Environmental Health Perspectives
Vol. 33, pp. 115-126, 1979

Intestinal Disease and the Urban Environment

by Harold P. Schedl*

Factors in the urban environments of highly industrialized societies are important causes of disease. This review examines urban diseases of small and large intestine. The urban environment is pervaded by chemicals including drugs, food additives, pesticides, industrial products, etc., which are potential causes of disease. Examples of typical urban, as contrasted with rural, intestinal disease are considered in terms of differing etiological factors. Urban intestinal disease is examined from the following standpoints: the population at risk; the chemical agents to which the population is exposed; a model for the physiology of distribution and metabolism of chemicals in relation to the alimentary tract; the application of this model to treatment of an industrial disease; a major urban disease of the alimentary tract, carcinoma of the colon, considered in terms of this model; approaches to characterizing, identifying, and controlling urban intestinal disease.

Introduction

The title of this paper implies that factors in the urban environment are important determinants of intestinal disease. What are the environmental factors and the diseases? How can we identify them as well as treat and prevent the diseases?

We must begin by defining the "urban environment" and its characteristics so that the term is useful for classifying diseases and understanding their relationships to the environment. The densely populated areas of highly developed industrialized countries of the West epitomize the urban environment. However, if we use this as a definition, cities in developing countries may show some of the worst features of the urban environment. In addition, if the urban environment is thus defined, the rural environment must comprise the sparsely-populated areas of developed and developing countries. Yet, it is well recognized that environmental factors causing intestinal disease differ in rural areas of developed as compared with developing countries. For these reasons, it is simplest to define the concept "diseases of the urban environment:" diseases determined by factors resulting from technological innovations.

The most striking difference between urban and rural environments is in intensity of exposure to technology-related chemicals. This exposure to chemicals pervades all aspects of urban society and is fortunately, but sometimes unfortunately, lacking in the rural environment. In addition to containing factors that cause disease, the urban environment may also lack factors that prevent intestinal disease, factors that are present in the rural environment, particularly rural developing countries. To provide background, some intestinal diseases associated with urban and rural environments are considered, using recent, widely publicized examples. For historical perspective, the first urban intestinal disease, rickets, is also considered.

Background

Diseases Caused by Presence of Factors

An environmental factor present in developed countries and deficient in developing countries is access to modern medical care. In many cases modern medical care focuses simply on greater use of

*Division of Gastroenterology-Hepatology, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242.

drugs, particularly antibiotics. Antibiotics alter the normal bacterial flora of the alimentary tract, leading to overgrowth by opportunistic organisms. Many antibiotic-treated patients develop watery diarrhea. Diarrhea with colitis develops in a smaller percentage of treated patients. Antibiotic-associated colitis is particularly associated with lincomycin and clindamycin and is characterized by severe diarrhea with pseudomembranous placques, confluent pseudomembranes, and/or diffuse hemorrhagic colitis (*1*). The etiologic organism appears to be *Clostridium difficile,* which produces an enterotoxin causing the secretory diarrhea (*2-4*).

Enterotoxin-induced diarrhea can also be contracted in developing countries (*5, 6*). In fact, it is one of their commonest diseases, and is called "travelers' diarrhea," when we contract it ourselves (*7, 8*). When this disease occurs in the indigenous population, it can be considered an intestinal disease of the rural, as contrasted with the urban, environment. Inadequate purification of the water supply, due in part to lack of chemical treatment, and poor sanitation, result in endemic gastrointestinal infection with bacteria that cause acute, watery diarrhea, with no specific pathologic lesion. Strains of *E. coli* producing enterotoxin are the most common pathogens (*5, 6*). These organisms are indigenous and are spread by the fecal-oral route through food and drink. This self-limited disease runs the shortest course if untreated, but certain antibiotics may be beneficial in prophylaxis (*9*). Obviously, too-liberal use of antibiotics for prophylaxis in developing countries would lead to the urban disease, pseudomembranous enterocolitis, even in the rural setting.

The list of urban diseases of medical progress is enormous, including drug reactions involving the gastrointestinal tract. Patients receiving anticoagulants may have intestinal obstruction from intramural hemorrhage (*10-12*). Patients taking oral potassium preparations may develop ulcers, strictures, and obstruction of the gastrointestinal tract. Enteric-coated potassium tablets, the worst offenders, have been withdrawn from the market. The currently available preparation of potassium chloride impregnated in a wax matrix has a much lower incidence of this complication, although it still occurs (*13, 14*).

Diseases Caused by Lack of Factors

Contrasting with urban intestinal diseases caused by the presence of specific factors in the urban environment are urban diseases caused by lack of factors abundant in undeveloped countries. These include the colonic diseases, diverticulosis and diverticulitis. Although cause and effect relationships are not firmly established, the increased incidence of diverticular disease in the populations of highly civilized societies as compared with undeveloped countries is attributed to lack of fiber or bulk in the urban diet (*15*). For example, diverticular disease of the colon occurs commonly in westernized populations eating little dietary fiber and rarely if at all in African communities where fiber consumption is high (*16*). Even in a high-incidence society, asymptomatic diverticular disease reflects fiber intake: fiber intake by vegetarians is twice that of nonvegetarians, whereas incidence of diverticular disease is one-third as frequent (*17*). In a society in which incidence was previously low, Africans (blacks) living south of the Sahara, urbanization associated with change from the traditional high to a low residue diet has been accompanied by emergence of diverticular disease (*18*). A striking feature of the incidence pattern is that of 16 patients, five were young (in their fourth decade) and only four were over the age of 60. Diverticulosis of the colon also occurs more frequently in the urban population of Greece, particularly in the more prosperous segment. In contrast with findings by other workers with respect to fiber, there is no relationship between diverticulosis and dietary fiber content (*19*).

The "irritable bowel syndrome" is probably the most common gastrointestinal disorder of the urban population of developed countries. Since low fiber intake is thought to be a contributing factor, case reports of irritable bowel syndrome in urban blacks consuming a low fiber diet are of interest (*20*). The psychosomatic component of stress of the urban environment in both irritable bowel syndrome and diverticulosis should also be emphasized.

