is difficult or the examination inadequate, barium enema can be performed promptly without the need to recleanse the colon. Another situation where colonoscopy may be preferable to barium enema is when polyps have been discovered on sigmoidoscopy. Regardless of X-ray findings, these patients will need colonoscopy with polypectomy. While it seems reasonable to go directly to colonoscopy in this situation, other argue that double-contrast barium enema should be performed before colonoscopy in all cases, allowing close endoscopic attention to any abnormal areas.

Colonoscopic polypectomy

Colonoscopic polypectomy is the diagnostic and therapeutic procedure of choice for large bowel adenomas. Whenever a polyp is discovered by sigmoidoscopy or barium enema, the usual policy is to perform total colonoscopy to the cecum and remove all polyps 5 mm in diameter or larger. The principle reason to perform polypectomy, of course, is to prevent the devel-

opment of invasive cancer. Forceps biopsy and cytology are not useful in the evaluation of benign-appearing polyps since they are not reliable in determining the histologic growth pattern or excluding malignancy.

Colonoscopic polypectomy has become a routine procedure which has virtually replaced abdominal surgery in the treatment of patients with benign-appearing polyps. The details of this procedure have been well described elsewhere and fall outside the scope of this discussion [107]. Nearly all polyps can be treated in this fashion; Gillespie *et al.* found 97% of 1,049 colorectal adenomas were amenable to colonoscopic removal or ablation [98]. Pedunculated polyps can generally be removed by snare electrocautery regardless of size, as can most sessile polyps 2 cm or less in diameter. Total excision of sessile adenomas larger than 2 cm is technically difficult and the likelihood of malignancy in such lesions is quite high. Surgery is generally recommended in these circumstances; however, in selected patients an aggressive endoscopic approach with 'piecemeal' snare excision has been accomplished. Other potential indication for surgery include inaccessible, multiple or 'cancerous' (see below) polyps.

The management of diminutive colorectal polyps (those measuring less than 6 mm in diameter) is somewhat controversial. Previously it had been felt that over 90% of such lesions were hyperplastic and lacking in malignant potential; however, there is recent evidence which challenges this concept. In several colonoscopic series, where all polypoid lesions were removed for histologic classification, the incidence of adenomas among diminutive polypoid lesions has varied from 37–72% [108–110]. Age over 60 years and location proximal to the splenic flexure are clinical features associated with a higher incidence of neoplasia. It is not possible to reliably differentiate small adenomas from hyperplastic polyps based on endoscopic appearance alone. Therefore, when diminutive polyps are encountered during colonoscopy, it is usually recommended that they be ablated with the 'hot biopsy' technique [11]. Whether the finding of diminutive polyps on barium enema should be an indication for colonoscopy is open to question, but this may be reasonable for lesions located in the proximal colon of patients over the age of 60, where the potential for neoplasia is the greatest.

The management of malignancy in colon polyps

The incidence of malignancy in colorectal adenomas varies with their size, histologic growth pattern and degree of epithelial atypia. Overall, the incidence of cancer in endoscopically removed adenomas is between 10–20%, with the majority of cases involving carcinoma *in situ* [97, 98]. According to the best available evidence, adenomas containing carcinoma *in situ*, i.e. carcinoma confined to the mucosa and not invading the muscularis mucosae, are incapable of metastasis and should be managed as if they were benign.

The diagnosis of carcinoma *in situ* can only be made by microscopic examination of completely excised adenomas; confusion may result based on superficial, small biopsy specimens. Whenever possible, complete endoscopic resection of adenomas containing carcinoma *in situ* will be curative, and further surgery will not be required.

Invasive carcinoma, crossing the muscularis mucosae, is found in roughly 5% of adenomas removed during colonoscopy [97, 98]. Such polyps have the potential for lymphatic metastasis, regardless of whether the carcinoma involves the resection margin, and their subsequent management is controversial. Obviously the 'safest' course is to recommend surgical resection of the involved bowel whenever invasive carcinoma is found in an adenoma; however, for individual patients the risk inherent in operative intervention must be weighed against the risk of cancer mortality from untreated residual tumor. Therefore, the salient issue in the management of polyps with invasive cancer is to determine the risks and histopathologic determinants of lymphatic metastasis.

Incomplete resection of an adenoma containing invasive carcinoma, i.e. microscopic evidence of carcinoma at the margin of resection or visually incomplete polypectomy, is plainly an indication for further therapy, often surgery. Cooper reported that in 75 patients with invasive carcinoma extending to the polypectomy margin, 13 had lymph node mestastases and 14 had recurrent tumor [112]. Although the finding of carcinoma at the resection margin has been associated with a high incidence of recurrent tumor and lymphatic metastases; in some such cases, bowel resection has been carried out and no tumor found. It is probable that the local, destructive effects of electrocautery can obliterate residual tumor even in the presence of positive polypectomy margins. While it might be possible to manage such patients with polypectomy alone, most would advise surgery in the absence of major contraindications. Endoscopic surveillance of the polypectomy site is of little use in these circumstances, since this may be normal even after metastasis has occurred. It should be noted that histological completeness of resection does not necessarily imply endoscopic completeness; there may be residual tumor at the primary site even when the resection margins are free of tumor.

More controversial is the proper management of the patient with an adenoma containing invasive carcinoma but with a free margin of resection. The bulk of the available evidence suggests that for the usual well-differentiated adenocarcinoma in a completely excised predunculated polyp, the risk of metastasis is very low and colonoscopic therapy alone is adequate. Morson *et al.* presented strong evidence supporting this view, provided the tumor is not poorly-differentiated or found to involve the margin of resection [113]. In this series, 60 patients with malignant adenomas (or polypoid carcinoma) were followed for 5 or more years after treatment. If local exci-

sion was judged to be complete (both endoscopically and microscopically) and the invading carcinoma was well- or moderately well-differentiated, polypectomy alone was advised. Forty-six patients were treated with polypectomy alone, of whom 37 were alive and well after 5 or more years and nine had died of unrelated causes without evidence of recurrent tumor. Fourteen patients were treated by polypectomy followed by powel resection, 11 because of doubtful completeness of excision and three because the tumor was poorly-differentiated. Two patients were found to have residual visible tumor at the polypectomy site but negative lymph nodes (in retrospect, these patients could have been managed endoscopically). Only one patient died with metastatic carcinoma, but in this case the operative specimen was free of residual cancer, and it is unlikely that operation affected the subsequent course.

In addition to the presence of poorly-differentiated tumor or invasion to the polypectomy margin, other morphologic features have been associated by various authors with an increased risk of lymphatic metastases. In a carefully done retrospective follow-up study, Haggitt *et al.* found the level of invasion to be the major factor determining the prognosis of adenocarcinoma arising in a colorectal adenoma [114]. Of the 64 patients in this study, eight had an adverse outcome (dead from colorectal cancer, alive with colorectal cancer, or presence of lymphatic metastases in colectomy specimen); seven of these had invasion to the level of the submucosa of the adjacent bowel wall. Among the following factors – location, gross appearance, histologic type, grade of carcinoma, vascular invasion, level of invasion and adequacy of excisional margins – invasion to the level of the submucosa was found to be the only independent variable associated with an adverse outcome. Submucosal invasion was more likely to be present in large (over 2.5 cm), sessile or villous lesions, but in its absence these factors did not appear to influence the outcome.

Although reliable data in large numbers of cases is unavailable, the risk:benefit ratio appears to favor surgery only when high risk factors are present in an otherwise completely resected adenoma with focally invasive carcinoma. This approach is outlined in Figure 12. While the majority of authors agree that a conservative approach to adenomas containing focally invasive carcinoma is justified, a notable exception is the report of Colacchio *et al.* in which six of 24 patients undergoing bowel resection after the finding of invasive carcinoma in a completely excised adenoma were found to have lymphatic metastases [115]. These authors were unable to reliably differentiate cases with and without metastasis based on such previously identified features of growth pattern, degree of differentiation or lymphatic invasion, leading them to argue stronly in favor of operative intervention for all cases of invasive carcinoma within colorectal adenomas regardless of other morphologic features.

Finding	Intervention
I. Carcinoma in situ	No further treatment
II. Invasive carcinoma	
A. Well-differentiated	
and	No further treatment
Resection complete (both endoscopic and microscopic)	
B. Poorly-differentiated	
or	
Tumor involving resection margin	Abdominal surgery
or	
Invasion to level of submucosa of the adjacent bowel wall	

Figure 12. Management of malignancy in adenomas removed during colonoscopy.

Follow-up after colonoscopic polypectomy

Patients with previously removed adenomas have an increased tendency to develop new (metachronous) adenomas and colorectal cancer. In an early study, over 400 patients were followed after removal of benign neoplastic polyps; metachronous adenomas were found in 41% and colorectal cancers in 3.2% of patients during the subsequent 4–9 years [116]. This study was based on proctosigmoidoscopy and barium enema, but several recent endoscopic studies also have found the incidence of metachronous adenomas to be 30% or greater [117–119]. The concept that colorectal carcinoma arises from pre-existing adenomas has given rise to the hope that detection and 'prophylactic' removal of metachronous adenomas will reduce subsequent cancer mortality. In spite of the intuitive rationale to this approach, at the time of this writing there is no firm evidence that routine follow-up polypectomy will reduce the incidence or improve the outcome of colorectal cancer. Nevertheless, until data become available from the ongoing National Polyp Study and the controlled screening studies from the University of Minnesota and the Sloan-Kettering program, most experts continue to recommend long-term surveillance after removal of benign colorectal adenomas. The form such surveillance should take, however, is a subject of considerable debate and uncertainty.

The optimal follow-up intervals and methods of examination after colonoscopic polypectomy need to be tailored to the individual patient. These will be influenced by the relative risk for metachronous polyps to develop, polyp growth rates, technical difficulty and risk associated with various examinations, and factors such as the patient's age, associated medical conditions and compliance. Critical studies on follow-up are scarce, but several general statements can be made. First, proctoscopy and fecal occult blood testing are too insensitive to be used alone in colon polyp surveillance; instead, the whole colon needs to be examined periodically. While colonoscopy is more sensitive than barium enema and allows removal of any

lesions detected, the combination of endoscopy and roentgenography will result in the greatest accuracy. An important concept underlying the following recommendations for follow-up relates to the ability of colonoscopy to detect and remove all neoplastic tissue of any size; only after a 'clean colon' has been achieved will a relatively lengthy interval before the next follow-up examination be safe.

To determine the incidence of metachronous adenoma formation, Waye and Braunfield retrospectively reviewed their experience with 227 patients who underwent follow-up colonoscopy after initial colonoscopic removal of benign neoplastic polyps [118]. Only patients felt to have had complete colonoscopy with total removal of all visualized lesions were included. During follow-up colonoscopy within the next 1 year, 56% of patients were found to have further adenomas. In an attempt to differentiate true, metachronous adenomas from 'missed' synchronous lesions, the size of the lesions detected on follow-up examination was analyzed – adenomas greater than 10 mm in diameter (presumed to have been missed during the initial endoscopy) were detected in 9% of patients. Of course, smaller polyps also may have represented overlooked lesions, but the 'miss' rate of 9% in this study is consistent with the false-negative rate for colonoscopic polyp detection based on the endoscopic-radiologic correlation studies discussed earlier. In this study, the risk of metachronous adenoma formation was strongly related to the original number of polyps. For example, in patients having a negative follow-up colonoscopy within 1 year after the initial examination, the incidence of metachronous polyps occurring within the next year was 13% for patients with a single index polyp, rising to 80% for those with multiple polyps originally. Similarly, the incidence of new adenomas occurring within 4 years of a negative colonoscopy varied from 35% for those with a single index adenoma to 63% for those initially found to have multiple adenomas. Based on these findings the authors proposed the following surveillance program after colonoscopic polypectomy: repeat colonoscopy within 1 year to detect 'missed' synchronous adenomas, to be followed by interval examination every 2 years for patients with multiple index adenomas or every 3 years for those with single adenomas on initial examination. While not stated explicitly, it seems logical that interval examinations should not begin until a 'clean colon' has been achieved, and that surveillance should continue indefinitely. These recommendations are presented in Figure 13.

In a pair of prospective studies, Kronberg *et al.* investigated the benefits of follow-up after colorectal polypectomy [120, 121]. In a randomized comparison of colonoscopy at 6 or 24 months following the removal of stalked polyps, the authors concluded that 6 monthly follow-up was too frequent. In the alternate group, one carcinoma (Duke's A) developed between initial colonoscopy and the first re-examination. No risk factors were associated

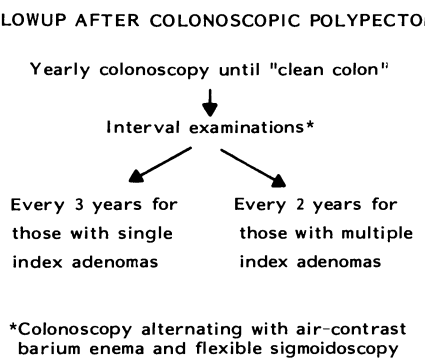


Figure 13. Following after colonoscopic polypectomy.

with an increased incidence of metachronous polyps after the removal of stalked polyps; however, among patients with previous sessile adenomas or adenomas containing carcinoma *in situ*, the risk of metachronous adenomas was directly related to the original size, number, villous growth pattern, and degree of dysplasia of the index lesions. An important feature of these studies relates to the morbidity associated with surveillance colonoscopy – six perforations (one fatal) occurred among the 789 follow-up examinations – emphasizing the need to critically justify the usefulness of this form of management.

None of these studies discusses the role for diagnostic modalities other than colonoscopy in post-polypectomy follow-up. In a unique study, Williams *et al.* subjected 330 patients who had previously undergone colonoscopic polypectomy to an extensive, 1-day evaluation, including: fecal occult blood testing, digital rectal examination, rigid proctosigmoidoscopy, fiberoptic sigmoidoscopy, total colonoscopy and double contrast barium enema [119]. Both the endoscopic and radiologic studies were done by experienced specialists; discrepancies between endoscopy and X-ray were rechecked by one or both techniques. Briefly, only total colonoscopy and X-ray were effective in evaluating the 37% of patients who were found to have further adenomas or carcinoma. The sensitivity of colonoscopy was 92% for detection of adenomas over 7 mm in diameter compared to 71% for double contrast barium enema. Unfortunately, two of the four cancers detected on follow-up were missed by X-ray. Based on these findings, colonoscopy was recommended by these authors as the primary procedure of choice for follow-up after polypectomy. An important feature of this study relates to the unusually high degree of colonoscopic proficiency demonstrated – total colonoscopy to the cecum was possible in 98% of patients (only 12% found the examination to be 'very uncomfortable') with a mean time taken of only 15.3 min. Nevertheless, 30% of colonoscopies were felt

to have been technically difficult by the endoscopist, and for these patients it was recommended that follow-up should be by fiberoptic sigmoidoscopy and double contrast barium enema, with colonoscopy reserved for abnormal findings by either study. Clearly, the diagnostic results with colonoscopy in this study may not be matched in many centers. It seems reasonable that after a negative follow-up colonoscopy has been achieved, further interval examinations should alternate the combination of fiberoptic sigmoidoscopy and barium enema with total colonoscopy.

Adenocarcinoma of the large bowel

Malignant disease of the large bowel is both common and associated with a high mortality. Nearly all large bowel tumors are adenocarcinomas, and other epithelial tumors such as epidermoid, carcinoid, and lymphoma will not be discussed below.

Approximately 120,000 new cases of colorectal adenocarcinoma are diagnosed each year in the US, making this the most common visceral malignancy when both sexes are considered together. Survival depends mainly on the stage at diagnosis, but most of the natural history of large bowel cancer is asymptomatic. Colorectal cancer should be suspected in patients presenting with altered bowel habits, abdominal pain, rectal bleeding, postive fecal occult blood test or unexplained iron deficiency anemia. Although the clinical presentation of large bowel cancer is well recognized, many patients delay for some time after the onset of symptoms before seeking medical attention [122]. Thus, most cases are referred for evaluation late in their symptomatic course, when the opportunity for cure is low. The overall 5-year survival for those with adenocarcinoma of the large bowel is 40–45%; unfortunately, the outcome with this disease has not changed significantly over the past three decades. What is disturbing about these statistics is that when colorectal cancer is detected before symptoms appear, 5-year survival rates of better than 80% have been achieved. At present, early detection of colorectal cancer, before the appearance of symptoms, offers the most realistic prospect for improved outcome with this disease. In practical terms, this will involve the identification and screening of populations at increased risk for the development of adenocarcinoma of the large bowel.

Appearance and distribution

Typical colonoscopic appearances for colonic adenocarcinoma include: a polypoid mass – with or without ulceration, or an annular, 'apple-core' lesion (Fig. 14). The finding of a flat, plaque-like growth pattern or of a stricture without apparent tumor mass is much less common for colonic cancer. In some cases, only the distal margin of the lesion can be visualized during colonoscopy and the gross appearance of the resected tumor may not

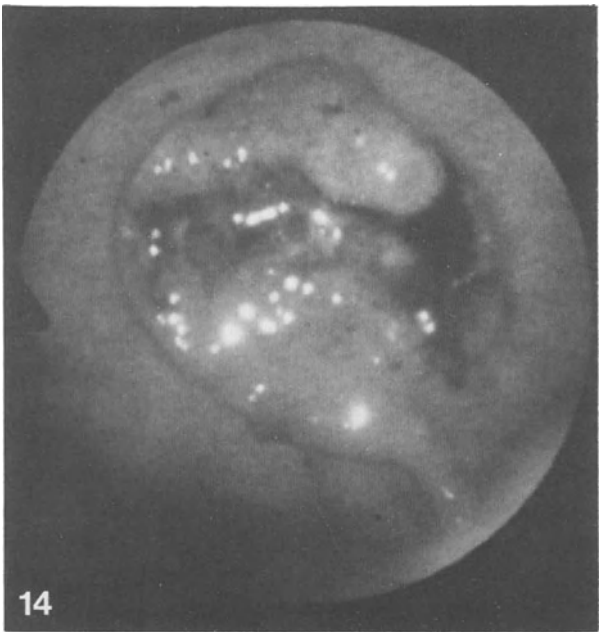


Figure 14. Carcinoma of the rectum; circumferentially encircling tumor.

correspond closely to the endoscopic description. The most common location for large bowel malignancy is in the distal colon; however, several studies have shown a proximal migration in the distribution of colonic cancer over the past two decades with a relative decline in the incidence of rectal carcinoma [123–125]. For example, in a prospective colonoscopic study of 39 cancers, Tedesco *et al.* found six cancers (15%) in the rectum, 14 cancers (36%) in the sigmoid colon, five cancers (13%) in the descending colon, five cancers (13%) in the splenic flexure-transverse colon, and nine cancers (23%) to be located in or proximal to the hepatic flexure [124].

A second cancer in the large bowel can be found at the time the primary lesion is discovered in up to 10% of cases. Several recent series emphasize the importance of whole colon examination in cancer patients, preferably preoperatively, because of the high incidence of synchronous cancers (3–7%) and adenomas (25–28%) [126–129]. The practical impact of this recommen-

dation was demonstrated by Langevin and Nivatvongs, who found that 88% of synchronous cancers and 67% of the synchronous adenomas identified by preoperative colonoscopy would not have been included in the standard resection for the index primary tumor [129]. Similarly, Pagana *et al.* reported that the planned surgical procedure was altered by the colonoscopic findings in 58% of patients discovered to have synchronous carcinomas [128]. Of note, 15% of patients in this study did not have complete colonoscopy because the index cancer was obstructing. In such cases, all authors recommend early postoperative colonoscopy for the identification of unsuspected synchronous neoplasms.

In addition to the high frequency of synchronous neoplasms, a personal history of colorectal carcinoma is a definite risk factor for subsequent development of metachronous adenomas and cancer. After initial curative treatment, patients with colorectal cancer should undergo a follow-up program of endoscopic and radiologic surveillance as described for post-polypectomy patients (see above).

Diagnosis

Proctosigmoidoscopy and barium enema are the traditional tools for the diagnosis of colorectal carcinoma. The flexible fiberoptic sigmoidoscope has a 2- to 3-fold increased diagnostic yield over the rigid proctoscope, chiefly due to the greater extent of colon examined. Patient acceptance is better than with the rigid instrument; and as a increasing number of 'non-endoscopist' primary physicians gain expertise in this procedure, flexible sigmoidoscopy will become the procedure of choice for pre-barium enema screening.

Current evidence suggests that the double-contrast technique has significantly improved the detection of colorectal cancer compared with the single-contrast barium enema examination. Gilbertson *et al.* reported that the single-contrast barium enema missed 35% of all proven colon carcinomas and 42% of early Duke's A or B lesions [130]. In comparison, Thorpe *et al.* found that air-contrast barium enema studies detected 96% of Duke's C and D lesions, and 91% of Duke's A and B lesions in their series [131]. It should be recognized that the relative diagnostic effectiveness of single and double-contrast barium enema studies is hotly debated by gastrointestinal radiologists, and strong proponents can be found for either study. Local expertise may be the determining factor in choosing which roentgenographic study to use.

In addition to its definite advantage in detection of small polyps, colonoscopy adds to the sensitivity of barium enema for the detection of cancer throughout the colon. Roentgenography and colonoscopy are best seen as complementary studies, with colonoscopy serving to clarify abnormal or equivocal barium enema findings, provide histologic confirmation and

identify and remove synchronous adenomas. Nevertheless, when the clinical suspicion is high, there should be no hesitation in performing colonoscopy, even when the barium enema study has been normal.

In most cases the endoscopic appearance of an exophytic or annular mass does not present any diagnostic difficulty. However, it is often helpful to confirm the malignant nature of the lesion before proceeding to surgery, particularly in the poor-risk patient. Even for exophytic lesions, the diagnostic yield of colonoscopic forceps biopsy is surprisingly low. In a series of 40 patients with colonic carcinoma, the yield of forceps biopsy was 72% for exophytic lesions, and only 60% overall [132]. The addition of brush cytology significantly increased the diagnostic yield – 94% for exophytic lesions and 89% for all cancers. Brushing was a more effective technique than lavage cytology in this study, and lavage cytology is currently reserved for high-risk patients with diffuse lesions, e.g. longstanding ulcerative colitis. For those with annular or constricting lesions, brushing within the stenotic area is definitely indicated; however, negative cytology results cannot exclude malignancy. A particular problem is the differentiation of benign strictures from malignancy in the presence of severe diverticular disease. Even after visual inspection combined with biopsy and brushing within the mouth of the stricture, bowel resection is often the only way to definitively establish the diagnosis. It should be reiterated that the superficial specimen obtained with the colonoscopic forceps does not provide enough tissue to differentiate invasive carcinoma from carcinoma *in situ* in otherwise benign-appearing polypoid lesions of the large bowel. Whenever possible, complete colonoscopic removal, rather than biopsy, of such lesions should be done.

The role of endoscopy in management of patients with lower GI cancer

In patients with large bowel adenocarcinoma, the primary role for endoscopy is diagnostic. However, in selected cases, laser ablation offers an alternative to conventional therapy such as surgery, radiation, and electrocoagulation in the management of local complications of unresectable colorectal cancer. Several reports have documented the safety and effectiveness of laser photocoagulation in the palliation of obstruction or bleeding from otherwise unresectable tumors [133–135]. Advantages of laser therapy include low-risk, good patient tolerance and suitability for outpatient use. Multiple interval treatments are usually required, but there is no dose limit to laser photocoagulation. The reported experience is very small, and careful clinical studies will be necessary to determine the indications, complication rate and cost-effectivenss of laser therapy in the palliation of colorectal cancer. At present it seems reasonable to consider the laser in cases where the risk of surgery is considered excessive, where surgery is refused, and for inoperable or recurrent tumor after prior nonlaser therapy.

Screening for colorectal cancer

Over the past two decades there has been growing interest in the idea of screening apparently healthy populations for the presence of large bowel cancer with the hope of identifying early, potentially curable lesions. In the context of this discussion, screening will refer to case finding within the context of medical practice, rather than mass detection in large populations. A large number of diagnostic techniques are applicable to cancer screening, and a considerable body of literature on this subject has been accumulated, much of it confusing. The concept of screening by fecal occult blood detection is reviewed elsewhere in this volume and will not be discussed in depth here. Issues to be discussed include the screening approach to average-risk and high-risk groups and the role of endoscopy in screening.

Using all currently available diagnostic methods, it is possible to detect asymptomatic colorectal cancer in nearly all instances. However, for routine screening purposes examination of the whole colon (by either endoscopy or roentgenography) is too complex and costly for general use. Winawer and co-workers have introduced the useful concept of modifying the screening approach based on the risk for development of colorectal cancer – while barium enema and colonoscopy may not be suitable screening tools for the average-risk population, they assume major importance in high-risk subgroups [136].

Average-risk patients

The vast majority of those who will develop colorectal cancer can be identified on the basis of age. The incidence of colorectal cancer rises sharply after age 40 years, doubling each decade thereafter to a peak around age 75 years. In the absence of other high-risk factors (see below) screening should begin between the ages of 40 and 50 years with yearly fecal occult blood testing and proctosigmoidoscopy every 3–5 years. It should be stated that the appropriate diagnostic workup of patients found to have a positive fecal occult blood test on screening includes evaluation of the whole colon, preferably by colonoscopy. Noninvestigation of patients with positive screening tests is a sizable concern. In one series, only one-third of patients with occult gastrointestinal bleeding were felt to have been 'properly' evaluated [137]. Physician misconceptions are clearly at fault in this matter, as demonstrated in a recent survey where only 33% stated they would recommend colonoscopy for occulty bleeding patients and less than 60% would proceed even as far as a sigmoidoscopy [138].

The benefits of proctosigmoidoscopic screening have been demonstrated in several long-term studies. Hertz *et al.* reported a 15-year survival rate of nearly 90% among patients with cancer detected by surveillance rigid proctoscopy, which is double the expected rate [139]. Gilbertsen suggested that

rigid proctosigmoidoscopy screening could be an effective secondary preventative approach to rectosigmoid cancer [140]. By detecting and removing benign adenomas during periodic rigid proctoscopy, he reduced the subsequent incidence of rectosigmoid cancer to 15% of the expected.

The principal limiting feature of rigid proctosigmoidoscopy for cancer screening is its high false-negativity above 16 cm, where the majority of cancers are located. There is considerable evidence that flexible fiberoptic sigmoidoscopy offers an increased diagnostic yield compared with rigid proctoscopy, chiefly due to the greater distance of colon examined [141–143]. For example, Marks *et al.* prospectively compared rigid proctosigmoidoscopy and flexible sigmoidoscopy done sequentially in 1,012 patients and found a 2.5-fold increase in the numer of polypoid lesions as well as a 3-fold increase in the number of cancers using the fiberoptic instrument [141]. Bohlman *et al.* reported a similar study involving 139 patients where significant pathology was found by fiberoptic sigmoidoscopy in 39% compared to 13% with a rigid instrument [142]. Strikingly, 56% of the neoplastic lesions detected with the flexible sigmoidoscope were located below the 20-cm level, within reach of but not seen by the rigid proctoscope. As more physicians are trained in the use of flexible sigmoidoscopes (either the standard 60 cm instrument or the recently introduced 35 cm scope) these instruments will eventually replace rigid proctosigmoidoscopy for screening purposes.

Unfortunately, the potential benefits of screening sigmoidoscopy have not been realized because of poor patient acceptance and physician overconfidence about the diagnostic accuracy of fecal occult blood screening. This was borne out in a recent survey of physician's attitudes and practices regarding early cancer detection [144]. The majority of physicians interviewed felt proctoscopy was an important tool for cancer detection (only 10% felt it was of no value for this purpose); however, only 18% followed or exceeded established guidelines for proctoscopic screening. In addition, 61% of physicians reported using the fecal occult blood test as a prescreen for proctoscopy, and would not recommend proctoscopy if the stool test was negative. In view of the high false-negative rate for fecal occult blood testing in patients with established neoplasia, this recommendation is difficult to justify. Indeed, based on a number of studies it appears that between 33 and 50% of patients with proven colorectal cancers and over 75% of patients with adenomas will have falsely negative Hemoccult screening [145]. Clearly, the addition of flexible sigmoidoscopy can greatly improve on the diagnostic yield over screening with stool occult blood testing alone.

The screening program recommended here can be carried out within the context of a general medical practice. If moderation is used in setting physician fees for sigmoidoscopy, the direct cost of screening can be kept within reason. Controlled clinical trials will be needed to determine whether screening asymptomatic patients in this fashion will achieve the aim of

reducing mortality from colorectal cancer. Two such studies are currently underway, and their mortality data is awaited with interest.

High-risk patients

As a generalization, it can be stated that in comparison to average-risk patients, those who are at a higher risk for developing colorectal cancer should receive more intensive investigation, at more frequent intervals, beginning at an earlier age. Subgroups of the population at increased risk for colorectal cancer include patients with prior colorectal cancer or adenomas, ulcerative colitis, female genital cancer, a family history of one of the polyposis syndromes, or inherited (nonpolyposis) colon cancer syndromes. In most cases, there is little scientific basis for specific screening recommendations, however, the following recommendations which are derived largely from Winawer and Sherlock have proven effective in practice [136, 146].

The appropriate follow-up for patients with prior colorectal cancer or adenomas has already been discussed. Those with a personal history of female genital or breast cancer should undergo screening as recommended for average-risk patients beginning as soon as possible after diagnosis. Patients with a family history of familial polyposis or Gardner's syndrome should have sigmoidoscopy to establish whether they are affected at least yearly, beginning around age 12 years.

The relative risk of developing colon cancer associated with having a 'strong family history' of colon cancer is discussed elsewhere in this volume. Members of genetically-defined cancer family syndrome kindreds are at especially high risk for the development of colon cancer. Such cases are characterized by early age of onset and high frequency of right-sided colon cancers; therefore, it is recommended that they undergo yearly fecal occult blood testing and colonoscopy at 3–5-year intervals beginning at age 20. Even among first-degree relatives of patients with sporadic colon cancer there appears to be an increased risk for development of colorectal cancer, and such patients should undergo screening as recommended for average-risk patients beginning at age 20 years.

The risk of colorectal malignancy is increased in patients with ulcerative colitis and is directly related to the duration of disease and the extent of colonic involvement [147, 148]. In the past, prophylactic surgery has been recommended for patients with extensive colitis, once chronicity has been established [149]. Based on the concept that the finding of epithelial dysplasia on colorectal biopsy can identify patients at increased risk to have or develop carcinoma [150], a number of investigators have recommended periodic colonoscopy and biopsy as an alternative to 'prophylactic' colectomy in patients with quiescent, long-standing, extensive colitis. There is fairly strong circumstantial evidence supporting the use of dysplasia as a marker for carcinoma. In several studies the prevalence of carcinoma in colons

removed because of the presence of dysplasia has been over 50% [147–150]. However, in most of these cases dysplasia was present on the initial evaluation, and there is little information concerning the incidence of dysplasia and carcinoma during follow-up for those patients who are initially 'dysplasia-negative'. In a long-term prospective study, Lennard-Jones *et al.* performed endoscopic surveillance on 303 patients with extensive ulcerative colitis, 186 of who had disease for over 10 years [151]. Nine of the 13 cancers detected were found on surveillance endoscopy, and only one death from colorectal cancer occurred. Twenty-eight colectomies were done in the 66 patients who developed dysplasia on biopsy; ten contained cancer. This study lends strong support to the concept that detection of dysplasia during endoscopic surveillence can serve as the basis for colectomy.

Currently available data do not allow firm conclusions as to when screening should begin or how frequently colonoscopy should be performed. A reasonable policy is to perform surveillance on those with extensive colitis (to or beyond the hepatic flexure) of at least 7 years duration. Colonoscopy should be done at 2-year intervals with biopsies taken from flat mucosa every 10 cm throughout the colon and from any suspicious macroscopic lesions. Sigmoidoscopy with rectal biopsy can be performed on alternate years. Barium studies are reserved for those in whom complete colonoscopy cannot be performed. Surveillance examinations should be scheduled when the patients are as well as possible to avoid difficulty in histologic assessment due to reactive epithelial changes. Confirmed severe dysplasia or any degree of dysplasia associated with a macroscopic lesion is taken as an indication for colectomy. Low grade dysplasia is an indication for short interval follow-up with repeat biopsy, rather than immediate surgery. The effectiveness of such a surveillance program as a means of cancer control in these patients remains to be established. Several practical points should be considered in weighing this approach to management. Most importantly, a high degree of patient motivation and compliance is necessary for such an extended follow-up program. It must be remembered that despite the inconvenience associated with an ileostomy, total colectomy reliably prevents subsequent mortality from colorectal cancer. The cancer risk in patients with left-sided ulcerative colitis or longstanding Crohn's disease of the colon is also increased, but to a lesser extent than in extensive ulcerative colitis [147, 152]. Although some authors have proposed surveillance programs for patients with these conditions, additional data will be required before such an approach can be generally recommended.

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7. The detection and surgical management of recurrent colon and rectal cancers

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Early aggressive surgery is not the universally accepted procedure of choice for the management of recurrent colorectal cancer. Barring patients with multiple, diffuse metastases, surgical excision for cure can be accomplished at a second operation, with one-third of the re-operated patients remaining free of disease indefinitely [1, 2]. Second-look operations and the pre-planned use of carcinoembryonic antigen (CEA) to indicate when to operate, though still questioned by some, is now showing significant clinical benefit along with long-term free-of-disease survival in many patients.

Wangensteen [3, 4] proposed the concept of the second-look operations for colorectal cancer in 1951 to locate metastatic tumor in asymptomatic patients. His original arbitrary 6-month intervals for the second-look operations were too brief. His change to a 9-month interval between the first operation and the second-look operation did little to improve survival. The problems he observed in a pre-scheduled program of second-look operations were these: (1) at the second operation, no tumor was discovered, (2) at the second operation, recurrent tumor was too extensive for resection, (3) some individuals with a negative second operation had tumor develop later. The variation in tumor-growth rates led to the abandonment of pre-scheduled second-look operative procedures, since the benefits to most patients were unrewarding.

In 1965, Gold [5] discovered a nonspecific antigenic tumor marker for colon and rectal cancers that could be detected in the serum of patients. Within 5 years of this discovery, preliminary CEA testing kits using a radioimmunoassay were available from the Hoffman LaRoche Company. This provided physicians with a tool to examine the serum of patients who had already undergone a colorectal cancer operation and to determine if the CEA value in their serum was increasing, decreasing, or staying the same. When an increasing CEA value was detected, the assumption was that the source of this CEA was recurrent cancer. This concept however needed verification. Early sequential studies on patients with rising CEA levels who

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

had previously been resected for cure indicated that this marker was an accurate means of discovering which patients had recurrent cancer [6–10]. Frequently, all the tests used to determine the presence and location of the recurrent cancer were negative. The physician was then placed in a new setting of clinical responsability. He had to make a decision to reexplore that patient only on the basis of a rising CEA, or to ignore the rising CEA and wait until some acceptable and familiar physical finding, laboratory test, or X-ray test became positive. This wait usually lost the opportunity to discover and treat resectable tumor.

