Environmental Contaminants and Intestinal Function

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The environmental contaminants which have their major effects on the small intestine may be classified into five major categories: (1) bacterial, viral, and parasitic agents, (2) food and plant substances, (3) environmental and industrial products, (4) pharmaceutical agents, and (5) toxic agents whose metabolic effects are dependent on interreaction with intestinal bacterial flora, other physical agents (detergents), human intestinal enzyme deficiency states, and the nutritional state of the host.

Bacterial, viral, and parasitic agents are the most important of all such agents, being responsible for significant mortality and morbidity in association with diarrheal diseases of adults and children. Several plant substances ingested as foods have unique effects on the small bowel as well as from contaminants such as fungi on poorly preserved grains and cereals. Environmental and industrial products, in spite of their widespread prevalence in industrial societies as contaminants, are less important unless unexpectedly intense exposure occurs to the intestinal tract. Pharmaceutical agents of several types interreact with the small bowel mucosa causing impairment of transport processes for fluid and electrolytes, amino acid, lipid and sugars as well as vitamins. These interreactions may be dependent on bacterial metabolic activity, association with detergents, mucosal enzyme deficiency state (disaccharidases), and the state of nutrition of the subject.

Environmental contaminants which have their major effect on the intestine are a disparate group of chemical agents which defy easy classification. Their study often requires the scientific disciplines of epidemiology, together with those of pharmacology, toxicology, bacteriology and biochemistry. They represent a challenge to a diversity of persons and different investigational techniques to provide the factual data with which to better the social environment. Information to determine whether they should be eliminated from the environment, monitored closely for possible deleterious effects, investigated for their role in disease causation or require development of practical methods for reducing their effects on the GI tract are the combined aims of these efforts.

The chemical agents affecting the intestine will be considered under five categories: bacterial, viral, and parasitic agents; food and plant substances; environmental and industrial products; pharmaceutical agents; and metabolic interreactions of toxic substances, i.e., toxic agents which are dependent on their interreaction with the intestinal bacterial flora, other physical agents, human enzyme deficiency states and nutritional status.

Several experimental model systems are applicable to the study of toxic compounds directed in their effect on the intestine and will receive mention and discussion as suitable practical techniques for evaluation of the toxic agents that may appear anew in the environment.

Bacterial, Viral, and Parasitic Agents

Bacteria

Bacterial, viral, and parasitic agents usually enter the GI tract in food and water. Acute infections of the intestinal tract are among the commonest in the population. Acute infectious diarrheal disease is the world’s leading cause of infant and child mortality and accounts for 8% of U.S. infant mortality. Bacteria within our environment that injure/infect the
intestine include Salmonella, Shigella, *E. coli*, Yersinia, Vibrios, *Bacillus cereus*, Campylobacter and many other organisms. They are known contaminants of our water supply, household pets, domestic and farm animals, and food (1). Over one half of the outbreaks of Salmonella gastroenteritis, for instance, are related to contaminated poultry products (2).

The mode of transmission, intestinal colonization, and pathogenesis of bacterial infections has received increased study in recent years. In general, such agents are either invasive organisms causing direct damage to the mucosal surface of the bowel (Shigella, Salmonella, and viruses), or toxigenic (Vibrio, *E. coli*) elaborating enterotoxins but with minimal invasive potential. Invasive organisms enter the plasma membrane of the mucosal cell, cause cell death and necrosis with further spread of the inflammatory response in the underlying submucosa, causing ulceration and inflammation of the bowel wall. Initial entry of the organism depends on their engulfment into phagosomes, division within the mucosal cell, which cause subsequent death of the enterocyte and release of organisms into the tissue. The inflammatory response is dependent on the presence of the live organisms. There is no definite pathogenetic role for any toxin generated by these invasive bacteria in this form of inflammatory reaction (3, 4).

On the other hand, toxigenic organisms exert their effect through the toxin's influence on the intestinal mucosal surface with the organism itself rarely gaining access to the host tissue. The enterotoxic injury is more subtle, often occurring without significant morphological changes in the mucosal surface, although functional changes causing massive fluid and electrolyte secretion accompany the intoxication (5).

It is of some general interest that the pathogenesis of these enterotoxic injuries to the intestinal cell provides a resemblance to other forms of bacterial protein exotoxic injury, as well as to that of certain food toxins. The toxic protein in each instance is represented by a binding protein moiety which binds to the cell surface, presumably to a specific receptor site which is not, in every instance, identified, and this binding component does not enter the cell. An additional moiety, an active toxic component, becomes released from the whole molecule to subsequently enter the cell, causing alteration in metabolic processes within by enzymatic mechanisms which alter cellular protein synthesis (6). For cholera toxin this process results in the activation of adenylate cyclase with the later effects of causing the cell to secrete large quantities of fluid and electrolytes which are recognized by the patient as diarrhea (7-9).