The complexity of urban intestinal disease can be illustrated by a malady that is ordinarily thought of as the bone disease, rickets. This disease appeared in epidemic form at the start of the industrial revolution, virtually disappeared, and now is returning (*21*). Rickets is caused by impaired intestinal calcium transport through lack of vitamin D action on the gut. Vitamin D is derived from endogenous and exogenous sources: the endogenous source is the vitamin D produced by exposure of the skin to ultraviolet light; the exogenous source is vitamin D in the diet. Either source can meet the body's needs. Rickets first became a notorious urban disease during the industrial revolution. The population moved from country to town and was housed in poorly lighted, multistoried dwellings set on narrow dark streets. The long working hours combined with the shaded environment were compounded by air pollution produced by the factories. Penetration of ultraviolet

light was so greatly reduced by air pollution that even animals in the municipal zoos — chimpanzees, lions, and tigers — developed rickets. This urban disease was eliminated by consumption of fish liver oil, irradiation of milk, and correction of air pollution. However, rickets has recurred with recent population movements: Indians and Pakistanis to Great Britain (*22*) and Turks to Germany (*23*). This can be explained by the following hypothesis: these groups normally consume a vitamin D-deficient diet and are sustained by the endogenous production of vitamin D in the skin by sunlight. Exposure to sunlight is minimal in their new cloudy, cool environment, and they have lost their normal supply of endogenous vitamin D from irradiation of skin.

Diseases Determined by Urban Population Groups

Certain diseases occur in both urban and rural environments, but have differing patterns in the two settings. For example, amebiasis is endemic in rural environments of developing countries because of poor sanitation and presence of amebae in the food and water supply. Endemic amebiasis has been almost eliminated from the urban environment, and is rare in the United States (*24*). Yet in two settings, custodial institutions and male homosexuals, the disease is epidemic in the urban environment. In custodial institutions for the retarded and for patients with mental disease, the inmates do not observe the usual precautions for prevention of fecal-oral contamination. One patient harboring amebae spreads infection among the others. Sexually transmitted amebiasis as well as other protozoan diseases are epidemic among male homosexuals in New York City (*25*). Pathogenic protozoa have been found in 26% of a sample of 100 homosexual men, not selected on the basis of symptoms. In San Francisco during a three year period, amebiasis, shigellosis, and viral hepatitis A and B increased four- to tenfold, most commonly in young men (*26*). Usually there was a history of frequent orogenital and oro-anal sexual contact between men, with no common food source. This contrasts with the previous foodborne or waterborne transmission with equal occurrence in both sexes, a pattern still prevailing in developing countries. In the male homosexual, persisting intestinal symptoms demand intensive investigation for parasites. Close sexual contacts of these patients are usually asymptomatic cyst passers. *Entamoeba histolytica* infection is frequently associated with *Giardia lamblia* or *Dientamoeba fragilis*. Rectal gonorrhea probably shows a similar distribution pattern.

Statement of the Problem

As just indicated, division of intestinal disease into urban and rural categories on the basis of etiologic organism or mechanism involved may be arbitrary. The same infectious disease, amebiasis, has a different distribution in urban and rural environments. Diseases caused by the same mechanism, e.g., toxigenic diarrheas, have different causes in the urban setting (antibiotics) and the rural setting (poor sanitation). Diseases thus far considered are primarily infections of known cause, present long before the transition from rural to urban environment. Their control can be approached through standard public-health preventive-medicine measures, which are already implemented in developed countries. Not yet considered are diseases unique to the urban environment, diseases as yet unidentified, caused by environmental chemicals. How are such diseases to be identified so that control and treatment can be implemented?

Some such diseases have already been identified and certain of their consequences defined. Acute severe lead poisoning with abdominal colic is classically an urban disease of children with pica living in buildings where the paint pigments are lead-based. As response to this knowledge, acute lead poisoning has recently become an urban disease of workers removing the lead from these buildings, "deleaders' intestinal colic" (*27*). Although acute lead poisoning is a well defined syndrome, blood lead is not a reliable index of past absorption and toxicity. The potential significance of elevated blood lead levels found in asymptomatic children through lead poisoning screening programs is only now beginning to be understood. The neuropsychologic effects of unidentified childhood exposure to lead have been examined by comparing performance of children with high and low levels of dentine lead (*28*). Dentine lead concentration is one of the best available indices of prior exposure. Children with high lead levels scored less well on an intelligence test, and frequency of nonadaptive classroom behavior increased in a dose-related fashion with dentine lead levels. Thus, lead exposure at doses below those producing symptoms sufficient for clinical diagnosis is associated with neuropsychologic deficits that may interfere with classroom performance. Vulnerability of children to lead is enhanced by their increased intestinal absorption. It is of interest that skeletal lead is currently three orders of magnitude greater in Americans and Britons that it was in Peruvians 1600 years ago (*29*).

Based on this experience with lead, how many other chemicals in the urban environment are caus-

ing undetected effects? Obviously, we cannot always expect well defined syndromes readily recognized by their dramatic acute effects or by standard toxicological procedures. With this background, what is the approach to intestinal diseases produced by chemicals, diseases so subtle that they are not recognized or only suspected? The remainder of the paper will attempt to define these problems as follows: to consider the population at risk; to examine the chemical agents; to outline the physiology of distribution of chemicals in the gut and in the body; to illustrate the application of this information to an industrial disease, Kepone poisoning; to consider the major urban disease of the alimentary tract, carcinoma of the colon; to characterize our present status with respect to identifying and controlling urban intestinal disease.

Characteristics of the Exposed Population

A systematic consideration of intestinal disease in the urban environment must begin by examining population at risk. Most of the characteristics that can be measured in a population bear some relationship to social classes within population. In Western societies the population is commonly divided into six social classes (Table 1). Class I comprises the leading professions and business executives, class III comprises two categories of skilled workers, nonmanual and manual, and class V is composed of unskilled workers. With regard to measures of health in a population, perhaps the most direct and least controversial indices are infant or neonatal mortality and post-neonatal mortality. Even during the middle of the 1970's, neonatal mortality was twice as great in class V as in class I (Table 1) (*30*). The post-neonatal death rate is one of the most socially sensitive health indicators in a society. Even in a welfare state such as Britain, post-neonatal mortality was three times as great in class V as in class I. This general pattern also holds true for many common diseases. Mortality rates from bronchitis and pneumonia, lung and stomach cancer, cerebrovascular disease, peptic ulcer disease, and motor-vehicle accidents show the classical one to five gradient.

With respect to intestinal diseases, cancer of the colon, a disease of western industrial societies, is unusual in that rates are level across the social classes. In contrast to the common diseases previously mentioned, leukemia and other malignancies of the lymphatic and hematopoetic tissues cause a sizable proportion of deaths, with the highest in class I and least in class V. Clearly, in examining intestinal disease in the urban environment, social class, with possible greatest incidence in class V, will have to be considered.

Table 1. Infant mortality by social class (1975-76 England and Wales).

Social class		Mortality (deaths/1000 live births)	
		Neonatal	Post-neonatal
I	Leading professions, business	7.4	2.8
II	Lesser professions, business	8.1	3.0
III	Skilled workers, nonmanual	8.5	3.3
III	Skilled workers, manual	9.5	4.2
IV	Semiskilled workers	10.9	5.4
V	Unskilled	14.4	8.6

Environmental Chemicals

The environmental setting of the population at risk for intestinal disease is filled with chemicals: earth, air, water, food, clothing, even newspapers, magazines and journals read for information about chemicals. How many chemicals are there? There is no definite answer. *Chemical Abstracts* lists over four million different chemical entities (Nov. 1977, quoted by Maugh, 1978), and the number in this register is growing at an average rate of about 6000 per week.