During this same period of time, surgeons were beginning to send their colorectal cancer patients with high risk for recurrence to medical oncologists for adjuvant treatments. Multiple cooperative groups were studying adjuvant chemotherapy and/or immunotherapeutic protocols throughout the country. Because these patients were admitted to randomized, prospective chemotherapy studies, the CEA second-look trial approved for study by the Southwest Oncology Group (SWOG) had an accrual rate which was too low to continue. The SWOG study #7830 [11] was terminated October, 1979. Thus the study, which could have scientifically answered the question of benefit from a CEA-directed second-look operation was never completed. The end result is that today, nearly 10 years later, the clinical benefits of CEA-directed operations have not been established in a randomized, prospective, study group trial. Several nonrandomized studies have reported long-term survivals and apparent cures in hundreds of patients [1, 2, 12]. So the question remains, should a rising CEA be used as an indicator for second-look surgery and will it benefit patients with long-term free-of-disease survival?

The Society of Surgical Oncology (SSO) carried out a prospective, nonrandomized study in which significant benefit to patients with recurrent colorectal cancer occurred only when second-look operative resection was done [1]. No 5-year survivals exist in the recurrent cancer patient population when the patient was treated with chemotherapy and/or radiation therapy alone. On the other hand, in a subgroup of CEA second-look operation patients, 40% of those patients with resected recurrent cancer are alive 5 years and longer free-of-disease if they were resected before their rising CEA had reached 11 ng/ml. When the CEA value was greater than 11 ng/ml, 22% of patients undergoing resection for cure at their second-look operation were alive free-of-disease 5 years later, irrespective of any other form of treatment. From the data of the SSO study, one might optimistically project that nearly 20,000 colorectal cancer patients per year could benefit from CEA-directed second operations.

With the discovery and use of CEA as a biologic marker to detect recurrence in asymptomatic patients, the percentages of patients reoperated on who actually have recurrence is at least 95% [2]. In the study by Martin *et*

al. [2], 31% of patients with recurrent disease are alive 5 years after curative resection. Others have reported less favorable results [13–15], but this may be due to the infrequent determinations of CEA in their follow-up protocols. In the study by Martin *et al.* [2], CEA analyses were done an average of every 1.8 months and operations performed on an average of 2.5 months after the first elevated CEA was detected. Resectability was highest (70%) when CEA was 11 ng/ml or less [1, 2].

Studies have shown that best results are obtained by reoperating soon after a persistent rise in CEA is detected [1, 2]. In these studies, CEA levels were obtained at one month, or at most, 2-month intervals for the first 2 years. In a clinical study by Lunde [13] 75% of patients with recurrence had abnormal CEA levels. Abnormal CEA was the first sign of recurrence in 59.1% of patients and transient CEA elevations were measured in 21.5% of patients (a CEA above 3.5 ng/ml was considered abnormal). Blood samples were collected postoperatively after 2 weeks, 1 month, 3 months, 6 months, and later, every 6 months. The mean time between the first abnormal CEA and clinical diagnosis of recurrence was 5 months. This study concluded by seriously questioning the routine use of CEA measurement in patients with colorectal cancer since the majority of their patients with elevated CEA had advanced metastatic disease not amenable to surgical treatment. In their study, a second-look operation with only an abnormal CEA as the indication for surgery was performed on nine patients. One resectable tumor was found. CEA levels were measured less frequently in the Lunde study than in more successful studies and a 5-month mean delay following a detectable CEA rise has been associated with unresectable recurrence in other studies [1].

In a 1984 study [14], 663 patients were followed with CEA testing. There was no mention of second-look surgery. One hundred and seventy-one patients (27%) had recurrent cancer, 114 (67%) had a CEA elevation as the first evidence of recurrence with an average time interval of 30 weeks before any other test became positive for recurrence. CEA testing was not started until the 3rd month after the curative resection. Instead of a second-look procedure, all asymptomatic patients with a rising CEA were randomized to receive chemotherapy. All but one demonstrated progressive disease and died. The authors concluded that an asymptomatic rise in CEA usually meant hepatic metastases, while a CEA rise with symptoms indicated extra-hepatic tumor.

In another clinical study on the use of CEA [15], CEA was measured in 102 patients at 6-month intervals over 3 years after curative resection. Twenty-seven patients demonstrated recurrence. Twenty-two of the 27 patients had an elevated CEA before recurrent tumor could be clinically detected. The time between primary tumor removal and the first CEA measurement was a median of 26 months. After a CEA rise was noted, an

additional delay of 5 months occurred before the second-look surgery. No patient was cured of recurrent disease. The upper limit of normal CEA was chosen as 10 nl/ml. The CEA was considered elevated when two serial measurements, taken one month apart, were both above the upper limit of normal. The authors of this article concede that more frequent CEA testing might improve the resectability rate, but from their own data they concluded that curative resection was not possible using CEA as an indicator for second-look surgery.

In an article in the September supplement of British Journal of Surgery 1985 [16], J.M.A. Northover outlines the current thought and attitudes towards CEA in Britain. He states... 'although there are several series indicating that such patients have a 30 percent chance of five year survival after resection, there is a reluctance in Britain to treat this condition aggressively'. A randomized prospective multi-center trial was started in Britain in 1983 in order to quantify the effect on mortality of CEA-prompted second-look surgery. Monthly CEA determinations are being done and surgery is required in approximately half of the patient population.

In general, the ability of a rising CEA to indicate recurrence is well accepted. Infrequent use of CEA determinations have already been demonstrated to be associated with poor clinical results for second-look surgery, whereas monthly or bimonthly testing followed by a minimal time delay before surgical exploration and aggressive, but safe and complete, resection of all recurrent tumor is associated with a significant 5-year free-of-disease survial [1, 2].

Surgeons planning to operate on an asymptomatic patient with a rising CEA will seek to locate the recurrence prior to the operation by a variety of studies. Since the liver is the most common site of metastases the surgeon will attempt imaging with a third generation CT scanner and an echogram or ultrasound scanner. The connection between Dukes' staging and/or differentiation of tumor and the likelihood of recurrence is quite clear, but where tumor will recur is not clear. The current literature is of some help in predicting anticipated sites of recurrence but far more prospective data analysis is necessary to map out the most common locations of recurrent tumor according to the primary tumor site, stage, and differentiation of the original tumor.

Most articles dealing with colorectal cancer surgery include a classification of tumors by Dukes' staging or some modification thereof. Unfortunately, comparisons become difficult or impossible because a common staging system is not used. Many use the Astler-Coller variation of Dukes' staging. Some use the original Dukes' staging, the Chinese have a 'Chinese Modification', and others. The American Joint Committee on Cancer (AJCC) is recommending a uniform staging system using the TNM system. An example of the problem of comparison and/or compilation of data can

be seen in Table 1 where the staging from several recent colon and rectal cancer studies is summarized. We recommend the TNM system be adopted for all future colorectal cancer publications [17].

Another problem in analyzing tumor recurrence and colon cancer operation failure rates is the nonspecific description of primary tumor locations. This may be due to an attitude that patterns of recurrence have little or nothing to do with the original site of the tumor. Stower and Hardcastle [18] report an approximate 26% survival rate for all colorectal malignancies, and find no relationship between the site of the original tumor and the high rate of tumor recurrence and patient mortality. Malcolm *et al.* [19] in 1981 noticed that tumors originating in the right colon had the highest failure rate but concluded that the differences were not statistically significant. In analyses of recurrence by site, authors tend to divide the colon as they see fit, once again, making comparisons difficult. For example, Malcolm *et al.* [19] divided the colon into five parts for analyses while the SSO study [1] divided it into nine divisions and Turunen *et al.* [20] into ten divisions.

Table 1. Comparative data table; recurrence statistics for several colon and/or rectal studies using different tumor classification systems

	A	B1	B2	B3	C1	C2	C3		
Willett *et al.* [27]	3%	9%	24%	37%	25%	51%	57%		
	Local fail			Total fail					
Koyama *et al.* [22][a]	B	C		B	C				
	8.4%	24.5%		15.4%	55.8%				
	A	B1	B2 (m)	B2 (m & g)[2]	B_3	C1	C2 (m)	C2 (m & g)	C_3
Chung *et al.* [28]	0%	9%	29%	44%	63%	28%	44%	67%	90%
	A	B1	C1	B_{2-3}	C_{2-3}				
Malcolm *et al.* [19]	13%	11%	32%	37%	56%				
	A	B1	B2	C1	C2	Unknown			
Minton *et al.* [1]	0%	23%	26%	26%	48%	86%			

Recurrence percentages – local and distance failure statistics are combined for curative colorectal resections unless otherwise specified.

[a] 5-yr cumulative curative results for patients with rectal cancer who underwent an extended lymphadenectomy.

(m) = microscopic only; (m & g) = microscopic and gross; B_3 & C_3 = adherence to or invasion of adjacent organs or structures.

Tumor differentiation is another factor predicting the risk of recurrence of colorectal cancer. It has been shown that the more poorly differentiated tumors have a greater tendency to recur [21]. Malcolm *et al.* [19] did not find tumor differentiation to be a significant factor and did not include this factor in their correlations of recurrence. Most other studies find a correlation does exist and include differentiation data [18, 1].

In our review of the current colorectal cancer literature, the detection of recurrent tumor is not a subject that authors devote much attention to unless the article is specifically concerned with recurrence detection, as in CEA studies. In a study of rectal cancers by Koyama *et al.* [22], it was stated that, 'periodic check-ups were usually performed every 3 months for the first 2 years, then every 6 months until the 5th year, and then at least every 12 months for the remainder of the patient's life. Measurement of serum carcinoembryonic antigen (CEA), chest X-ray, and ultrasonography of the liver were included in the routine check-up'. In another rectal cancer study by Pilipshen *et al.* [23] it was stated, 'Criteria for establishing recurrent pelvic disease included: histological confirmation; palpable disease, or disease evident on radiographic studies with subsequent clinical progression; and supportive biochemical data, i.e., rising level of carcinoembryonic antigen (CEA)'. This particular study seriously doubts the early detection capabilities of CEA. Our clinical experience, for example, shows that rectal cancers don't tend to produce elevated CEA levels and in our experience is not often rewarding for early detection. Most articles which deal with colon or rectal cancer survival do not specify their use of CEA as a follow-up test or the results of their second-look surgery if it was even done.

In most studies, how recurrent cancer is detected and how soon it is discovered after the primary operation is not discussed, or only minimal details are given. This lack of information, we believe, reflects a general attitude that recurrent colorectal cancers are essentially untreatable, except in a palliative sense, and aggressive surgical management for cure is an exercise in futility.

Scant attention has been directed at the time to recurrence following primary surgery. Some studies do not even include this information or give only a mean time for all recurrent cancer patients. In contrast, the SSO study [1] presents average times to recurrences according to Dukes' classification. An important aspect in dealing with patients with a high probability for recurrent cancer is recognizing not only where recurrence will most likely occur, but when. In the SWOG 7510 study entitled 'Intensive Adjuvant Chemotherapy With or Without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel', Frank Panettiere [24] points out the majority of recurrent colorectal cancers occurred before 2 years had elapsed following the original operation. As a matter of reference, two out of three recurrences had already occurred during the first

18 months of this study and by the end of 5 years, nine our of ten recurrences had already occurred. This emphasized a need for intensive patient monitoring in the first 2 years following the original operation. In this SSO study [1], it was recommended that CEA values be obtained on Dukes' B2, C1, and C2 colorectal cancer patients every month after the original operation, but it was more acceptable for economic reasons for CEAs to be obtained every 2 months during that first 2-year period and then every 3 months during the next 3 years with no detectable loss in clinical benefit.

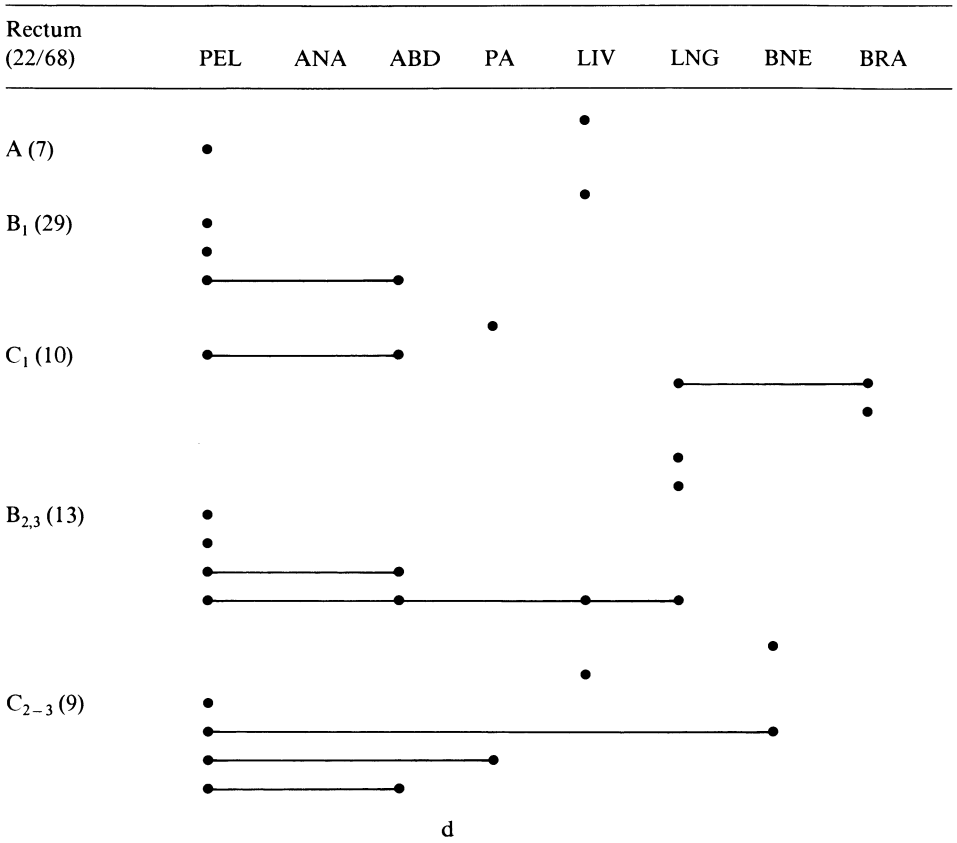
Most studies report 5-year survival data according to Dukes' classification, others by primary tumor site. Unless a study specifically deals with surgical recurrent cancer management, the 5-year survival data for patients with recurrent tumor is usually not given. One assumes all patients with recurrence die. But in contrast, other studies [1, 2] find that around 30% of asymptomatic patients who have their recurrence resected are disease-free 5 years later. Pilipshen *et al.* [23], in an article on pelvic recurrence of rectal cancer, reported an ultimate disease-free survival of 3.8% of patients with pelvic recurrence. Other studies simply do not given statistics like these. Usually the percentage of recurrences are stated and the overall 5-year survivals are given.

As can be seen from this overview of some of the current literature, a more comprehensive and unified approach to recurrence data needs to be done. In the 1981 study by Malcolm *et al.* [19], a correlation between primary site, stage, and site of recurrent tumor is presented. In this analysis, the colon was divided into several sections (e.g. left colon, right colon, etc.). For each site of the original tumor the recurrence pattern was listed according to Dukes' stage and site(s) of recurrences. Table 2 is an example recurrence table taken from this study.

If surgeons wish to predict with considerable accuracy the site of recurrent cancers according to the first tumor location, Dukes' staging and differentiation, a more comprehensive variation of this table will be necessary. The colon and rectum should be divided into 12 sites: cecum, ascending colon, hepatic flexure, right and left transverse colon, splenic flexure, descending colon, sigmoid, rectosigmoid, and upper, middle, and lower third of rectum. A uniform staging system should be used by everyone, preferably the TNM system [17]. Further stratification needs to be included within each staging category by the tumor differentiation (AJCC) [17]. Five-year survival for each sub-category as well as average duration of time to recurrence and method of detection should be included. Operative mortality should also be reported.

In addition to providing excellent stratification and cross correlation of data, these charts could be used to further divide the patient into risk of recurrence subsets. For instance, separate charting can be done for patients under 40, black/white female etc. The usefulness of knowing where and

Table 2. Malcolm *et al.* 1981 study correlation between primary sites, Dukes' classification, and location of recurrence(s)



PEL = pelvis; ABD = abdomen; LIV = liver; BNE = bone; ANA = anastomosis; PA = para-aortic; LNG = lung; BRA = brain; • = only site of recurrence; •—• = multiple sites of recurrence.
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when a tumor is statistically likely to recur is important in planning post-operative therapy, management and follow-up. Follow-up protocols can be more highly specialized to detect recurrences if one has a good idea of where and when to look. Charting one's data in this manner may provide information that would dictate changes in the surgical technique(s) at the original operation.

Differences in recurrence patterns and survival statistics should become apparent with the data obtained from uniform charting procedures. Differences in surgical techniques may produce variations in recurrence and survival data. In the study by Koyama *et al.* [22], the use of a meticulous,

Table 3. Sample recurrent chart – colon or rectal area e.g. cecum; proposed variation of A.W. Malcolm chart to be used to record and correlate recurrence statistics

	Tumor diff	Tot rec	OB L	OB R	HY L	HY R	SH L	SH R	DP L	DP R	UI L	UI R	PA L	PA R	LV	LG	BN	BR	SR L	SR R	IR L	IR R	OM	DI	MS	ST	OA	5-yr surv	Time to rec	How det	Op mort	Size	Pre & post op CEA
Stage 0	GX																																
	G1																																
	G2																																
	G3																																
	G4																																
Stage IA	GX																																
	G1																																
	G2																																
	G3																																
	G4																																
Stage IB	GX																																
	G1																																
	G2																																
	G3																																
	G4																																

L = left; R = right; OB = obturator area; HY = hypogastric area; LG = lung; SH = sacral hollow; IR = infra renal; DP = deep pelvis; UI = ureteral involv; SR = supra renal; OM = omentum; PA = paraaortic; LV = liver; MS = mesentery; DI = diaphragm; BN = bone; BR = brain; ST = suture line; OA = other areas not on chart; GX = grade or differentiation not determined, not stated or not applicable; G1 = well differentiated; G2 = moderately well differentiated; G3 = poorly differentiated; G4 = undifferentiated.

This chart is an example of the way recurrences should be recorded for statistical and computer analysis as well as peer review. For each patient in a given subset (e.g. 'stage III GI' subset), a dot is placed on the chart in each area of recurrence. There could be many patients in each subset. The dots are connected for a patient with multiple recurrences. This method is essentially the same as they are used in the Malcolm *et al.* chart (Table 12).

For example, a hypothetical, single patient has been recorded on the sample chart. The sample chart is the 'cecum chart' thus the patient had a primary tumor in the cecum. It was a stage IA tumor which was moderately well differentiated. The patient had recurrence in three areas. These areas were the left obturator, the right sacral hollow, and the liver. The last five columns are numbers that need to be averaged for each subset and are not filled in on this sample chart. However, for a single patient, it is possible to fill in most of this data.

Table 3. (continued)

	Tumor diff	Tot rec	OB L	OB R	HY L	HY R	SH L	SH R	DP L	DP R	UI L	UI R	PA L	PA R	LV	LG	BN	BR	SR L	SR R	IR L	IR R	OM	DI	MS	ST	OA	5-yr surv	Time to rec	How det	Op mort	Size	Pre & post op CEA
Stage II	GX																																
	G1																																
	G2																																
	G3																																
	G4																																
Stage III	GX																																
	G1																																
	G2																																
	G3																																
	G4																																
Stage IV	GX																																
	G1																																
	G2																																
	G3																																
	G4																																

extended lymphadenectomy for primary rectal cancer produced about a 20% better 5-year survival rate than the standard operations for Dukes' B & C cancer. Special surgical considerations need to be taken for dealing with cancer of the colon as well as the rectum. Phillips *et al.* [25] deals with this problem quite frankly. They state:

> However, as previously reported, there is considerable inter-surgeon variation in the incidence of local recurrence such that the surgeon is an independent prognostic variable that needs to be considered *para passu* with Dukes' staging. Some surgeons consistently have an increased incidence of local recurrence for both sexes and for each level of the Dukes' classification. Although this information will be readily accepted by some and be distasteful to others, it represents an important problem which we should not attempt to avoid. It raises issues for surgical training, patient management and the conduct of large multi-centre trials, the last because the object of study may be overwhelmed by the background 'noise' of such surgeon related variables.

the article then goes on to state:

> In the meantime, surgeons should be aware that a small group of our colleagues are obtaining results substantially better than those for the majority, which is not explained by any system of patient stratification that we have used. We conclude that these good results have been achieved by meticulous attention to detail. Although there is no evidence to indicate which technical aspect is the more important, we must assume that overall technical expertise is an essential ingredient for the best results and emphasizes the special requirements for those who wish to practice colon and rectal surgery.

In the postoperative period, the question of dealing with recurrent tumor must always be considered in relation to the risk of surgery versus the benefits of the operation to the patient. There is little reward to the patient to have a magnificent curative procedure when the patient does not survive the operative procedure. So judgment is exceedingly important in selecting which patients have an amount of recurrent tumor that can be safely resected. Training programs in cancer surgery emphasize the biological differences of different malignancies and points out the mistaken, but generally accepted concept that all cancers are equally bad. With clinical experience, surgeons learn that many cancers present a slow, indolent growth capability which, especially in colon cancers, provides the surgeon with the opportunity to safely remove all recurrent detectable tumor at a second operation.

Since 1971, I have been actively performing CEA directed second-look operations. With the exception of the 20% of the cancer patients whose cancer does not produce CEA, a rising CEA has been a reliable indicator of recurrent colon and rectal cancer. As a result of a thorough exploration of the abdomen after all other tests have been negative, I have been impressed

at the futility of additional roentgenograms in demonstrating the location of recurrent tumor in most patients with rising low levels of CEA. More recently, the CT scan has proved itself to be unrewarding as well in the search for recurrent cancer, with the exception of an occasional pulmonary and liver metastases. Ninety-five percent of patients explored because of rising CEA have demonstrable tumor. My current rule-of-thumb is that in the presence of a persistently rising CEA, preferably one below 11 ng/ml, a second-look operation is the earliest and most reliable method to establish the presence of a recurrent cancer and to definitively treat it.

Care must be taken that the patient has not received chemotherapy within the 3 weeks prior to the operation, since bleeding and clotting abnormalities are quite prevalent especially in patients who have been receiving long-term chemotherapy. Some patients may develop CEA elevations to 7 or 8 ng/ml as a result of adjuvant chemotherapy. Usually this is associated with the administration of 5-FU and mitomycin-C or methyl-CCNU. It is preferable that these drugs be terminated at least 3 weeks before the second-look and that a CEA be obtained and evaluated before the second-look operation is done since occasionally the CEA will begin to drop after termination of the chemotherapeutic agents. If the downward trend continues surgery should be delayed 1 month and the CEA repeated to confirm this trend. Unnecessary second-look operations can be avoided by this cautious re-evaluation.

Other times when a change in CEA may be erroneous are around the months of December and January, and June and July. These months are the times when personnel come to and leave laboratories. We have experienced major CEA changes in the longitudinal course of patients who have been normal for a long time when laboratory personnel change. Frequently we have notified the laboratory personnel of the erratic changes in CEA values they reported.

When I have decided that all the potential false-positive elevated CEA tests have been eliminated, then the patient and frequently the referring physician need to be educated on the necessities of reoperating on the patient who feels and looks perfectly healthy. The old adage 'if it doesn't hurt don't fix it' is fatal in our experience for these people.

My next major concern is that CEA-directed second-look operations be performed by surgeons who are comfortable with the rigors of aggressive cancer surgery. If the surgeon has been properly trained in *en bloc* excision of recurrent disease and surgical excision of liver metastases, the patient has an opportunity to receive curative therapy at the second operation. If the surgeon is not comfortable with resection of liver metastases, retroperitoneal metastases, omental metastases, mesenteric node metastases, etc., a referral to an appropriate surgical colleague should be done.

The preoperative preparation includes a 2-day liquit diet, ingestion of a

5-L 'go-lightly' mechanical prep, oral erythromycin and kanomycin, and a systemic cephalosporin. I always obtained, preoperatively, permission to perform a colostomy if it becomes necessary. Once the patient is on the operating table the colon is irrigated with a 1000 cc Betadine ® solution. In females a Betadine ® vaginal prep is done. A Foley catheter is always inserted and a nasogastric-tube placed after the patient is given an endotracheal anesthesia. When hepatic metastases are suspected, an arterial-line is inserted as well as a large bore central venous catheter. The abdomen is prepped with Betadine ® and alcohol.

Sterile paper drapes are applied from the pubis to nipples. An instant iodoform-impregnated Vi-drape® covers the operating site. A xiphoid to pubis mid-line incision is made, which points out another area of concern. The 4 inch para-median incision, all too often used at the time of the original cancer operation, jeopardizes wound healing because of the two parallel abdominal wall incisions less than an inch apart. Often I am forced to make an unattractive incision which opens the midline and then swerves over to accommodate the para-median incision. My plea is that surgeons who operate on cancers do midline incisions and do incisions that are generous enough so that an adequate mesenteric node excision can be accomplished as well as a thorough exploration of the abdomen and liver.

As the xiploid to pubis incision is being made, the electrocautery is put on coagulation only to complete the dissection below the skin, since it provides immediate coagulation of blood vessels and can be used to dissect through the fascia and peritoneum with care. Almost all these patients will have dense intraabdominal adhesions. An assistant holds three or four Kocher's clamps that are placed on the fascia opposite the surgeon and retracts superiorly in order to provide countertraction so the needle point can dissect the omentum and the small and large bowel free from the anterior abdominal wall peritoneum. With the abdomen open and the adhesions detached from the abdominal wall, the omentum must be freed up from its adhesions to the colon, bladder, cul-de-sac, and small bowel. Meticulous dissection is required and once it is totally freed, it should be laid as an apron upon the chest. I do not use self-retaining retractors during this part of the dissection. I recommend Richardson retractors be used to appropriately expose and provide countertraction in the area of dissection. Electrocautery dissection with the needle-tip at a 32–45 setting is generally safe for division of small bowel adhesions. Electrocautery is preferred because of the time it saves in dealing with oozing blood loss from dissected tissue surfaces. Sharp dissection with scissors or knife occasionally can be accomplished without the generalized ooze seen in the patients who have received long-term chemotherapy, but is uncommon.

Once all the small bowel has been mobilized out of the pelvis and away from its lateral adhesion to the cecum and the sigmoid, the mesenteric

leaves should be carefully dissected and inspected from the ligaments of Treitz to the ileocecal valve. Then the small bowel should be dislocated on its mesentery out of the abdomen and up on to the omentum lying on the chest. A warm moist towel covering the bowel will help it stay in place. The cul-de-sac, parailiac nodes, pararectal nodes, paraaortic and caval nodes from the pelvis to the diaphragm, and inferior mesentery artery must be inspected for recurrent tumor. Evidence of the presence of these nodes below the inferior mesenteric artery implies incomplete nodal excision at the first operation. Firm nodes must always be excised meticulously from the iliac vessels, the aorta, and vena cava, and sent for frozen section confirmation of recurrent diseases. If retroperitoneal tumor involves the ureter, a segment should be resected along with adequate proximal and distal margins, confirmed by frozen section, and where possible the ureter reanastomosed or sewn into the nearest corner of the bladder. Most recurrences involving the ureter are seen near the pelvic brim and require an ureterovesical anastomosis. This procedure should be done with 5–0 absorbable suture and swedged-on needles in two or three layers and always using a ureteral mucosa-to-bladder mucosa suture. A wrap of bladder around the vesico-ureterostomy minimizes the risk of leak. Anywhere the surgeon finds recurrent tumor in the peritoneum, muscle, fascia or mesentery, excision of the tumor should be accomplished with a 1 cm margin of normal tissue; the needle point Bovie is an efficient tool for this dissection. Tumor in the pelvis should be approached with the long Bovie blade extension and long Russian forceps. If the tumor is unresectable it should be meticulously outlined with Titanium metal clips so that focused, intense radiotherapy can later be applied. These clips do not present or create a large artifact to surveillance with CT scan. When metastases involve the omentum it must be removed. Metastases involving the ovary or fundus or the uterus requires a total bilateral ovariosalpingohysterectomy. Tumor involving the vaginal wall or the residual rectal or colon tissue requires an appropriate wide resection and when feasible an end-to-end or end-to-side colorectal anastomosis. Tumor involving the bladder can usually be excised locally with an adequate 1–2 cm margin of bladder wall free-of-disease with a triple layer closure of the bladder. Recurrent disease on bone should be removed. Metastases to retroperitoneal fat, muscle, and nerves must be excised with an adequate margin of normal tissue. In the upper abdomen, the liver and diaphragm, retrogastric and lesser curvature nodes should all be examined and if suspect, biopsied.

The falciform ligament must be taken down from its attachments to the diaphragm. If adhesions exist between the liver and diaphragm, they must be dissected away. The right lobe of the liver should then be detached from its retroperitoneal attachments and separated from the bare area of the diaphragm. The liver can then be dislocated out of the retroperitoneum into

the upper abdominal wound. The triangular ligament attached to the left lateral segment of the liver should be taken down as well. A careful bimanual palpation of each lobe of liver must be done. Any suspicious area should be excised for biopsy and stem cell culture. Occasionally multiple small (1–3 cm) metastases are found in the liver. These can be safely removed surgically using the electrocautery unit set at 100+ coagulation. A suture passed through the tumor in a figure 8 fashion is helpful in providing countertraction. Meticulous dissection with the electrocautery using the blade should minimize blood loss during the dissection. A 1/2–1 cm margin of normal liver tissue should be excised from around the tumor nodule. Larger nodules can be excised in a similar way even when both lobes are involved. We have removed up to and including 12 metastatic lesions from both lobes with minimal blood loss, no postoperative mortality, and significant extended survival (100% alive at 1 year) [26]. Metastatic cancer from the colon does not usually involve the spleen but, if it does, a splenectomy should be performed.

When metastatic tumor in the liver is unresectable, I place a Broviac catheter in the gastroduodenal branch of the hepatic artery and a Hickman catheter in the gastroepiploic vein which drains to the portal vein. I inject fluorescein (2–3 cc) dye to determine if there is uniform flow to both lobes of the liver through the hepatic artery. The portal vein catheters are then filled with 2 cc of sodium heparin (1000 unit/cc). Both catheters are inserted through stab wounds in the right upper abdomen before placement into the vessels. Residual areas of tumor in the liver are carefully outlined with titanium silver clips.

Mestastases to small bowel, colon, stomach, or any hollow viscus are resected with an adequate margin of normal tissue. Excised tumor is taken for stem-cell culture in order to assess the sensitivity of the tumor to chemotherapeutic agents. When peritoneal lesions are noted, the CO_2 laser can vaporize them; one or two Tenkhoff catheters may also be sewn into the peritoneal cavity as a route for intraperitoneal chemotherapy. Selective chemotherapeutic agents are administered through the heparic artery and portal vein lines or into the peritoneal cavity, depending on their demonstrated kill capability with the culture tumor cells.

Once all tumor has been surgically removed from the abdomen or residual tumor carefully marked with clips, the abdomen is closed with #1 Surgilon®. My experience with this suture indicates extremely low risk of hernia and almost nonexisting risk of infection, especially if the wound has been irrigated with generous amounts of Chloropactin® during the operation and at the closure of the wound. The skin closure is optional but I prefer a subcuticular running 3-0 Dexon closure with Betadine® impregnated Steristrips® placed over the incision. A compression dressing on the skin completes the operation.

Following the procedure, CEA determinations are performed at one week, and then at one month intervals. If all detectable disease was removed, the same sequence of follow-up is reinstituted as though a primary operation had taken place. When tumor is left behind, the CEA can monitor the tumors' response to other forms of therapy.

Acknowlegments

Supported by Public Health Service Grant CA-16058-11 from the Division of Extramural Activities, National Cancer Institute; by American Cancer Society Grant RF712349; The Grand Chapter of Ohio, Order of the Eastern Star; The Ohio State University Development Fund; and, Phi Beta Psi Sorority.

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8. Systemic and regional chemotherapy in advanced colorectal carcinoma

NANCY KEMENY

Introduction

Colorectal carcinoma afflicts more patients in the United States than does any other malignant neoplasm, excluding skin cancer, and accounts for 15% of all cancer deaths [1]. At the time of initial surgery, almost half of the patients with colorectal carcinoma have some evidence of lymph node involvement [2], and 10 to 25% of those patients already have liver metastases [3, 4]. To improve survival, earlier detection and treatment more effective than surgical resection of the primary must be developed. This chapter will describe the role of chemotherapy – singele agents, combination chemotherapy, and regional therapy – in the management of large bowel cancer.

Single agents

5-Fluorouracil

5-Fluorouracil (5FU) has been the drug of choice for the treatment of colorectal carcinoma. The clinical usefulness of this agent was first reported by Ansfield who obtained a 15% response rate using 5FU at 15 mg/kg intravenously for 5 consecutive days, and then half doses until toxicity (the standard loading dose). Twenty-three percent of the patients had severe leukopenia (white blood cell count below 2000 cells/mm^3) and 3% died from drug toxicity [5]. A less toxic schedule was developed using 12 mg/kg intravenously for 5 consecutive days and is now referred to as the standard loading dose. Early work with the standard loading dose showed a great variation in response rate, 8–85% [6], which may reflect differences in patient population and response criteria. In studies in which the measure-

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

ment of response was clearly defined, the average response rate was 15% [7].

The optimal method of 5-FU administration is still controversial. Oral administration would be easier on the patient, but 5-FU is absorbed erratically. In the only randomized study comparing oral to a weekly IV dose and the standard loading dose, the response rates were 13%, 13%, and 33%, respectively. One of the problems with the study is the relatively high response rate obtained with the standard loading dose, but the study does suggest the standard loading dose method gives a higher response rate [8].

There has been recent interest in administering 5FU by continuous infusion. This method favors the catabolic degradation of 5FU and allows a much higher dose to be given with less hematologic but greater gastrointestinal toxicity [9]. Seifert in a randomized study of 70 patients, compared continuous infusion of 5FU versus bolus 5FU for 5 days, and obtained response rates of 44 and 22%, respectively [10]. It is important to note that patients were not stratified for sites of metastases and there were more patients with lung metastases in the bolus group. The relationship between the site of metastases and response rate for 5FU had been previously demonstrated. Lung metastases responded at a much lower rate than abdominal or liver metastases, 6% versus 32 and 24%, respectively [6]. Lokich has advocated using a protracted infusion program in contrast to short-term infusion so that there would be a constant availability of drug to affect cells which may enter into a certain phase of the cell cycle at various times. For a drug such as 5FU used over a 30-day period, the accumulative dose for the infusion is approximately four times that which could be delivered by the standard bolus dose. In a phase II study, the responses with protracted 5FU infusion were 8/21 in previously treated patients, and 13/34 in previously untreated patients [11]. Two other reports suggest increase activity for 5FU infusion. Ausman [12] reported a 36% response rate using 300 mg/m^2 of 5FU administered daily [13]. Protracted infusions require an external pump and catheter and more extensive patient training. Randomized studies, comparing protracted infusion to short-term infusions or bolus therapy, are necessary to see if the method is really superior.