For other toxins, effect is more likely to result in cell death and tissue necrosis (Diphtheria) (Table 1). It is, therefore, entirely possible that other bacterial toxins, as yet unidentified, will have similar intercellular sites of action.

Other more recently identified bacterial toxins may exert their effects primarily at the cell membrane. The stable toxin of *E. coli* (ST), which also causes intense fluid secretion in man or experimental animals, activates guanylate cyclase and causes rapid induction of fluid secretion. However, rapid reversal and return to normal absorptive function, occurs when toxin exposure is discontinued (unlike cholera toxin). Such agents may, therefore, act primarily outside of the cell membrane in a manner similar to bacterial neurotoxins and hemolysins (10, 11).

**Viruses**

Viruses are a ubiquitous cause of diarrheal disease and may account for 50-80% of all infant and childhood diarrhea. Reo viruses are a major component of these agents. Similar species can be identified in piglets, calves and foals, but it is not yet known

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**Table 1. Protein toxins which act within the cell.**

| Receptor                        | Whole molecule MW | Active fragment | Effect                   |
|---------------------------------|-------------------|-----------------|--------------------------|
| Diphtheria                      | ?                 | 63,000          | 24,000                   | ADP-ribosylation [EFII] |
| Cholera                         | Ganglioside       | 84,000          | 21,000                   | ADP-ribosylation        |
| *E. coli* (LT)                  | GM₁ter-Galactose  | 65,000          | 30-32,000                | Protein inhibition      |
| *Ps. aeruginosa*                | ?                 | ?               | 27,000                   | ADP-ribosylation [EFII] |
| Abrin-Ricin                     | ?                 | ?               | ?                        | 16S ribosome inhibition |
| Colicin 3                       | ?                 | ?               | ?                        |                           |
whether these animal viruses are the same (12). Their identification, growth in tissue culture, and vaccine prevention present an important present challenge in our management of diarrheal disease. Adult diarrheal disease is rarely due to reo viruses. Parvo viruses may be more important at this age, but their reservoir is, at present, unknown and means for their culture less well defined than those for reoviruses (12).

Parasites and Protozoa

_Ca. lambia_, a protozoal organism, is an environmental contaminant in mountain streams and even in city water supplies and may cause a chronic diarrheal illness (13). Its natural reservoirs are poorly understood, and factors in its transmission require clarification. It is usually a noninvasive organism resident on the mucosal surface of the duodenum and jejunum where surface destruction of microvilli may be identifiable but where gross inflammation and necrosis are not to be found. The mode of its pathogenicity in causing diarrhea and malabsorption of nutrients is poorly understood. The surface properties of this agent and its epidemiology require further elucidation.

Natural Food and Plant Substances

In addition to the microbiological contaminants which enter food, as it were by natural contamination, nature has introduced many more toxic substances into food than has man (Table 2). Usually by trial and error man has, in the past, discovered how to avoid, minimize, and eliminate these agents, and, perhaps, may even have become adapted to traces of such compounds (14). Many of these toxic compounds present in plants have recognized toxic effects after absorption by the GI tract. However, few of these agents have as their main target the GI tract. Likewise, carcinogens in food are recognized but have their major effect as primary liver carcinogens after absorption by the intestine.

Present interest in enhancement of the nonabsorbable dietary fiber content of the diet has led to renewed interest in compounds that may be altered in their absorption by the fiber content of the diet or which are available in greater quantity in such diets. High fiber ingestion may enhance sodium, potassium, magnesium, phosphorus, calcium, and water loss in the feces by passive (gel filtration or passive water-holding capacity) or other (cation exchange, bile acid absorption) processes (15). Fiber diets may have antioxidant effects (16) and antitoxic effects on other dietary materials present, particularly carcinogens (17). However, studies have not clearly defined the specific agents of the fiber diet which have such effects owing to the varied composition of dietary fiber used in different systems. In future work it will be important to utilize standard, pure forms of dietary fiber to define the exact nature of the fiber used and its quantity. This is especially clear now that it is recognized that fiber is often partially degradable by bacterial action; and, thereby, alters bacterial flora considerably, both quantitatively and qualitatively (18).