Current estimates by the Environmental Protection Agency (EPA) indicate that there may be as many as 50,000 chemicals in everyday use, not including pesticides, pharmaceuticals, and food additives. EPA estimates that there are as many as 1,500 different active ingredients in pesticides. The Food and Drug Administration (FDA) estimates that there are about 4,000 active ingredients in drugs and about 2,000 other compounds are used as excipients in the drugs to promote stability, cut down on growth of bacteria, and so on. FDA also estimates that there are about 2,500 additives used for nutritional value and flavoring in foods, and 3,000 chemicals are used to promote product life. This totals about 63,000 chemicals in common use. Obviously, the task of determining the safety of all commonly used chemicals could never be completed, only the scope of the task has been defined.

Why are there so many chemicals? We have accepted the use of manufactured chemicals to the extent that we hardly recognize them as such because they are integral to the innovations that make our urban society possible. Some chemicals are produced in response to legislation. For instance, flame retardants added to sleepwear for infants and chil-

dren are the response of the textile industry to flammability standards. When it develops that the flame retardants are mutagens (*32*), one may question how to assign responsibility.

Physiology of Distribution of Chemicals in the Body

Since chemicals are integral to the home and work environments, their potential for producing intestinal disease depends on their properties, how they enter and are distributed in the body, and how they are excreted. Chemicals must enter the body in order to cause intestinal disease and effects will depend in part on portal of entry. The major portal of entry of food and water-borne chemicals is ingestion (Fig. 1). Secondary portals are the lungs and skin. Pulmonary-to-alimentary tract exchange occurs as inhaled substances are coughed into the pharynx and swallowed. This may be particularly important for inhaled particulates and substances bound to them. Alimentary tract contents progress from pharynx to esophagus, stomach, small intestine and finally to colon. Absorption of toxins (as well as food and water) is chiefly from the small intestine, and for nearly all absorbed substances except fats the distributive pathway is via the portal system to the liver, where transformation, conjugation, and re-excretion into the alimentary tract take place (Fig. 2). Within the gut, the conjugates may be hydrolyzed by pancreatic and bacterial enzymes and be reabsorbed, or may remain within the lumen and be excreted in the feces. This enterohepatic cycle may be repeated many times, e.g., for bile salts and drugs such as indomethacin. Some metabolites pass from the liver

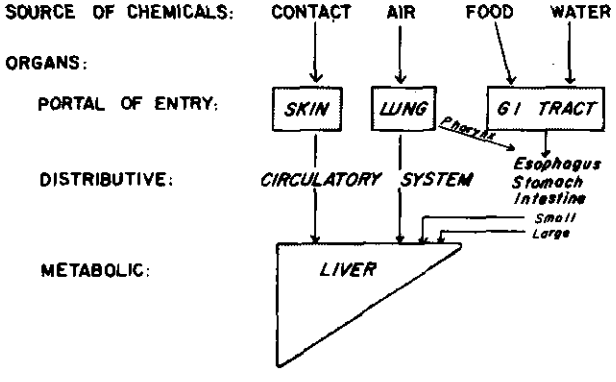

FIGURE 1. Environmental chemicals: portals of entry and initial distribution. Skin, lung and gastrointestinal tract are the portal of entry organs for environmental chemicals. The entering chemicals are carried in the circulatory system to the liver, a major organ of metabolism.

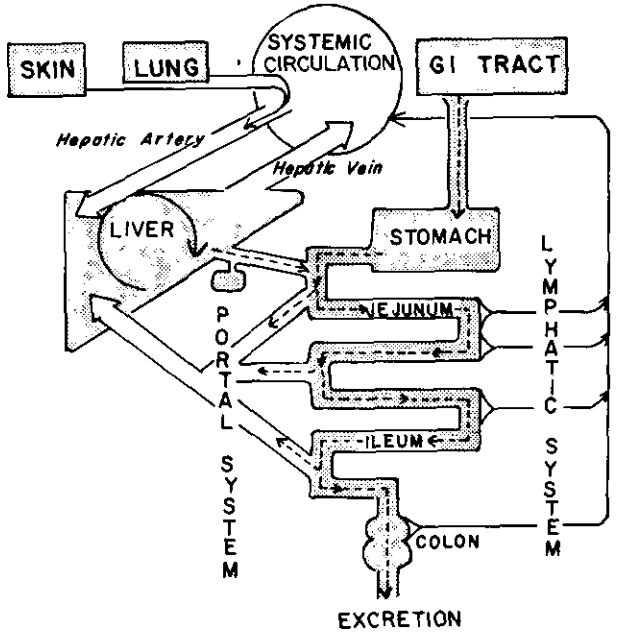

FIGURE 2. Environmental chemicals: distribution, cycling and gut excretion. Absorption of chemicals in food and water is chiefly from small intestine. The portal venous system carries nearly all absorbed substances to the liver except for fats and lipoidal compounds which are carried in lymphatics to the systemic circulation. Here they join chemicals taken up by skin and lungs to be carried in the arterial circulation to the liver. In the liver chemicals are transformed, conjugated, and re-excreted into the alimentary tract. Within the lumen, conjugates are hydrolyzed and the deconjugated compounds are reabsorbed, completing an enterohepatic cycle which may be repeated many times.

into the hepatic vein and enter the systemic circulation.

Chemicals taken up by lung and skin are also carried to the liver and participate in this cycle. Lipids in alimentary tract contents as well as lipoidal compounds such as DDT (*33*) and carcinogenic hydrocarbons (*34*) follow the alternate distributive pathway, the lymphatic system which discharges into the central venous system. From this locus they are pumped by the right heart through the lungs and join substances absorbed by the lungs in being carried to the liver.