The suggestion that the dose response curve for the antitumor effectiveness of 5FU is steep has lead some investigators to using higher doses of 5FU again. In a study by the Southwest Oncology Group (SWOG) patients were treated with 5FU at 550 mg/m^2 intravenously for 5 consecutive days, and the response rate was only 13%; 50% of the patients developed life-threatening bone marrow toxicity [15]. In another study, 5FU in doses ranging from 575–689 mg/m^2 for 5 consecutive days increased the response rate to 26% but the toxicity was significant: 61% of the patients developing granulocyte counts less than 500 cells/mm^3 [16]. The dose response rela-

tionship for 5FU was actually demonstrated many years ago by Horton, in a study in which a weekly dose of 5FU at 7.5 mg/kg yielded only a 6% response rate while 15 mg/kg weekly yielded a 20% response rate [17].

In summary, the average response rate of 20% quoted for 5FU is most likely lower unless very high doses of 5FU which produce considerable toxicity, are used. The optimal method of administration of 5FU is still not clear. In order to improve the response rate investigational drugs, new methods of delivering drugs, or new combinations of drugs should be used.

Other single agents

No other single agent has produced a consistently higher response rate than 5FU. Of the agents tested, one of the more promising group of drugs is the nitrosoureas: BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), CCNU (1-(2-chloroethyl)-3-cyclohexyl-l-nitrosourea), and MeCCNU (1-(2-chloroethyl)-3-4-methylcyclohexyl-l-nitrosourea). This group of drugs has response rates ranging from 11–25% in untreated patients [17]. These drugs are ineffective in previously treated patients. Mitomycin C has an overall response rate of around 18%, but the average duration of response seems to be short (2 months) and the margin between therapeutic dose and toxicity is narrow [18]. Other drugs with about a 10–15% response rate include methotrexate [19], streptozotocin [20], Baker's Antifol [21] and ICRF-159 [22]. Cis-diamminine-dichloroplatinum (cis-platinum) has activity in many solid tumors but as a single agent it has very little activity in colorectal carcinoma. In a randomized study comparing cis-platinum with 5FU, the response rates were 3 and 17.5%, respectively [23]. Adriamycin which has produced responses in hepatoma and carcinoma of the stomach, has only a 9% response rate in colorectal carcinoma [24]. Unfortunately, none of the new drugs tested in the last few years have proven to be effective in this disease.

Several derivatives of 5FU have been tested; FUDR has been compared to 5FU in four studies and has given comparable response rates with an average response rate of 23%. Ftorafur, another derivative, has the advantage of being able to be used orally and has less myelosuppression than 5FU, but some investigators have noted increased neurologic and gastrointestinal toxicity [25].

Combination chemotherapy

There has been a multitude of trials with combination chemotherapy in colorectal carcinoma. One could list the various trials and their results, but

because of variations in patient population and the method of measuring response, such data may not be meaningful. Therefore, only a few combinations have been selected for discussion. The first combination that seemed to be effective was methyl-CCNU, 5FU, and vincristine (MOF). In a randomized study of this combination versus 5FU alone, Moertel obtained a 43% response rate with MOF and a 19% response rate with 5FU [26]. Two other randomized studies, one by Faulkson and the other by SWOG, doubled their response rates with the MOF-type combination though vincristine was excluded from the latter study [27, 28]. As work continued with this combination on more than 700 patients, the mean response rate decreased to 23% with four groups obtaining response rates of less than 16% (Table 1). The overall response rate approximates that seen with 5FU alone; however, in the first three studies using the combination, there was a significant increase in response rate with MOF over 5FU alone, though there was no increase in survival.

At MSKCC, streptozotocin was added to the MOF combination to increase the amount of nitrosoureas in the combination without increasing hematologic toxicity [36]. Methyl-CCNU was administered at 30 mg/m^2 p.o. for 5 consecutive days, 5FU at 300 mg/m^2 IV for 5 consecutive days, vincristine 1 mg every 5 weeks, and streptozotocin 500 mg/m^2 weekly (MOF-Strep). In the first study of 74 evaluable patients, there were two complete and 22 partial responses with a 32% response rate. A subsequent randomized study of MOF versus MOF-Strep [37] yielded a significantly higher response rate with the MOF-Strep, 6% vs. 32%, respectively

Table 1. 5-FU + MeCCNU vincristine in the treatment of advanced colorectal carcinoma

Investigators	Total Pop.	MeCCNU (mg/m^2)	5 FU (mg/m^2)	Vincristine (mg/m^2)	No. of responding patients	% of responding patients
MacDonald [29]	25	150	500	1	10	40
Posey [30]	35	175	12/kg	—	12	37
Falkson [27]	46	100	12/kg	1	17	37
Baker [28]	152	175	400	—	49	32
Moertel [31]	127	175	10/kg	1	34	27
Buroker [32]	133	150	1000 [a]	—	21	16
Engstrom [33]	81	150	325	1	10	12
Kemeny [34]	69	150	300	1	7	11
Lokich [35]	52	150	300	—	2	4
Total	720				162	23%

[a] Continuous 24-h infusion.
Adapted from Kemeny [7].

Table 2. MOF-Strep [a] chemotherapy for colorectal cancer

Investigators	No. of patients	No. of responding patients	% of responding patients
Kemeny	74	24	32
Kemeny	35	12	33
Kemeny	17	6	35
Weltz	40	10	25
Smith	40	3	9
Winn	18	5	28
Buroker	22	7	32

[a] Methyl-lomustine, 5-fluorouracil, vincristine and streptozotocin.
Adapted from Kemeny [39].

($p = 0.001$). Other studies using MOF-Strep are listed in Table 2 and demonstrate a mean response rate of 28%. In one small randomized study comparing 5FU to MOF-Strep, the response rates were 15 and 30%, respectively, but there was no increase in survival [38]. If the three studies using MOF or MOF-Strep at MSKCC are combined, a statistically significant increase in survival with the MOF-Strep regimen over MOF was observed [37].

One concept in designing new drug combinations is to use one drug to biochemically modulate the effect of the second drug; an example of this is sequential methotrexate and 5FU. Methotrexate blocks purine metabolism and thereby causes an increase in the level of phosphoribosylpyrophosphate (PRPP) which is a substrate required for the conversion of 5FU to its active metabolite. Methotrexate given prior to 5FU may therefore enhance 5FU activity. Numerous studies have been done with this combination but there is quite a variation in response rate. One of the factors which may affect this variation is the difference in the time intervals between the administration of methotrexate and 5FU. In reviewing all the studies [40], it seems that the studies with the longer time interval have a higher response rate. In studies in which the time interval between methotrexate and 5FU is greater than 3 h, the mean response rate is 37% while the mean response rate was only 16% in studies where the interval between the two drugs was only 1 h (Table 3).

Other attempts at modulation of 5FU metabolism include the use of thymidine, PALA, leucovorin, dipyridamole and allopurinol. Thymidine decreases plasma clearance of 5FU [41] and PALA inhibits *de novo* pyrimidine biosynthesis by blocking the activity of aspartate carbamoyl transferase, one of the first steps in pyrimidine metabolism [42]. Although both drugs increase incorporation of 5FU into RNA, they do not increase the response

Table 3. Results of MTX and 5FU trials in colorectal carcinoma

Study	MTX (mg/m^2)	Leucovorin rescue(mg)	5FU (mg/m^2)	Interval hours	Response
1-h interval					
Alan *et al.*	250	15 q6h × 6	600	1	3/5
Tisman + Wu	1500	15 q6h × 6	1500	1	2/7
Cantrell	250	$10/m^2$ q6h × 5	600	1	1/16
Blumenreich	200	$10/m^2$ q6h × 6	600	1	0/7
Panasci	200	20 q6h × 6	1000	1	2/9
Panasci	200	20 q6h × 6	600	1	0/5
Hansen	100	$10/m^2$ q6h × 4	600	1	5/20
Burnet	250	$10/m^2$ q6h × 5	600	1	1/18
				Total	14/87 (16%)
3 or more hours [a]					
Drapkin	200-600	$12/m^2$ q4h × 6	300-600	7	6/19
Drapkin	200-600	$12/m^2$ q4h × 6	300-600	7	9/24
Weinerman	20	$10/m^2$ q4h × 4	600	4	10/29
Solan	200	yes	600	4	2/6
Solan	40	none	600	4	3/8
Mehotra	100	$10/m^2$ q6h × 11	600	4	8/10
Hermann	200-300	$14/m^2$ q6h × 8	900	3	5/8
Kemeny	40	none	600	24	14/43
				Total	57/147 (37%)

[a] Time between MTX and 5FU.
Data are of number of patients responding / total number of patients in schedule.
Adapted from Kemeny *et al.* [40].

Table 4. 5-FU plus citrovorum factor (CF) for metastatic colorectal carcinoma

Investigators	5-FU (mg/m^2)	CF (mg/m^2)	No. of patients	Previously treated	Response PR
Petrilli [44]	600	500	24	20	9 (38%)
Betrand [45]	370	500 [a]	15	0	6 (40%)
Budd [46]	1000 [a]	200	53	0	12 (23%)
Budd [46]	375	200	54	0	12 (22%)
Mortimer [47]	600	60 [b]	23	4	3 (15%)
Machover [48]	400	200	85	25	(41%)
Denny [49] [c]	400	20	16	12	5 (31%)

[a] Continous 24-h infusion.
[b] q6h.
[c] Methotrexate also used in this study.

rate in colorectal carcinoma. In an MSKCC study the addition of thymidine to 5FU increased toxicity but not the response rate [43]. With PALA and 5FU, Bedikian obtained a 16% partial response rate in 24 patients treated with a weekly schedule, and a 11% response rate with a 5-day schedule of the two drugs [42].

Leucovorin forms a ternary complex with thymidylate synthetase, and theoretically should increase 5FU activity. Studies using the combination are listed in Table 4. Such reports are encouraging but most of the studies are small and more work has to be done to verify these results. Allopurinol reduces the toxicity of 5FU and allows the use of a higher dose of 5FU but the combination has not significantly increased the response rate obtained with 5FU alone [50].

Another approach to finding effective combinations is to look for synergism between the various drugs. Cis-platinum alone has no activity in colorectal carcinoma but 5FU and cis-platinum are highly synergistic in animal models. In a recent clinical trial by Einhorn [51], there was a 32% response rate in 38 patients treated with cis-platinum at 60 mg/m^2 every 3 weeks and 5FU at 15 mg/kg weekly. Hematologic toxicity was severe with 65% of the patients having granulocyte counts less than 1000 cells/mm^3. Other recent reports with this combination have not yielded such high response rates. O'Connell, combining 5FU at 300 mg/m^2 and cis-platinum at 20 mg/m^2 for 5 consecutive days, obtained a 25% response rate in 28 patients [52]. Shepard had no responses in 20 patients [53]. The doses were different and further work with this combination will have to be done to know if it is effective.

How does one decide which drug or combination of drugs to use? The advocates of 5FU therapy state that no combination chemotherapy has clearly shown a survival advantage over 5FU; therefore, there is no reason to use any of the more toxic combinations. If a patient has a small amount of disease and is asymptomatic, one could possiblely advocate this approach. However, if the patient has a large volume of disease and a poor performance status, one has to get a response quickly. I feel that some of the combinations that offer at least a 30% response rate, would be more useful at this time.

Regional infusion

Although the liver has a dual blood supply, there has been evidence to suggest that hepatic tumors derive their blood supply primarily from the hepatic artery [54]. Infusion of chemotherapy directly into the hepatic artery exposes these metastases to a high drug concentration and perhaps spares the normal liver tissue which is supplied primarily by the portal vein. There

is also evidence to suggest that certain drugs have a higher hepatic extraction. Ensminger *et al.* demonstrated differences in extraction of 5FU and FUDR by measuring hepatic venous effluent [55]. There was a four fold higher extraction of FUDR, and 1.5 fold higher extraction of fluorouracil when the drugs were given by the hepatic arterial route compared to the systemic route.

The first trials with hepatic artery perfusion used external pumps or required hospitalization and patient immobilization. The mean response rate for previously untreated patients was 58%, but because of the hindrance to normal activity, few oncologists advocated the use of hepatic artery therapy despite the apparently higher response rates [56]. The development of a totally implantable infusion device provided a new stimulus for the infusion advocates [57].

Use of an implantable pump delivery system offers several potential advantages: reduction in catheter-related sepsis, ease of drug administration, and greater patient acceptance without bulky external devices. Direct placement of the catheter negates the problem of catheter displacement and allows better determination of the presence of intra-abdominal extrahepatic disease.

The first study with the infusaid pump and continuous FUDR therapy produced an 83% response rate [58]. Most of the other investigators using this method could not reproduce these results (Table 5) but the mean response rate of 44% (in eight trials where 42% of the patients were previously treated) is higher than the mean response rate with systemic chemotherapy trials.

Although the operative and technical complications with the use of the implantable pump have been minimal, there have been chemotherapy com-

Table 5. Hepatic arterial FUDR infusion responses

Investigators	No. of patients	% Prior chemo.	% Resp.	% CEA	Surv. med. (months)	% Liver mets. (> 50%)
Ensminger [58]	60	45	83	—	21	—
Balch [59]	50	40	—	83	26	—
Kemeny [60]	41	43	42	51	12	53
Shepard [61]	53	42	32[a]	—	17	—
Weiss [62]	17	85	29	57	13	—
Schwartz [63]	25	—	15	75	18[b]	—
Johnson [64]	40	—	47[a]	—	12	34
Cohen [65]	69	49	51[a]	—		24

[a] More than on drug given.
[b] Survival from diagnosis of liver mets.
— = Not mentioned.

plications. In our original pilot study, 30% of the patients developed significant endoscopically documented gastrointestinal ulcerations. If severe gastritis and duodenitis were included, about 50% of the patients developed significant gastrointestinal disease [60]. A summary of the gastrointestinal toxicities noted by the other investigators is listed in Table 6. The rate of ulcer disease is higher in the MSKCC study. However, this was one of the only trials that thoroughly investigated patients with endoscopy whenever they had abdominal pain. In the study from the Farber Center [62], pain was reported in 50% of the patients but rarely was endoscopy done. In the study by Ensminger's group, pain was assumed to be due to gastritis, and very rarely was endoscopy done. These variations in patient followup may explain the higher reported rate of ulcer disease seen in the MSKCC study.

Hepatic toxicity was also frequent. Bilirubin elevations above 3 mg/ml were seen in 20% of the patient and transaminase elevations in 71%. Two patients developed strictures of the bile ducts resembling biliary sclerosis. Hepatic toxicity was quite similar in the different pump studies and in most studies, one-fourth to one-third of patients had elevated bilirubin. Toxicities obtained by the various investigators are listed in Table 5.

At MSKCC it was found that the most useful laboratory test to help monitor and avoid some of these side effects was the serum glutamic oxalactic transaminase (SGOT). A review of the liver function tests obtained every two weeks, revealed a certain pattern of SGOT elevation in 23 of the original 45 patients: an increase of SGOT at the end of FUDR infusion (2 weeks after initiation of treatment) and then normalization prior to the next dose (4 weeks after initiation). This pattern occurred in all of the patients who later developed severe hepatic toxicity (bilirubin 3 mg/ml) and in 11 of 12 who developed ulcers.

Table 6. Toxicity from hepatic arterial FUDR

Investigators	No. of patients	% Toxicity				% Extra hepatic disease
		Gastritis	Ulcer	SGOT	Bil.	
Ensminger [58]	60	60	8	46	23	—
Balch [59]	50	—	6	23	23	—
Shepard [61]	53	—	20	49	24	—
Cohen [65]	69	—	40[a]	10	25	—
Kemeny [60]	41	29	29	71	22	32
Johnson [64]	40	—	8	50	13	—
Schwartz [63]	25	53	—	77	20	76
Weiss [62]	17	50	11	80	23	—

[a] Most of the pumps were placed by transbachial route.

Since our initial report there has been an increase in the recognition of the serious side effects, including biliary sclerosis, seen from infusional therapy. Hohn has documented this side effect in 12 of 45 patients [66]. Since the ducts are sclerotic, sonograms are usually normal and the diagnosis has to be made by endoscopic retrograde cholangio-pancreatogram. Close monitoring is necessary to try to avoid this complication. If the bilirubin becomes elevated, no further treatment should be given until the bilirubin comes back to normal, and then only with a very small dose (0.05 mg/kg/day). If there is no increase in liver function tests after a test dose, the dose can be slowly escalated. In some patients who cannot tolerate a low dose for 2 weeks, it is possible sometimes to continue administering treatment by giving the FUDR infusion for only 1 week rather than the usual 2 weeks.

Attempts to modify the GI toxicity have included extensive dissection of the upper border of the distal stomach and the duodenum with ligation of all regional vessels. Careful reduction of the dose with any gastrointestinal symptoms or SGOT elevation may also decrease the side effects. Drugs such as cimetidine, ranitidine and antacids have been used but they have not prevented the development of ulcers in these patients though these drugs may decrease the rate.

It is difficult to interpret the true impact of hepatic infusional therapy on tumor response and patient survival without a prospective randomized study comparing it to systemic infusional therapy. In such a study, patients would need to be stratified for parameters known to influence tumor response rates and patient survivals, such as, performance status, percent of liver involvement and initial lactic dehydrogenase levels. In many hepatic infusional studies, patients with poor performance status are not included because surgery is required. In contrast even patients with poor performance status are usually entered in the systemic chemotherapy trials.

The influence of the percent of liver involvement on survival has been shown by many investigators as noted previously. Patients in our original hepatic infusion study were evaluated to see if there was an association between the extent of metastases and survival. The estimation of tumor involvement was done both medically and surgically; both estimations were then compared to survival. The median survival for patients with less than 20% involvement was greater than 29 months for both medical and surgical involvement, and only 6 months for those with greater than 60% involvement [64].

The influence of certain laboratory parameters on tumor response and patient survival was evaluated in a study of 220 patients with advanced metastatic colorectal carcinoma at MSKCC [65]. The initial lactic dehydrogenase (LDH) level proved to be the most significant factor affecting both response and survival. Patients whose initial LDH and carcinoembryonic

antigen (CEA) levels were normal had a median length of survival of 32 months versus only 8 months for those who originally had abnormal plasma values. In reviewing the patients who received hepatic infusion via the pump at MSKCC, the median survival for patients with a normal LDH was 28 months, while it was only 6 months for patients with an LDH greater than 700ng/L [64].

Because of variation in patient survival based on these various patient characteristics, a prospective randomized study was initiated at MSKCC comparing intrahepatic infusion to systemic infusion applying the same chemotherapeutic agent (FUDR), drug schedule, and method of administration [66]. Patients with measurable metastatic colorectal carcinoma to the liver without extrahepatic disease are eligible for the trial. Patients are stratified by plasma LDH level and the percent of liver involvement.

All patients randomized to the study underwent exploratory laparotomy to assess the percent of liver involvement and to be sure that there is no extrahepatic disease. Patients randomized to intrahepatic therapy had the hepatic artery catheter connected to the pump. In the systemic group, the hepatic artery catheter was connected to an infus-a-port, and he pump was connected to an additional catheter placed in the cephalic vein. If the disease progressed in a patient in the latter group, a minor surgical procedure would allow a crossover to the intrahepatic arterial therapy; thereby also allowing further evaluation of the efficacy of regional thearpy.

The drug, FUDR, was administered by continuous infusion for 14 days via an Infusaid pump in both groups. However, the starting dose was 0.3 mg/kg/day for the intrahepatic group and 0.125 mg/kg/day for those receiving systemic infusion.

One hundred and forty-three patients have already been referred for entry into the study. Nine patients refused randomization, and three were

Table 7. Intrahepatic vs. systemic FUDR infusion

Referred			143
Refused randomization		9	
Two or more arterial supply		3	
Randomized			131
Excluded		45	
Resected	17		
Extrahepatic disease	24		
Infection	1		
No tumor	3		
Entered			86

Table 8. Intrahepatic vs. systemic FUDR infusion

		Patient characteristics	
		Intrahepatic (n = 41)	Systemic (N = 45)
Age (years)[a]		60	62
KPS[a]		80	80
% liver involvement		40	45
Sex (M/F)		28/13	26/19
Initial laboratory data			
LDH	> 500 U/L	14	16
CEA	> 100 ng/ml	16	19
WBC	> 10,000 cells/mm^3	7	9
Albumin	< 4.0 g/dl	14	17
Alk Phos	> 300 U/L	11	11

[a] Median.

excluded because of anomalous arterial blood supply, i.e. more than three vessels perfused the liver. Therefore, 131 patients were randomized preoperatively.

Forty-five patients were excluded from the study after surgical exploration for the following reasons: resectable disease in 17 patients, extra-hepatic disease in 24, no tumor in three, and intra-abdominal infection in one. Eighty-six patients, therefore, have had the pump placed in the randomized study (Table 7). The two groups were comparable; they were well matched with respect to percent of liver involvement, initial laboratory values, performance status, age and unfavorable prognostic factors (Table 8).

To date there are 16 PRs in 32 evaluable patients in the intrahepatic group and nine PR's in 34 evaluable patients in the systemic group. The median duration of response is 10 and 7 months for the two groups, respectively. There were two MR's in each group. In both groups, there were three

Table 9. Intrahepatic vs. systemic FUDR infusion

	Intrahepatic	Systemic
Total entered	41	45
Too early	6	9
Inadequate trial	3	3
Evaluable	32	34
Partial response	16	9
Minor response	2	3
Stable	3	3
Reduction of CEA (> 50%)	21	13

patients with stable disease. Twenty-one patients in the intrahepatic group and 13 patients in the systemic group have had more than 50% reduction in CEA level (Table 9).

In evaluating the patients who had a crossover from the systemic to the intrahepatic infusion, there seems to be some relationship between initial tumor response to systemic treatment and the ability of obtaining a tumor response from the crossover to arterial infusion. Five patients who responded and then failed systemic treatment have been crossed-over to the intrahepatic treatment. Three of the five patients responded and one had a transient improvement which was followed by thrombosis of the hepatic artery and progression of disease. Six of seven patients who originally failed systemic infusion also failed intrahepatic arterial infusion.

The toxicity has been quite different between the two groups (Table 10). In the intrahepatic group, the toxicity has been mainly gastrointestinal and hepatic. Five of 32 patients developed significant gastrointestinal ulcers documented by endoscopy, and another four patients had severe gastritis. Twenty patients developed an elevation of SGOT greater than 100% over baseline value, and ten developed a significant elevation of serum bilirubin (as high as 10.0 mg/dl in one patient). Four of the ten had abnormal ERCPs suggesting biliary sclerosis. In the systemic group, the major toxicity has been diarrhea, seen in 25 patients. In three patients, sigmoidoscopy revealed sigmoid ulcerations suggestive of colitis. Both patients required hospitalization for supportive care including intravenous hydration.

Although the starting dose for the intrahepatic therapy was twice as high as the systemic therapy, doses in both arms were quite similar after the third cycle of treatment. In the intrahepatic group, six patients required reduction in the dose after the first treatment, eight after the second and four after the third, so that the median dose after the third treatment was 0.2 mg/kg. In the systemic arm, the starting dose was 0.15 mg/kg/day × 14 days in the first nine patients. After two patients developed severe diarrhea, the FUDR

Table 10. Intrahepatic vs. systemic FUDR infusion: toxicity in evaluable patients

	Intrahepatic (n = 41)	Systemic (n = 45)
Ulcer	5	0
Diffuse gastritis	4	1
SGOT > 2 × baseline	20	4
Bilirubin > 3.0 mg/dl	10	1
Diarrhea	1	25
Colitis	0	4
Bil. sclerosis	4	0

dose was reduced to 0.125 mg/kg/day. Thirty-four patients have been entered on this dose and 13 have already tolerated an increase in dose, two patients to 0.2 mg/kg. Therefore, the median dose at the present time for the systemic group is 0.15 mg/kg/day.

Another significant difference between the two groups was the development of extrahepatic disease. In the intrahepatic group, 18 patients have already developed extrahepatic disease (ten lung, three intra-abdominal, four bone, one pelvis, adrenal, lymph node and spine). At the present time, seven patients in the systemic group have developed extrahepatic disease (two lung, one bone, four pelvis).

There has been no difference in survival between the two treatment groups. The median survival, at the present time, for the intrahepatic and systemic groups is 15 months and 14 months, respectively.

A similar study initiated by the Northern California Cooperative Cancer Group presently has response rates of 41% in the intrahepatic infusion group and 35% in the systemic FUDR infusion group [70]. Ensminger's consortium included four institutions but they were unable to enter enough patients and the study closed after 43 patients were entered into the three arm study. Of the 13 patients receiving only systemic 5FU, 38% responded. Of the 12 patients receiving FUDR infusion 58% responded and of the 18 patients receiving combined systemic and intrahepatic therapy 56% responded. In the three groups, respectively, one, three and seven patient have developed extrahepatic disease [71].

It is still to early to reach definite conclusions about the use of intrahepatic infusional therapy. These randomized studies have to be completed before we can decide whether intrahepatic infusional therapy truly has a place in the treatment of this disease. There are certain points that are obvious even at this time: (1) the development of extrahepatic disease is more common with intrahepatic infusion than with systemic infusion; (2) gastrointestinal toxicity is common with both types of infusion; diarrhea with systemic infusion and gastrointestinal ulceration with intrahepatic infusion (which remains a problem even with correct surgical manipulation and careful follow-up). Hepatic toxicity is a major problem of intrahepatic therapy. Using a dose of 0.3 mg/kg every day for 2 weeks of each month can lead to severe toxicity, if the patient is not monitored very carefully with frequent liver function tests. It may be that in the future, with modulation of doses, i.e. lower doses or shorter intervals of treatment such as one week of therapy, we may see less hepatic toxicity. The ease of delivering chemotherapy via the Infusaid pump makes this a very attractive way of treating patients, and if this method of treatment produces higher response rates, either by intrahepatic or by systemic infusion, it may be an ideal way to treat these patients.

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9. Anal canal and esophageal squamous cell carcinomas: the role of combined modality treatment

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Introduction

Over a decade ago, Nigro *et al.* [1] pioneered the efficacy of simultaneous radiation therapy (RT) and chemotherapy in the treatment of anal canal squamous cell carcinomas at Wayne State University. Using bolus mitomycin C and a 96-h infusion of 5-fluorouracil (5-FU), these investigators have demonstrated that this protocol obviates the need for an abdominoperineal resection in the majority of patients [2–5]. In addition, the simultaneous use of chemotherapy and pelvic irradiation provided greater local disease control than for the same dose of radiation alone.

The success of the Wayne State protocol of combined modality treatment for anal canal carcinoma led our clinicians to extend the use of mitomycin C and 5-FU infusion with simultaneous RT to the treatment of esophageal squamous cell carcinoma [6, 7]. This work has been extended, replacing mitomycin C with cisplatin, based on the latter drug's activity in esophageal carcinoma, *in vitro* radiation enhancement property, and low incidence of myelotoxicity [8].

The results of the esophageal protocols [9, 10] and the anal canal studies resulted in complete erradication of carcinoma in individuals whose disease would not have been controlled by the administered radiation dose alone. These preliminary clinical models serve as the rationale for the use of simultaneous RT therapy and chemotherapy.

The 'biological basis' of combined modality treatment

Most clinical examples of combined modality interactions have taken advantage of 'spatial cooperation' [11, 12]. This concept implies that chemotherapy and RT act on malignancies at different sites to improve tumor control. The use of RT to control disease 'bulk' at the primary site and the

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

implementation of chemotherapy targeted against micro- and macroscopic distant metastases is a familiar clinical example. 'Spatial cooperation' has been designed in the therapeutic management of Wilm's tumor, Ewing's sarcoma, rhabdomyosarcoma, Hodgkin's disease, bronchogenic small cell carcinoma, and breast carcinoma.

In experimental model systems of combined modality treatment, Steel and Peckham [12] developed the concepts of 'additive effects', 'synergestic effect', and 'sensitization'. Sensitization refers to the enhanced effect of a combination when one element of the combination has no clinical antitumor activity when used alone. An example is the hypoxic cell radiosensitizer, misonidazole.

In contrast, additive and synergistic effects refer to the combined use of independently active agents whose dose-response curve is known and approximates linearity [12]. Synergistic effects are 'supra-additive' and exceed the expected results of merely adding therapies together. Since linear dose response curves are unavailable in clinical practice, the term 'enhancement' rather than additive and synergistic should describe clinical situations where an augmented clinical response is observed with combined treatment.

Most clinical prescriptions of combined radiation therapy and chemotherapy have utilized chemotherapeutic agents with known activity against the tumor in a sequential or alternating manner with RT [11, 13]. This clinical design has been constructed to avoid overlapping toxicities; usually myelosuppression or pulmonary toxicity. Although an improved clinical response in using sequential RT and chemotherapy may be noted, little direct interaction between drug and RT is observed. Results of combined sequential therapies are usually additive.

Our protocols of irradiation and chemotherapy have differed from other conventional combined modality studies since RT and chemotherapy are given simultaneously. Compared to bolus administration, continuous infusion 5-fluorouracil alters the drug toxicity allowing greater total drug delivery and minimal myelosuppression [14]. This altered toxicity pattern permits the simultaneous use of irradiation and drug. The results of our anal canal protocol express a direct interaction between the drugs and RT. Results of experimental models have demonstrated greater than a simple additive effect of simultaneous 5-FU, cisplatin, and RT [8, 15–18].

Possible mechanisms of interaction between RT and chemotherapy have been recently reviewed [11]. Mechanisms of interaction include increasing the slope of radiation dose-response curves, inhibition of repair of radiation-induced sublethal damage, and inhibition of recovery from potentially lethal damage of irradiation. Another postulated mechanism is altering the cell cycle by increasing the number of cells in a sensitive phase to induce maximal cell kill. Also, combined modality therapy may decrease tumor size allowing improved blood supply and an increased drug delivery.

5-FU may interact with irradiation by increasing the slope of radiation response curve after drug exposure. Cisplatin may reduce both sublethal radiation damage repair and radiation-induced potentially lethal damage repair. When combined with irradiation, cisplatin may increase the slope of the hypoxic cell radiation dose response curve [11, 19].

As with 5-FU in our clinical protocols, prolonged exposure of the drug may be of importance in combined modality. Work by Byfield *et al.* [15] suggested that 'enhanced cell killing is maximized if cells are continuously exposed to 5-FU for 48 hours following X-ray exposure'. Recent work by Fu *et al.* [11] demonstrated a similar phenomenon for cisplatin. In studies of cisplatin and continuous low dose rate irradiation on the SCC VII/SF tumor, a supra-additive effect was recognized with continuous infusion of cisplatin in contrast to only an additive effect with cisplatin given before or after continuous low dose rate irradiation.

In both our anal canal and esophageal cancer studies, combined chemotherapy-RT have permitted the use of less irradiation than 'standard' to obtain satisfactory local control. Clinically, an enhancement phenomenon has been observed; defining these effects as additive and/or synergistic is difficult since dose response curves do not exist in this clinical setting. The success of 'spatial cooperation' (chemotherapeutic control of micrometastases with RT control of primary disease) of our protocols can be judged by examining our local failure rate, sites of distant failure, and ultimately, our survival rates which will serve as the focus of subsequent discussion.

Anal canal carcinoma

The conventional treatment for squamous cell anal carcinoma had been an abdominoperineal resection (APR) with an extensive perineal phase; 5-year survival rates have ranged from 30–60% [20–23]. APR necessitates a permanent colostomy with a postoperative mortality estimated at 5%. Frequent urinary and sexual dysfunction are long-term sequelae. Local recurrence after an APR is recognized to be greater than that of rectal adenocarcinoma due to extensive vascular and lymphatic supply of the region and difficulty in excising large areas of margins around the primary site.

Primary radiotherapy for the treatment for this disease consists either of external RT [24–28], interstitial therapy alone [29, 30] or a combination of the two techniques [31–35]. Although external RT is effective in controlling local disease, especially lesions less than 4 cm, complications of radiation necrosis may be seen in as high as 15% of patients requiring operative intervention. Most external RT studies have employed doses between 6000–7000 total cGy dose with 5-year disease-free survivals of 30–70%. This wide variation in survival reflects the differing sizes of the lesions studied.

Interstitial therapy alone can produce severe necrosis ranging from 5–20%; this technique should be performed on selected small carcinomas. In an effort to increase local control, the combined use of external RT and interstitial implants have been used. In the largest series of 97 patients, Papillion *et al.* [30] noted that over 80% of patients had local control with a 67% disease-free 5-year survival. Only 7% had complications requiring surgery. Puthawala and associates [35] noted a 70% complete response (CR) rate using 4000–5000 cGy of external RT and a boost of 3000–4000 cGy delivered by interstitial ^{192}Ir implants. Complications included hemorrhage (5%), necrosis (15%), infection (2.5%), and rectovaginal fistula (2.5%).

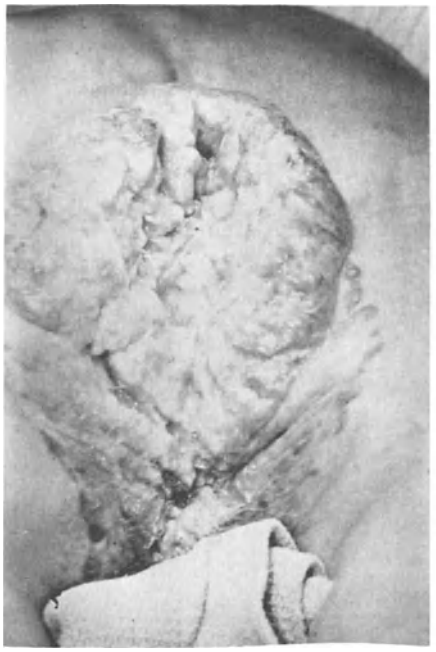
It is somewhat difficult to review the results of RT, surgery, and combined modality studies of anal canal carcinomas. First, some studies combine anal margin cancers with true anal canal cancers, the former tumor carries a more favorable prognosis regardless of therapy. Secondly, varying sizes and stages are included in the various series. Unlike colorectal carcinomas, anal canal carcinomas are difficult to stage on the basis of penetration into the bowel wall. The anal canal lacks clearly defined separated components of its wall. A 'TNM' staging system exists with T defined in terms of external sphincter involvement and extension into adjacent structures. Tumor size is not specified in this system. Yet, most investigators group their patient population based on tumor size, usually separating patients with tumors greater than or less than 4 cm.