Animal nutritionists have been aware that extracts from plants have properties of agglutinating red blood cells, features which led to the isolation in food and purification of many different phytohemagglutinins or lectins. The antinutritional feature of these compounds in the red kidney bean (Phaseolus vulgaris) and soybean (Glycine max) particularly have been recognized for a long time (19). Certain lectins, such as ricin, from the castor oil bean (Ricinus communis) are very poisonous in very small quantities (20). Many others have antinutritional effects; impairing weight gain, growth, protein and fat absorption, and inducing pancreatic hypertrophy. These effects have largely been avoided by heat treatment or presoaking of beans. Such measures remove most plant agglutinins (PHA), trypsin inhibitors, and other complex proteins which cause these effects. The fact that some lectins, ricin, for example, are very toxic in minute quantities is very different from the antinutritional effects of these other more widely used dietary agents which cannot strictly be viewed as being toxic. For instance, growth inhibition and pancreatic hypertrophy are both reversible with restitution of a normal diet after PHA feeding (21-23).

The importance of these dietary antinutritional factors has received little attention in human nutri-

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**Table 2. Toxic chemicals in food.**

| Origin     | Type                                                      |
|------------|-----------------------------------------------------------|
| Natural    | Natural contaminants of natural food                      |
|            | Microbiological                                           |
|            | Nonmicrobiological                                        |
|            | (mercury, selenium consumed by animals)                   |
|            | Normal components of natural foods                       |
| Human      | Agricultural chemicals                                    |
|            | Food additives                                            |
|            | Chemicals from food packaging                             |
|            | Chemicals from food processing (heat, etc.)               |
|            | Food preparation                                          |
|            | Contaminants of utensils                                  |
|            | Environmental pollution                                   |
|            | Contamination during storage or processing               |

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tion. Potent effects of these mitogenic compounds in other organ systems and the binding affinity of their carbohydrate end groups suggest they may have importance in the GI tract as well. Pathogenesis of the malabsorptive process which accompanies the impaired nutritional state has not been well defined which raises the possibility that comparable transient or sustained dietary induced malabsorption may accompany ingestion of complex proteins in man, and may, indeed, occur but are, as yet, unrecognized.

It is noteworthy that a complex sulfated polysaccharide — carrageenan — will cause ulcerating lesions in the cecum of the guinea pig and rabbit but not in man (24). This effect is ameliorated by Clindamycin and Cotrimoxazole therapy, suggesting a synergistic effect of anaerobic organisms in this inflammatory process (25). A similar interrelationship with bacterial action is present in the antinutritional effects of phytohemagglutinin in animal studies. The germ-free state or antibiotic administration restore growth rates to normal in PHA-fed animals (26).

Mycotoxins

Mycotoxins, the toxic agents of fungi, are toxic to the intestine only in the condition of alimentary toxic aleukia which in the period of 1943-47 was widely present in certain states of the USSR following the consumption of bread made from grain that had over-wintered in the snow (27, 28). The disease is caused by eating adequate quantities of contaminated grain over a period of weeks. Contamination with Fusarium was identified and the toxic materials identified as tricothecenes or scerpenes. The cat has proved to be an acceptable animal model for this disease. These agents cause a burning sensation in the throat, esophagus, and stomach, causing vomiting, abdominal pain, and diarrhea before later features of depression of the bone marrow, leucopenia, anemia, and the development of hemorrhagic phenomena on the body surfaces occur (28). No specific studies are available to determine the effect of these agents on the alimentary tract prior to causing bone marrow depression. It would be of interest to define carefully their mode of action on the intestinal mucosa.

Scombrotoxin

Intoxication by eating fish is named ichthysarcoxin. Symptoms of scombroid, that form associated with ingestion of contaminated mackerel or tuna, are abdominal cramps, vomiting, diarrhea, flushing, and hypotension. These manifestations are thought to be due to the release of histamine by bacterial enzymatic breakdown of histidine present in the flesh of these fish. Treatment with H1 receptor antagonists moderates symptoms. Outbreaks of this problem have been recognized in this country in recent years (29).

Environmental and Industrial Products

The occurrence in food and water of chemical substances used as preservatives, contaminants introduced in farming, as insecticides, or in other ways, have been identified by routine surveillance in food sources for many years. The identity of those materials which are toxic to the small bowel is difficult to define. Epidemiological data has been able to identify intestinal illness associated with gross contamination in occasional instances [Epping jaundice due to diaminodiphenylmethane contamination of flour (30)] but rarely in situations where an exposure to low concentrations of chemicals has occurred. At this time there is evidence for many hundreds of chemical substances, ranging from insecticides, pesticides, polychlorinated biphenyls to heavy metals, such as lead, cadmium, and mercury, causing contamination of the environment and entering the digestive tract from the mouth or even via the respiratory tract (31). Their target effects on the small intestine are, if any, unknown. Two agents, of general toxicological interest, asbestos and mineral oil, may depend on general processes by which particular materials are absorbed from the intestine.