Luminal Contents

Nonabsorbed Chemicals

Luminal contents of the alimentary tract are often considered "outside" the body until they are absorbed. Even if not absorbed, compounds in the lumen can exert significant effects. Although environmental chemicals are not usually taken in

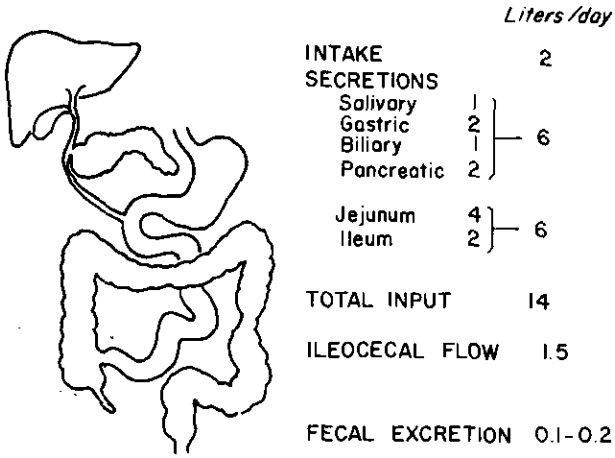

FIGURE 3. Intraluminal fluid volume in the gastrointestinal tract. Fluid intake of 2 liters/day added to salivary, gastric, biliary, and pancreatic secretions totaling 6 liters/day introduces a total of 8 liters/day of fluid into the proximal jejunum. To this is added six liters/day of secretions by the small intestine. This total volume of input into proximal small intestine represents the potential volume containing environmental chemicals. This volume has been reduced to 1.5 liters/day at the time of exit from the small intestine at the ileocecal valve. The greatest increase in concentration of environmental chemicals that remain unabsorbed occurs in the colon where the intraluminal volume is reduced to 0.1-0.2 liters/day by the time the contents are excreted in stool. This volume-flow pattern is consistent with presentation of the highest concentration of unabsorbed chemicals to the colon.

amounts sufficient to cause osmotic actions that change intraluminal fluid distribution, unabsorbed chemicals in solution could react with other compounds in the lumen or with the limiting membrane of cells lining the alimentary tract, e.g., altering membrane permeability, without being absorbed. Unabsorbed compounds could also alter the indigenous bacterial populations in the lumen. Concentrations of the chemicals in luminal contents will be relatively low because of the large volumes of fluid entering the alimentary tract (Fig. 3) (*35*). Added to the water intake of 2 liters/day are secretions (salivary, gastric, biliary, pancreatic) amounting to 6 liters/day. Small intestinal secretions add another 6 liters/day. This represents a total input of 14 liters/day. When the luminal contents leave the small intestine to enter the colon, however, the total volume has been reduced to 1.5 liters/day, and by the time the contents are finally excreted in stool the volume of water is 0.1-0.2 liters/day. Thus, concentrations of unabsorbed chemicals in luminal contents increase in distal small intestine and reach their highest levels in the colon where luminal volumes are lowest.

Solid and Particulate Components of Luminal Contents

Luminal contents of the alimentary tract are a multicompartmental system with solid and liquid (aqueous solution and lipid) components. The chief solid components remaining after digestion are those in fiber or bulk. In smaller amounts and of unknown significance are particulates such as asbestos fibers and fly-ash. These substances may be ingested directly as in drinking water or inhaled and subsequently coughed up and swallowed. Human studies have shown that at least a small fraction of ingested asbestos fibers is absorbed: fibers originating in drinking water are excreted in urine (*36*). Penetration of asbestos fibers (introduced intragastrically) through the digestive tract and accumulation in tissues has been shown in the rat (*37*). Other particulates such as coal fly-ash are mutagenic (*38*), and there is evidence that membrane uptake of chemical carcinogens may be particle-mediated (*39*). Thus, the possible role of the particulate component of the solid phase in the luminal contents in intestinal disease must be considered. The unabsorbed fiber component of the solid phase adsorbs bile acids and facilitates their excretion in the stool.

The bacterial ecosystem comprises another particulate component of luminal contents. The normal stomach and proximal small intestine contain few bacteria. The normal jejunum contains up to 10^4 organisms/g, the ileum up to 10^8/g, and the highest concentrations are found in colon (10^9-10^{11}/g). Because of the relatively low counts and species present, bacterial action on luminal contents proximal to the cecum is limited under normal conditions. Stasis of luminal contents (caused by blind loops, diverticula, strictures, fistulas, autonomic neuropathy, etc. in the proximal small intestine) prevents normal clearing of bacteria and allows bacterial overgrowth. These bacteria frequently have the capacity to deconjugate and dehydroxylate bile salts and hydroxylate unsaturated fatty acids. The resulting products inhibit water and electrolyte absorption and cause diarrhea, delivering nutrients to the colon. Bacteria exert major actions on the contents of the colon. Normally, nutrients do not reach the colon in appreciable amounts and flora of the normal bacterial ecosystem prevails. In the presence of stasis with bacterial overgrowth, digestive (pancreatic, biliary), or absorptive (nontropical sprue, intestinal resection) disease, or combinations thereof, nutrients reach the colon, changing the bacterial flora. Relations between alterations in flora and environmental chemicals are only beginning to be evaluated with respect to intestinal diseases.

Liquid Luminal Contents

The liquid phase of luminal contents is chiefly an aqueous electrolyte solution containing digestion products of food, chiefly carbohydrate and protein. Most components of the liquid phase are absorbed before the stool is excreted. Lipids and lipoidal substances insoluble in the aqueous phase begin as a lipid phase and after the digestion process are chiefly in the form of micelles. The lipid phase contains fatty acids, monoglycerides, bile salts, cholesterol, hydrocarbons, etc. Most of the lipids in the micelles are absorbed proximal to the ileum where the bile salts necessary for maintenance of micelles are absorbed.

Adsorption

Adsorption of gut contents to the intestinal wall also occurs: for example mineral oil can coat the alimentary tract, metabolic products of senna laxatives can be bound by the colonic mucosa (melanosis coli), and bacteria, particularly pathogens have the ability to attach to the gut wall. Some substances adsorbed to and taken up by cells lining gut wall may traverse the wall so slowly that a large proportion re-enters the lumen as the mucosal cells age, die, and slough into the luminal contents. Iron taken up by duodenal mucosal cells is an example.

Limiting Membrane and Lining Cells

Contents of the alimentary tract are in contact with the luminal surface of cells lining each organ, e.g., the brush border membrane of the small intestine. During absorption substances pass through the luminal membrane to enter the cell, although small molecules (e.g., urea) and ions (e.g., sodium and chloride) may also enter the body through intercellular pathways. Once within the absorbing cells, e.g., small intestinal mucosa, chemicals are subjected to intracellular processes including metabolism by enzymes and conjugation (*40*). Activity of enzymes in intestinal mucosal cells that metabolize chemicals is altered by the ingested chemicals themselves (enzyme induction) as well as by composition of diet and other factors.