Combined modality treatment

Since Wayne State University's introduction of combined chemotherapy and RT in the management of squamous cell carcinomas, several other investigators [36–41] have implemented studies using mitomycin C, continuous infusion 5-FU, and RT in the treatment of this neoplasm. Our proto-

Table 1. Therapy for anal canal tumors Wayne State University

External RT
3000 cGy to primary tumor, pelvic, and inguinal nodes days 1–21 at 200 cGy/day
Chemotherapy
5-FU 1000 mg/m^2/24 h as a continuous infusion for 4 days
Sart on day 1
Mitomycin C: 15 mg/m^2 IV bolus day 1
5-FU: repeated days 28–31
Deep biopsy under Anesthesia of the scar in the anal canal
Negative biopsy: no APR
Positive biopsy: APR



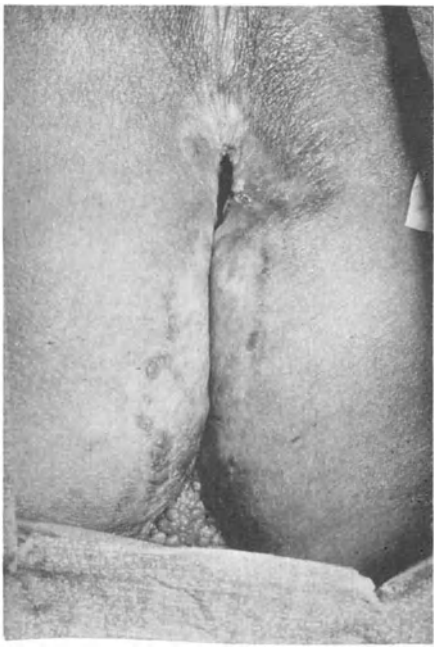


Figure 1. Extensive squamous cell carcinoma of the anal canal pre-treatment.
Figure 2. Post-treatment of carcinoma depicted in Figure 1. Results of combined treatment of 5-Fluorouracil, Mitomycin C, and radiation therapy (3000 cGy).

col is provided in Table 1; Figures 1 and 2 demonstrate a clinical response which has been achieved with this regimen.

The results of the Wayne State study have been recently updated [5] and disclosed that 84% of patients [38, 45] were rendered free of cancer by the described treatment regimen. In the protocol's original design, APR was indicated after the completion of chemotherapy and radiation; however, five of the six initial patients treated had no evidence of tumor in the operative APR specimen. Therefore, APR was deemed necessary only for those patients with carcinoma on the deep biopsy specimen post-chemotherapy-RT. Eighty-four percent of the patients had no disease in the biopsy specimen and 89% of these patients are disease-free with a median of 50 months follow-up. The four deaths occurring in this group were not related to carcinoma.

Fifteen percent of our patients (seven patients) had either macroscopic or microscopic disease on deep biopsy specimens and all developed distant metastatic disease (two patients had both local recurrence and distant metastases). Sites of distant metastatic disease were bone, liver, lung, and pericardium. Tumor size influenced response to the chemotherapy-RT regimen and, ultimately, survival. The median size of carcinomas was 5 cm in

patients whose post-therapy biopsies disclosed residual carcinomas; in patients who had no evidence of tumor in the biopsy specimens the median size was 3.5 cm. The prognosis of patients was dictated by the results of the post-therapy biopsy. This data *may* suggest that negative biopsy specimens are *in vivo* predictors of eradication of systemic microscopic disease.

Toxicities were usually mild and included myelosuppression, stomatitis, and diarrhea. 5-FU infusions were terminated early in the event of stomatitis (or oral mucosal erythema) during the infusion. In a group of 122 patients treated at multi-institutions using a similar protocol (specifics of RT differed), Nigro [42] commented on increased toxicity. The information on these patients was collected by questionnaire and the increased toxicity appeared to be related in part to a higher dose of radiation (4500–5000 cGy) employed. Toxicity in this group included re-hospitalization for gastrointestinal symptoms, APR for necrosis of the rectum, colostomy for severe rectal stricture, sigmoid resection secondary to perforation, and massive internal hemorrhage. Little is to be gained by exceeding the 3000 cGy dose of pelvic RT and potentially local complications escalate rapidly with higher RT doses.

In this questionnaire study, 113/122 patients had no gross tumor. APR was performed in 40/122 with no tumor in 27, microscopic disease in four, gross disease in nine. In another 40 patients whose primary lesions grossly disappeared but underwent wide local excision, 36 had no tumor in the resected specimen and four had microscopic disease.

In contrast to the Wayne State study of simultaneous chemotherapy and RT, investigators at Memorial Sloan-Kettering [37] employed sequential radiation starting 1–3 days after completion of chemotherapy. Mitomycin C and 5-FU infusion were initiated on day 1. RT consisted of parallel opposing pelvic fields anteriorly and posteriorly at 200 cGy/day for 15 fractions. Two to four weeks later a local excision or APR was performed depending on the discretion of the individual surgeon.

In the Memorial Sloan-Kettering study, 37 patients were entered on the study, 30 had newly diagnosed disease and seven had been previously treated. Thirty-one patients had measurable disease; of these, 52% had complete clinical response and 43% had a clinical partial response. Complete pathological response was documented in 53% of patients. Median follow-up in this study was 28 months with seven patients having recurrent disease. Of these seven, three occurred following APR with all of these patients demonstrating positive pathological biopsies following pre-operative treatment. Four of these seven patients had recurrence following local excision despite no pathological evidence of disease in initial post-chemo-RT specimen. Of patients with known tumor size, 26 had lesions greater than 2 cm with five of these having recurrences; nine patients had tumor size less than 2 cm with two patients of this group having recurrence.

Reports from Princess Margaret Hospital [40] commented on the results of a non-randomized study treating patients with radical external beam RT alone versus combined modality treatment of 5-FU, mitomycin, and RT. Radical RT consisted of multiple field external RT to a tumor dose of 4500 to 6000 cGy in 4–6 weeks. The combined modality used a 5000 cGy tumor dose in 4 weeks in 250 cGy fractions with 5-FU and mitomycin C initiated on day 1 of therapy. The final 2500 cGy dose was delivered to a reduced field encompassing only the anal region. Because of the intestinal toxicity, RT was altered allowing a 4-week rest interval between large-volume and reduced volume treatment. Chemotherapy was again begun with initiation of RT. Surgical resection was reserved for patients with residual disease; however, no post-therapy biopsies were performed. Tumor size of the RT alone group was not specified in 10/15 patients. In the combined modality treatment 15 patients had tumors less than 5 cm; 11 had tumor size between 5–10 cm and four patients had tumors greater than 10 cm. Primary tumor control was achieved in 93% of patients with combined modality arm in contrast to 60% treated with RT alone. Serious late toxicity requiring surgical intervention occurred in 3/25 patients in the RT alone group, 5/30 patients following combined modality treatment. Colostomies were required for residual carcinoma or management of toxicity in 11 patients treated by RT alone and four patients in the combined modality.

The superiority of combined modality treatment in controlling local disease versus RT alone was further substantiated by work by French investigators [33, 43]. Patients with anal tumors greater than 4 cm were treated with radiation therapy alone (external RT and Iridium-192 implants) versus chemotherapy plus the identical RT regimen. As delineated in Table 2, the combined modality treatment had a significantly lower rate of local recurrence.

Implementing higher doses of radiation therapy than the Wayne State study, Sischy *et al.* [38, 44] noted complete tumor regression in 23/27 patients (85%) with a 5-year adjusted survival of 77%. However, unlike the

Table 2. Anal canal tumors: effectiveness of Chemotherapy as adjuvant to radiotherapy for tumors > 4 cm: 5-FU (600 mg/m^2/24 h, days 1–4) Mitomycin C (10 mg/m^2, day 1)

	No. of cases	Rate of local failures
1st group		
Radiotherapy alone	77	31%
2nd group		
Chemotherapy associated with RT	70	13% p = 0.01

Presently all patients receive RT and chemotherapy.
(Courtesy of Dr. Jean Papillion, Lyon, France, June 1985).

Wayne State study, complete tumor response was clinical and not based on a deep pathological biopsy specimen. None of the patients who had a complete response had a recurrence with a median follow-up period of 2 years. Although chemotherapy was identical to the Wayne State study, RT was given to a total anal dose of 5500–6000 cGy. In addition, if residual nodularity was encountered on digital examination, an implant was administered delivering an additional 1000–1600 cGy.

The above studies differed in RT technique and dose, size of lesions, and the use of pathological determination of complete response, however, several features emerge. First, APR is unnecessary in squamous cell anal cell carcinomas when the tumor is completely eradicated by the chemotherapy and RT. Contrasting simultaneous RT and chemotherapy to their sequential use, simultaneous use *may* achieve a greater degree of local control (84% complete pathological response in the Wayne State study versus 53% in the Memorial Sloan-Kettering study). The local effect of combined modality treatment exceeds the expected additive effect of the modalities.

In addition, exceeding 3000 cGy pelvic RT dose is of little therapeutic gain. The Wayne State study demonstrated 84% of patients had a *pathologically* confirmed complete response with 89% of these patients disease-free at 50 months. This data compares favorably with results employing larger RT doses (5500–6000 cGy) providing an 85% *clinical* complete response rate with a median follow-up of 24 months [44]. Although toxicity in exceeding 3000 cGy has been 'acceptable' in reported studies [37–39, 44], this 'acceptable toxicity' may reflect the expertise of individual radiation oncologists and may not be evidenced in all institutions as suggested by Nigro's review of over 120 patients treated in multiple institutions with the combined modality approach [42].

Esophageal squamous cell carcinoma

Like anal canal tumors, the success of treating esophageal carcinoma depends on controlling both local tumor and distant metastases. The survival statistics for esophageal carcinoma are far more dismal than those for anal canal carcinoma with less than 10% of patients alive 5 years from diagnosis [45, 46]. Most symptomatic patients probably have metastatic disease at diagnosis. Review of autopsy records indicates that over 85% of patients have metastatic disease at post-mortem predominantly with liver, lung, and nodal involvement. The median interval between diagnosis and death was only 4 months suggesting the advanced nature of this tumor at presentation [47].

The virulence of this tumor may reflect the special anatomic features of the esophagus. The esophagus is distensible allowing significant tumor

growth before the onset of symptoms. In addition, the absence of a fibrous stroma and an abundant lymphatic supply permits early tumor dissemination.

Results of treatment of esophageal carcinoma with RT or surgery have been recently reviewed [45, 46, 48, 49]. Patient selection influences the results of any series; however, cumulative reviews suggest little difference on survival between the two modalities. RT alone has never been directly compared to surgery for minimal lesions.

Because of poor results of primary treatment with RT or surgery, investigators have attempted to combine these modalities. The most commonly employed technique is the use of pre-operative RT with 5-year survivals ranging from 2–11.5% [50]. Launois and co-workers [51] presented the results of 124 patients treated in a randomized study of pre-operative RT and surgery versus surgery alone. The RT regimen was unconventional administering 4000 cGy in 8–12 days. The 5-year survival rate was similar between the two arms (11.5% for the surgery alone arm and 9.5% for combined RT-surgery). The resection rates were also similar, (67% versus 70% for the RT-surgery and surgery arms, respectively) with no apparent differences in operative mortality. The median survival was only 4.5 months for the pre-operative RT group and 8.2 months for the surgery alone patients.

Most other studies of pre-operative RT have not been randomized. One of the largest series, which included 332 patients was reported by Marks and associates [52]. These investigators used 4500 cGy in 18 fractions with surgery 1–2 months after completion of RT. Only 41% (137 patients) actually underwent surgery; the remaining patients were inoperable at pre-operative evaluation based on disseminated disease or local extension. At the time of surgery, only 101/332 patients had resectable disease.

The average survival of patients with resectable disease was 25 months and only 8 months for inoperable patients. A Stanford study [53] using 5000–6000 cGy over 7 weeks noted substantial toxicity of combined modality treatment. An operative mortality of 28% was reported; 3/21 patients who survived surgery died of radiation pericarditis or myocarditis, reflecting an overall treatment-related mortality of 31%. Only 4.7% of patients were alive at 5 years.

The benefit of pre-operative RT remains unclear. One randomized study [51] did not confer any advantage and preliminary results from a randomized European Organization for Research on Treatment of Cancer (EORTC) study [54] have not shown a difference between combined RT-surgery, and surgery arms. In addition, the treatment mortality of pre-operative RT-surgery studies are cited at approximately 20% or higher [51, 52, 55–57]. Similarly, the post-operative use of RT in patients who have undergone esophagectomy remains to be clarified. A randomized study addressing

the value of RT in the post-operative setting does not exist. Using 6000 cGy post-operatively over a 6-week period, Kasia *et al.* [58] treated patients with and without lymph node mestasases. Survival was improved only in the group without lymph node metastases; local relapse rate was 14% in patients receiving RT after a curative resection.

Chemotherapy + RT → surgery

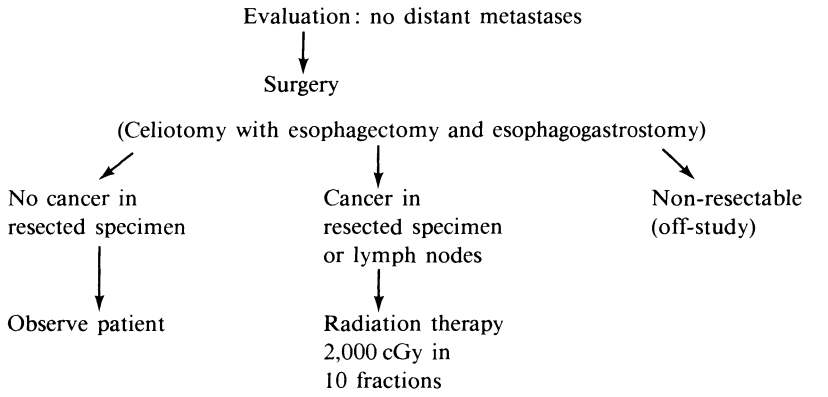
Since many of esophageal carcinoma patients have early dissemination of disease, systemic chemotherapy should theoretically be introduced early in the therapeutic prescription for this disease. Encouraged by our early success in the treatment of squamous cell carcinomas with mitomycin C, continuous infusion 5-FU, and simultaneous RT, this treatment was extended to squamous cell carcinomas. Although mitomycin's efficacy was unknown in esophageal carcinoma, 5-FU had shown single agent activity [60]. The protocol regimen is delineated in Table 3 [7, 9, 10].

Beginning in 1977, 30 patients were entered on the mitomycin C, 5-FU, and RT protocol. Of these 30 patients, 23 underwent surgery. Six patients had no evidence of tumor in the resected specimen, three had microscopic

Table 3. Wayne State University combined modality treatment: esophageal protocols

Protocol 1

- Mitomycin C 10 mg/m^2 IV bolus day 1 *only*
- 5-FU 1000 mg/m^2 IV continuous infusion days 1–4 and repeated days 29–32
- Radiation therapy, 3000 cGy, delivered in 15 fractions starting day 1 and completing day 19



Protocol 2

As above, however, mitomycin C is eliminated and replaced by cisplatin 100 mg/m^2 IV days 1 *and* 29

disease confined within the esophagus, nine had microscopic disease beyond the esophagus, and five had residual gross tumor post-operatively.

No patient with microscopic disease is alive. Four of six patients who demonstrated no tumor in the resected specimen are disease-free at 5 years. The operative mortality was 30% in this series.

Because of the activity of cisplatin in esophageal carcinoma [61] and its *in vitro* radiation enhancement property [8, 17, 19], the protocol was altered substituting cisplatin for mitomycin as shown in Table 3. Since 1979, 21 patients were entered on this pilot study. Of these patients, 15 were resected for cure with five of them (33%) having no evidence of carcinoma in the histologic examination of the resected esophagus. Four patients were unresectable at the time of thoractomy. As in the previous study, the operative mortality approximated 30% [9, 10].

Based on the above pilot data, the Southwest Oncology Group (SWOG) and the Radiation Therapy Oncology Group (RTOG) instituted group-wide studies, identical to our pilot study with the dose of cisplatin modified to 75 mg/m^2 (from 100 mg/m^2) intravenously, day 1 and 29. The SWOG data has recently been updated with 128 patients entered on the study; 76 patients are evaluable for response. Of these 76 patients, 18 had a complete response to the pre-operative regimen with no demonstrated tumor on histological sectioning of the esophogectomy specimens. Forty-three percent of patients had stable disease while 14% showed increasing disease [62].

Of interest is the toxicity data of the group experience. First, our 30% operative mortality rate reported in the pilot study was not observed in the group experience; the post-operative mortality rate was only 12%. Secondly, the SWOG toxicity data corroborated our pilot study showing only mild toxicity. In the SWOG toxicity data (76 patients), the most consistent toxicities were nausea and vomiting, as expected, from cisplatin. Severe toxicity manifested as leukopenia (granulocytes less than 500) was observed in only four patients; mucositis (unable to eat because of oral ulcers), three patients; pancytopenia, one patient.

For patients in the Wayne State pilot study who underwent curative resections and were treated with our cisplatin combination, the median survival was 24 months; in contrast, individuals in our earlier mitomycin C protocol resected for cure had a median survival of 12 months. Patients who had microscopic tumor in their resected specimens or nodes were destined to relapse in both pilot protocols. However, patients rendered disease-free by the pre-operative regimens possessed a favorable prognosis. Consistently, approximately 20% or greater of patients treated in either of our two pilot studies or in the cooperative group studies had complete pathological eradiation of their malignancy by our pre-operative treatment regimens. In our first pilot study, four of the five patients who survived greater than 5 years, belonged to the histologically negative tumor group. Similarly, in our cis-

platin pilot study, the four patients who are disease-free also belonged to this group.

The impact of pathologically tumor-free esophagectomy specimens on long-term survival needs clarification. In the SWOG study, 7/18 patients labeled as complete pathological responses in the esophagectomy specimens have died with the median survival of 25+ months; 3/7 deaths were tumor-related. In addition, Parker and colleagues [63], using a protocol similar to our first mitomycin study (days 29–32 of 5-FU were omitted), believed that the absence of residual carcinoma in the resected specimen did *not* confer improved long-term survival status.

The percentage of surgical specimens showing residual carcinoma was 65% (20/31 patients) in Parker's study, which was an improvement from an earlier pre-operative RT study using 4500 rads in 3 weeks (no chemotherapy), which demonstrated 87% of patients had residual carcinoma [64]. Unfortunately, patients who had no carcinoma in the resected specimen, developed distant metastases. Their disease-free status rendered by chemotherapy-RT was not a predictor for long-term survival. The 2-year survival for patients finishing the pre-operative chemotherapy, radiation, and surgery, was 33% (7/21 patients). Table 4 provides survivorship status with results of the pathological evaluation of surgical esophagectomy specimens.

Chemotherapy → surgery

Another treatment strategy is the use of chemotherapy alone followed by surgery. Early Japanese studies [65, 66] in the 1970s used bleomycin prior to surgery with demonstrable tumor shrinkage.

Table 4. Pathological analysis of resected esophageal specimens from Parker *et al.* [63]

	Positive specimen	Negative specimen
3-year survivors	1	1
2-year survivors	1	1
1-year survivors	2	1

Positive resections / total resections	
1980	5/8
1981	5/8
1982	6/9
1983–84	4/6
Total	20/31 (64%)

Treating 43 patients with loco-regional disease with a combination of cisplatin and bleomycin, investigators at Memorial Sloan-Kettering [67] noted a 14% response rate to this regimen. After one course of chemotherapy, surgery was performed followed by another course of chemotherapy. RT was administered to patients with regionally positive nodes or with disease

Table 5. Esophageal carcinoma: preoperative chemotherapy

Investigator	Drug(s)	No. of patients	Response	Comments
El-Akkad [69]	Cisplatin Vincristine Bleomycin 5-FU	10	50%	No increase in operative mortality Survival data lacking
Kukla, Lad [70]	Cisplatin Mitomycin Prednisone Bleomycin	15		High operative mortality of 45%
Forestiere [71]	Cisplatin Bleomycin VP-16	16	2 PR	
Kelsen [72]	Cisplatin Vindesine MGBG	5	3PR	
Carey [73]	Cisplatin 5-FU (by continuous infusion)	20	40% clinical CR and 20% clinical PR (1/20 pathological CR)	Similar to the Wayne State pilot *without* simultaneous RT
Gennis [74]	Cisplatin MGBG Vinblastine	7 pts. with squamous cell ca. 15 pts. adeno ca.	9 PR 1 CR	65% response rate for squamous cell cancer (included metastatic and recurrent tumors in this response rate)
Advanti [75]	Methotrexate	44	48%	Pt. underwent surgery or chemotherapy (37 pts. were radiated)
Desai [76]	Methotrexate Cisplatin	88	75%	As above; 4/9 pts. who underwent surgery, had pathological CR at surgery 3 years: 10/60 disease-free

found to be penetrating into paraesophageal tissue at surgery. The median survival for patients treated with this regimen was 10 months, which did not differ from a historical control group treated at that institution with pre-operative RT.

After recognizing the activity of vindesine in the esophageal carcinoma, Kelsen and associates [50, 68] designed a study giving two courses of DVB (cisplatin, vindesine, bleomycin) prior to surgery. Patients with N_2 or T_3 disease were given post-operative RT of 5500 cGy over 5–6 weeks. Pre-operative chemotherapy demonstrated down-staging of the primary tumor in 10/34 treated patients. No residual tumor was noted in three surgical esophagectomy specimens. Twenty-eight of 34 patients had resectable tumor; 32% of these are alive with a median follow of 36 months [50].

Table 5 summarizes selected studies using chemotherapy prior to surgery. The study from Massachusetts General Hospital [73] is similar to the Wayne State pilot study using continuous 5-FU and cisplatin. However, simultaneous RT is not give preoperatively. This study provides direct evidence for the activity of our chemotherapy without RT. Complete radiologic and gross clinical disappearance of tumor post chemotherapy was seen at surgical resection in 8/20 (40%) patients and an additional 40% had a partial response (greater than 50% reduction in the tumor mass). Only one patient had a complete pathological complete response. Selected patients received post-operative chemotherapy for four additional courses with radiation therapy. Seventy-five percent of the patients are alive with a median duration of follow-up of 9.5 months.

Chemotherapy → radiation (no surgery)

Table 6 provides selected studies of radiation therapy and chemotherapy without surgical esophagectomy. Radiation therapy can provide relief of dysphagia as evidenced by the study of Coia *et al.* [78] using 5-FU and mitomycin schedule identical to the Wayne State regimen previously cited in Table 1. However, RT was given at 200 cGy daily to total dose of 6000 cGy over a 6–7 week period. If the patient was deemed 'palliative' (not curable) a lower dose of RT was administered (5000 cGy). Excellent palliation was achieved in both groups of patients. Of the 13 patients, 11 are evaluable (two deaths from early cardiovascular disease) and all had improvement in swallowing. Of the four patients who have relapsed, only one patient had an in-field relapse; three had loco-regional failures outside of ports. All patients with local failure also had distant metastases discovered.

What is the role of surgery in esophageal carcinoma? Esophagectomy palliates the majority of patients with esophageal carcinoma, but carries a high

Table 6. Esophageal carcinoma: chemotherapy and RT (no surgery)

Investigator	RT + drugs	No. of patients	Response	Comments
Resbeut [77]	Vincristine Methotrexate Folinic acid Cisplatin 2 cycles of chemotx, then RT started	28	For chemo only: 6% CR, 7% PR Post RT: 32% CR, 43% PR	Median duration of response 8 mo., median survival, 11.6 mo.
Coia [78]	5-FU Mitomycin plus RT: - 6000 rads for stage I and II pts. (curative) - 5000 rads stage III	11 6	10/11 clinical CR	Relief of dysphagia in 16/17 pts. 10/11 treated definitively alive from 4–32 months
Earle ECOG [79]	Randomized: 5000–6000 rads over 5–6 wks. vs RT + Bleo.			No difference in survival Median survival 6.4 vs 6.2 months
Marcial [80]	Methotrexate Bleomycin 5-FU, Vincristine prior to 5000 rads	26	55% tumor shrinkage after chemo; after RT 66% clinical CR	Median survival 11 months
Kolaric [81]	Bleomycin Adriamycin	15		27% survival at 1 yr.

operative mortality approximating 30% in some series. If patients who have negative histologic esophagectomy specimens are the only patients destined to be long-term survivors, then removal of a 'normal' esophagus is clearly unwarranted. As discussed above, the answer to the correlation between long-term survival and histologically negative esophagectomy specimens is conflicting. Maturation of the SWOG and RTOG studies do not appear to support the initial impression of this correlation. In addition, several earlier RT studies [49, 50, 64] have shown RT alone can eradicate carcinoma in esophagectomy specimens. Therefore, the expection of the histologically negative esophagectomy specimen to be an *in vivo* predicator of long-term survivorship and potential systemic efficacy of chemotherapy may not be realized.

Future directions

Combined modality treatment using surgery, RT, and chemotherapy, have many variables which can influence response. As discussed by Fu [11], factors which may influence the combined effects of chemotherapeutic drugs and RT include (1) tumor and normal tissue type, (2) drug type, (3) drug dosing and schedule, (4) time sequence between drug and radiation administration, (5) radiation dose and fractionation schedule, and (6) radiation dose rate.

Identification of new agents effective against esophageal and anal canal carcinomas continues to be the focus of phase II studies. Cisplatin has identified activity in anal canal cancer [82] and its substitution for mitomycin in the anal canal studies with continuous infusion 5-FU and RT may be the next evolution in the study. Cisplatin analogues require investigation in phase II setting. 5-FU is administered as a 'low dose' continuous infusion at 200 mg/m^2/day for 26 consecutive days with cisplatin administered days 1–5. RT is given throughout the 5-FU infusion. This continuous 26 day regimen of 5-FU and RT exploits the 'simultaneous' nature of combined modality treatment which was initiated by our 4-day infusion of this drug over a decade ago.

Anal canal and esophageal carcinomas are clearly different neoplasms with different patterns of dissemination and natural histories. However, since both are squamous cell carcinomas with sensitivity to RT and similar chemotherapeutic agents, a combined modality strategy has emerged. Both local control and eradication of systemic micrometastases must be accomplished. This treatment philosophy has involved systemic chemotherapy with RT for local control. Although the majority of patients can be spared an APR for anal canal cancer with our 5-FU-mitomycin-RT regimen, the role of definitive surgery in esophageal cancer is unanswered. The work in the next decade of combined modality treatment will focus on the six variables listed above, identifying new agents, and their delivery sequence in relationship to differing radiation dose schedules.

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10. Adjuvant therapy of gastrointestinal cancer

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Introduction

Cancer will continue to be second to heart disease as cause of death in the United States in 1986 [1]. Twenty-two percent of all deaths will result from neoplastic disease. The major adenocarcinomas of the gastrointestinal tract, stomach, pancreatic and colorectal carcinoma, will afflict 190,000 Americans in 1986 and these diseases represent 88% of all gastrointestinal cancer. Of more importance than incidence rates, is the fact that upper abdominal and colorectal adenocarcinoma will result in 90,100 deaths this year. The deaths from these cancers will represent 20% of all cancer deaths [1].

The standard treatment of adenocarcinoma of the gastrointestinal tract is surgical resection of the primary tumor. However, this approach is at best partially effective and at worst woefully inadequate therapy. For example, deaths from cancer [1] occurs in 58% of patients with gastric cancer, 95% of those with pancreatic cancer and 37% of those with colorectal cancer. The reason that patients who have had 'curative' resections of gastrointestinal cancer die of metastatic disease is that microscopic dissemination of cancer has occurred before surgical resection. Strategies aimed at treating microscopic residual or metastatic disease include adjuvant chemotherapy, radiation therapy, and the adjunctive use of biological response modifiers. Approaches using adjuvant chemotherapy have been explored in patients with breast cancer. Successful adjuvant treatment after mastectomy in patients with high risk (lymph node positive) breast cancer has been described [2]. This chapter will describe the natural history and prognoses of adenocarcinomas of the gastrointestinal tract and the strategies and results of adjuvant therapy in stomach, pancreatic, and colorectal carcinomas.

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

Gastric carcinoma

The only treatment which currently results in a significant cure rate in gastric cancer patients is well-planned, aggressive surgical resection. In patients with resectable localized disease as many as 30–50% can be cured with carefully planned and executed radical subtotal or total gastrectomy [3]. However, only one-half to two-thirds of patients with gastric cancer have grossly localized disease at the time of diagnosis [3]. Thus, only a minority of gastric cancer patients can be cured with the best application of current therapy.

Obviously one of the major problems in successful treatment of stomach cancer is that surgical resection, even with clear margins, does not remove all tumor. Disease relapse, in particular, local-regional relapse, is an all-too-common occurrence following subtotal gastrectomy with curative intent. As early as 1951 McNeer *et al.* reported that 74/92 (80%) of patients undergoing autopsy after gastric cancer surgery had evidence of local-regional recurrence [4]. In the University of Minnesota reoperation series Gunderson and Sosin reported that after curative resection, 86 of 107 (80%) evaluable patients had recurrent cancer [5]. Of the patients with recurrent tumor, 72/86 (84%) had evidence of local recurrence and, of these, 44 (51% including 20 with localized peritoneal spread) had local-regional recurrence as their only site of disease relapse.

More effective control of local-regional as well as distant microscopic residual disease following surgery would clearly improve the prognosis for the majority of patients with gastric cancer. Attempts to prevent relapse after gastric resection have led to efforts to develop effective surgical adjuvant therapies. In general, treatment regimens which are evaluated as adjuvant therapy for cancer are derived from protocols which have demonstrated anti-tumor activity in patients with advanced disease. In gastric cancer several chemotherapeutic agents, especially when used in combination, as well as radiation therapy, have provided successful palliative therapy for some patients with advanced disease [6–11]. Appropriately, these treatment modalities have been and continue to be studied in adjuvant protocols based on the hypothesis that the cure rate of gastric cancer is most likely to increase by applying agents with demonstrated therapeutic efficacy in the treatment of patients with the least tumor burden, namely, those with occult, local and/or disseminated micrometastatic disease.

Although this approach appears to be logical and simple to apply, the design of adjuvant therapy protocols is problematic because of several prognostic variables which may bias the interpretation of treatment results. The Veterans Administration Surgical Oncology Group reviewed 503 patients who underwent gastrectomy for stomach cancer and identified five major variables affecting survival [12]. These included preoperative performance

status, the presence of locally advanced disease, the tumor size and position in the stomach, and the pathologic characteristics of the tumor. Thus, patients with significant weight loss and anorexia were more likely to die of recurrent cancer. Similarly, curative results were achieved in less than 20% of patients whose tumors involved serosa, blood vessels, lymphatics, or regional nodes. Also, only half as many patients survived 5 years when the tumor was either greater than 3 cm in diameter or located proximally and requiring total gastrectomy. Furthermore, patients whose tumors showed a histologic pattern of linitus plastica had only a 2% 5-year survival compared to a 28% 5-year survival for those with other histologies.

Because imbalances of these important prognostic factors in patients in gastric adjuvant therapy studies could bias outcome, reliable information about the efficacy of specific treatment regimens can only be obtained from prospective randomized protocols. With such protocol design there is the greatest probability that prognostic variables will be balanced between treatment and control groups.

Table 1 summarizes prospective randomized studies [13–19] which have been designed using one-, two- or three-drug chemotherapy compared to a

Table 1. Gastric cancer – prospective randomized adjuvant trials with controls treated by surgery alone

Treatment	(Study group)	Patients randomized	Survival benefit	Reference
Single agents				
Thiotepa	(VASOG)	194	NS	13
Fluorodeoxyuridine	(VASOG)	276	NS	14
Mitomycin; Thiotepa	(SCSG-J)	209	NS	15
Mitomycin	(SCSG-J)	472	NS	15
Two-drug combination				
5-FU + Mitomycin	(SCSG-J)	460	NS	15
5-FU + Methyl-CCNU	(VASOG)	134	NS	16
5-FU + Methyl-CCNU	(ECOG)	160	NS	17
5-FU + Methyl-CCNU	(GITSG)	142	$P < 0.03$	18
5-FU + Doxorubicin	(NCCTG)		ongoing	—
Three-drug combination				
FAM	(SWOG)	148	ongoing	19
FAM	(MAOP)	295	ongoing	—
FAM-RT-FAM	(ECOG)		ongoing	—

5-FU = 5-Fluorouracil; FAM = 5-FU + Doxorubicin + Mitomycin; RT = radiation therapy; VASOG = Veterans Administration Surgical Oncology Group; SCCG-J = Stomach Cancer Study Group-Japan; ECOG = Eastern Cooperative Oncology Group; GITSG = Gastrointestinal Tumor Study Group; NCCTG = North Central Cancer Treatment Group; SWOG = Southwest Oncology Group; MAOP = Middle Atlantic Oncology Program.

surgery only control arm. The data show that in the adjuvant setting single agents, which have demonstrated activity against metastatic disease, do not improve survival of gastric cancer patients more than treatment with surgery alone. Studies of two-drug combination therapies have usually involved the combination of fluorouracil with another active agent. It is disappointing that, in general, these studies also have failed to show a benefit in patient survival although one study by the Gastrointestinal Tumor Study Group (GITSG) did demonstrate some benefit in the chemotherapy arm [18]. It is possible that the GITSG study showed an advantage for chemotherapy because, compared to other studies, there was a higher proportion of patients on this trial with favorable prognostic factors such as distal lesions. Thus, chemotherapy would be tested in a somewhat better risk group of patients, and a partially effective therapy might therefore improve the survival of patients who have an intrinsically less aggressive tumor.

Another adjuvant approach to the treatment of gastric cancer has been underway for several years in Japan where patients were studied in a prospective but non-randomized trial and received either surgery alone or intraoperative radiation in addition to surgery [20]. Although no advantage to radiation was seen in patients with stage I disease, the 5-year survival of irradiated patients with stage II, III, and localized stage IV disease was 78%, 45%, and 20% respectively, compared to 55%, 37%, and 0% respectively in patients treated with surgery only. Thus intraoperative radiation seemed to benefit some patients at high risk for local-regional treatment failure. It is important to emphasize that these data are from a non-randomized study and the true value of intraoperative therapy will only be learned when larger prospectively randomized studies can be performed. Such a study will only be possible when multiple centers have developed the capability to perform intraoperative irradiation.

Combined modality approaches may have a significant role to play in the adjuvant therapy of gastric cancer. A study performed by the GITSG [7] in patients with locally residual or recurrent gastric cancer demonstrated the efficacy of combinations of chemotherapy and irradiation. In this study patients with locally residual or recurrent gastric carcinoma were randomly allocated to receive either 5-FU + methyl-CCNU or 5000 rads split course irradiation to the gastric bed followed by 5-FU + methyl-CCNU. The results after 5 years of follow-up demonstrate that 25% of patients receiving combined modality therapy for small amounts of recurrent or residual cancer in the gastric bed are alive and free of disease. This apparently curative combined modality approach could be adapted to the adjuvant situation.