Asbestos is an agent of long-term health consequences which has been shown to pass through the intestinal wall and to disseminate to other organs. Suggestions have been made that it may be epidemiologically related to colon cancer as well as to peritoneal mesotheliomas. In spite of difficulties with identification of fibers in small numbers in tissue, fibers have been identified in the bowel wall of experimental animals challenged with asbestos (32). In this context asbestos may, therefore, be similar to other macromolecules which, in man, can be shown to cross the mucosal barrier under normal physiological conditions. The mechanisms of translocation of such agents has been reviewed recently (33). The initial effect is one of adsorption of the macromolecule to the microvillus membrane. Subsequently, invagination of the membrane occurs, and small vesicles are formed. Macromolecules migrate within this membrane bound vesicle (phagosome) to coalesce with lysosomes to form larger vacuoles within which intracellular digestion may occur. Small quantities of material may be observed
to migrate to the lateral basal surface of the cell to be deposited in the intercellular space by exocytosis. At the present time very little is known about the processes involved in these steps of translocation. Studies with macrophages and the intestinal mucosa have largely been devoted to the absorption of protein molecules which after absorption may induce antibody responses which may then modify uptake. There is little understanding of factors which may modify invagination uptake or transport across the cell or release in the lymphatic or blood system. Several general factors affecting the host or intraluminal environment are known to control passive transfer, but understanding of this metabolic process is not well understood.

A similar entry of lipid droplets through the human intestinal wall may occur. Droplets are readily detected in lymph nodes of the mesentery and of the porta hepatis in autopsy studies. Saturated hydrocarbons, resembling mineral oil, have been frequently identified in these tissues and postulated to originate from the petroleum wax employed in food packaging. While the significance of this material is unknown and may not have any interest other than curiosity, such a lipid transport system might facilitate passage of other fat soluble toxins. It is unknown whether this particulate fat enters by a mechanism similar to that for other macromolecules.

**Pharmaceutical Agents**

The intestine is a known target organ for toxic effects of two major groups of pharmaceutical agents: a heterogenous group of compounds, including antibiotics, identified as causing intestinal malabsorption, and the overuse of laxative agents (laxative abuse).

**Drug-Associated Malabsorption**

Drug-induced malabsorption may result from a variety of compounds shown in Table 3. The effects are often dose-dependent and reversible on withdrawal of the drug. With cholestyramine and neomycin malabsorption is common; with phenytoin and contraceptive pills malabsorption is the exception. Neomycin administration produced morphological changes in the mucosa, increase in fecal bile acid excretion, reduced disaccharide activity, inhibited fat-soluble vitamin absorption, and caused steatorrhea when administered at high doses (> 10 g/day). Phenytoin and salicylsulfasalazine have more specific effects acting as competitive inhibitors of the intestinal folate binding protein for monoglutamate folate.

**Table 3. Drug-induced intestinal malabsorption.**

| Drug                          | Absorptive defect |
|-------------------------------|-------------------|
| Alcohol                       | Folic acid        |
| Calcium carbonate             | Fat               |
| Cholestyramine                | Fat, bile acids, vitamins |
| Clofibrate                    | Sterols           |
| Colchicine                    | Fat, B12, xylose  |
| Contraceptive pills           | Xylose, folate    |
| Indomethacin                  | Xylose            |
| Kanamycin                     | Fat, protein, electrolytes |
| Methotrexate                  | Xylose, Vitamin B12, Vitamin K |
| Neomycin                      | Fat, B12, etc.    |
| Phenformin                    | Fat, xylose, folate |
| Phenindandione                | Fat, xylose       |
| Phenytoin                     | Xylose, folic acid |
| Phenolphthalein               | Fat               |
| PAS                           | Fat, Vitamin B12, xylose |
| Polymyxin                     | Fat, protein      |
| Quinacrine                    | Fat               |
| Sulfasalazine                 | Folate            |
| Triparanol                    | Fat, protein, carotene |