Application to Treatment of Urban Intestinal Disease

Information on pathways of distribution and enterohepatic cycling of chemicals is basic to understanding chemically-induced intestinal disease. This information has already been applied to treatment of a systemic disease induced by a pesticide. The organochlorine pesticide Kepone (chlordecone) produces a toxic syndrome involving the nervous system, testes, and liver. In poisoned patients, elimination in urine and sweat is negligible, and fecal excretion accounts for an average of 0.075% of the estimated body burden per day (Fig. 4) (*41*). However, fecal excretion accounts for only one-tenth to one-twentieth of the load delivered into the alimentary tract by biliary excretion (determined by duodenal drainage). Unless Kepone has been converted intraluminally into unmeasured chemical compounds, major enterohepatic recycling must have occurred. To test the hypothesis of recycling, cholestyramine, an anion exchange resin that precipitates Kepone from bile, was administered orally (Fig. 4). Fecal excretion of Kepone increased sevenfold as compared with the control condition prior to treatment. Thus, cholestyramine blocks reabsorption of Kepone, possibly by preventing deconjugation. The effectiveness of cholestyramine in depleting body stores of Kepone depends on the equilibrium between tissue stores of Kepone and blood. Blood Kepone concentration is directly proportional to its concentration in fat, a major body depot. Rapid movement of Kepone from fat to blood to liver makes this detoxification possible. DDT in human body fat also established a dynamic equilibrium with the blood, permitting elimination via the alimentary tract (*42*).

Studies of distribution of Kepone in tissues and enhancement of its excretion by cholestyramine in a rat animal model showed that cholestyramine depleted Kepone from all body tissues in proportion to tissue concentration; and total fecal excretion of Kepone was greater than biliary secretion, suggesting excretory pathways other than bile (*43*). These pathways might be direct secretion by intestine into the lumen, possibly of a conjugate formed in intestinal mucosal cells, or loss through desquamation of Kepone-laden cells lining the alimentary tract during the normal cell renewal process. Thus, particulates in luminal contents of the alimentary tract can function as if effectively outside the body and provide a means for treatment of chemically-induced disease.

Colon Cancer

General

Carcinoma of the colon may be the most important intestinal disease of the urban environment. Undoubtedly, the greatest expenditure of time, effort and money has been devoted to this disease.

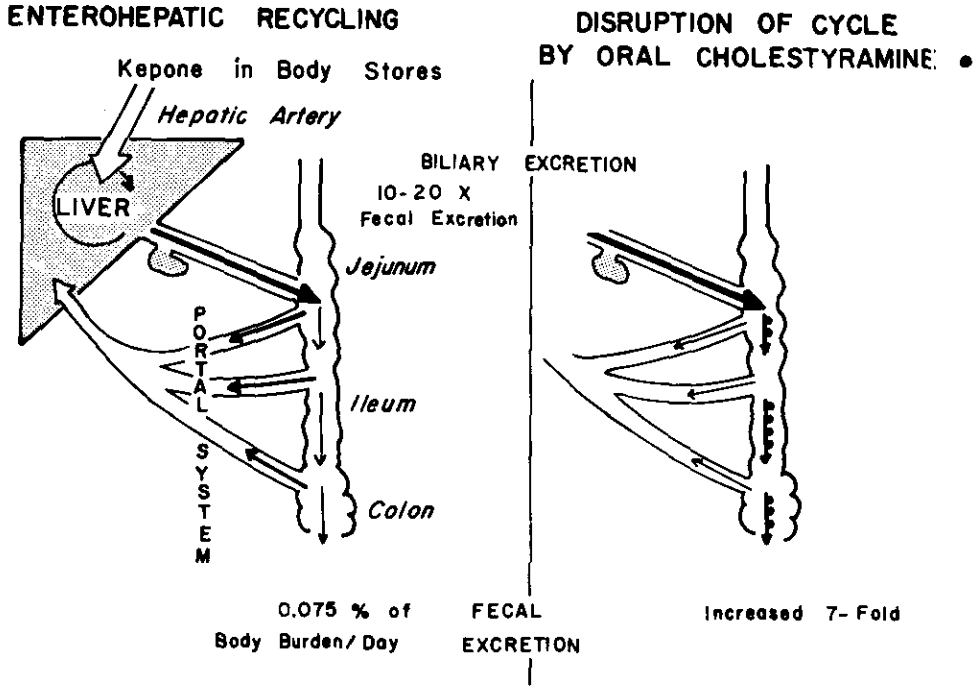

FIGURE 4. Kepone poisoning. Enterohepatic recycling and its disruption by cholestyramine. In poisoned patients biliary excretion of Kepone measured by duodenal drainage is 10-20 times greater than the fecal excretion rate of 0.075% of the body burden per day (left). This enterohepatic recycling of Kepone is interrupted by the anion exchange resin cholestyramine given orally (right). Increased fecal excretion lowers Kepone levels in the circulation, mobilizing it from body stores.

Pathophysiologic considerations just discussed are uniquely applicable to colon cancer, and the status of current knowledge has recently been summarized (*44*). Incidence and mortality of large bowel cancer varies markedly among populations (*45*). There is a sevenfold range in age-adjusted incidence rates, with high rates in populations of high socioeconomic standards and low rates in populations of undeveloped countries. The mortality pattern follows the same distribution. This urban distribution for colon cancer represents an epidemic pattern and holds for all highly developed countries except Japan. There is no socioeconomic gradient in incidence within populations of high risk (*46*), as mentioned previously (*30*). In populations at low risk a socioeconomic gradient is present: cancer of the intermediate portion of the colon (ascending colon through sigmoid) is increased in social classes I, II, and III, but there is no increase in cancer of cecum or rectum (*47, 48*).

Migrants from countries where the risk of large bowel cancer is low to countries where the risk is high acquire the high risk of the host country within their lifetime: rates for the first and second generation of migrants from Japan to Hawaii are considerably higher than for Japanese remaining in the country of their birth (*49*). The timing of the increase in incidence conforms to an incubation period of 20 years or more (*49*). In undeveloped countries, carcinomas of the cecum and ascending colon are more frequent than carcinomas of the left colon. In developed countries, cancers are predominantly in the left colon (sigmoid) (*50*).

Rectal cancers appear to comprise two populations (*44*). Cancers of the upper rectum have the epidemiologic distribution of colon cancer, i.e., highest incidence in developed countries. Cancers of the lower rectum have the highest incidence in developing countries. Thus, lower rectal cancers have a different set of etiologic factors as compared with upper rectal cancers, which appears to be those of colon cancer generally.

Etiology

Diet. The dynamics of the epidemic type of colon cancer of highly developed societies can be explained by the action on the intestinal tract of an environmental carcinogen that becomes more potent (e.g., concentrated or activated) as it passes from cecum to rectosigmoid. Thus, it is logical to consider differences in the diet as etiologic factors. No

specific carcinogen has been demonstrated in the highly refined diets of developed countries which contain food additives, and are characterized by high fat, sucrose and meat content. Because the colon is the most distal site in the alimentary tract, an ingested procarcinogen could be inactive in the proximal gut and might be activated when it reached the colon. Factors that might modify incidence or be causal in carcinoma of the colon include bulk, fat, and meat in the diet and their effects on the bacterial flora.