To effectively study surgical adjuvant therapy of gastric cancer in an expeditious manner requires large numbers of patients. These patient numbers can best be achieved by inter-institutional cooperative studies. The designs of current cooperative studies are based on positive and negative

results from earlier trials in both early and advanced disease. Protocols testing a combination of three drugs against surgery alone are now underway in the Middle Atlantic Oncology Program (MAOP) and the Southwest Oncology Group (SWOG) (Table 1). These trials are testing the efficacy of fluorouracil, doxorubicin (Adriamycin), and Mitomycin-C (FAM), a combination which has demonstrated approximately 35% objective response in at least five studies in advanced disease [8–11]. Another protocol in progress in the Eastern Cooperative Oncology Group (ECOG) further addresses the problem of local regional recurrence by incorporating radiation to the tumor bed after the first cycle of FAM chemotherapy. These studies are important because they evaluate in patients with minimal disease some of the most effective combination therapies for patients with advanced disease. The completion of accrual and analysis of these patients is awaited with great interest.

In summary, gastric cancer is a disease for which surgery remains the only proven initial therapy. Only one prospective, randomized trial to date has demonstrated any advantage for use of another modality of treatment after surgical resection when there is no detectable residual disease remaining. In patients with residual or recurrent cancer, combined radiation plus chemotherapy may cure some patients [7]. One could make the argument that the standard adjuvant therapy today *is* participation in ongoing clinical trials. Uncontrolled use of adjuvant therapy is hardly appropriate until benefit for such treatments are proven. It should be clear that the potential toxicity of 'routine' adjuvant treatment in addition to surgery is not justified until proof of benefit is available.

Pancreatic carcinoma

Adenocarcinoma of the pancreas represents a very significant problem in cancer medicine since this disease is increasing in incidence and is highly lethal [21]. Less than 5% of all patients survive 2 years and only 1% of cases survive 5 years. Obviously since this disease is so highly lethal, it is clear that treatment strategies are currently inadequate.

Although irradiation and chemotherapy may be palliative for patients with adenocarcinoma of the pancreas [21], these strategies are not curative and have little, if any, significant impact on survival. The only known curative therapy for pancreatic cancer is resection. The two procedures that are commonly used are either total pancreaticoduodenal resection or the Whipple procedure in which pancreaticoduodenal resection is performed for carcinoma of the head of the pancreas. However, rather than totally resecting the pancreas, the pancreatic tail is preserved and anastomased to the small bowel utilizing a pancreaticojejunostomy. Although pancreatic resection

may result in disease-free survival in as many as 45% of patients with carcinoma of the ampulla of vater [22, 23], pancreaticoduodenectomy is rarely curative in carcinomas of the head, body or tail of the pancreas. There are several reasons for the ineffectiveness of surgery. These include the poor resectability rate of patients with pancreatic cancer, the high operative mortality associated with these procedures and an unacceptably high rate of cancer relapse after surgery [21, 24].

Patients with adenocarcinoma of the pancreas are commonly poor candidates for resection for a variety of reasons. For example, pancreatic neoplasms are 10-fold more common in the seventh compared to the forth decade of life [21]. The typical patient with pancreatic cancer is 60–70 years old, has had significant weight loss from his disease and is in an age group where significant medical problems including coronary artery disease, hypertension and chronic pulmonary disease are common. All of these conditions increase the risk of major surgery. Also early in its course, pancreatic adenocarcinoma results in local invasion of the duodenum, retroperitoneum and major vessels in the area of the celiac axis. These manifestations of locally extensive disease make many patients technically unresectable. Table 2 reviews the resectability rate in five series [25–29] in which 1,587 pancreatic resections were reviewed. As may be seen only 15% of patients evaluated for surgery were candidates for curative resection. Thus of 10,580 patients with pancreatic cancer, only 1,587 were appropriate candidates for curative surgery. These data confirm that the great bulk of patients with pancreatic cancer never come to potentially curative surgery.

The issues of operative mortality and overall survival after pancreatic resection are dealt with in Table 3. The data in Table 3 are a summary of information from 20 series of patients treated with either total pancreatectomy or Whipple procedures for pancreatic carcinoma. The data demonstrates that the two procedures are very similar in efficacy and operative mortality. One of five (20%) patients undergoing surgery died as a result of the operation. The overall 5-year survival was less than 10% for operated

Table 2. Resectability rate in pancreatic cancer

No. of resections	Year	Resectability rate (%)	Reference
119	1964	10.0	25
430	1977	15.4	26
10	1979	7.2	27
23	1983	11.8	28
1005	1983	15.0	29
1587 (Total)		14.6 (Total)	

Table 3. Operative mortality and survival after pancreatic resection

Procedure	No. of patients	Operative Morality (%)	Survival (%)		Reference
			3-year	5-year	
'Whipple' pancreatectomy	814	19.5	13.1	8.1	21
Total pancreatectomy	300	21.7	18.4	9.3	21

patients. It should be emphasized that this 10% survival is actually 10% of the 15% of patients who could undergo resection and therefore the survival for all patients with adenocarcinoma of the pancreas is approximately 1%. Of the 90% of patients dying after pancreatic resection who do not experience operative death, the vast majority die of recurrent disease [21, 24]. This is an important observation since it means that if effective post-operative adjuvant therapy were available a large percentage of resectable patients with pancreatic cancer could be helped.

Adjuvant therapy

Data documenting careful clinical trials assessing adjuvant therapy of pancreatic cancer are scanty. Most information available describes the use of radiation or radiation plus chemotherapy. There are no available data on randomized trials testing radiation therapy as an adjuvant to surgery in pancreatic cancer. Most data are ancedotal and report small numbers of patients. For example, Pilepich and Miller [30] reported on the use of preoperative irradiation in 17 patients with potentially resectable pancreatic cancer. These patients received up to 5,000 rads preoperative irradiation over 5 weeks. Eleven patients underwent surgical exploration and six patients were resected for cure. Two of those patients survived greater than 5 years. This was an uncontrolled study and it is impossible to attribute the survival of two patients to the preoperative irradiation. Another small experience using irradiation was reported by Kopelson [31]. Seven patients were treated with 4,500 rads over 6 weeks. These patients all underwent pancreaticoduodenal resection. Five patients were treated preoperatively and two patients received postoperative therapy. Two cases survived disease-free for greater than 5 years, but again it is not possible to attribute this finding to the adjuvant irradiation. Of potential interest however, is the fact that no patient developed recurrent cancer in the irradiated field. This suggests benefit in preventing local failure since at least 50% of patients failing after pancreatectomy who have no adjuvant therapy have local/regional tumor recurrence [24].

The use of chemotherapy as adjuvant treatment has not been systematically investigated. Although both [21] single chemotherapeutic agents and combination chemotherapy programs are effective in producing partial remission of advanced pancreatic cancer, it is unknown whether chemotherapy used alone will improve postoperative survival and decrease recurrence rates after pancreatectomy.

There has been one prospective randomized clinical trial of adjuvant combined modality treatment in patients with resected pancreatic cancer. This study [21, 32] was carried out by the Gastrointestinal Tumor Study Group (GITSG) and is illustrated in Table 4. In this clinical trial initiated in 1974, 43 patients were randomized between pancreatic resection only (total or Whipple's) or resection followed by 4,000 rads of split course irradiation and 5-fluorouracil. The results of this clinical trial indicate that survival was significantly better (42% vs. 18%) at 2 years post resection when adjuvant combined modality therapy was used. This difference was lost at 5 years demonstrating that the adjuvant therapy utilized was capable of delaying but not eliminating the emergence of recurrent cancer. A subsequent national cooperative trial of adjuvant therapy of pancreatic cancer has been mounted. This study is illustrated in Figure 1. In this clinical trial, 5-FU plus irradiation as utilized in the GITSG study is being compared to a combined modality program including 4,000 rads of irradiation plus a combination chemotherapy regimen of streptozotocin, 5-fluorouracil and Mitomycin-C (SMF). The SMF regimen was chosen because it appears to be the most consistently active combination chemotherapy regimen in patients with advanced pancreatic cancer. SMF produces partial response in 30–40% of patients with measurable metastatic pancreatic cancer [33]. The SMF plus irradiation adjuvant study is being performed as an intergroup study by a number of clinical cooperative groups in the United States. The results of this study will be awaited with interest although it will take several years before sufficient numbers of patients will be accrued to this clinical trial.

Table 4. GITSG[a] pancreatic adjuvant trial

Treatment	No. of patients	Survival (%)		Reference
		2-years	5-years	
Surgery	21	18 $P < 0.03$	8 $P < 0.2$	32
Surgery + irradiation and 5-Fluorouracil	22	43	14	

[a] Gastrointestinal Tumor Study Group.

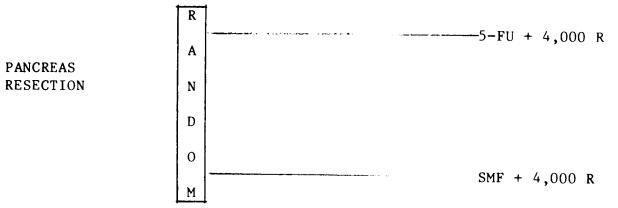

Figure 1. Intergroup phase III clinical trial for patients with resected pancreatic cancer. This study compares 5-Fluorouracil (5-FU) +4,000 R of split course irradiation to the same irradiation program combined with chemotherapy utilizing streptozotocin, Mitomycin-C and 5-FU (SMF).

It should be clear that adjuvant therapy in pancreatic cancer is at an early stage and no firm conclusions in regard to efficacy can be drawn. Before truly effective adjuvant therapy strategies can be developed for adenocarcinoma of the pancreas, it will be necessary to develop new and more effective approaches to the therapy of advanced disease. Unfortunately at present we have few approaches which produce significant responses or prolongation of survival in advanced pancreatic cancer and thus have no effective therapy to apply to the adjuvant situation. It is hoped that early clinical trials in new approaches [21] including brachytherapy, intraoperative irradiation, hyperthermia and monoclonal antibody applications will lead to the development of effective strategies for adjuvant therapy.

Colorectal cancer

Colorectal cancer is a most common malignancy in the United States for both males and females and is second in incidence only to lung cancer [1]. The survival rates of patients with colorectal cancer undergoing surgical resection have changed little during the last thirty years. In 1986, there will be approximately 140,000 new cases of colorectal cancer and approximately 60,000 deaths will result from this disease in this year [1]. Although prevention of colorectal cancer, as well as detection and treatment at an early stage, would be the most preferable means of reducing the mortality due to the disease, it is clear that effective post-surgical adjuvant therapy aimed at preventing recurrence would be a major advance.

The likelihood of long-term disease-free survival after undergoing colon resection for cancer depends upon stage of disease. Common staging classifications are modifications of that proposed by Dukes in 1932 [34]. This classification has four major subdivisions: Dukes' A – mucosal tumor only; Dukes' B – bowel wall involvement; Dukes' C – pericolic lymph nodal extension; and Dukes' D – Metastatic cancer (Table 5). Prognosis worsens

Table 5. Dukes' classification: Astler-Coller modification

		% 5-year survival
Initial extension		
A	Mucosa only	95
B_1	Within wall	85-90
B_2(m)	Microscopically through wall	60-70
B_2(g)	Grossly through wall	50
B_3	Involves adjacent structures	30
Lymph nodes positive for tumor		
C_1	Within wall	40-50
C_2(m)	Microscopically through wall	40-50
C_2(g)	Grossly through wall	15-25
C_3	Involves adjacent structures	10-20
D	Distant metastatic disease	< 5

with increasing bowel wall and local lymph node tumor extension. Bowel wall invasion appears to be an important pre-condition for nodal tumor spread, since only 4% of cancers are classified as C_1 (positive nodes without complete bowel invasion). As demonstrated in Table 5, tumor confined to the submucosa (Dukes' A) is surgically curable greater than 90% of the time. Deeper penetration into the bowel wall results in a 60–90% survival at 5 years, whereas penetration through the serosa into the pericolic fat is associated with a 30–50% 5-year survival. Regional lymph node involvement (C_1 or C_2) results in an average 25% 5-year survival. Fifty percent of all patients have serosal penetration, nodal involvement or both at the time of their initial surgery [34]. It is clear that until effective screening results in early diagnosis, adjuvant therapy of colorectal cancer will be actively explored in an attempt to reduce deaths due to this tumor.

In order to appreciate strategies for adjuvant therapy in colorectal cancer, it is necessary to understand how and where surgical failure occurs in patients with large bowel cancers. Several authors have demonstrated that for both rectal and colon cancer, local recurrences of tumor at the resection site is common. Important evidence for this finding in rectal cancer comes from the second-look surgery experience performed by Wangensteen, Gilbertsen and co-workers at the University of Minnesota [35–37]. Analysis of these data demonstrate that distant metastases alone was uncommon (< 10% of cases), but occurred as a component of failure in approximately 50% of the group with failure. Peritoneal seeding was uncommon. Local failure (including regional lymph node metastases) occurred in nearly 50% of patients as the only site of failure, and in combination with distant metastases, in approximately 90%.

Taylor [38] performed an autopsy study on 125 patients whose deaths

were related to cancer of the colon and/or rectum. Seventy-two percent died of intra-abdominal causes of death, either intestinal obstruction due to tumor or infection. Only 3% of patients died of lung metastases and 25% of liver metastases [38]. These data again suggests the high rate of local intra-abdominal recurrence in patients with colorectal cancer. Cass, Million, and Pfaff [39] retrospectively studied 165 patients who had recurrent colon and rectal cancer. Sixty percent had local recurrence alone, and 14% had distant metastases alone. Ninety-two percent of the local recurrences developed in structures contiguous with the operative site. These authors found that through 5 years of follow-up, local recurrence without clinical evidence of distant metastases was the most common cause of death [39].

Based upon these data, one may only conclude that when primary surgical resection is likely to fail further treatment must be directed both to the site of the original tumor as well as systemically if survival rates are to be improved. The issue of local recurrence is particularly important in patients with rectal cancer [36–38]. It is reasonable to assume that efficacious adjuvant therapy with irradiation or chemotherapy could be a major factor in improving long-term survival in rectal cancer patients.

Indications for adjuvant treatment – prognosis

Currently, treatment for disseminated colon cancer is not highly successful and is associated with significant morbidity. Data in regard to the benefit of adjuvant therapy in colorectal cancer is inconclusive at present. However, it is very reasonable to select patients who are at high risk of relapse for entry into well designed clinical trials to test potential adjuvant therapies.

Based on presentation alone, patients who are asymptomatic and whose tumors are diagnosed during the course of routine examination have been demonstrated to have better prognoses than symptomatic patients [40–44]. This finding is logical since symptomatic disease is frequently the result of local or distant metastases. Patients who are younger at time of diagnosis are more likely to die of colon cancer than are patients who are elderly when diagnosed. Patients older than 70 years when their tumors are diagnosed have a decreased likelihood of dying of cancer since they are likely to die of other causes [45–47]. On the other hand, patients less than 30 years old with colorectal cancer have a very poor 5-year survival rate of less than 20% [48]. This may result from the rarity of this disease in this age group leading to delayed diagnosis. Also as noted elsewhere in this volume, patients below the age of 40 frequently have hereditary colon cancer with autosomal dominant patterns of inheritance.

The presence of an elevated CEA pre-operatively or post-operatively in either Duke's B or Duke's C colorectal cancer is clearly associated with a

worse prognosis. Wanebo *et al.* [49] and Goslin *et al.* [50] have shown that patients with Dukes' B cancer and a post-operative CEA of > 5 ng/ml, have a significantly decreased disease-free survival (40%) compared to that (80%) seen in patients without elevated CEA. For patients with Dukes' C cancer and elevated post-operative CEA levels, there were no 5-year survivors [49, 50]. It is also clear that patients presenting with obstructing and/or perforating tumors have poor prognoses. This is due to the locally advanced nature of these tumors and the consequent increased risk of local, regional, and metastatic recurrent disease [51, 55].

Another important prognostic indicator is location of the primary tumor. Some studies suggest that survival with rectal cancer is poorer than with colon cancer [56, 57]. Furthermore, survival diminishes as rectal tumors are located more distally in the rectum. This finding results from the propensity of rectal cancer to recur locally. Also low lying rectal cancers, particularly in a patient with a narrow pelvis, may present complex surgical problems and make complete resection difficult.

The most important prognostic indicator remains the presence or absence of lymph node metastases (Table 5). The extent of lymph node involvement is important. When only a few regional lymph nodes contain metastases, as many as 40–50% of patients survive disease-free after appropriate surgery. Survival diminishes greatly when there is more extensive nodal involvement or nodal metastases plus extensive local tumor invasion (Dukes' C_2) [57, 58].

The conclusion that may be drawn from the above discussion of prognostic factors is that certain subgroups of patients do poorly with surgery only and would be good candidates for effective adjuvant treatment. Groups of patients that may benefit from adjuvant therapy include those with:

1. a locally extensive tumor with lymph node involvement, regardless of histologic type, especially patients with C_2 lesions;
2. patients who present with obstruction or perforation;
3. those patients with locally advanced and low lying rectal lesions;
4. patients with an elevated post-operative CEA regardless of whether they have Duke's B or C lesions initially.

However, from a practical standpoint, patients are generally considered candidates for adjuvant therapy if the primary tumor demonstrates Duke's B or C pathology.

Adjuvant chemotherapy

The potential effectiveness of adjuvant chemotherapy in patients with colorectal cancer is compromised by the fact that response rates to chemotherapy in patients with advanced disease are poor. There have been extensive trials using single drug and combination chemotherapeutic regimens in

advanced colorectal carcinoma. Partial response rates have varied from 10 to 40% [34, 59].

Although improvement in patient survival has not been documented clearly for chemotherapeutic treatment of advanced colorectal cancer, it is clear that there are agents with activity. 5-FU alone has a well documented response rate between 15 and 30% [34]. Other active agents [34] include Methyl-CCNU and Mitomycin-C. Combination chemotherapeutic regimens have not shown, to this date, consistent superiority over single agent treatment. Regimens of 5-Fluorouracil plus Methyl-CCNU with or without Vincristine, have demonstrated response rates varying between 11 and 43% [34, 59]. Such disparity among treatment results has been the rule rather than the exception. The conclusion that may be drawn from these variable results is that there are no consistently effective chemotherapy regimens for advanced colorectal cancers. Even with the relative ineffectiveness of chemotherapy of disseminated colon cancer, there has been continued interest in the use of adjuvant therapy after surgical resection.

One must be cautious in interpreting the results of clinical trials on adjuvant therapy of colon cancer since it is clear that some studies have problems in design [60]. It is not appropriate to utilize non-randomized study design to evaluate adjuvant therapy. A phase III prospectively randomized design must be employed if data on survival and recurrence rates are to be valid. The largest phase III adjuvant trials have employed fluorinated pyrimidines. More than 1,500 patients have been entered into well designed controlled clinical trials, and to date, there has been no evidence of statistically significant survival benefit for those receiving treatment [60]. The results of these studies indicate a general trend for treated groups to have slightly improved survival, but these differences do not reach statistical significance.

Most of the early work in adjuvant therapy of colorectal cancer was done by the Veterans Administration Surgical Oncology Group (VASOG). The early trials used single agents such as FUDR and Thiotepa. In these early studies, neither drug improved 5-year survival [61, 62]. The VASOG also studied 5-FU as a single agent and demonstrated a suggestion of benefit from treatment. In a study in which a short course of post-operative 5-FU was used, the survival at 5 years was 58% for 152 patients receiving adjuvant therapy versus 49% for 146 control patients. These differences were not statistically significant [63]. A subsequent VASOG trial examined a prolonged intermittant drug schedule in which 5-FU was given daily for 5 days and repeated at 6 to 8 week intervals. At 7 years of follow-up, there is some survival benefit for the treated group. Thirty-three percent of patients receiving 5-FU are alive at 7 years versus 25% of the control patients [63]. However, this result is not statistically significant if only completely resected, i.e. true adjuvant cases, are considered.

The Central Oncology Group (COG) also completed a phase III study of 5-FU versus surgery only [64]. In this clinical trial, 56% of the 5-FU treated patients remain disease-free versus 50% of surgery only control group. Although this result is not statistically significant, it does demonstrate a trend in favor of those patients receiving treatment. When the COG study was analyzed for benefit in subgroups of patients, it was found that patients receiving 5-FU with Duke's C rectal lesions did have a statistically significant improvement in survival [64].

The VASOG and COG studies are well designed phase III studies. As noted previously, the literature [65] is replete with studies purportedly showing the benefit of adjuvant chemotherapy or chemoimmunotherapy in colorectal cancer. These studies do not utilize a prospectively randomized design but rather compare survival in a treatment arm to that of historical control patients. Such clinical trials are not reliable since they are not prospectively randomized and thus subject to a variety of biases. It has also been demonstrated that current controlled randomized trials are reporting better survivals with all forms of treatment including surgery only than results seen in historical patients treated in the past [66]. Thus the use of as historical control populations for present studies is invalid and potentially could incorrectly suggest that the treatment arm under evaluation is active.

Recently several groups have mounted carefully controlled adjuvant trials in colorectal cancer (Table 6). The Gastrointestinal Study Group (GITSG) initiated a four-armed study in August 1975 for patients with B_2 and C colon lesions. This trial compared 5-FU plus Methyl-CCNU, plus or minus the methanol extracted residue of BCG (MER), and MER alone to patients treated with surgery only. This clinical trial failed to show any advantage for treated patients versus surgery only patients. The results did demonstrate that all patients experience better survival than would have been predicted by historical data. There was a 77% 5-year survival for patients with B_2 lesions and a 47% survival for those with Duke's C_2 lesions [66].

Preliminary results from a Southwest Oncology Group (SWOG) study [67] have suggested improvement in relapse-free survival with the addition of BCG to Methyl-CCNU and 5-FU when compared to combination chemotherapy alone or surgery alone. The differences in disease-free survival are statistically significant for some subgroups in this study. For example, Duke's B_2 cases benefit from chemoimmunotherapy while other subgroups do not. It is difficult to be sure of the significance of this finding since other studies [64] noted benefit of adjuvant chemotherapy confined to Duke's C patients. Another study that has recently been reported which is of interest is the NSABP trial [68]. This three-armed study randomized 1166 patients to surgery only or BCG or 5-FU + Methyl-CCNU + Vincristine chemotherapy. There is marginal disease-free survival benefit ($P = 0.07$) in patients receiving chemotherapy. There is no apparent benefit for immuno-

Table 6. Chemoimmunotherapy adjuvant studies in Duke's B and C colon cancer

Regimen	No. of patients	Duration of therapy	Median follow-up (years)	Results	Group reference
5-FU + Methyl-CCNU vs. control	659	52	5	Negative	VASOG [69]
5-FU + Methyl-CCNU vs. MER vs. 5-FU + Methyl-CCNU + MER vs. Control	621	70	5-5	Negative	GITSG [66]
5-FU + Methyl-CCNU vs. 5-FU + Methyl-CCNU + BCG vs. control	626	52	7	Chemoimmuno-therapy superior to surgery only in Duke's B_2 ($P = 0.003$) in disease-free survival	SWOG [67]
BCG vs. 5-FU + Methyl-CCNU + Vincristine vs. control	1166	52	3-4	Marginal disease free survival benefit ($P = 0.07$) for chemo group	NSABP [68]
Levamisole vs. Levamisole + 5-FU vs. control	430	52	N/A	Pending	NCCTG
5-FU + Heparin via portal vein vs. control	300	7 days	3/84 study started	Pending	NSABP

therapy. Clearly the NSABP result is difficult to reconcile with the SWOG data suggesting benefit for a BCG arm treatment. With large well designed studies reporting inconsistent results both in regard to benefit from types of therapy and benefit for particular prognostic groups, one must draw the conclusion that no effective therapy has been demonstrated.

There are on-going studies by a number of groups investigating adjuvant therapy of colon cancer (Table 6). One of particular interest is being performed as an intergroup study by the North Central Cancer Therapy Group (NCCTG), the Eastern Cooperative Oncology Group (ECOG), and the Southwest Oncology Group (SWOG). The immunomodulator Levamisole is being evaluated by these groups. The results of this study will not be available for several years.

The conclusion that may be drawn regarding systemic adjuvant therapy of colon cancer is that slight improvements (5–10%) in survival may be seen in treated groups. However, these results have not been highly statistically significant and have been sporadic and thus may represent chance occurrence. Clearly there is a need for further investigation utilizing the application of agents or techniques that have significant activity in wide spread disease to the adjuvant situation.

As a result of the poor response rates with systemic chemotherapy, there has been considerable interest in regional infusional chemotherapy in colorectal cancer [70–72]. Because of the frequency of liver metastases seen with this disease, it is reasonable that intra-arterial therapy, using direct injection of the agent into vessels (hepatic artery or portal vein) supplying the tumor would result in markedly increased delivery of drug to the malignancy. Although hepatic artery infusion for liver metastases from colon cancer has been performed for some time, it it still unclear whether this approach is truly superior to systemic therapy. Huberman [70] reviewed ten series in which 840 patients were treated, and found at least a 50% response rate in these patients. Median survivals ranged between 7 and 17 months. Other studies [71] confirmed a 40–50% response rate and significantly improved survival in responding patients. In the one completed randomized study performed comparing intravenous and hepatic artery perfusion chemotherapy with fluorinated pyrimidines, the response rate was higher for the intra-hepatic group, but the median survival was not statistically different [72]. This study compared short-term hepatic artery 5-FU infusion for 3 weeks only with systemic 5-FU therapy.

Two studies [73, 74] are underway currently in which patients are randomly allocated to intra-arterial FUDR (Fluorodeoxyuridine) via an implantable pump or to systemic FUDR. Both these studies have small numbers of patients (< 40). Both also demonstrate increased rates of hepatic tumor regression in the intra-arterial arms, but no significant difference in overall survival. These clinical trials are on-going. The final results of these

studies will be important because phase II studies suggest marked benefit for continuous hepatic artery infusion chemotherapy with implanted pumps. For example, the University of Michigan group reported 60 patients treated with FUDR at 0.3 mg/kg per day for 14 days of each month. The overall response rate was 83% and the median survival was projected to be in excess of 21 months [75]. What these results may mean for chemotherapy in the adjuvant setting is currently unsettled.

Intra-hepatic chemotherapy has been used in the adjuvant situation. A study performed in Liverpool by Taylor *et al.* [76, 77] compared adjuvant intra-hepatic chemotherapy versus surgery only. The initial report of this study was published in 1977 [76]. Twenty-six patients served as controls and 24 received 5-FU 1 g daily as continuous infusion into the portal venous system during the first 7 days after resection of colorectal carcinoma. The immediate post-operative mortality and morbidity did not differ significantly between the two groups. During the follow-up period, six deaths occurred in the control group and only one in the perfusion group. At autopsy, four of the controls had multiple liver metastases, two of the surviving controls developed evidence of liver metastases, and two had local recurrence. No patient in the perfusion group developed evidence of hepatic metastases. Taylor *et al.* concluded that adjuvant portal venous perfusion with 5-FU may reduce the incidence of liver metastases in colorectal cancer [76]. An analysis of this study in 1984 [77] reported results in 250 patients. Although there were decreases in liver metastases in all patients receiving perfusion, survival benefit was limited to patients with Dukes' B cancer. The portal vein infusion study is currently being repeated by the National Surgical Adjuvant Breast Project (NSABP). The NSABP clinical trial was initiated in March 1984, results of this study will clarify the use of portal vein infusion for adjuvant therapy.

Several other adjuvant approaches to preventing liver metastases are being evaluated. For example, adjuvant hepatic irradiation is being explored by the GITSG utilized doses of 2200 rads to the liver. It is too early to conclude anything in regard to efficacy of this approach.

Adjuvant radiation therapy

The use of adjuvant radiation therapy in locally advanced (Duke's B_2 and C) rectal carcinoma has been evaluated for a number of years. It is assumed that either pre-operative or post-operative radiation therapy on an adjuvant basis may decrease local recurrence of rectal carcinoma. The basis for the use of irradiation is the relatively high local recurrence in rectal cancer patients. As noted previously, Gunderson and Sosin [36] analyzed the sites of recurrence in a series of 75 patients undergoing second-look surgery after

curative resection for rectal carcinoma. Forty-eight percent of cases with relapse were found to have only local or regional tumor recurrence. Distant metastases as a sole pattern of recurrence was uncommon (7%) and local or regional failure represented some component of recurrence in 92% of the cases. These data suggest that if local/regional metastasis could be prevented, as much as 50% of rectal cancer recurrences could be prevented.

Irradiation has been used both pre- and post-operatively as an adjunct to surgery in patients with rectal cancer. The advantages of pre-operative irradiation may be at least two-fold [60]. Pre-operative irradiation may damage tumor cells so that the metastatic potential is decreased. Therefore, malignant cells disseminated at the time of surgery may be less likely to grow into clinical metastases. It is also possible for pre-operative irradiation to reduce tumor bulk, thus increasing the likelihood of complete surgical resection. Most recent studies have utilized post-operative radiation therapy. This approach has advantages since it is applied only to patients with high risk of recurrence (Dukes' B_2 and C). Since careful intraoperative staging is carried out, patients who are found to have low risk lesions (Dukes' A and B_1) and those with metastatic disease (Dukes' D) will not be subjected to unnecessary radiation therapy.

In a large randomized trial from the VASOG, results of pre-operative irradiation were reported by Higgins *et al.* [78]. In this study, 700 patients with rectal or rectosigmoid cancers were randomized to receive either 2000 or 2500 rads of pre-operative irradiation versus surgery alone. The survival at five years in the 453 patients who were able to undergo curative resection was 48.5% for the irradiated group and 38.8% for the surgery only patients. This difference was not statistically significant.

Recently a randomized trial evaluating post-operative adjuvant irradiation was reported by the GITSG [79]. One hundred ninety-two patients were randomized to surgery only, surgery with 5-FU and Methyl-CCNU adjuvant chemotherapy, surgery with 4000 to 4800 rads irradiation or surgery with combined chemotherapy and radiation therapy. The GITSG study demonstrated that patients treated with chemotherapy plus irradiation had a significantly ($P = <.03$) lower relapse rate than patients treated with surgery only (Table 7). The relapse rates were 55% for surgery only and 30% for the combined modality group. There was no benefit in survival for any treatment but without doubt if the differences in relapse persist, differences in survival will follow. The use of radiation or chemotherapy alone did not either decrease relapse or improve survival. Although this study is of interest it must be stressed that there are relatively few patients on each arm (<60) and that several more relapses in the combined modality arm would erase any statistical significance. A study being performed by the NSABP in which patients are randomized to surgery only, chemotherapy (5-FU + Vincristine + Methyl-CCNU) or post-operative radiation (3200 to 4000 rads)

Table 7. GITSG rectal cancer study

Number of patients with recurrence (%)

Stage	Treatment groups			Radiotherapy + Chemotherapy	Total
	Control	Chemotherapy	Radiotherapy		
B_2	7/21(33)	3/16(19)	6/19(32)	4/16(25)	20/72(28)
C_1	16/24(67)	12/24(54)	10/19(53)	6/19(32)	45/86(52)
C_2	9/13(69)	6/8(75)	8/12(67)	5/11(45)	28/44(64)
Total	32/58(55)*	22/48(46)	24/50(48)	15/46(33)*	93/202(46)

* $P = .03$.

will be very helpful in defining the role of post-operative radiation in rectal cancer patients. This study has 550 patients already enrolled and remains blinded at present.

Conclusions

This chapter has reviewed the rationale for and results of adjuvant therapy of the three major adenocarcinomas of the gastrointestinal tract: stomach, pancreatic, and colorectal cancer. It should be clear that surgical therapy of these diseases, although curative in some instances, is frequently inadequate. The reason for this inadequacy is the presence of locally and/or widely disseminated microscopic metastases at the time of surgical resection. The adjuvant approaches that have been used including radiation, chemotherapy and various immune manipulations, are aimed at destroying locally residual and/or disseminated metastases. In some instances, notably gastric and rectal carcinoma, combined modality approaches with radiation and chemotherapy have been effective in decreasing relapse rates and resulting in prolongation of survival. However, generally the adjuvant therapy of gastrointestinal cancer must be thought of as an approach which currently is limited by less than adequate treatment strategies.

It is clear that we now understand the prognoses and natural history of gastrointestinal cancer. To improve the effectiveness of adjunctive therapy we must first continue to develop innovative strategies utilizing combined modality studies incorporating the currently available treatments of surgery, radiation, chemotherapy, and biological response modifiers. As noted above, these approaches have already shown some evidence of benefit. Efforts to develop more effective adjuvant treatment through research at a more basic level must continue. Thus, we must develop new approaches to

the earlier diagnosis of stomach, pancreatic, and colorectal carcinomas. This will first insure a greater likelihood of surgical cure and secondly decrease the amount of microscopic metastatic disease present at diagnosis and thus optimize the likelihood that adjuvant therapy will be effective. Finally, more effective chemotherapy, better ways of applying radiation therapy and evaluations of strategies to use new biological response modifiers must be developed to give clinical investigators the tools they need to improve adjuvant therapy of gastrointestinal cancer.

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11. Primary hepatobiliary carcinoma

BLAKE CADY

Introduction

The liver and biliary tract can be considered as a single anatomic area, although primary cancers that arise in these two structures differ markedly in etiology, incidence, treatment, and response to various therapies. Unfortunately the results of treatment of all of these tumors are extremely poor in terms of cure. All primary cancers of the liver and biliary tree offer challenging surgical problems and thus have elicited more interest in the field of surgery than their numbers would indicate, as many workers have struggled to develop surgical techniques, radiotherapy, and chemotherapy as well as combined modality techniques in an attempt to offer palliation and cure to these cancers that cause such difficult clinical problems.

Incidence and epidemiology

While the incidence of primary cancers of the liver, gallbladder, and biliary tract are low in this country overall, there are remarkable geographic and racial differences across the world that substantiate the impressions that these three cancers are highly related to environmental conditions. For instance, in the United States cancers of the liver, gallbladder, and biliary tract make up 1.5% of cancers and approximately 2.3% of fatal cancers [1]. However, in both east and west Africa, primary liver cell cancer alone may make up 10% of all cancers diagnosed, and in some areas of east Africa primary liver cell cancers may constitute an even higher percentage of overall cancer cases [2]. Furthermore, within a specific defined geographic area such as the island of Mozambique vast differences in incidence may occur between separate races. In Mozambique the Africans have an incidence of primary hepatocellular carcinoma of 1.1%, the Arabs 4%, and the Asian population had no cases recorded [3]. Similarly, in Hawaii the age-adjusted

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

incidence of primary hepatocellular carcinoma in males varies among the different racial groups from 13.3 per 100,000 per year in Filipinos, to 12.6 per 100,000 in Hawaiians, to 0.3 per 100,000 per year in Chinese, 7.5 per 100,000 in Japanese and 2.9 per 100,000 per year in Caucasians. Similar ratios are also noted in the female population [4].