High-residue diets characterize developing countries where incidence of colon cancer is low. The more rapid transit time of gut contents resulting from such diets is thought to minimize effects of luminal carcinogens (*51*). However, no clear association between undigestible fiber content of diet, transit time, and colon cancer risk has been established. The amount of fat in the diet correlates well with risk of colon cancer (*50*). Blood cholesterol levels in cancer patients, however, tend to be low rather than high (*52*), although this may be secondary to other effects of the disease. Parallelism of colon cancer with cholesterol-linked disease such as myocardial infarction is to be expected, since both correlate with high socioeconomic status. For dietary components, meat consumption shows the best correlation with colon cancer: the colon cancer rate in Argentina, a developing country with high meat consumption, is as high as in the United States (*53*). The positive correlation of colon cancer with meat has also been shown by case-control studies (*54*) and in social class correlations (*47*).

Bacteria. Bacterial flora may play a key role in development of colon cancer. Related in part to differences in diet, feces of people from highly developed countries such as Britain and the United States have higher counts of bacteroides and lower counts of enterococci and other anaerobic bacteria than feces from people of Uganda, South India, and Japan, where frequency of colon cancer is low (*55*). Some species of clostridia have been reported to be of excessive frequency in patients with colon cancer (*55, 56*), but this finding has not been confirmed in subsequent studies (*57, 58*). Bacteria have the capacity to metabolize a wide variety of chemical compounds, and are exceedingly adaptable to substrate. An example of such bacterial action is the deconjugation of the noncarcinogenic glycoside cycasin to its carcinogenic aglycone. Cycasin, the β-D-glucoside of methylazoxymethanol, is not carcinogenic in the germ-free rat (*59*). In rats monocontaminated with bacteria having β-D-glucosidase activity and in conventional rats, cycasin given orally is carcinogenic and produces carcinoma of the large intestine. Under these conditions, only a small portion of administered cycasin is recovered unchanged in urine and feces, whereas in germ-free animals recovery of the intact β-D-glucoside is virtually complete. The product of cycasin hydrolysis, methylazoxymethanol is a potent carcinogen in germ-free animals, as well as in monocontaminated and normal animals. The requirement for presence of bacteria for carcinogenesis in the large bowel has also been shown for a synthetic compound, 3,2′-dimethyl-4-aminodiphenyl. This agent is not carcinogenic in the germ-free rat (*60*). Production of cancer of the large bowel by this agent requires the presence of feces, and cancer is not induced in segments of the large bowel by-passed by the feces (*61*).

Bacteria are not necessary for carcinogenicity of agents with target organ specificity for the colon, as demonstrated by production of cancer of the large bowel by methylazoxymethanol in germ-free rats (*59*). A related compound which is also a large bowel carcinogen in normal rats, methylazoxymethane, has been studied in operated conventional animals (*62*). Segments of colon were transposed to the level of the small intestine and segments of small intestine were transposed to the level of the colon. On treatment with methylazoxymethane, carcinoma developed in the transposed colon segments, but not in the transposed small intestine. Thus, colonic mucosa is susceptible to this carcinogen, regardless of its location in the alimentary tract, but the small intestine is not.

Steroids, which are also metabolized by gut bacteria, are procarcinogens, and their concentration in luminal contents is largely determined by amount of fat ingested. The steroid concentrations in feces are higher in people from developed western countries than from African or Oriental countries (*63*).

Colon Polyps

It is necessary to consider adenomatous polyps of the colon in connection with carcinoma of the colon as a disease of the urban environment of the highly developed western countries. Adenomatous polyps are probably causally related to colon cancer and both correlate strongly with respect to geography, anatomic location, socioeconomic class, migration experience, and time trends. Incidence of adenomatous polyps appears to be a good epidemiologic indicator of colon cancer risk (*44*).

Particulates and Cocarcinogens

This approach and these studies have not elucidated the cause of the epidemic of colon cancer in urban societies of the west. It is clear that the

alimentary tract, in particular the colon, offers an exceedingly complex setting for a chemically induced disease. Many factors, known and as yet unknown, remain to be investigated. The interactions of particulates (e.g., asbestos and fly-ash) carrying carcinogens, cocarcinogens, and enzyme induction require further study. Certainly, lung and colon cancers may share common etiologic factors. Cocarcinogenesis may be an important factor in colonic carcinoma. This phenomenon is well illustrated by asbestos and cigarette smoke (*39*). Some cancers, such as mesothelioma of the pleura and probably some gut carcinomas, result from exposure to asbestos alone. With bronchogenic carcinoma, the problem is different. Asbestos insulation workers taken as a group have a seven- to eightfold higher probability of dying from bronchogenic carcinoma than persons from the general population. However, when asbestos workers are divided into nonsmokers and smokers, nonsmokers have no increased disposition to lung cancer, while the smokers have a 92-fold increased disposition. This suggests that asbestos-induced lung cancer results from synergistic effects of the polynuclear aromatic hydrocarbons in cigarette smoke and particulate asbestos. Polynuclear aromatic hydrocarbons and particulates other than asbestos are also synergistic. To induce an increased incidence of lung cancer in experimental animals, it is necessary to disperse benzo[a]pyrene on the particulate, hematite. Intratracheal injection of benzo[a]pyrene alone resulted in only a low incidence of lung cancer in animals unless asbestos or india ink was also injected. The particulates did not induce cancer if benzo[a]pyrene was not also injected.

Why do particulates and polynuclear aromatic hydrocarbons act as cocarcinogens? Since particulates adsorb these hydrocarbons, they can function as carriers. Particulates also damage the target tissue. Both the damage to the target tissue and the enhanced transport, increasing availability of the polynuclear aromatic hydrocarbons for microsomal activation, could augment carcinogenicity. Mechanisms such as these may be important in colonic carcinogenesis. In particular, increased incidence of carcinoma of the colon in chronically inflamed mucosa of patients with chronic ulcerative colitis and regional enteritis may result from such mechanisms.

Conclusions

These concepts about urban disease in general and even about carcinoma of the colon are not new to our era. The dictum of Paracelsus, who was born in 1490, is basic to our thinking: "What is it that is not poisonous? All things are poisonous, and nothing is without toxicity. Only the dose determines that a substance is not a poison." Despite the magnitude of the problem of urban disease, there are reasons for optimism. The recent studies correlating classroom performance of children with their dentine lead concentration (*28*) demonstrates that toxicity can be measured in clinically undetectable disease. Awareness that such conditions may be widely prevalent should lead to greatly expanded efforts at identification and prevention. The example of rickets, the first disease of air pollution, illustrates another reason for optimism. The problem of rickets was solved without requiring the understanding of vitamin D we have today. We have only to consider our present state of scientific knowledge in comparison with that prevailing during the epidemic of rickets. The organization of this conference testifies to the knowledge and expertise that are currently available. Problems can be solved even if information is incomplete.