For primary carcinoma of the gallbladder, rates also vary dramatically across the world [5, 5a]. In particular, there is a high incidence in Latin America, Japan, and Southeast Asia. In the United States primary gallbladder carcinoma seems to be common among North American Indians, where it may make up as much as 2.3% of cases operated upon for biliary tract conditions [6]. Among the Caucasian population of the United States, it has generally been estimated to make up between 1.2 and 1.4% of all biliary tract operations [6a]. In New Mexico, carcinoma of the gallbladder made up 8.5% of all cancers of American Indian women and was exceeded in frequency only by cancers of the uterine cervix and breast [6]. It was estimated in the New Mexico Tumor Registry that age-adjusted incidence rate among women for carcinoma of the gallbladder was 1.7 per 100,000 per year for Caucasions, 13.2 per 100,000 per year in Spanish Americans, and 19.4 per 100,000 per year in American Indians [6].

Primary carcinoma of the extrahepatic biliary tree excluding the gallbladder also shows wide geographic and racial variations. For instance, in Hawaii, Japanese patients have six times the incidence of extrahepatic biliary tree carcinoma compared to the Caucasian population and other racial groups [7]. Overall the incidence of extrahepatic bile duct carcinoma in the Orient is much higher than in other places in the world [5]. There are other relationships to underlying diseases, so that patients with congenital choledochal cysts have a high incidence of bile duct carcinoma later in life [8]. Furthermore, patients with chronic ulcerative colitis are recognized as having a marked increase in the incidence of primary extrahepatic bile duct carcinoma [9].

Time trends in incidence of disease are almost impossible to decipher from data regarding gallbladder and extrahepatic bile ducts, but in primary hepatocellular carcinoma in the United States it has been observed that, for a period of 30 years, there has been a 30% reduction in incidence in men and a 56% reduction in women [10]. Thus primary hepatocellular carcinoma, which ranked as the fourth leading cancer cause of death in men and the fifth leading cancer cause of death in men and the fifth leading cancer cause of death in women in 1930, now ranks as tenth and ninth respectively [10]. In the United States at the present time, utilizing the SEER data, primary cancer of the liver and biliary passages makes up 0.7% of white male, 1.2% of black male, 0.4% of white female, and 0.7% of black female primary cancers [11]. It has also been shown that the age-adjusted rates for these four racial and sex groups are, respectively, 2.6, 5.2, 1.2, and 2.1 per

100,000 per year [11]. The age-specific incidence rates indicate that there is a constant rise with age to at least 80 for both white and black, males and females in the United States [11].

Etiology

Primary hepatocellular carcinoma has strong correlations with several well-defined environmental agents [12]. These include alcohol ingestion, infection with Hepatitis B, ingestion of food contaminated with Aflatoxin, and, in specific histologic types, exposure to thorotrast and vinyl chloride manufacturing. Other dietary contaminants and agents may well be associated, but the data is less clear-cut. In carcinoma of the gallbladder, the only specific etiologic agent pinpointed so far is the presence of gallstones, which in turn seem to be related to the incidence of dietary fat, the presence of obesity, and female sex [13]. No reports of case control studies of other etiologic agents have been reported.

In carcinoma of the extrahepatic biliary tree, it has been postulated that biliary parasites are etiologic agents, since patients with cancer seem to be clustered in areas of the world where these parasites are common, and conversely these parasitic infestations are frequently found in patients with bile duct carcinoma [5].

In specific terms, it is expected that roughly 13,600 cases of carcinoma of the liver and biliary passages will occur in the United States in 1986 [1]. It is also expected that approximately 10,500 patients will die of these diseases.

It is vitally important that continued studies of relationships between specific dietary and environmental agents and the cancers of the liver and biliary tree be continued for it is known that the liver, because of its enormous metabolic role in human physiology, may well be exquisitely sensitive to environmental agents as it apparently is in various animal systems. For instance, in fish, extraordinarily minute quantities of Aflatoxin in the water have been associated with dramatic increases in primary liver cancers [14]. In addition, primary liver cell cancer in indigenous fish of the Atlantic coast of America have been shown to havy widely based on general water contamination with pollutants [15]. Furthermore, the entire epidemiological and etiological relationship to Alfatoxin was first discovered by a dramatic epidemic of liver cell cancer in turkeys raised commercially in Great Britain which were traced back to the contamination of a shipment of peanuts for poultry feed from Brazil in a remarkable example of epidemiological surveillance.

The possibility of immunization against Hepatitis B virus, which is now possible, offers the hope of a specific attack on what may be one of the

prime etiologic agents in primary liver cell cancer in the third world and perhaps even in this country [16]. Since most primary hepatocellular carcinomas in the third world and many in this country are associated with evidence of previous infection with the Hepatitis B virus, even if the overall epidemiology may well be multifactorial, immunization offers hope of a public health control of this disease.

Clinicians need to be aware of the general data regarding race, geography, and epidemiological features to aid in their assessment of patients in clinical practice.

Clinical features in diagnosis

Primary hepatocellular carcinoma

Primary liver cancer in the United States and western countries can be classified in two different major types: those arising on the basis of cirrhotic liver and those arising without pre-existing cirrhosis. In patients with a pre-existing cirrhosis, which may be of a variety of etiologies or types, there is a risk of eventual hepatoma development in up to 40% of cases in patients with alpha-Antitrypsin deficiency [17], 20% of cases with postnecrotic cirrhosis, and 10% of cases with Laennec's cirrhosis. The specific etiology of the cirrhosis has major implications, as can be seen furthermore in the fact that Wilson's disease seldom results in primary liver cell cancer, whereas cirrhosis associated with hemachromatosis has a very high incidence of eventual development of primary liver celll cancer [18].

Patients with a relatively stable pre-existing cirrhosis frequently have the onset of hepatoma announced by a sudden deterioration in long-term compensated liver physiology. For instance, the sudden appearance of ascites on the basis of hepatic-venous tumor thrombus is not uncommon. Sudden gastrointestinal bleeding from esophageal varices on the basis of sudden worsening of portal hypertension from portal-venous invasion by tumor is also seen. The appearance of liver pain, increased liver size, or sudden worsening of liver function tests may all be manifestations of liver carcinoma. Liver cell cancers may also rupture intra-abdominally causing acute hemoperitoneum with right upper quadrant and/or shoulder pain.

Pain syndromes associated with the growth of primary hepatocellular carcinoma may be dull and aggravating, but not severe, right upper quadrant pain and right shoulder pain from growth of disease into the diaphragm, and the appearance of peritonitis from rapid bleeding into the peritoneal cavity with marked tenderness, guarding, and rigidity of the abdominal wall.

Other less common clinical presentations for primary liver cell cancer include jaundice from pressure obstruction of the intrahepatic biliary tree or even direct intrabiliary growth of tumor to form intraluminal obstruction within the liver. Fever as a presenting complaint is uncommon but possible and would usually be accompanied by some other clinical manifestation.

Postnecrotic cirrhosis of extremely long standing either previously diagnoses or not and with no apparent laboratory or clinical manifestations may also result in the development of primary liver cancer and present with dramatic or stubtle clinical manifestations such as rupture of the primary tumor or right upper quadrant or shoulder pain. These preliminary time durations of cirrhosis may run to three, four, or five decades. Primary liver cell cancer with a background of cirrhosis is generally a disease of older people, and will generally manifest itself in the sixth, seventh, and eighth decade.

In contrast, primary liver cell cancer arising on a liver unaffected by cirrhosis generally occurs in younger patients, sometimes even in the late teenage years. Liver cell cancer manifesting itself in infants and very young children can be either a hepatoblastoma or hepatocellular carcinoma. These patients without the pre-existing forms of cirrhosis will present clinically in many of the same ways as the patients previously described. Pain arising in the liver and manifesting itself in the right upper quadrant or shoulder or flank would be the most common presenting clinical symptomatology, but sudden appearance of ascites or even bleeding may also be noted. Enlarged abdominal girth on the basis of massive enlargement of the liver itself without ascites can also be seen. Jaundice would be an uncommon initial symptom of these cancers, but can occur on occasion because of intrabiliary growth of the primary liver cancer or biliary tract compression.

Diagnosis

The diagnosis of primary hepatocellular carcinoma is based on clinical manifestations as described previously plus the physical examination that would reveal signs of an enlarged liver, ascites, or portal hypertension. Non-specific diagnostic tests would include measurements of liver function, particularly serum albumin and hepatic enzymes such as alkaline phosphatase, transaminase, LDH and bilirubin. Specific blood tests include the presence of alpha-fetoprotein, which is found in significant numbers of patients, both in the cirrhotic patients and less commonly in the patient with a non-cirrhotic liver. Because primary hepatocellular carcinoma is a common cause of paraneoplastic syndromes, other biochemical evidence of disease can be sought in terms of hypercalcemia, hypoglycemia, anemia, and other syndromes.

Anatomic diagnostic studies include radionucleide liver scans, computer tomography liver scans, ultrasonography of the liver, and, more invasively, angiography of the liver. Since most primary hepatocellular carcinomas are hypervascular, the angiographic appearance of the liver is usually quite characteristic, in contrast to the mere space-occupying mass that would be seen on the less invasive liver scans. Needle aspiration cytology or core-needle cutting biopsy by random or radiographically directed needles can confirm the histologic diagnosis of hepatocellular carcinoma in many cases. It should be recognized however that liver biopsy by needle techniques can be extraordinarily hazardous because of the hypervascular nature of most primary liver cell cancer. Needle biopsy of such suspected primary liver cancer should be reserved for those cases that are clearly inoperable by clinical evaluation. Liver biopsy should also be done with the smallest size needle possible to minimize possibility of trauma to these vascular tumors with resultant intrahepatic or intraperitoneal bleeding. In the presence of cirrhosis and elevated alpha-fetoprotein and a liver mass by scan with an angiographic appearance that is characteristic of hepatoma, histologic confirmation is not required for diagnostic accuracy, although attractive from an academic point of view.

It should be recognized that the ultimate diagnosis of hepatoma in those patients who are clinically operative candidates should be obtained at surgery where exploration will determine the ultimately resectable nature of the primary liver cancer.

Differential diagnosis

For the most part, differential diagnosis involves only the distinction between metastatic liver cancer from a variety of primary sites but usually the gastrointestinal tract, and the presence of cirrhosis without the superimposition of hepatoma. Particularly in patients who are alcoholic, the sudden decompensation of the liver may represent continued insult to the liver from drinking.

Mestastatic liver carcinoma is rarely hypervascular angiographically and would rarely be manifested on the background of cirrhosis. The only specific biochemical differentiation between metastatic liver cancer and primary hepatic cell carcinoma however would be the presence of alpha-fetoprotein at diagnostically high levels. For instance, in one study 69% of patients with primary liver cell cancer had an alpha-fetoprotein level higher than 400 ng/ml whereas none of 66 patients with metastatic carcinoma and only one of over 200 patients with non-malignant liver disease had an alpha-fetoprotein level greater than 400 ng/ml [19]. It must be remembered, how-

ever, that a normal alpha-fetoprotein level does not eliminate the possibility of a primary hepatocellular carcinoma. Clearly the presence of a previously known cancer suggests that a primary hepatoma would be unlikely. Although metastatic cancer to the liver from an unknown primary site is not at all uncommon, such cases would rarely occur on the background of a cirrhotic liver. Primary organ sites of liver metastases of obscure origin would include lung, adrenal, colon, breast, esophagus, pancreas, and stomach. In addition, hepatic metastases from lymphomas or even rare primary lymphomas of the liver may occur [20].

Gallbladder: diagnosis

The pre-operative diagnosis of carcinoma of the gallbladder is uncommon since benign conditions of the gallbladder leading to surgical operation are extremely common in the United States and other western countries, and the symptoms of gallbladder carcinoma almost totally mimic those of cholelithiasis. These would include right upper quadrant pain, jaundice, palpable right upper quadrant mass, and hepatomegaly. Similarly, functional laboratory tests in carcinoma of the gallbladder would rarely distinguish these lesions from benign gallbladder disease. Abnormal liver function tests, elevated bilirubin, and manifestations of infection in the gallbladder all fail to distinguish benign from malignant disease. Rarely gallbladder carcinoma may present as ascites with transerosal spread of disease into the peritoneal cavity. Anatomic diagnostic tests also rarely distinguish benign from malignant lesions of the gallbladder in the absence of liver metastases at a distance from the gall bladder. These would include radionucleide scans, including Hyda scans; ultrasonography usually would show gallstones but may reveal an unusually thickened gallbladder wall or mass which would alert the radiologist to the presence of something other than a benign cholelithiasis and cholecystitis. Invasive studies such as percutaneous transhepatic cholangiogram or endoscopic retrograde cholangiography in the presence of jaundice might show anatomic obstruction of the biliary tree that would more closely resemble malignant encroachment than benign obstruction by stones. But of critical importance is the fact that most curable gallbladder carcinomas will arise as an incidental finding in a gallbladder removed for apparent benign cholelithiasis or cholecystitis [21]. In these lesions, of course, there will be no specific clinical manifestations of the cancer. In operations on cholelithiasis and cholecystitis roughly 1% of cases will ultimately be found to be carcinoma of the gallbladder.

Differential diagnosis

As suggested, the principal differential diagnosis is that of benign biliary tract disease. Since it is not critical that the differentiation between benign and malignant biliary tract disease be established prior to surgery as most of these patients will warrant exploration, the accuracy of pre-operative diagnosis is not of major concern. The major differential diagnosis would be the presence of a liver metastasis or a liver tumor when a primary gallbladder carcinoma invades the hepatic bed and presents as a large mass in the gallbladder fossa. Again, since most of these patients will require surgery, the accuracy of the pre-operative diagnosis or differential diagnosis is not critical, but the surgeon must be experienced enough to have a full range of surgical options available during operation.

Extrahepatic bile duct carcinoma

Clinical presentation

Almost without exception, the clinical manifestation of carcinoma of the extrahepatic bile ducts is that of obstructive jaundice [22]. This would be true of lesions arising at the hepatic duct bifurcation or anywhere in the common bile duct itself. If the lesion arises in the area below the takeoff of the cystic duct, an enlarged gallbladder palpable in the right upper quadrant in the presence of obstructive jaundice might well be noted. Carcinomas obstructing the bile ducts above the level of the cystic duct takeoff present the anomalous situation of obstructive jaundice without gallbladder or common bile duct distention. This presentation is characteristic of carcinomas of the Klatskin variety at the hepatic duct bifurcation. Other clinical manifestations include hepatomegaly and derangements of the liver function tests. Seldom will these cancers manifest themselves as clinically apparent masses, because of the early obstruction of the biliary tree. Occasional extrahepatic or intrahepatic bile duct carcinomas will obstruct only the lobar biliary tree and therefore not present with obstructive jaundice but will be manifested by cholangitis, enlargement of the hepatic lobe, abnormal liver function tests in the absence of bilirubinemia, or even a liver abscess [23].

Differential diagnosis

Differential diagnosis of distal common bile duct carcinoma lies primarily in distinguishing it from carcinoma of the pancreas and other periampullary primary sites such as the ampulla of Vater. Frequently this distinction can-

not be made even with endoscopic retrograde cholangiography and pancreatography; it may be apparent only by inspection of the resected surgical specimen when that is possible. In cases of obstructive jaundice, a differential diagnosis between cancer and benign lesions of the biliary tract such as common bile duct stones or pancreatitis will always be a problem in distal obstruction. In the proximal extrahepatic bile ducts there is only one disease that clinically offers diagnostic confusion from primary bile duct carcinoma – that is sclerosing cholangitis [24, 25]. In Oriental patients who have emigrated from Asia, a rare differential diagnosis would be primary intrahepatic stones with cholangitis, which is a disease particularly of young adult males and should be recognized in this country with the increasing immigration of people from endemic areas for this unusual disease [26, 27]. Sclerosing cholangitis is almost always manifested by widespread abnormalities in the intrahepatic and extrahepatic bile ducts as viewed anatomically by percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography. This beading, irregular obstruction, and lack of distention of the intrahepatic bile ducts would be a classical radiological appearance for sclerosing cholangitis whereas a focal lesion at the hepatic duct bifurcation or upper common hepatic duct would be nearly diagnostic of primary bile duct carcinoma.

Pathology

Primary hepatocellular carcinoma presents as three major anatomic types [28]. Two-thirds of these cancers are of the nodular form in which the liver has multiple nodules scattered throughout its substance. The massive form of primary hepatocellular carcinoma presents as a large primary mass with associated multiple satellite lesions near its periphery within the liver substance. Approximately 5% of hepatocellular carcinomas present as a diffuse form with virtual suffusion of the entire liver substance by hepatocellular carcinoma. This latter form arises only in association with cirrhosis. In addition there are two other types that need to be separately recognized. These are the fibrolamellar type [29], which forms a distinctive histologic entity, and the encapsulated form [30, 31], in which the tumor grows as a large mass with a pseudocapsule but does not spread to other parts of the liver or extrahepatically for long periods of time. These latter two varieties may make up as much as 10% of cases in Japan and perhaps as many as 4% of cases in the United States. These are the cases that primarily lend themselves to surgical resection and offer a good enough prognosis to justify their aggressive surgical resection. Both these latter two presentations present as inherently more benign forms of primary hepatocellular carcinoma and even in the absence of treatment have been recognized as displaying a more prolonged survival and even occasional 5-year survivals [32].

Histologically, hepatocellular carcinoma presents in widely varying patterns. Well differentiated carcinomas may be difficult to distinguish from regenerative nodules or liver cell adenomas. The diagnosis of well differentiated liver cancer will be suggested by histologic features such as minimal nuclear abnormalities, absence of bile ductules, and the absence of Kupfer cells. Poorly differentiated hepatocellular carcinoma may be difficult to distinguish from epithelial or mesenchymal malignancies and offer diagnostic difficulties for the pathologist.

Intrahepatic cholangiocarcinomas may also arise as mixed cholangiocarcinoma and hepatic cell carcinoma [33]. These two cancers generally manifest themselves as solitary lesions that are unifocal, avascular, and without background cirrhosis. Angiosarcomas are extremely uncommon [34] and have been reported as a late consequence of exposure to thorotrast and to vinyl chloride in its manufacturing process [35]. Hepatoblastoma is an unusual low-grade, unifocal, primary hepatic cell cancer of infants and young children with characteristic histologic features [36].

The exact histologic differentiation between liver cell adenoma and focal nodular hyperplasia is a matter of debate among pathologists, but in general revolves around differences in clinical appearance, vascularity, and the presence of bile ductules. Liver cell adenomas are generally larger clinically, have a high incidence of spontaneous rupture, are associated with previous prolonged steroid use, and display an absence of bile ductules in a well differentiated hepatic parenchymal cell pattern [37].

Gallbladder carcinoma

Carcinoma of the gallbladder overwhelmingly presents as adenocarcinoma of moderate to poor differentiation. Anaplastic carcinomas, squamous cell carcinomas, and adenoacanthomas are uncommon variations of histology. Gallbladder carcinoma frequently extends into surrounding anatomic structures, in particular, the liver, bile ducts – frequently at the level of the hepatic duct bifurcation – and the duodenum and colon. It is frequently accompanied by lymph node metastases in the portahepatis, and by transserosal peritoneal metastases because of the large peritoneal surface as it lies on the inferior aspect of the liver. Hepatic metastases are common, but usually not as a feature of the initial disease presentation.

Extrahepatic bile duct carcinoma

There may be a variety of histologic presentations of extrahepatic bile duct carcinoma. Though almost exclusively adenocarcinomas, their manifesta-

tions in the bile duct itself may range from papillary varieties with soft, frond-like, non-obstructing, extensive involvement of the biliary tract lining to lesions that display scant cancer cells in a diffuse desmoplastic reaction that causes sclerosis and obstruction of the bile duct. It is not uncommon to find bile duct carcinomas multicentric in origin [38]. On occasion it is extremely difficult histologically to distinguish between sclerosing cholangitis and a sclerosing variety of bile duct adenocarcinoma with extensive desmoplastic reaction [24]. It is occasionally noted that a patient originally diagnosed as sclerosing cholangitis will eventually develop frank bile duct adenocarcinoma. Because of the early appearance of biliary obstruction and jaundice it is uncommon to find primary extrahepatic bile duct carcinomas as a large lesion, clinically, in contrast to primary cancers of the gallbladder.

Staging and prognosis

While staging systems for primary cancers of the liver, gallbladder, and extrahepatic bile ducts have been evolved by the American Joint Committee on Cancer Staging [39], in practice the overwhelming majority of cancers of all three sites are of such poor prognosis that exact staging has woefully little clinical benefit or impact on decision making in treatment. Overall, the prognosis of hepatocellular carcinoma is extremely bleak with perhaps no more than 3 to 5% of all cases surviving 5 years. The vast majority of these survivors will be patients with the 'encapsulated' or the fibrolamellar type of hepatocellular carcinoma arising in normal liver without cirrhosis. Even when primary liver cancer arises in a unifocal fashion on a background of cirrhosis, it is uncommon for the patient to survive for 5 years because of the long-term poor prognosis of the underlying cirrhosis, as well as the carcinoma. Although unusual hepatocellular carcinomas survive for over 5 years with no treatment whatsoever, surgery is the only curative form of therapy and the vast majority of treatments will be for palliation only.

Carcinoma of the gallbladder is seldom cured. Because of its occult nature with symptoms mimicking that of benign cholelithiasis and cholecystitis, delayed diagnosis, and early spread to adjacent, non-resectable organs, carcinoma of the gallbladder is cured by surgery only when found in unsuspected fashion with disease confined to the gallbladder wall or a small contiguous extension to immediately adjacent tissue. Cures have not been reported with treatment other than surgery.

Extrahepatic bile duct carcinoma also has an extremely poor prognosis as only about 10% of cases can be completely resected, and the vast majority of these will succumb from disease within a few years. The bulk of the survivors for primary carcinoma of the bile ducts will be those cases that

present with obstructive jaundice resulting from a tumor in the head of the pancreas or periampullary area of a sclerosing variety of a relatively small size. In such circumstances, cure rates of over 30% have been reported [40]. Survivors of other bile duct carcinomas are uncommon despite their early clinical manifestations, because of the immediately surrounding unresectable vital organs such as hepatic artery, portal vein, and liver.

Treatment

Hepatocellular carcinoma

Although vigorous efforts should be made to work up patients with primary hepatocellular carcinoma for attempted cure through surgical resection, it must be recognized that the vast majority of patients present as candidates only for palliation of symptoms. Surgical resection of more than a limited extent is not possible in patients with underlying cirrhosis, since that fibrotic process prohibits hyperplasia of the remaining liver cells to compensate for the anatomic loss in addition to the reduced liver function from cirrhosis itself. Thus seldom will a patient with underlying cirrhosis be a candidate for surgical resection and even the possibility of cure. In contrast, solitary lesions arising on the background of a non-cirrhotic liver, as might be seen as the fibrolamellar or encapsulated varieties of hepatoma and in hepatoblastoma, may provide significant opportunities for surgical resection and cure. Patients with hepatoma should be evaluated for the possibility of surgical treatment by the use of the anatomic studies described previously and careful clinical assessment. Patients who have evidence of portal hypertension, ascites, esophageal varices, or distant metastases are categorically incurable and inoperable. In the absence of the ability to prove the diagnosis by non-operative needle biopsy, ascitic fluid cytology, or biopsy of metastases, it is not necessary, except for academic or research protocol purposes, to confirm the diagnosis by open surgical laparotomy in a typical case with diagnostically elevated alpha-fetoprotein. Laparoscopy and direct biopsy is sometimes a method of achieving biopsy without formal laparotomy in such patients. Patients without evidence of significant cirrhosis or complications of cirrhosis, such as portal hypertension or ascites or metastatic disease, are candidates for surgical exploration for the determination of resectability. When laparotomy is carried out on such patients, provision should be made for hepatic resection. Conduct of the exploratory laparotomy merely for obtaining a biopsy on a patient who is suitable for resection without being prepared to perform that major operation at the same time is to be condemned. At exploratory laparotomy, evidence of cirrhosis is determined by gross examination of the liver and evidence of secondary deposits in the

liver or in the porta-hepatis lymph nodes is sought for. Direct extension of the hepatoma to diaphragm, abdominal wall, or adjacent viscera is not grounds for unresectability if the cancer arises in a non-cirrhotic liver and is unifocal, since some adjacent organs or abdominal wall can be resected *en bloc*. If all evidence by exploration of the abdominal cavity is that the primary hepatocellular carcinoma is unifocal in origin and the liver is non-cirrhotic, conditions are appropriate for a surgical resection. At this point, technical considerations involving the location of the primary cancer and the extent of the hepatic resection necessary to remove it determine the eventual surgical approach. Lesions that are well lateralized and do not abut the interlobular fissure can be resected with a generous wedge resection or an hepatic lobectomy with relative safety and significant expectation of cure. However, lesions that involve more than one lobe or are located high in the liver adjacent to the superior hepatic hilum may preclude a logical anatomic hepatic resection. Occasionally trisegmental resection may be necessary to remove the larger, more strategically placed hepatocellular carcinomas. Because of the indolent nature of fibrolamellar and encapsulated varieties of hepatocellular carcinoma and hepatoblastoma, size alone is not a contraindication to hepatic resection [41]. Indeed, data indicates that survival rate for lesions greater than 10 cm or even 20 cm in diameter is nearly as good as for lesions that are smaller, indicating the more indolent nature of these specialized varieties of hepatocellular carcinoma. Although the logical extension of this biological finding would indicate that total hepatectomy and liver transplantation would be a method of dealing with unusually large or strategically placed hepatocellular carcinomas, the success rate with such efforts has been poor except in the indolent types [29, 41, 41a].

Resectability rates reported in the surgical literature vary considerably based on the geographic area of the report as well as the selection process that preceeds the exploratory laparotomy. It also, of course, is dependent on the relative incidence of hepatomas that arise on the background of cirrhosis. Since hepatectomy is a major surgical undertaking, clearly the seriousness of the surgical approach depends greatly on the facilities available in the hospital. Unfortunately, most hepatomas arise in third world countries where such major surgical procedures are unduly hazardous because of less adequate blood bank and intensive care facilities.

Although most authorities consider the presence of cirrhosis as a contraindication of major hepatic resection, occasionally patients with peripheral unifocal hepatoma can be resected from a cirrhotic liver if the amount of normal liver substance removed is kept to a minimum. Such a situation would obtain in a lesion of the left lateral segment or a peripheral lesion of the right lobe which could be treated by a large wedge resection.

In the absence of the ability to resect a primary hepatoma, either because

of the presence of cirrhosis or the large bulk or strategic location of the primary hepatic cell carcinoma arising in a non-cirrhotic liver, consideration should be given to implanting an hepatic artery catheter for constant infusion of chemotherapeutic agents, particularly 5FUDR. Regional chemotherapy given through such an intrahepatic arterial chatheter has been demonstrated to be more effective than systemic chemotherapeutic agents [42]. In the absence of the ability to conduct a program of regional infusion chemotherapy, hepatic dearterialization at the time of the surgical exploration should be considered since palliation and apparently prolonged survival has been reported in series of cases so treated [43]. Such surgical dearterialization is accompanied by a very significant postoperative mortality and morbidity, however, and should be reserved for institutions and surgical teams that are prepared for intensive post-operative care for support during a period of extensive hepatic necrosis. Clearly, the presence of cirrhosis and portal hypertension would contraindicate any attempt at hepatic dearterialization since in such cases the hepatic artery supplies almost all of the oxygen and nutrition for the normal hepatic cells. This is in contrast to the normal liver, where the portal venous flow supplies the majority of oxygen and metabolic substrates for the normal liver, and the liver tumors whether primary for metastatic are supplied largely by the hepatic artery.

Response rates of 30 to 70% have been reported in programs of hepatic arterial infusion chemotherapy and surgical dearterialization [42, 43]. Median survival durations up to 16 months for groups of patients who respond to these therapies have been reported [44, 45] and may double, triple, or even quadruple the expected life survival. Systemic chemotherapy with a variety of agents has been utilized to treat patients with primary hepatocellular carcinoma with variable success but generally low rates of response and short survival durations. As a result, in the absence of programs of regional chemotherapy for patients with primary liver cancer, standard chemotherapeutic regimens have not generally been accepted and such patients are candidates for experimental trials and protocols.

Radiotherapy of hepatic cell carcinoma can also be performed but offer the problem of normal liver tolerance to large doses of radiation [46, 47]. Local radiation therapy would primarily be indicated in patients with well-localized pain from extension of the hepatic cell carcinoma into the diaphragm, chest wall, or abdominal wall. In these situations a more localized field could be administered to relieve symptoms while not injuring normal liver. Occasional reports of combined treatment with chemotherapy and radiotherapy of a low dose have been published [47].

Experimental programs of anti-ferritin antibody used as a homing agent to carry radioactive iodine or specific anti-cancer agents have been reported by Order [48], but these techniques have been applied only to a very limited

subset of patients with primary hepatocellular carcinoma and are still totally experimental. Trials with interferon have been reported with uncertain results [49].

Gallbladder carcinoma and extrahepatic bile duct carcinoma

Gallbladder

The surgical treatment of gallbladder carcinoma is frustrating since the vast majority of cases are unresectable for cure because of local extension to liver, porta-hepatic, bile duct, or adjacent duodenum and colon. In addition, extensive lymph node metastases in the porta-hepatis and celiac axis are a common accompaniment of gallbladder carcinoma and preclude successful *en bloc* resection. Most curative resections for gallbladder carcinoma are carried out in ignorance under the belief that the gallbladder resection was for benign disease and only after removal is the carcinoma noted in the open specimen or pathology laboratory. However, in the unusual case of carcinoma of the gallbladder recognized at surgery and known to be only locally invasive, surgical resection should be carried out in the vain hope of cure. Although gallbladder carcinoma invading the liver and cured by right hepatic resection have been reported [50], in general this additional resection is to be avoided. If the primary gallbladder carcinoma is small, localized, and involving the liver parenchyma, wedge resection of an appropriate amount of liver tissue to provide a margin of a centimeter around the local invasion would be appropriate; hepatic lobectomy to accomplish this will yield no additional success.

The primary surgical objective in the vast majority of cases of gall bladder and extrahepatic bile duct cancers will be to provide surgical palliation of obstructive jaundice as well as the definitive diagnosis. Jaundice usually results from extensive carcinoma invading the porta-hepatis which would preclude a complete removal. In these situations, techniques of peripheral hepaticojejunostomy [5, 51, 52] to distended biliary radicals in the periphery of the left lobe in particular [53, 54], but occasionally the right lobe [55], are extremely useful in providing relief of jaundice and itching without indwelling, long-term percutaneous catheterization whether provided by radiological or surgical techniques. It is often forgotten how close to the surface of the liver significantly dilated intrahepatic biliary radicals lie in cases of obstructive jaundice. These ducts can be dissected out with relatively minor resections of the edge of the liver substance [53]. More importantly, it is frequently possible to do an anastomosis between a loop of intestine and the horizontal portion of the left hepatic duct several centimeters proximal to the hepatic duct bifurcation to provide one of the most efficacious biliary decompressions [51, 53]. The major surgical chore is to prevent the

symptom of itching from obstructive jaundice, and this can almost always be achieved by draining just the left lobe of the liver [23]. So long as the remaining obstructed portion of the liver does not get infected by repeated or persistent percutaneous catheterization, no major surgical problems ensue. The drained portion of the liver will hypertrophy and the obstructed portion will atrophy over time, so that the bulk of the liver mass will have adequate biliary drainage [23].

One absolute necessity in the performance of the surgical decompression operations is the avoidance of pre-operative radiological biliary decompression through percutaneous catheterization. It has been shown in recent controlled trials that preliminary biliary decompression does *not* decrease operative mortality although it may relieve obstructive jaundice [56–58]. Increased morbidity and prolonged hospitalization actually result. Of particular concern is the fact that pre-operative decompression obliterates the distended biliary tree which permits such an easy peripheral hepaticojejunostomy to be performed and prevents the effective use of the most reliable and trouble-free internal decompression that is available for palliation. Thus it should be emphasized that pre-operative diagnostic studies of obstructive jaundice should avoid percutaneous needle puncture of the intrahepatic biliary tree. Since the only diagnostic possibilities that exist in the clinical situation of a collapsed gallbladder and common bile duct with distended intrahepatic ducts is either primary or secondary malignant obstruction of the hepatic duct bifurcation or proximal common hepatic duct, it is unnecessary preoperatively to exactly define the anatomic appearance of the bile ducts in the area of the porta-hepatis. Ultrasonic demonstration of dilated intrahepatic ducts and an absent or small distal common bile duct and collapsed gallbladder are diagnostic. No other conditions exist in the area of the hepatic duct bifurcation that have that particular constellation of findings. Therefore, appropriate diagnostic studies in a patient with obstructive jaundice should consist of, sequentially, ultrasound of the liver and porta-hepatis and CT scan of that area. Endoscopic inspection of the ampulla of Vater and duodenum with retrograde cholangiography should also be considered, since it is helpful to rule out the possibility of ampullary or periampullary carcinomas and to indicate, from below, the level of biliary tract obstruction. Operation should be performed at this point without a percutaneous transhepatic cholangiogram with or without drainage, which has become so popular that it is performed without second thought by gastroenterologists, internists, and radiologists. The concept that this destroys the principal effective avenue of surgical palliation of the obstructive jaundice has yet to be widely appreciated in the medical community.

Extrahepatic biliary duct

Although elaborate schemes of anatomic classification of bile duct lesions

exist, carcinomas of the extrahepatic bile ducts can be separated for surgical purposes into two main categories. First, carcinomas of the distal common bile duct in the peri-ampullary area should be approached as any peri-ampullary carcinoma. However, unlike carcinomas of the head of the pancreas, where opportunities to avoid surgery should be sought by sampling for lymph node metastases in the common duct and peri-pancreatic area because the results of resection are so dismal, cancers of the distal common bile duct should be resected if at all possible because of the substantial cure rates that can be obtained. Thus an immediate peri-pancreatic lymph node metastasis would not be a contraindication to performing a radical pancreaticoduodenectomy for this cancer. Obviously if nodes at a more distant echelon are involved or if other evidence of extensive intraabdominal disease exists, resection is contraindicated. However, in true cancers of the distal common bile duct in the peri-ampullary or pancreatic head area, the vast majority of lesions are resectable because jaundice appears relatively early in the course of disease, and even if immediately adjacent lymph nodes are positive cures are still possible [59].