The number of scientists working directly on the intestinal tract and having this area as their primary interest is limited. These scientists are fully committed to relatively narrow disciplines, e.g., transport physiology, morphology, embryology, focused on the intestine. What is their role in detection, diagnosis, treatment and prevention of intestinal disease of the urban environment? Even the small amounts of environmental chemicals that we are constantly exposed to are probably toxic to the alimentary tract. If this toxicity produces urban diseases of the intestine, then like all toxicity syndromes the effects must range from acute to chronic with consequences that may be immediate or long-term. Some of these toxic effects must be very common, others exceedingly rare, occurring only in the genetically susceptible individual. This approach to seeking new intestinal disease is analogous to surveying for toxicity.

A diversity of toxic effects dictates a diversity of strategies for their detection. Clinicians are familiar with rare diseases that are most efficiently approached through case reports and case-control studies. These rare conditions must be relatively striking in order to be identified. Rare conditions that lack unique characteristic features usually remain undiagnosed. Common conditions may be so mild that associations with characteristics of the urban environment may be difficult to establish. It is possible that such associations can only be identified by prospective studies. Data sets may have to be developed in anticipation of the eventual need for prospective investigations. The alimentary tract is an exceedingly complex highly integrated system. The precise knowledge of the function of the subsystems

within this system is outside the expertise of the toxicologist. The researcher working in depth in a specific area is more likely than the toxicologist to recognize a new disease, but the approach must be multidisciplinary. This conference carries us a long way toward knowing how we must proceed.

In trying to plan our future course the following guidelines seem to be axiomatic:

1. There is no risk-free environment.
2. Removal of one chemical that is a specific risk-factor is followed by its replacement by another agent whose potentialities have not been defined.
3. We must identify noxious environmental chemicals and monitor for their adverse effects on the intestinal tract and other organ systems.
4. A diversity of approaches must be used, and this conference provides a focal point for identifying these approaches.

This study was supported in part by National Institute of Health Research Grant AM 02534.

REFERENCES

1. Tedesco, F. J., Stanley, R. J., and Alpers, D. H. Diagnostic features of clindamycin-associated pseudomembranous colitis. New Engl. J. Med. 15: 841 (1974).
2. Rifkin, G. D., Silva, J., Fekety, F. K., and Sac, R. B. Antibiotic-induced colitis: implication of a toxin neutralized by Clostridium sordelli antitoxin. Lancet II: 1103 (1978).
3. Bartlett, J. G., Chang, T. W., Gurwith, M., Gorback, S. L., and Onderdonk, A. B. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. New Engl. J. Med. 298: 531 (1978).
4. George, W. L., Sutter, V. L., and Finegold, S. M. Toxigenicity and antimicrobial susceptibility of *Clostridium difficile*, a cause of antimicrobial agent-associated colitis. Curr. Microbiol. 1: 55 (1978).
5. DuPont, H. L., Formal, S. B., Hornick, R. B., Snyder, M. J., Libonati, J. P., Sheahan, D. G., LaBrec, E. H., and Kalas, J. P. Pathogenesis of *Escherichia coli* diarrhea. New Engl. J. Med. 285: 1 (1971).
6. Guerrant, R. L. Role of toxigenic and invasive bacteria in acute diarrhea of childhood. New Engl. J. Med. 293: 567 (1975).
7. Gorbach, S. L., Kean, F. H., Evans, D. G., Evans, D. J., and Bessudo, D. Travelers's diarrhea and toxigenic *Escherichia coli*. New Engl. J. Med. 292: 933 (1975).
8. Merson, M. H. Travelers' diarrhea in Mexico, a prospective study of physicians and family members attending a congress. New Engl. J. Med. 294: 1299 (1976).
9. Sack, D. A., Kaminsky, D. C., Sack, R. B., Ititia, J. N., Arthur, R. R., Kapikian, A. Z., Ørskiv, F., and Ørskov, I. Prophylactic doxycycline for travelers' diarrhea. Results of a prospective double-blind study of Peace Corps volunteers in Kenya. New Engl. J. Med. 298: 758 (1978).
10. Yvars, A. M., Eckert, B., and Kane, A. A. Small bowel obstruction following anticoagulant therapy. Report of a case and review of the literature. Am. J. Gastroenterol. 44(6): 572 (1965).
11. Killian, S. T., and Heitzman, E. J. Intramural hemorrhage of small intestine due to anticoagulants. J. Am. Med. Assoc. 200(7): 591 (1967).
12. Crisler, C., Stafford, E. S., and Zuidema, G. D. Intestinal obstruction in patients receiving anticoagulants. Surg. Clin. North Am. 50(5): 1009, (1970).
13. Howie, A. D., and Strachan, R. W. Slow release potassium chloride treatment. Brit. Med. J. 26: 176 (1975).
14. Heffernan, S. J., and Murphy, J. J. Ulceration of small intestine and slow-release potassium tablets. Brit. Med. J., 28: 746 (1975).
15. Trowell, H. Definition of dietary fiber and hypothesis that it is a protective factor in certain diseases. Am. J. Clin. Nutr. 29: 417 (1976).
16. Painter, N. S., and Burkitt, D. P. In: Refined Carbohydrate Foods and Disease D. P. Burkitt and H. C. Trowell Eds., Academic Press, London, 1975, p. 99.
17. Gear, J. S. S., Fursdon, P., Nola, D. J., Ware, A., Mann, J. I., Brodribb, A. J. M., Vessey, M. P. Symptomless diverticular disease and intake of dietary fiber. Lancet I, 8115: 511 (1979).
18. Segal, I., Solomon, A., and Hunt, J. A. Emergence of diverticular disease in the urban South American black. Gastroenterol. 72: 215 (1977).
19. Manousos, O. N., Vrachliotis, G., Papaevangelou, G., Detorakis, E., Doritis, G., Stergiou, L., and Merikas, G. Relation of diverticulosis of the colon to environmental factors in Greece. Dig. Dis. 18: 174 (1973).
20. Segal, I., and Hunt, J. A. The irritable bowel syndrome in the urban South African negro. South African Med. J. 49: 1645 (1975).
21. Loomis, W. F. Rickets. Sci. Am. 223 (No. 6): 76 (1970).
22. Anonymous. Rickets and osteomalacia. Lancet I:1168 (1962).
23. Offermann, G., and Manhold, C. Immigrant osteomalacia: occurrence in Turkish guest workers in Germany. Abstracts, Fourth Workshop on Vitamin D. Berlin, West Germany, Feb. 18-22, p. 287 (1979).
24. Krogstead, D. J., Spencer, H. C., Jr., and Healy, C. R. Amebiasis. New Engl. J. Med. 298: 262 (1978).
25. Unger, K. W. Amebiasis (letter). New Engl. J. Med. 298: 1148 (1978).
26. Dritz, S. K., Ainsworth, T. E., Back, A., Boucher, L. A., Garrard, W. F., Palmer, R. D., and River, E. Patterns of sexually transmitted enteric diseases in a city. Lancet 2(8027):3 (1977).
27. Feldman, R. G. Urban lead mining: lead intoxication among deleaders. New Engl. J. Med. 298: 1143 (1978).
28. Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., and Barrett, P. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. New Engl. J. Med. 300: 690 (1979).
29. Erickson, J. E., Shirahata, H., and Patterson, C. C. Skeletal concentrations of lead in ancient Peruvians. New Engl. J. Med. 300: 946 (1979).
30. Morris, J. N. Social inequalities undiminished. Lancet I:87 (1979).
31. Maugh, T. H., II. Chemicals: How many are there? Science 199: 162 (1978).
32. Gold, M. D., Blum, A., Ames and B. N. Another flame retardant, tris-(1,3-dichloro-2-propyl)-phosphate, and its expected metabolites are mutagens. Science 200: 785 (1978).
33. Sieber, S. M. The lymphatic absorption of *p,p'*-DDT and some structurally related compounds in the rat. Pharmacol. 14: 443 (1976).
34. Kamp, J. D., and Newman, H. G. Absorption of carcinogens into the thoracic duct lymph of the rat: aminostilbene derivatives and 3-methylcholanthrene. Xerobiotica 5: 717 (1975).
35. Schedl, H. P. Water and electrolyte transport: clinical aspects. Med. Clin. North Am., 58: 1429 (1974).
36. Cook, P. M., and Olson, G. F. Ingested mineral fibers: elimination in human urine. Science 204: 195 (1979).
37. Pontefract, R. D., and Cunningham, H. M. Penetration of