Cancers of the extrahepatic bile ducts anywhere except within the pancreatic portion of the common bile duct are infrequently resectable for cure; therefore surgical procedures are largely exercises in effective surgical palliation of obstructive jaundice. Because these tumors lie so immediately adjacent to the hepatic artery and portal vein, they frequently can be only incompletely resected or bypassed as described previously. One notable exception would be lesions of the right or left hepatic ducts or hepatic duct bifurcation which are very small or which grow anteriorly into the substance of the liver rather than posteriorly into the vascular structures of the portahepatis. In such situations, the resection might include either the right or left lobe of the liver to provide an adequate surgical margin for curative resection [60, 61]. In these unique situations, the posterior border against the major vessels may well be clear of the anteriorly growing carcinoma. Usually, these primary carcinomas of the extrahepatic biliary tree are quite small in overall dimensions because of the early appearance of jaundice, but still unresectable in toto because of the direct involvement of neighboring vital structures. The cure rate in all cancers of the extrahepatic biliary tree is extremely low although it has been the surgical custom to resect these whenever possible, even when leaving residual gross tumor. It is not unreasonable to consider as an option the peripheral bypass through hepaticojejunostomy to a dilated hepatic duct in right and/or left lobes of the liver and treatment of the undisturbed primary carcinoma itself with radical radiotherapy, either intraoperatively with radioactive seeds, intraoperative radiation machines [62], or externally through small fields [46]. It may well be that the disruption of the tissue planes around these small primary cancers by operation disseminates disease through surgical trauma. Several reports

of intraluminal therapy with cesium or other radioactive sources placed in tubes penetrating the obstructing primary bile duct carcinoma indicate the possible benefit of such programs of non-resection [63, 64].

If these primary extrahepatic bile duct carcinomas can be resected for cure, the second major surgical challenge is to provide effective drainage by means of an hepaticojejunostomy to the divided extrahepatic bile ducts high in the porta-hepatis of the liver. Sometimes it is necessary to core out a portion of the liver high in the porta-hepatis to provide enough duct to enable construction of a reasonable anastomosis. In carcinomas of the common hepatic duct or mid common bile duct, the hepaticojejunostomy is easily performed near the level of the hepatic duct bifurcation.

Radiotherapy of the biliary tree cancers

In contrast to primary hepatocellular carcinomas, radiotherapy should play an active role in the treatment for palliation of primary carcinomas of the gallbladder or extraheptic biliary ducts and perhaps cure of extrahepatic bile duct cancers. These tumors have been demonstrated to be radiosensitive in a number of reports [46], and significant shrinkage of tumors and even opening of obstructed bile ducts can be achieved by high dose radiotherapy. Innovative techniques of after-loading radiotherapy sources in tubes placed through obstructing extrahepatic bile duct carcinomas offer opportunities of achieving extremely high radiotherapy doses to these tumors, particularly when supplemented by external beam radiotherapy to small portals. Whether such innovative radiotherapy techniques can actually cure small, localized primary bile duct carcinomas remains to be seen however.

Chemotherapy of bile duct and gallbladder carcinomas

There is no standard chemotherapy for carcinomas of the gallbladder or extrahepatic biliary tree. A variety of agents have been utilized with modest response rates, but experience in any one of these treatment programs is limited [46]. These patients should all be candidates for protocol and experimental chemotherapy in attempts to achieve palliation of metastatic or symptomatic local disease extension.

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12. Islet cell and carcinoid tumors of the gastrointestinal tract

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Introduction

Islet cell tumors and carcinoid tumors of the gastrointestinal tract represent unique opportunities for the oncologist to fully integrate an array of surgical and internal medicine modalities. Arising from the APUD (amine precursor uptake and/or decarboxylation) system [1], these tumors frequently present with protean symptoms, often representing exaggerations of normal homeostatic mechanisms. Pathologists may have great deal of difficulty clearly distinguishing islet cell tumors from carcinoids. Indeed, examination of pathologic specimens alone may fail to predict the malignant potential for these tumors, which may only become known when metastatic disease is manifested [2]. Physicians who manage these patients require a full awareness of the biologic potential of these tumors as well as a proper balance of therapeutic restraint and aggressive medical and surgical management.

Islet cell tumors

Since the identification of the intestinal regulatory hormones, secretin and gastrin, three-quarters of a century ago [3, 4], much information has become available concerning the normal physiologic role of these and other peptides secreted by the gut and the pancreas. Not all gut peptides are, in fact, classically-defined hormones, which are defined by the ability to demonstrate release by a physiologic stimulus and effect response on a distant organ, with these effects mimicked by exogenous infusion of the hormone [5, 6]. Of the many peptides identified, only gastric inhibitory peptide, cholecystokinin, secretin and gastrin fulfill the criteria for a classical hormone, and only gastrin has been associated with a pathophysiologically abnormal tumor state. Other nonclassical peptides have been identified by histochemical techniques and electron microscopy in the pancreas and from the sto-

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

mach to the anus (Table 1) [7]. These peptides "are 'hormones' only in the pathophysiological sense and the normal physiologic function extrapolated from observations of their oversecretion" [5]. Complicating the correlation of these hypersecretory states with tumors of the APUD system is the observation that such tumors may produce no recognizable peptide, may produce a single peptide with or without a specific clinical syndrome, or may produce a large number of diverse peptides. Careful review of pathologic material from patients with apudomas reveals that most endocrine tumors may be composed of a number of cell types, each responsible for release of a particular peptide [8]. This heterogeneity should serve as a caution to avoid oversimplifying the syndromes produced by tumors or overemphasizing the differences between islet cell syndromes and carcinoid tumors [9].

Incidence and epidemiology

The diverse clinical presentations of islet cell tumors and their frequently silent and benign pathologic presence make an accurate determination of their true incidence very difficult. A great proportion of islet cell tumors probably remain asymptomatic and undiagnosed, as indicated by the high prevalence of these tumors in autopsy series (1500/100,000) compared to the reported clinical incidence of islet cell carcinoma (1/100,000) [10, 11]. As previously noted, the frequently benign histologic appearance of these tumors, which may belie their true metastatic potential, makes it likely that islet cell tumors are both underrecognized and underreported. There appear to be two different groups of patients with apudomas. The first group consists of those patients who evidence their tumors as a sporadic event, without significant personal or family history of endocrine disorders [7]. The second group comprises those patients who have clear evidence of an inherited predisposition to multiple neoplasias of the endocrine system, manifested in an autosomal dominant fashion. Since Wermer's and Sipple's

Table 1. Gastrointestinal endocrine tumors

Secretory cell	Normal peptide produced	Associated syndrome
alpha	glucagon	glucagonoma
beta	insulin	insulinoma
delta	somatostatin	somatostatinoma
D1 (?)	VIP	VIPoma; WDHA
G (intestinal)	gastrin	gastrinoma; Zollinger-Ellison
D (pancreas)		
intestinal crypt	5-HIAA	carcinoid
	5-HTP, others	

descriptions of two inherited syndromes with multisystem hyperfunction, a number of kindred with these disorders have been described [12, 13]. Wermer's syndrome – now termed multiple endocrine neoplasia (MEN) type I – is characterized by the presence of tumors of the pituitary gland, parathyroid gland and pancreas. Sipple's syndrome – MEN type II – typically present with parathyroid tumors, pheochromocytomas and medullary carcinomas of the thyroid, but without pancreatic tumors. However, the distinction between these syndromes is often blurred, such that pheochromocytomas, neurofibromas and carcinoids may be seen in either [5]. These association of apudomas suggests a common neuroectodermal origin for islet cell tumors, carcinoids and other cytochemically similar tumors [1]. Although these syndromes are rare, the physician presented with a patient with an islet cell tumor should be aware of these associations and should be prepared to evaluate family members for the presence of one or more manifestations of the MEN syndromes.

Pathology

Pathologists utilize a number of methods to characterize islet cell tumors. The classic Grimelius' silver impregnation stain [14] is now only part of a panel of studies used to identify pancreatic endocrine tumors, which may also include electron microscopy and immunohistochemistry. In poorly differentiated tumors, electron micrographs may aid in determining an endocrine origin by depicting characteristic ultrastructural features. Two histochemical studies which may also be useful are antibody-derived stains against specific peptides and against a nonspecific marker of the neuroendocrine system. The latter, neuron-specific enolase (NSE), is considered to be a simple and reliable way of detecting the presence of neuroendocrine tissue throughout the body [7]. The specific pathologic features of each of the islet cell tumors may vary in regard to location, multifocality, and malignant potential and will be discussed in regard to individual clinical syndromes.

Clinical features of islet cell syndromes

Zollinger-Ellison syndrome (ZES)

Since the original description of this syndrome by Zollinger and Ellison in 1955, the clinical features of gastrinoma-associated gastric hyperacidity have been extensively reported [15]. Although the original case reports were characterized by extensive gastric ulcer disease, a heightened index of suspicion and early detection have altered this pattern of disease presentation. The

typical patient today presents with a relatively short period of recurrent ulcer pain, frequently without an active ulcer present at the time of diagnosis [16, 17]. Other common clinical associations include diarrhea, secondary to rapid intestinal transit time, or other manifestations of the MEN-I syndrome [17].

The complete diagnosis of ZES is based upon four steps [18]: (1) identification of hypersecretion of gastrin, (2) evaluation of peptic ulcer disease, (3) localization of the primary tumor and (4) assessment of benignancy versus malignancy. Hypersecretion of gastric acid is the cardinal sign of ZES, and the demonstration of basal acid output > 15 mEq/h is essential to the diagnosis. The combination of an increased gastric acid output and a fasting serum gastrin level of > 1000 pg/ml is virtually pathognomonic for ZES. Borderline elevations of fasting serum gastrin must be further evaluated by the secretin test, in which a peak level of serum gastrin of > 200 mg/ml over baseline after administration of secretin is considered diagnostic [19]. Endoscopy is the most accurate means of assessing the extent of peptic ulcer disease, and may also allow for idenfication of the small proportion of extrapancreatic primaries, which chiefly occur in the duodenum [17]. Although CT scanning, ultrasonography and selective angiography may all be utilized to localize the primary tumor site, it is estimated that less that 50% of primaries are identified by any combination of these imaging modalities prior to surgical exploration [18]. Two other techniques which are being evaluated include percutaneous transhepatic portal venous sampling for gastrin and intraoperative pancreatic ultrasonography to detect sonolucent gastrinomas [18]. The assessment of malignancy of this tumor may be inferred from these same noninvasive techniques, but may also require surgical exploration to establish metastatic potential. Recent reports indicate that the incidence of rate of malignancy among gastrinomas is approximately 25% [17].

Insulinoma

Insulinomas are the most common islet cell neoplasms and are almost always confined to the pancreas. Unlike gastrinomas, these tumors are virtually always unifocal and benign in appearance and behavior [20]. As one would expect, the presenting symptoms of insulinomas are those of hypoglycemia and the associated laboratory findings are those of fasting hypoglycemia in the presence of an inappropriately high insulin level. In patients with suspected exogenous insulin administration or equivocal fasting insulin levels, proinsulin levels and calcium provocative testing may be performed [21, 22]. Because of the unifocal and predictable location of this tumor, selective arteriography is more likely to predict preoperative localization than similar studies in patients with gastrinomas [23].

Glucagonomas

One of the roles of glucagon is to counteract the effects of insulin by increasing serum glucose levels by promoting gluconeogenesis and glycogenolysis. The effect of hypersecretion of this hormone, therefore, is to cause hyperglycemia and carbohydrate intolerance, both of which may be relatively mild. The original description of this rare tumor included the characteristic skin rash, a necrolytic migratory erythema [24], in addition to which patients may present with generalized symptoms such as weight loss, anemia and diarrhea [25]. Another relatively constant feature of this tumor is the presence of hypoaminoacidemia, resulting from the effects of glucagon on glucose metabolism [26]. Although the true malignant potential of this tumor is not known, most patients present with high-bulk disease metastatic to the liver and with grossly elevated plasma glucagon levels, averaging 2110 ± 334 pg/ml in one series [27, 28].

VIPoma

This islet cell tumor is most notable for its presenting symptom of profuse watery diarrhea, from which it has also become known as the WDHA (watery diarrhea, hypokalemia and achlorhydria) or pancreatic cholera syndrome. Although other islet cell tumors – such as gastrinomas, which characteristically do *not* have achlorhydria – are associated with diarrhea, studies of VIP infusions in healthy volunteers have supported the concept that the diarrhea in VIPoma patients is clearly caused by elevated VIP levels [29]. Clinically, it is not always possible to differentiate VIPoma from gastrinoma, although abdominal pain is far more common in the latter [30]. In addition, measurement of high gastric acid, low stool pH and lack of metabolic acidosis will favor gastrinoma over VIPoma; however, the definitive diagnosis requires measurement of the appropriate hypersecreted peptide. The majority of patients with this syndrome have metastatic disease at presentation, chiefly to the liver [30].

Somatostatinoma

These extremely rare islet cell tumors were first reported in 1977 [31]. Boden and Shimoyama recently reviewed 20 cases in the literature with either plasma elevations of somatostatin or with islet cell tumors containing this hormone [32]. Eleven patients had diabetes, 13 had gall bladder disease and seven had diarrhea. Half of the patients had evidence of other endocrinopathies in addition to their somatostatinoma. In most cases (80%) malignancy was present at the time of diagnosis, although the majority of pancreatic primaries appeared to be solitary. Interestingly, all of the patients in this review were somewhat unintentionally diagnosed during searches for other endocrinopathies or gallbladder symptoms.

Therapy of islet cell tumors

Given the diversity of presentations of apudomas, their rarity and their frequently metastatic nature it is not surprising that the therapy of these tumors must be highly individualized. As with most other neoplasms, surgery is the most curative modality, but both chemotherapeutic and nonchemotherapeutic medical management may have significant roles to play in patients with these disorders.

Surgery

Surgical therapy of this disease may be performed for purposes of cure or to palliate tumor bulk or syndromes of hypersecretion. Surgical features common to all islet cell tumors are: (1) surgical extirpation should be performed when possible, (2) benignancy and malignancy may be difficult to establish by nonsurgical means, (3) because of the slow growth rate of these tumors, gross metastatic disease is not a contraindication to debulking, and (4) there may be no definite relationship between tumor mass and symptomatology [33]. Since insulinomas are the most localized, they are most frequently cured by resection, although attempts should be made to resect other islet cell tumors after appropriate noninvasive localization. The situations in which this may be considered are those in which obstructing lesions are present or when debulking is required to decrease symptoms from excess hormone production [64]. A recent review of 62 patients with metastatic insulinomas reported that the median survival of 17 such patients surgically treated with curative intent was 7.5 years, with 63% recurring at a median of 2.8 years [35]. Patients who had palliative resections had a median survival of 4 years, although no information was made available concerning the symptomatic benefit of this surgery.

The surgical management of ZES requires special consideration since, in addition to tumor-directed surgery, removal of the target organ may be considered. As previously noted, preoperative localization of tumor should be performed, but available techniques may frequently be inaccurate. Prior to the availability of H2-receptor antagonists, surgical management alone was considered standard therapy. However, in a large series of patients reported in 1974, the mortality associated with total gastrectomy was 30% [36]. The majority of patients died of postoperative or ulcer complications, and only 16% died of progressive disease. Of the 187 patients surviving total gastrectomy, 60% were alive at 5 years. The availability of newer forms of medical management and better surgical supportive care mandate a review of these options for the individual patients, recognizing that a large group of patients may still require total gastrectomy because of failure of nonsurgical measures to control ulcer disease.

Hepatic-directed therapy

The liver represents the most frequent site of metastatic disease from islet cell tumors. Although surgical removal of metastases may afford the best control of these metastases, the extent of such disease may mitigate against surgical approaches. In these indolent, symptomatic tumors, attempts at debulking may be made by nonsurgical techniques such as hepatic artery embolization and hepatic radiation therapy [37, 38]. Each of these techniques offer the possibility of symptom control in selected symptomatic patients with liver-dominant metastases.

Nonchemotherapeutic medical management

Medical management of islet cell tumors is frequently required because of their high likelihood of unresectable disease and prolonged survival with symptoms related to hypersecretion of active hormones. The most widespread example of such therapy is that of the H2-antagonists in patients with ZES, first reported in 1977 [39]. Both cimetidine and ranitidine, utilized in doses much higher than those required for peptic ulcer disease, have a high degree of success in controlling the gastric hyperacidity associated with gastrinomas [18]. Collected series show uniform control of abdominal pain after one month of therapy, with evidence of ulcer healing in half of treated patients [40]. Side effect of cimetidine in these studies included gynecomastia and male sexual dysfunction.

Although the majority of patients with insulinoma can be managed with a combination of surgery and high carbohydrate diet, some patients with unresectable disease may have profound hypoglycemia in spite of these measures. Diazoxide, an antihypertensive agent with hyperglycemic properties, may be utilized with some success in such patients [41].

More recently, data concerning the activity of a long-acting somatostatin analogue (SMS 201-995) in islet cell tumors has been reported. Somatostatin has the ability to decrease peptide release from tumors, but until a long-acting analogue became available its clinical effectiveness was limited by the 2 min half-life of the naturally-occurring hormone [42]. Beneficial antidiarheal effects associated with VIPomas have been observed, as well as tumor regression in a single patient [43, 44]. Individual patients with insulinoma and ZES have also shown some benefit from this drug [45]. Although the mechanism of action is not known, two cases of patients with WDHA secondary to VIPomas have been reported to respond to human leukocyte interferon [46]. Each of these patients had MEN-I, failed standard therapies, and responded within 3–5 days to interferon. Each of these latter new therapies will require further investigation to learn their ultimate role in the management of islet cell tumors.

Chemotherapy of islet cell tumors

In addition to the rarity of these tumors, there are a number of features of islet cell neoplasms which has made it difficult to perform and interpret clinical trials of chemotherapeutic agents [47]. Since these tumors are quite indolent, few investigators wish to expose patients to the toxicity of such drugs. When chemotherapy is utilized, patients have usually exhausted all other modalities of treatment and may be very late in the course of their disease, biasing against success. Finally, the nature of these syndromes allow for variable criteria of response, which have not been well codified; some investigators may report only objective responses in tumor size or hormone levels, whereas others may report subjective improvements in symptoms as well. In fact, both methods of determining response may be valid in these tumors. The first chemotherapy drug used against an apudoma was streptozotocin, an antitumor antibiotic chosen because of its known toxic effects on the pancreatic β-cell of animals [48]. In this situation, a patient with an islet cell tumor secreting multiple hormones responded to the administration of streptozotocin with a decrease in both tumor size and hormone production. Investigators at the Mayo Clinic subsequently demonstrated objective tumor regressions in five of eight patients with nonfunctioning tumors treated with this drug [49]. In 1973, the National Cancer Institute reviewed the results of streptozotocin therapy, demonstrating that approximately two-thirds of patients with functioning tumors demonstrated a decrease in hormone levels, and half of the patients with measurable masses demonstrated objective shrinkage [50]. The majority of the benefits were seen in patients with insulinoma, who comprised the largest proportion of those who received the drug. Although survival was significantly longer in responding patients than nonresponding patients (744 days versus 298 days), the survival advantage to therapy cannot be clearly established since the patients with more indolent tumors may also be those who are more likely to respond to therapy. Although significant improvement in quality of life for patients who respond may be expected, it is not without toxicity. In addition to the typical side effects of chemotherapy, including nausea and myelosuppression, nephrotoxicity – in the form of proteinuria and renal tubular damage – is dose-limiting [51].

Few other single agents have been adequately tested in islet cell tumors. Doxorubicin demonstrated four responses in 20 evaluable patients, 18 of whom had previously been treated with streptozotocin [52]. Chlorozotocin also has shown two complete and four partial responses in 17 evaluable patients; this drug has potential utility because of the absence of significant nephrotoxicity compared to streptozotocin [53]. DTIC, a drug with known activity against two other tumors of presumed neuroectodermal origin – oat dell carcinoma of the lung and malignant melanoma – has shown surprising activity in glucagonomas [54]. The prolonged and often complete remis-

sions seen in patients with glucagonomas after treatment with DTIC suggests that it be considered the initial drug of choice in patients requiring therapy. A clinical trials within the Eastern Cooperative Oncology Group (ECOG) is attempting to establish the use of DTIC in glucagonomas and other islet cell tumors.

There have been few organized attempts to evaluate the role of combination chemotherapy in apudomas. Following initial reports of success with a combination of 5-FU and streptozotocin from the Mayo Clinic – six of eight responses – a large randomized trial comparing streptozotocin (500 mg/m_2/day × 5 d q 6 weeks) to streptozotocin plus 5-FU (400 mg/m_2/day × 5 d q 6 weeks) was undertaken [55]. The combination was superior to streptozotocin in overall (63% versus 34%) and complete (33% versus 12%) response. Patients who received the combination also survived longer – 26 months versus 16.5 months –although this difference was not significantly different. In 1978, a new ECOG study was begun, comparing the best treatment from its previous study – 5-FU plus streptozotocin – to a combination of doxorubicin and streptozotocin or to chlorozotocin alone. This study also will evaluate prospectively the role of DTIC in the large group of patients who progress on these regiments. The data from these studies typically require a number of years to acquire because of the rarity of the tumors, the heterogeneity of the patients population and the typical long survivals observated with these tumors. In addition to systemic chemotherapy, there are isolated reports of hepatic infusions of chemotherapy, the goal of which is to spare systemic toxicities of chemotherapy, while increasing concentrations of drug within the liver [56].

Carcinoid tumors

Although carcinoid tumors are often discussed separately from islet cell tumors, they are also thought to be derived from neuroectodermal tissue and may frequently be associated with other endocrine tumors in MEN-I and MEN-II [5]. Although carcinoids may arise from any portion of the gastrointestinal tract, the majority arise in the rectum, the small intestine and the appendix. Also in common with islet cell tumors is the inability of the pathologist to distinguish malignant versus benign forms of this tumor by standard microscopy or to distinguish carcinoids from other apudomas [57]. Series of autopsies from the Mayo Clinic suggest that only 3% of carcinoids are symptomatic during life, and the vast majority of these tumors are found incidentally during autopsies or surgery performed for other reasons.

The carcinoid syndrome is the endocrinologic manifestation of this particular apudoma [59]. Unlike the syndromes observed in islet cell tumors,

the carcinoid syndrome may not be as clearly ascribed to a single hormone. Rather, the syndrome manifested by flushing and diarrhea has been attributed to a wide variety of chemicals, including histamine, bradykinin, serotonin and prostaglandins [57]. Moertel states that 'symptomatic therapy of the malignant carcinoid syndrome at present is in a fascinating state of confusion reflecting a parallel state of confusion regarding the pathophysiologic mechanisms involved in generating the flush, the diarrhea, the pulmonary symptoms, and the cardiac symptoms' [57]. Characterizing the indolent nature of these tumors are the long survivals of patients reported, even when classic features of carcinoid syndrome are present [60].

Surgical therapy of carcinoid tumors

Nearly half of all carcinoids occur in the appendix, and most of these will be less than 1 cm and diameter [61]. Such lesions are cured by local therapy, as will small lesions of the rectum. Larger tumors (greater than 2 cm), however, require standard cancer operations for their locations because of high risk of recurrent disease [57]. Of note is the observation in the series of patients from the Mayo Clinic was the high incidence of multicentric tumors (29%) in patients undergoing surgery or autopsy [58]. Because of the indolent nature of this disease and the tendency for locally recurrent disease to cause symptoms, removal of regional tumor metastases should also be performed when surgically feasible. In addition, repeated bypass procedures of obstructed bowel may be required because of regional metastases [62].

The principles of surgical management of hepatic metastases from carcinoid tumors are similar to those for islet cell tumors [62]. Such resections should be reserved for selected patients whose syndrome cannot be controlled by other means, and whose tumors are relatively well confined to an isolated portion of the liver. Because of the prominent hepatic involvement of this tumor, other liver-directed therapies have been utilized in these patients. In a review of the literature, Moertel reports 32 cases of surgical ligation of the hepatic artery for treatment of carcinoid syndrome [57]. Among the 25 patients who survived the initial complications of the procedure, 18 demonstrated significant benefit. A further 11 cases from the Mayo Clinic also showed an improvement in the manifestations of the syndrome, but the duration of response was typically quite short (median, 5 months). Embolization of the hepatic arterial circulation has also been reported to demonstrate responses in patients with carcinoid syndrome, although also of relatively short duration [63, 64].

Nonchemotherapeutic treatment of carcinoid tumors

Symptomatic relief of the patient with carcinoid syndrome may be achieved by a number of drugs. Simple antidiarrheal medications are frequently useful in the therapy of diarrhea associated with this syndrome. A wide variety of agents have been suggested for their benefits in preventing flushing and diarrhea, including cyproheptadine, methysergide, corticosteroids and adrenergic blocking agents; however, the response to these drugs may be unpredictable and the side effects relatively intolerable [57]. The proper use of such agents requires a great deal of expertise on the part of the treating physician and forbearance on the part of the patient.

Recently, as with islet cell tumors, the use of long-acting somatostatin analogues has been explored. Reports of six patients indicated rapid and complete response in five, with evidence of inhibition of release of tumor products [65, 66]. Evidence also exists in these studies for a refractoriness to somatostatin and a possible rebound effect when the drug is discontinued. Interferon has also been tested in nine patients with carcinoid tumors; benefits were observed in carcinoid syndrome in six patients, but none were observed to demonstrate a decrease in tumor size [67].

Chemotherapy of carcinoid tumors

The first report of the chemotherapeutic management of carcinoid tumor was the use of intraarterial nitrogen mustard in a patient with liver metastases [68]. Subsequently, such patients were included in trials of hepatic infusions of 5-FU, with variable responses in objective measurement and symptoms [69]. In the 1970s, reports of systemic therapy with single agents began to appear. The Mayo Clinic noted six of 15 responses with 5-FU and three of six responses with streptozotocin [70]. Isolated reports of activity of doxorubicin, DTIC and tamoxifen also appeared in the literature, but with less striking results than those seen with the same drugs used in islet cell tumors [71–73]. Subsequent reports have failed to confirm the initial observation for the effectiveness of tamoxifen in carcinoid. The Mayo Clinic chemotherapy experience in over 200 patients suggests that the activity of single agent chemotherapy in this disease is quite low, with response rates of $> 10\%$ seen in only three adequately drugs: doxorubicin, 7/33 (21%); 5-FU, 5/19 (26%); and DTIC, 2/15 (13%) [57]. The full evaluation of drugs in these patients is hindered by variable definitions of response criteria, the heterogeneity of the patient population and the hesitance of physicians to administer chemotherapy to patients except those with far-advanced disease.

Based on initial reports of six of nine responses from the Mayo Clinic with 5-FU and streptozotocin, further evaluation of this combination was

undertaken [60]. Ultimately, the Mayo Clinic reported an overall response rate of 33% with this combination (14/34 patients) [57]. A larger series of patients has been reported from a randomized study in the ECOG of 5-FU plus streptozotocin compared to a combination of cyclophosphamide and streptozotocin [60]. The response rate for the two arms were not significantly different (33% vs. 27%, respectively) nor were the significant differences in survival time. The ECOG continues to evaluate these complex tumors in a series of stepwise trials; the most recent of these studies is designed to assess the contribution of doxorubicin when combined with 5-FU and compared to the 5-FU and streptozotocin combination. These trials are rigidly controlled for proper eligibility and are stratified for multiple variables to allow for more sophisticated data analysis than has generally been available in these tumors. Other studies of combinations of 5-FU, doxorubicin, streptozotocin and cyclophosphamide have shown results similar to those in the ECOG [74]. Generally, the use of chemotherapy for carcinoid tumors has not been as successful as similar therapies in islet cell tumors, either for controlling syndromes or for reducing tumor bulk. Patients with carcinoid tumors should be managed initially with aggressive surgical techniques balanced by an appreciation of the long natural history of these tumors. Nonchemotherapeutic measures should be used to control symptoms of the carcinoid syndrome as long as possible. If possible, patients who fail standard measures should be treated within the confines of a clinical trial; when this is not possible, the use of chemotherapy should be restricted to practicing oncologists with broad experience in the management of these tumors.

Summary

Islet cell tumor and carcinoid tumors of the gastrointestinal tract share many features of etiology, natural history and therapeutic management. Because of their common origin in the APUD system, they may present with fascinating, interrelated syndromes attributable to a myriad of tumor products. More often than not, many of these tumors may never produce recognizable hormones or metastasize; in fact, the distinction between benign and malignant forms of these tumors may be blurred, only to be demonstrated by longitudinal evaluations.

Given these variables, it is not surprising that a single therapeutic approach to these tumors cannot be advocated. For certain stages of disease, aggressive surgical extirpation is mandatory, while in other – ironically, frequently advanced stages – a policy of nonintervention is most appropriate. Management of these tumors in 1986 requires not only the traditional skills of the oncologist in surgery, chemotherapy and radiotherapy, but also calls upon a background of general medical knowledge and should be associated with a future of exciting medical advances.

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13. Lymphomas of the gastrointestinal tract

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Introduction

Lymphomatous involvement of the gastrointestinal tract occurs with greater frequency than is generally appreciated, demonstrable in 30–50% of patients with non-Hodgkins lymphoma at post-mortem examination [1–4]. Although primary gastrointestinal involvement is less prevalent (3–11% overall frequency), the gastrointestinal tract is the most common primary site of extranodal lymphoma [1–3, 5–10]. Non-Hodgkin's lymphoma accounts for less than 20% of primary bowel malignancies [2] and fewer than 5% of neoplasms of the stomach and colon [11–15]. Roughly 1,300 new cases of primary gastrointestinal lymphoma are seen in the United States each year.

Like their nodal counterparts, primary gastrointestinal lymphomas comprise a heterogeneous group of lymphoid malignancies. Despite aggressive histologic features, gut lymphomas are frequently unicentric (focal) at presentation lending themselves in many instances to local control by surgical excission alone [8, 16–18]. Nevertheless, a quarter of patients may present with extensive disease spread. The applications of sophisticated histochemical and immunologic techniques to the classification non-Hodgkins lymphoma in recent years has led to the recognition of distinct biologic subtypes of lymphoid malignancies [19–22]. Gastrointestinal lymphomas are no exception, and in fact, demonstrate immunologic phenotypes which appear to be unique to this group of lymphoid malignancies [23–26]. In Western countries, high grade lymphomas of the large cell variety (diffuse histiocytic lymphoma in the Rappaport classification system) predominate [1, 2, 17, 18, 27–31]. Geographic and ethnic differences in both the incidence and histology of gut lymphomas corroborate potential underlying etiologic, histologic, and prognostic differences [31–37].

Since primary gastrointestinal lymphomas are a relatively uncommon tumor type comprising several histologic varients, large prospective ran-

John S. Macdonald (ed) Gastrointestinal Oncology: Basic and Clinical Aspects.
 ISBN-13: 978-1-4612-9209-8.

domized therapeutic trials of specific histologic subtypes are non-existant. Prognostic variables and treatment recommendations can be based only on retrospective data accrued at single institutions. Early studies utilize histologic classifications which are now outdated (such as giant follicular lymphoma or reticulum cell sarcoma). Other reports group a variety of histologic subtypes by site of gastrointestinal involvement. More recent papers employ the Rappaport or Lukes-Collins systems but direct comparison of these classification methods may be difficult.

Despite the above noted difficulties in interpreting the literature, a large amount of information is available concerning primary gastrointestinal lymphomas and several conclusions and generalizations can be made. In this review, gastrointestinal lymphomas have been categorized into three distinct epidemiologic types: (1) Mediterranean lymphoma; (2) sprue-associated lymphoma; and (3) Western lymphomas. In the United States, the Western or sporadic type of gut lymphomas predominates. It is this specific category to which the major focus of this discussion will be directed. A brief discussion of the other two types of gut lymphoma will be made early in the chapter because of their interesting epidemiology and unique clinical features. Particular characteristics of lymphocytes present within the gastrointestinal tract will also be described in an attempt to better understand the histogenesis of tumors arising in this area.

Histogenesis of gastrointestinal lymphomas

B-cell neoplasms derived from follicular center cells (FCC) account for the majority of lymphomas arising in the gastrointestinal tract [23, 25, 26, 29, 37–41]. Lymphoid follicles are normally distributed along the interface between the submucosa and muscularis throughout the small and large intestine, but are identifiable in the stomach only with advancing age [42]. This lymphoid network, termed the gut-associated lymphoid tissue (GALT) by Isaacson, exhibits a unique pattern of FCC migration [26]. Antigenically-stimulated FCCs in animals gain entry into the enteric lymphatics where they pass into the systemic circulation via the mesenteric lymph nodes and thoracic duct [43–45]. These lymphocytes then return to the lamina propria of that region of the gastrointestinal tract from which they arose, as active IgA secreting plasma cells. This specific homing characteristic of lymphocytes derived from GALT appears to persist in the neoplastic cells of gut lymphomas, accounting in part for the pronounced tendency of these tumors to remain localized for prolonged periods of time and for their distinct proclivity for local relapse.

FCC lymphomas of the gastrointestinal tract initially evolve by lateral expansion along the lamina propria, explaining their often large size at diag-

nosis [31, 38, 39]. Concentric expansion into the base of the mucosa follows with glandular disruption and secondary necrosis and ulceration of the mucosal surface. Invasion of epithelial glands is a characteristic feature of these tumors and serves as a useful aid in distinguishing FCC lymphoma from benign or reactive lymphoid proliferations [26, 48]. As the tumor grows, penetration into the muscularis eventually occurs, resulting in transmural tumor extension and perforation in 5 to 15% of patients at presentation [2, 12, 47–49] and in 10–30% of patients following cytotoxic therapy. The minimal desmoplastic response elicited by such tumors compared to gut carcinomas contributes to the risk of this potentially fatal complication [2].

Mediterranean lymphoma

Mediterranean lymphoma refers to the malignant variant of a lymphoproliferative disorder of the small bowel known as immunoproliferative small intestinal disease (IPSID) or alpha-chain disease [23, 32, 50]. This disorder exhibits a curious geographic distribution, restricted primarily to underdeveloped countries of the Middle East and Northern Africa. A recent report of gut lymphomas treated at Stanford University, however, suggests that IPSID may also occur in Mexican-Americans of lower socio-economic status [2].

IPSID may occur at any age, but tends to affect young adults in the second and third decades of life. The clinical features are generally those of malabsorption with episodic diarrhea, weight loss and abdominal pain, often occurring in association with clubbing of the digits of the upper and lower extremities [32, 51–55]. Contrast radiographs of the small intestine resemble those of celiac disease, with dilatation and segmentation of the upper bowel loops, thickened mucosal folds, and multiple nodular defects [56, 57]. Histologically, a mature plasma cell infiltrate can be demonstrated diffusely involving the mucosa of the second and third portions of the duodenum and upper jejunum, as well as the mesenteric lymph nodes [26, 50–54, 58, 59]. The plasma cells characteristically secrete an abnormal immunoglobulin of the alpha-heavy chain class which lacks conjoined light chains and amino acid sequences localized to the variable region [23, 50, 53, 54, 60]. Alpha-heavy chain is detectable in the serum of up to 70% of patients early in the disease course [21, 53, 54, 61].

Left untreated, progression to malignant lymphoma inevitably occurs. Diarrhea becomes continuous and a mass may be palpable on physical exam. Radiographs demonstrate longitudinal extension of the infiltrate throughout the small bowel accompanied by nodular or polypoid mucosal lesions [57]. Intestinal obstruction or perforation, however, are rarely en-

countered. Histologic sections reveal infiltration of the intestinal wall by cytologically dysplastic plasma cells and immunoblasts, a picture morphologically resembling immunoblastic B-cell sarcoma [54–58]. Although alpha-heavy chain is generally not detectable in the serum of patients with frank lymphoma, it is demonstrable within the cytoplasm of neoplastic lymphocytes using immunoperoxidase staining techniques [50–60].

IPSID appears to arise as a reactive lymphoid proliferation, possibly in response to a bacterial pathogen. Tetracycline alone, or when used in conjunction with prednisone, effects complete clinical and histologic remissions in the majority of patients with early stage disease [53, 59, 62]. As the plasma cell infiltrate becomes more dysplastic, response to tetracycline diminishes, but the disease may continue to be controlled with the addition of cyclophosphamide [23]. Combination chemotherapy with or without abdominal radiation results in much higher response rates and more durable remissions than single agent therapy in patients with malignant lymphoma [23, 52, 53, 63, 64]. The inclusion of anthracyclines into such chemotherapy regimens appears to increase the proportion of complete responders at the expense of increased toxicity [64].

Sprue-associated lymphoma

The association of malignant lymphoma of the small intestine with the malabsorption syndrome celiac sprue (gluten-sensitive enteropathy or ulcerative jejunitis) was first described in 1937 [65]. Lymphomatous involvement generally appears as a late complication of the disease, following the onset of malabsorptive symptoms by 6 to 20 years, affecting patients in their fourth to sixth decades [66–70]. The risk of lymphoma appears to increase with time. Among 210 patients with celiac disease followed prospectively at the University of Birmingham, the incidence of lymphoma reached 10% following 13 years of observation [33]. Adherence to a strict gluten-free diet was not protective. Although sprue-associated lymphomas represent over one-third of non-Hodgkin's lymphomas in Great Britain [24, 71], they are uncommon in the United States, accounting for fewer than 5% of cases [17, 72].

The predominant site of lymphomatous involvement typically parallels that of sprue, affecting the upper jejunum in 60% of cases. Villous atrophy with crypt hyperplasia is readily identified in jejunal mucosa remote from areas of tumor involvement. In approximately one-third of patients, however, lymphoma may be limited either entirely to the mesenteric lymph nodes or ileum, or may demonstrate multifocal small bowel involvement [71]. The morphologic appearance of these tumors resembles that of large cell immunoblastic lymphoma. Nevertheless, distinct cytologic differ-

ences are readily appreciated. Tumor cells are large with abundant cytoplasm and bizarre pleomorphic nuclei [24, 71]. Erythrophagocytosis is frequently observed and immuno-histochemical staining for lysozyme (muramidase) or alpha-I-antitrypsin is typically positive suggesting that these tumors may arise from cells of true histocytic lineage [24, 71]. The clinical pattern of tumor dissemination supports this notion demonstrating a distinct predilection for liver, spleen and bone marrow involvement. On the basis of the similarities to malignant histiocytosis, Isaacson has proposed that these tumors be termed malignant histiocytosis of the intestine [24, 71]. Recent reports, however, have challenged Isaacson's claims, suggesting that many of these lymphomas may actually represent 'histiocyte-rich' lymphomas exhibiting an intense proliferation of reactive histiocytes [41]. More recent investigations employing nucleic acid hybridization techniques to detect. Immuno glubolin and T-cell receptor gene rearrangements suggest that the majority of these lymphomas are of T-cell lineage [141].

Western lymphomas of the gastrointestional tract

Incidence

Non-Hodgkins lymphomas arising in extranodal sites account for up to one-third of lymphoid malignancies seen at Western institutions [9, 10, 73]. Among 1,467 extra-nodal lymphomas reviewed by the End Results Group of Cancer Registeries in 1972 (Table 1), 538 (37%) arose from a primary

Table 1. Sites of involvement in 1,467 primary extranodal lymphomas

Site	No. of patients	(%)
Gastrointestinal tract	538	(37)
Stomach	346	
Small intestine	110	
Colon	59	
Rectum	23	
Tonsil	162	(11)
Skin	110	(8)
Salivary glands	69	(5)
Bone	69	(5)
Lung	53	(4)
Breast	33	(2)
Brain	32	(2)
Eye	32	(2)
Testis	23	(2)
Other	346	(24)

[a] End results group of Cancer registries [9].

gastrointestinal focus [9]. The stomach is by far the most common site of gut involvement, representing between one-half to two-thirds of gut lymphomas in most series [1, 2, 7, 38, 71, 74]. Approximately 30% of cases originate in the small intestine, with 10 to 15% confined solely to the ileocecal junction. Colorectal lymphomas account for less than 10% of cases in most series.

Significant differences in both the incidence and distribution of gut lymphomas are demonstrable between patients of differing age groups. In the pediatric population for example, gastrointestinal primaries account for 20–30% of all non-Hodgkin's lymphomas and are almost without exception restricted to the distal ileum or ileoccal junction [2, 8, 13, 75]. Although gastric primaries predominate in adults, they account for only 6–10% of adult lymphomas [2, 17] and fewer than 5% of gastric malignancies [3, 7, 11–15]. Interestingly, more recent reports suggest an increasing proportion of lymphoma (8–11%) among gastric malignancies [76, 77]. The relative rise in frequency of gastric lymphoma may be attributed in part to the steady decline in rates of gastric carcinoma in this country, rather than a true increase in lymphomatous involvement per se [78].

Etiologic considerations

Association between Western lymphomas of the gastrointestinal tract and antecedent prelymphomatous states is less firmly established than in the other epidemiologic types. Retrospective analyses of surgical specimens and isolated case reports have linked gastrointestinal tract lymphomas with a broad spectrum of potentiallyrelated disorders. As with other primary extranodal lymphomas, a distinct pattern has emerged suggesting that the pathogenesis of many of these tumors may be related to pre-existing immunoregulatory disturbances (Table 2).

Brooks and Enterline reviewed surgical specimens obtained from 48 patients with gastric lymphoma for associated histologic lesions [18]. The

Table 2. Western lymphomas of the gut: clinical associations

Waldeyer's ring lymphoma
Atrophic gastritis
Crohn's disease
Ulcerative colitis
Nodular lymphoid hyperplasia
X-linked lymphoproliferative syndrome
Acquired immune deficiency syndrome (AIDS)
Allograft recipients
Hodgkin's disease

vast majority of cases (79%) occurred on a background of prior gastric damage. Specifically, histologic evidence of chronic gastritis of the lymphoid hyperplasia type was demonstrable in 60% of cases in areas of the stomach remote from the primary neoplasm. In 14 of these speciments, a florid transmural lymphocytic infiltrate was superimposed upon a subtle pattern of interstitial fibrosis, consistent with a so-called pseudolymphoma-like reaction. Chronic benign gastric ulcers were identified in nine specimens slightly removed from the lymphomatous infiltrate. In some instances, however, focal tumor invasion was demonstrable at the periphery of the ulcerative lesion. Similar findings have been reported by other investigators. Vimadalal and coworkers found histologic evidence of atrophic gastritis in 53% of surgical specimens [29]. Gastric achlorhydria, a frequent accompaniment, was identified in 164 (85%) of 194 patients with gastric lymphoma seen at the Mayo Clinic on preoperative evaluation [79]. Loehr *et al.* [12] found absent or diminished acid output in 35 of 36 patients tested.

Because lymphoid tissue is intrinsically foreign to the stomach, several authors have proposed that chronic follicular gastritis may in fact represent a precursor lesion with malignant biologic potential [18, 29]. Its temporal relationship to that of malignant lymphoma is certainly supportive, developing on the average a decade earlier than its malignant counterpart [46]. Likewise, Brooks *et al.* in reviewing 15 cases of gastric pseudolymphoma, found foci of malignant lymphoma in five of the specimens examined [46]. Although circumstantial, these data suggest that prolonged antigenic stimulation may, in some instances, result in emergence of a malignant clone, analogous to the lymphomas arising in a milieu of chronic thyroiditis [80–82], and sialadentis of Sjogren's syndrome [83–85].

Primary lymphoma of the small or large intestine has been reported to occur in association with Crohn's disease and ulcerative colitis [35–37, 86–89]. The risk of this complication remains to be defined, but is considerably lower than that reported for adenocarcinoma [86]. Nonetheless, the clinical profile of both malignancies is quite similar. Progression to lymphoma generally follows long intervals of symptomatic disease, ranging from 10 to up to 30 years in published series [37, 87, 89].

Nodular lymphoid hyperplasia (NLH) is a benign proliferative disorder of gut-associated lymphoid tissue which characteristically involves the entire length of the small bowel or colon of patients with common variable immunodeficiency [90–92]. Less frequently, adults or children without identifiable immune defects may be affected [92–94]. In both groups of patients, intestinal infestation with *Giardia lamblia* is routinely demonstrable at presentation suggesting a possible causal relationship. Not infrequently, however, NLH persists following eradication of the intestinal parasite [34, 96]. Progression to intestinal lymphoma occurs only rarely in immunodeficient subjects [97–99], but may be an important complication in immunocompe-

tent adults [34, 94, 95]. Tumors of both B and T cell lineage have been described, the majority of which arise from a solitary focus in the proximal jejunum or duodenum [34]. Mucosal biopsies of uninvolved intestine are characteristically normal.

Other states of immune dysfunction display a heightened risk of lymphoid neoplasia, with a particular propensity for digestive tract involvement. Approximately 35% of males with the x-linked lymphoproliferative syndrome develop malignant lymphoma, the vast majority of which originate in the terminal ileum or ileocecal junction [100]. Malignant lymphoma also represents an important complication in patients with the acquired immunodeficiency syndrome (AIDS) [101–103]. Among 90 lymphoma cases in AIDS patients reviewed by Zeigler and associates, either gastrointestinal or primary central nervous system involvement was reported in 75% of patients [103]. Exogenous immunosuppressants employed in the prevention of organ rejection in allograft recipients [104, 105], or as primary cytotoxic therapy in other forms of malignancy carry a recognizable risk of secondary extranodal lymphoma [106–109]. Patients treated for Hodgkin's disease, for example, have an estimated risk of metachronous lymphoma as high as 4.4% at 10 years of observation [108]. High grade lymphomas of the distal small bowel or colon predominate [108, 109].

Lastly, lymphomatous involvement of Waldeyer's ring may share pathogenetic features common to other lymphomas of the aerodigestive tract. Banfi *et al.* [110], in reviewing 292 cases of Waldeyer's ring lymphoma treated with local irradiation, found that 18% of patients developed subsequent disease limited to the gastrointestinal tract. Although less frequently found, the reverse is also true. Waldeyer's ring is not an uncommon site of isolated relapse in patients treated for primary gut lymphoma [17, 18, 31, 111, 112].

Histology

The histologic classification of non-Hodgkin's lymphomas has undergone considerable modification during the past decade. The Rappaport schema widely used in the United States has demonstrated consistent clinical and prognostic utility [114]. However, other useful immunologic classifications (such as the Lukes-Collins classification) have emerged based upon cell lineage within the immune system and the stage of lymphoid cell maturation [19–22]. The Working Formulation proposed by the National Cancer Institute represents a compromise of the more popular classification systems [115].

Large cell lymphomas of diffuse morphology (diffuse histiocytic lymphoma) represent the most common histologic type among primary gastrointestinal lymphomas. Among 117 gut lymphomas reviewed by Lewin and asso-

ciates at Stanford University [2], over 60% of cases were categorized as diffuse large cell lymphoma. Hodgkin's disease, which only rarely involves the aerodigestive tract, accounted for only two or 1.7% of cases overall. Similar figures have been reported by other investigators [1, 2, 11, 17, 18, 31, 35, 39–41].

The designation large cell or histiocytic lymphoma, however, encompasses a biologically diverse group of lymphoid malignancies. At Vanderbilt University, we have employed the Lukes-Collins classification system since 1974 [19]. Table 3 summarizes the immunohistologic classification of 247 primary gastrointestinal lymphomas seen at our institution during the 10-year interval between 1974 and 1984. As with their nodal counterparts, B cell lymphomas of follicular center cell origin predominate, accounting for roughly 70% of cases overall. T cell lymphomas were distinctly unusual, identified in only two patients with disseminated lymphomatoid granulomatosis. There were no lymphomas of true histiocytic lineage. Hodgkin's disease accounted for only four, or 1.6% of cases.

The distribution of histologic grades among gut lymphomas contrasts sharply with those of nodal origin, demonstrating a clear preponderance of high-grade histologic types [17, 18, 30, 31, 39–41]. Approximately two-thirds of gut lymphomas seen at Vanderbilt were classified as unfavorable-histology tumors, including large non-cleaved cell lymphoma (41%), small non-cleaved lymphomas (12%), and immunoblastic B cell sarcoma (14%). Overall, tumors of large cell histology comprised 61% of gastrointestinal lymphomas. Large cleaved cell lymphoma (6% incidence), although included within the descriptive category of histiocytic lymphoma, is consid-

Table 3. Lukes-Collins classification of 247 primary gastrointestinal lymphomas (Vanderbilt University, 1974–1984)

	Number	(%)
B cell type		
Small lymphocytic	16	(7)
Plasmacytoid lymphocytic	18	(8)
Follicular center cell		
Small cleaved	29	(13)
Large cleaved	13	(6)
Large non-cleaved	94	(41)
Small non-cleaved	28	(12)
Immunoblastic sarcoma	32	(14)
T cell type	2	
Histiocytic	—	
Malignant lymphoma unspecified	7	
Hodgkin's disease	4	
Pseudolymphoma	4	

ered by many investigators to represent a low grade or indolent variety of B cell lymphoma [116]. Both histology and grade of GI lymphomas vary sharply with anatomic site. Roughly three-quarters of gastric lymphomas are large cell malignancies [8, 14, 16–18, 30, 31, 117, 118], 70% of which were found to be of non-cleaved cell origin in our series. The histologic spectrum of small bowel lymphoma generally parallels that of nodal primaries [2, 7, 15, 75], although small non-cleaved cell (Burkitt and non-Burkitt type) or diffuse undifferentiated lymphoma accounts for the major portion of lymphoid malignancies arising in the distal ileum or ileocecal junction. Similar histologic types are reported for lymphomas confined to the cecum or ascending colon.

Clinical features

Gastric lymphoma

Like epithelial malignancies of the stomach, gastric lymphoma is a disease generally observed in the elderly population. The peak incidence occurs in the seventh decade of life [8, 14, 16–18, 29–31, 117], and demonstrates a clear male predominance (male:female = 1.2–3.0:1). The clinical presentation as a rule is indistinguishable from that of carcinoma. Up to 90% of patients complain of epigastric discomfort [1, 8, 11, 27, 118]. In approximately two-thirds of such patients, symptoms mimic those of peptic ulcer disease, characterized by postprandial exacerbations and transient response to antacids [2, 8, 17]. Weight loss, seemingly out of proportion to symptoms, may be prominent [1, 8, 11, 18, 27, 118]. Early satiety and dysphagia, however, are uncommon except in patients with proximal gastric lesions or esophageal extension [17, 27]. The physical examination is often unrevealing. Peripheral lymphadenopathy is observed in fewer than 10% of patients [18, 118]. In one-third of cases, an abdominal mass, epigastric tenderness, or occult fecal blood loss is demonstrable [1, 8, 11, 18, 27, 30, 118]. Approximately 5% of patients present with acute abdominal pain as a result of visceral perforation [2, 18, 27, 118].

Barium contrast studies of the upper gastrointestinal tract are abnormal in the overwhelming majority of patients [2, 7, 8, 11, 17, 18, 118]. Roughly 40% will reveal a discrete mass and an equal proportion a diffuse pattern of tumor infiltration [7, 121, 122]. Overall, a diagnosis of neoplasm is suspected in 70–80% of cases. Nevertheless, the distinction between lymphoma and carcinoma remains a more difficult task, with the former diagnosis entertained in fewer than 20% of cases [2, 7, 11, 18, 120]. Several recent studies have attempted to more accurately define the radiographic features of gastric lymphoma [120–122]. Using the criteria outlined in Table 4, the diagnosis of lymphoma could be established in 71% and suggested in 86%

Table 4. Radiographic features of gastric lymphoma

Diffuse mucosal hypertrophy with irregular thickened folds
Multiple ulcerations
Single ulcer with diffuse mucosal thickening
Absence of luminal narrowing
Preservation of wall pliability
Mass or ulcer > 10 cm
Transpyloric extension

of cases reviewed by Craig and associates [122]. The radiographic appearance of gastric lymphoma generally reflects the gross pathologic features. Lymphomas are large compared to most carcinomas, with two-thirds of lesions greater than 10 cm in diameter at initial presentation [121]. Extensive submucosal infiltration is manifested as nodular, thickened, rugal folds with multiple foci of superficial ulceration [121–123]. The minimal desmoplastic response evoked by non-Hodgkin's lymphomas infrequently produces significant luminal narrowing or loss of distensibility, despite extensive organ involvement [121–123]. The predilection of gastric lymphoma to arise in the antrum or distal third of the fundus [8, 11, 30, 38] results in contiguous spread to the duodenal bulb with concomitant duodenal ulceration in 33% of patients [120, 123]. Adenocarcinoma, by comparison, exhibits transpyloric extension in fewer than 5% of cases [124, 125].

Fiberoptic gastroduodenoscopy has proven an extremely useful tool in the preoperative evaluation of patients with gastric malignancies, potentially altering the primary surgical approach and improving operative staging. Among six recently published series, an accurate diagnosis of malignant lymphoma was established in greater than 60% of patients via endoscopic directed biopsy [2, 7, 27, 30, 31, 126]. The addition of cytologic analysis of gastric washings appears to increase the diagnostic yield to 90% in patients with exophytic tumors [31, 126]. Nevertheless, the characteristic submucosal spread of gastric lymphoma results in a consistent false negative rate of approximately 33% in most series [2, 7, 27]. Difficulty also arises in the preoperative distinction between malignant lymphoma of small B lymphocytes (i.e. diffuse, well-differentiated, lymphocytic lymphoma) and reactive lymphoid proliferations [31]. Generally, histologic concurrence with surgical specimens is high. Among 24 patients with gastric lymphoma seen at the M.D. Anderson Cancer Institute, endoscopic evaluation established a preoperative diagnosis of lymphoma in 21 [31]. In only four patients (19%) was the histologic type of lymphoma altered postoperatively.

Small bowel lymphoma

The Western variety of small intestinal lymphoma has a clinicopathologic profile readily distinguishable from that of the Mediterranean or sprue-

associated lymphomas [1, 2, 63]. The disease occurs predominantly in middle-age and shows a striking male preponderance (male:female ratio in adults 3:1, children 9:1) [2, 75]. Over 70% of tumors arise in the distal ileum, approximately one-third of which are confined to the ileocecal junction [2, 38, 74, 75]. Abdominal pain, typically periumbilical in location, is a prominent presenting feature in nearly all individuals [1]. In one-half of cases, it is accompanied by nausea and vomiting secondary to small bowel obstruction [2, 63]. Diarrhea and malabsorption, although prominent features of Mediterranean lymphoma, occur in fewer than 15% of patients with lymphoma of the small intestine found in Western countries [1, 2, 51]. Visceral perforation is not uncommon, noted in 10–15% of cases at presentation [2, 63].

A preoperative diagnosis of malignant lymphoma is infrequent in patients with small bowel primaries. Radiographic features are nonspecific and often indistinguishable from that of malabsorptive states or regional enteritis demonstrating aneurysmal dilatation, thickening of the bowel wall, and mucosal nodularity or ulceration [122, 127, 128]. A discrete mass may be appreciated in patients with obstructing bowel lesions. In patients with ileocecal lymphoma, over half will have radiographic evidence of intussusception, accompanied by a palpable mass in the right lower quadrant on physical examination [2]. Peroral biopsy, although useful in patients with Mediterranean lymphoma, is generally unsuccessful in the more distal lesions of Western small bowel lymphomas [51, 129].

Colorectal lymphoma

The large intestine is the least frequent gastrointestinal site to be involved by primary lymphoma [1, 2, 7, 17, 38, 41, 71, 74]. Among 247 gastrointestinal lymphomas seen at Vanderbilt University between 1974 and 1984, 13% had primary colorectal involvement. The anatomic distribution of 34 of these tumors is illustrated in Figure 1. Over 70% of lesions were confined to the right side of the colon; 16 (47%) of which involved the cecum. Interestingly, of the remaining lesions, all but one arose within 10 cm of the anal verge. The sigmoid, descending and transverse colon gave rise to only one or 3% of all colorectal primaries. This pecular pattern of distribution of colorectal lymphoma has also been described by other investigators [7, 38] and sharply contrasts with that observed in carcinoma of the large intestine.

The peak incidence of colorectal lymphoma occurs in the sixth to seventh decade of life, with both sexes being equally affected. The majority of patients present with rectal bleeding [1, 2], but up to 50% of cases are accompanied by diarrhea. Rectal pain and tenesmus may be prominent features in patients with rectal lesions. There are no specific radiographic features differentiating colonic lymphoma from other large bowel neoplasms.

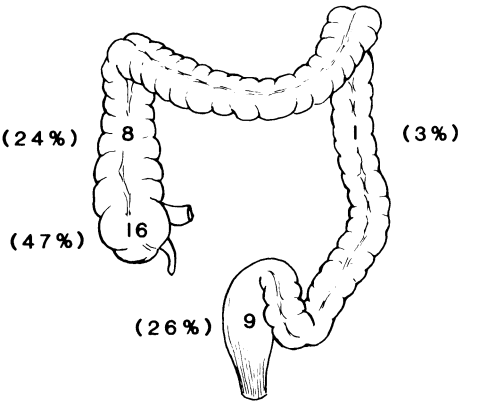

Figure 1. Regional distribution of 36 primary colorectal lymphomas seen at Vanderbilt University (1974–1984).

Most are discrete polypoid masses [38, 127, 130], but concentric mural invasion is not uncommon and may mimic the annular napkin-ring lesions of carcinoma of the large intestine [86, 130, 131].

Staging and prognostic factors

Careful clinical staging should be performed in all patients with non-Hodgkin's lymphoma to accurately define prognosis and tailor individual therapy. In patients with gastrointestinal lymphoma particular attention should be directed to Waldeyer's ring because of its high frequency of associated involvement and to peripheral lymph node chains. Peripheral blood smears in patients with small B-cell lymphoma (diffuse well-differentiated lymphocytic lymphoma) may reveal an absolute lymphocytosis, suggesting secondary gut involvement by chronic lymphocytic leukemia. Extreme elevations in serum LDH may be indicative of advanced tumor burden or lymphomas of high histologic grade. Every effort should be made to demonstrate lymphomatous spread beyond the abdominal cavity by physical examination, bone marrow aspiration and biopsy, chest X-ray, and abdominal CAT scanning or lymphangiography. The majority of patients with gut lymphomas ultimately come to laparotomy for either resection of the primary lesion or histologic diagnosis. Complete pathologic staging should be attempted in all such patients in a systematic fashion, including liver biopsy and sampling of both contiguous and non-contiguous lymph node groups. More often than not, however, the diagnosis of primary gut lymphoma is not suspected preoperatively, resulting in incomplete surgical staging. The benefits of accurate staging in this disease should be clearly understood by surgeons. Abdominal

Table 5. Modified Ann Arbor staging system for extranodal gastrointestinal lymphoma

Stage	Area of involvement
I_E	Solitary GI focus without lymph node involvement
II_E	GI focus plus lymph node involvement below the diaphragm
II_1E	Nodal involvement limited to immediately draining lymph nodes
II_2E	Involvement of contiguous and noncontiguous lymph nodes
IV	A dominant GI focus with lymph nodes involved on both sides of the diaphragm, or other extranodal sites

E = extranodal; GI = gastrointestinal.

CAT scanning provides an alternative method of assessing nodal involvement in patients unable to tolerate a major surgical procedure [132].

The staging system most often employed is a modification of the Ann Arbor classification adopted for Hodgkin's disease and non-Hodgkin's lymphoma with extranodal involvement (Table 5) [133]. In general, stage of disease at presentation is the single most important factor influencing survival [1, 11, 25]. Patients with disease confined to the gut wall (stage IE) have a consistently better prognosis than those with nodal or extranodal involvement (stages IIE and IV), regardless of histologic type [1, 7, 17, 25, 27, 28, 31]. In patients with primary gastric lymphoma for example, 5-year disease-free survival ranges from 60 to 85% for stage IE disease compared with figures lower than 50% for patients with concomittant nodal involvement [1, 7, 17, 18, 27, 28]. Discrimination between the pattern of lymph node involvement in patients with stage IIE disease appears to be of further prognostic importance [1, 17, 25, 30, 72, 134]. Among 51 patients with gastric lymphoma treated at Memorial Hospital, disease-free survival in stage II_1E disease was twice that observed for II_2E (50% vs. 25%) [30], and statistically identical to that observed in patients with disease limited to the gut wall (stage IE) [25]. Similar findings have been reported by other investigators [1, 17, 134].

Clinicopathologic stage generally varies with site of gut involvement. Approximately one-quarter to a third of patients with gastric lymphoma will have stage IE disease at diagnosis [2, 11, 17, 27, 28]. Another 50% of patients will have regional lymph node involvement (stage IIE), over half of which have disease limited to contiguous nodal structures (II_1E) [1, 17, 25, 134]. Approximately 25% of patients have disseminated disease at diagnosis, although higher figures may be reported in patients undergoing more intensive staging. The frequency of lymph node involvement increases with lesions located more distally in the GI tract, reflecting both the later detection of intestinal neoplasms and their more aggressive biologic nature [37, 38]. Among 109 surgically staged gut lymphomas seen at the Univer-

Table 6. Prognostic factors

1. Stage
2. Size of the primary lesion
3. Depth of invasion
4. Site of involvement
5. Polypoid lesions
6. Extension to adjacent structures
7. Histology
8. Cytoplasmic immunoglobin
9. Perforation
10. Age

sity of Michigan over a 40-year period, regional lymph node involvement was found in nearly 75% of all intestinal lymphomas, in 88% of tumors confined to the ileocecal junction, and in virtually all patients with colorectal lesions [72]. Site-specific figures for patient survival generally paralleled advancing stage, with over 55% of patients with gastric lymphoma alive at 2 years follow-up, compared with figures of 23 and 10% for patients with ileocecal and colorectal lymphoma, respectively.

Other variables have been reported to carry prognostic significance (Table 6), although few have been analyzed with respect to tumor stage. Favorable prognostic features include small (< 5 cm diameter) or polypoid lesions [12, 17, 18, 25, 30, 38, 39, 117], presence of cytoplasmic immunoglobulin in histologic specimens [38, 39], and indolent tumor histology [1, 11, 18, 25, 30]. Advanced age [30, 135], bulky tumor masses (> 10 cm) [17, 18, 25, 30, 38], and high-grade lesions [1, 17, 18, 25, 30] adversely influence relapse-free survival. Although intimately related to stage and histology, depth of mural invasion inversely correlates with survival. Prognosis sharply diminishes with penetration through the muscularis [11, 18, 38, 72]. Transmural invasion, in particular, results in an exceedingly high morbidity from hemorrhage or perforation upon institution of cutotoxic therapy [8, 28, 118, 135]. Likewise, extension of lymphoma to adjacent structures decreases relapse-free survival by 50% [11, 17, 72].

Management

The patient with primary gastrointestinal lymphoma poses a particular therapeutic challenge to the clinical oncologist. Prospective data on the management of gut lymphomas are not available, and retrospective studies from single institutions form the basis of treatment recommendations. Interpretation of such data is inherently complicated by small patient numbers and differences in patient selection, stage and treatment. Despite these short-

comings, several conclusions can be derived from this collective experience. Optimal management of the patient with gastrointestional lymphoma demands not only an accurate assessment of histology and stage, but an understanding of the pathophysiology and potential complications that may occur as a result of both the disease and its treatment.

Tables 7 and 8 summarize results obtained for early stage gastric lymphoma from six recently published series [1, 7, 17, 27, 28, 31]. It is apparent from these data that pathologic stage IE lymphoma may be successfully managed by surgery alone, with 75% of patients achieving relapse-free survival at 5 years observation. Postoperative irradiation appears to offer little if any additional benefit in this setting. However, in patients with local extension (serosal penetration or involvement of adjacent structures) or incomplete surgical excision, upper abdominal irradiation may decrease the risk of local relapse [1, 11, 17]. The same is not true, however, for patients

Table 7. Stage IE gastric lymphoma: treatment and freedom from relapse

Reference	Patients treated by resection only	5-yr RFS	Patients treated by resection + RT	5-yr RFS
Rosenfelt *et al.* [28]	—	—	6	5 (85%)
Novak *et al.* [7]	10	7 (70%)	6	5 (67%)
Paulson *et al.* [27]	2	2 (100%)	3	3 (100%)
Maor *et al.* [31]	9	6 (67%)	3	3 (100%)
Herrman *et al.* [1]	5	3 (60%)	4	3 (75%)
Weingrad *et al.* [17]	13	11 (85%)	11	9 (82%)
Total	39	29 (75%)	33	27 (81%)

RFS = relapse-free survival at 5 years of observation; RT = abdominal irradiation.

Table 8. Stage IIE gastric lymphoma: treatment and freedom from relapse

Reference	Patients treated by resection only	5-yf RFS	Patients treated by resection + RT	5-yr RFS
Rosenfelt *et al.* [28]	—	—	9	4 (44%)
Novak *et al.* [7]	2	2 (100%)	7	3 (43%)
Paulson *et al.* [27]	2	0	4	2 (50%)
Maor *et al.* [31]	3	2 (60%)	9	4 (44%)
Herrman *et al.* [1]	5	2 (40%)	6	6 (100%)
Weingrad *et al.* [17]	11	5 (45%)	21	13 (62%)
Total	23	11 (48%)	56	32 (57%)

RFS = relapse-free survival at 5 years of observation.

with ileocecal or small bowel lymphoma of comparable stage. Herrman *et al.* reported relapses in each of eight patients treated with resection alone, and in four of seven patients receiving adjuvant abdominal irradiation [1].

In general, surgical management alone appears to be ineffective in patients with regional (stage IIE) lymph node spread (Table 8). Although postoperative irradiation diminishes local recurrence [1, 11, 17], approximately 40 to 60% of patients will relapse outside the abdominal cavity [2, 17, 25]. In patients with stage II_1E disease, however, locally directed therapy may be curative.*En bloc* resection of the primary lesion and immediately draining nodal structures results in long-term disease control in 50% of patients [1, 17, 25, 134]. Post-operative radiotherapy controls an additional 30 to 40% of patients, acheiving results that are comparable to those obtained for patients with stage IE gastric lymphoma [1, 17]. Whether adjuvant chemotherapy can further improve disease-free survival in patients with resected II_1E disease as reported for patients with early stage node-based large cell lymphoma remains to be established [140].

Chemotherapy regimens used effectively in the treatment of large cell, nodal lymphomas such as CHOP, BACOP, M-BACOD and COMLA have been employed in patients with gastrointestinal lymphoma of similar histology. The specifics of these treatment regimens have been described elsewhere and will not be reviewed in detail here [136–139]. Results of treatment with these drug combinations has been less successful in primary gastrointestinal lymphoma compared with lymphomas presenting in other sites. Currently available drug combinations result in sustained complete

Table 9. Chemotherapy of advanced large cell GI lymphoma (biopsy only)

Reference	No. of patients	Chemotherapy	Relapse-free survival[a] (%)	Patients with major hemorrhage or perforation (%)
Hande *et al.* [134]	6	C-MOPPr	0	3 (50%)
	7	BACOP	1 (14%)	4 (57%)
Flemming *et al.* [8]	6	CHOP	1 (16%)	4 (67%)
Rosenfelt *et al.* [28]	23	CHOP, COP	7 (30%)	7 (30%)
Paulson *et al.* [27]	8	CHOP, BACOP, C-MOPPr	1 (13%)	NR
Maor *et al.* [31]	4	CHOP-B	0	0
Total	54		10 (19%)	18 (33%)

[a] Relapse-free survival at 2–5 years of observation.
C = cyclophosphamide; M = nitrogen mustard; O = vincristine; P = prednisone; Pr = procarbazine; B = bleomycin; A or H = doxorubicin; NR = not reported.

remissions in 40–70% of patients with advanced stage nodal large cell lymphomas [136–139]. Unfortunately, fewer than one-third of patients with gastrointestinal lesions achieve sustained clinical remissions [8, 27, 28, 135]. The reasons for this appear to be two-fold. As illustrated in Table 9, among patients with advanced disease in whom the primary lesion is left intact, approximately 33% of patients fail to enter remission as a result of perforation or gastrointestinal hemorrhage. However, with resection of the primary gastrointestinal focus (Table 10), a durable complete remission can be obtained in over 90% of patients. Although these are not randomized comparisons, such findings suggest that surgical resection remains an integral part of the management of individuals with advanced stage gut lymphoma with potentially resectable primary lesions. Initial surgical resection appears to reduce the risk of local complications, and by removing the site of tumor bulk, lowers the risk of local failure. Chemotherapy following surgery can then be more safely and effectively administered.

Although most patients with gastrointestinal lymphoma require aggressive therapy, some patients may be better managed in a more conservative fashion. Gastric lymphomas of indolent histology, for example, may have a lower risk of local complication than tumors of higher grade. Symptomatic patients with localized disease may benefit from regional irradiation alone. In more advanced disease, an oral alkalating agent such as chlorambucil or a non-anthracycline containing chemotherapy combination may offer significant palliation. Similarly, patients with large cell gastric lymphomas of small tumor diameter (< 5 cm) may be spared the risk of surgical intervention. Maor *et al.* [31] reported durable remissions in six unresected patients with clinical stage IE disease treated with four cycles of CHOP-Bleo (cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin) alternated with involved-field radiotherapy. Treatment of each patient with gastrointestinal lymphoma must be individualized. Carefully performed retro-

Table 10. Chemotherapy of advanced large cell GI lymphoma (primary resected)

Reference	No. of patients treated	Chemotherapy	Relapse-free survival[a] (%)	Patients with major hemorrhage or perforation
Hande *et al.* [134]	5	BACOP	0	0
Paulson *et al.* [27]	10	BACOP, C-MOPPr, CHOP	10 (100%)	NR
Maor *et al.* [31]	3	CHOP-B	3 (100%)	0
Total	18		17 (94%)	0

[a] Relapse-free survival at 2–5 years of observation.
NR = not reported.

spective studies with meticulous comparison of patients by stage, performance status, histology and treatment will continue to provide useful clinical information for planning individual therapy, and form the basis for much-needed prospective cooperative group investigations.

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