asbestos through the digestive tract of rats. Nature 243: 352 (1973).
38. Chrisp, C. E., Fisher, G. L., and Lammert, J. E. Mutagenicity of filtrates from respirable coal fly ash. Science 199: 73 (1978).
39. Lakowicz, J. R., McNamara, M., and Steenson, L. Particle-mediated membrane uptake of chemical carcinogens studied by fluorescence spectroscopy. Science 199: 305 (1978).
40. Schedl, H. P. Environmental factors and the development of disease and injury in the alimentary tract. Environ. Health Perspect. 20: 39 (1977).
41. Cohn, W. J., Boylan, J. J., Blanke, R. V., Fariss, M. W., Howell, J. R., and Guzelian, P. S. Treatment of chlordecone (kepone) toxicity with cholestyramine. Results of a controlled clinical trial. New Engl. J. Med. 298: 243 (1978).
42. Morgan, D. P., and Roan, C. C. The metabolism of DDT in man. In: Essays in Toxicology. W. J. Hayes, Jr., Ed., Academic Press, New York, 1974, pp. 39-97.
43. Boylan, J. J., Egle, J. L., and Guzelian, P. S. Cholestyramine: use as a new therapeutic approach for chlordecone (Kepone) poisoning. Science 199: 893 (1978).
44. Correa, P. Epidemiology of polyps and cancer. In: The Pathogenesis of Colorectal Cancer, B. C. Morson, Ed., Saunders, Philadelphia, 1978, p. 126.
45. Haenszel, W., and Correa, P. Cancer of the colon and rectum and adenomatous polyps. A review of epidemiologic findings. Cancer 28: 14 (1971).
46. Doll, R., Muir, C. S., and Waterhouse, J. A. H., Eds. Cancer Incidence in Five Continents, Vol. 2, UICC, Geneva, 1970.
47. Correa, P. Comments on the epidemiology of large bowel cancer. Cancer Res. 35: 3395 (1975).
48. Haenszel, W., Correa, P., and Cuello, C. Social class differences in large bowel cancer in Coli, Columbia. J. Natl. Cancer Inst. 54: 1031 (1975).
49. Haenszel, W., and Kurihara, M. Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. J. Natl. Cancer Inst. 40: 43 (1968).
50. Wynder, E. L. The epidemiology of large bowel cancer. Cancer Res. 35: 3388 (1975).
51. Burkitt, D. P. Epidemiology of cancer of colon and rectum. Cancer 28: 3 (1971).
52. Rose, G., Blackburn, H., Keys, A., Taylor, H. L., Kannel, W. B., Paul, O., Reid, D. D., and Stamler, J. Colon cancer and blood cholesterol. Lancet 1: 181 (1974).
53. Puffer, R., and Griffith, G. W. Patterns of urban mortality. Pan American Health Organization Scientific Publication 151, Washington, D.C., 1967.
54. Haenszel, W., and Berg, J. W. Large bowel cancer in Hawaii Japanese. J. Natl. Cancer Inst. 51: 1765 (1973).
55. Hill, M. J., Drasar, B. S., Aries, V., Crowther, J. C., Hawksworth, G., and Williams, R. E. O. Bacteria and the etiology of cancer of the large bowel. Lancet 1: 95 (1971).
56. Hill, M. J. Colon Cancer. A disease of fibre depletion or of dietary excess? Digestion 11: 289 (1974).
57. Finegold, S. M., Flora, D. J., Attebery, H. R., and Sutter, V. L. Fecal bacteriology of colonic polyp patients and control patients. Cancer Res. 35: 3407 (1975).
58. Moore, W. E. C., and Holdeman, C. V. Discussion of current bacteriological investigations of the relationship between intestinal flora, diet and colon cancer. Cancer Res. 35: 3418 (1975).
59. Lacquer, G. L. Contribution of intestinal macroflora and microflora to carcinogenesis. In: Carcinoma of the Colon and Antecedent Epithelium. W. J. Burdette, Ed., Charles C. Thomas, Springfield, Ill., 1970.
60. Cole, J. W. 2,3-dimethyl-4-aminobiphenyl: absence of carcinogenicity in germ-free rats. Quoted by Wynder et al. Environmental factors in cancer of the colon and rectum. Cancer 23: 1210 (1969).
61. Spjut, H. J. and Spratt, J. S., Jr. Endemic and morphological similarities existing between spontaneous neoplasms in man and 3:2'-dimethyl-4-aminodiphenyl induced colonic neoplasma in rats. Ann. Surg., 161: 309 (1965).
62. Gennaro, A. R., Villaneuva, R., Sukonthaman, V., and Rosemond, G. P. Chemical carcinogenesis in transposed intestinal segments. Cancer Res. 33: 536 (1973).
63. Hill, M. J. Steroid nuclear dehydrogenation and colon cancer. Am. J. Clin. Nutr. 27: 1475 (1974).