**Laxatives**

Laxatives represent a major toxic influence on the human small intestine. In 1974, 42 pharmaceutical companies manufactured 132 O.T.C. agents at a total cost of $241 million. The major compounds of interest as toxic agents are stimulant laxatives and surfactants or lubricant laxatives. Stimulant laxatives of the anthraquinone type alter sodium water transport in intestinal loops, and inhibit mucosal sodium and potassium ATPase activity. Ricinoleic acid, bisacodyl, and phenolphthalein have similar effects in increasing fecal water and in their effects on mucosal fluid transport. These effects on fluid transport are not dissimilar to those of the surfactant compounds, such as dioctyl sulfosuccinate. Their exact mode of effect on fluid transport remains in dispute. Some workers favor the idea that structural alteration in the mucosa may be the important factor in their effect. Others favor a role for cyclic AMP-mediated stimulation of active fluid secretion, since activity of cyclic AMP is elevated in mucosa exposed to ricinoleic acid. Impairment in absorption of other agents (glucose, xylose, lysine, and folic acid, as well as increased permeability to inulin) favor a less specific mechanism for the effect associated with tissue damage as the prominent feature. Additional work is necessary to define the mechanism of these effects. Life-threatening effects of laxative abuse may occur due to fecal fluid and electrolyte loss, or enhanced absorption of other agents known to have human toxicity. Dioctyl sulfosuccinate enhanced Danthon and Quinidine absorption and their toxicity in the liver. In addition, the colon may
undergo dilatation and the loss of contractility in chronic laxative abuse. Smith (39) demonstrated damage to and loss of myenteric neurons in cathartic colon patients. She induced similar lesions in mice by chronic senna administration. The nature of the toxicity of anthraquinone laxatives for the intestinal myenteric plexus is poorly understood and would repay further research. A further observation of some interest in relation to environmental toxicity directed against the visceral nervous system is that various population groups are predisposed to the development of volvulus of the sigmoid colon. This may cause acute intestinal obstruction and present as a surgical emergency in these communities. In colonic specimens resected, abnormal degeneration was noted in the myenteric plexus, and impaired colonic motility was documented when studied with intraluminal pressure recordings. Anthraquinones occur naturally and have featured as toxic materials in foodstuffs contaminated by fungal toxins (40).

**Metabolic Interactions of Toxic Substances**

Metabolic effects related to the intestine, per se, may occur intraluminally by reaction with intraluminal bacteria, at the brush border membrane interface between mucosal cell and the lumen, and within the mucosal cell itself.

**Bacterial Metabolism**

The metabolism of ingested compounds by gastrointestinal organisms has received considerable attention in recent years, and many metabolic reactions are defined as occurring in this environment (41). Several examples of the pharmacological significance of these reactions with bacterial organisms are available. Sulfasalazine undergoes cleavage of the azo bond with release of 5-aminosalicylate and sulfapyridine. Sulfasalazine is relatively insoluble. Sulfapyridine appears to be well absorbed and is recovered in the urine either as the free drug or its metabolite. 5-Aminosalicylate, on the other hand, seems to remain in the colon and to be excreted in the feces, whereas its acetylated derivative can be recovered in both urine and feces. The disposition of sulfasalazine and its metabolites is, therefore, complex and at this time the definition of the major therapeutic agent responsible for improvement of patients with ulcerative colitis remains uncertain (42). It is likely, however, that deconjugation is a prerequisite for its target effect on the bowel mucosa. Anthraquinone laxatives, likewise, require deconjugation and release of free anthraquinone from the glucuronide prior to exerting their cathartic effect on the colonic mucosa (41).

The importance of these bacterial metabolic pathways in toxicology is of intense interest in regard to conversion of drugs, chemical substances, and additives in food to toxic products or carcinogens and the prolongation of action of environmental factors by deconjugation causing reabsorption of an agent secreted into the gut after prior conjugation in the liver. Several examples of these actions are not known. The glycoside of cycasin found in cycad plants in Guam is hydrolyzed to methylazoxymethanol which is both hepatotoxic and carcinogenic (43). Nitrosamine formation may result from the conversion of nitrates to nitrites and secondary amines; such agents are thought to play a role in carcinoma of the stomach (44). The development of new short-term tests assaying for mutagenicity which can readily identify environmental mutagens and carcinogens will be of great use for early detection of hazardous environmental chemicals (45). Identification of the dangers from low or high dose toxicity unrelated to mutagenicity still require screening procedures which are less practical.

**Brush Border Enzymes**

Reactions between dietary agents and the brush border membrane may be deleterious. This is well illustrated in conditions of congenital or acquired enzyme deficiency associated with lactase or other disaccharidase deficiency. Under such conditions orally ingested disaccharides, such as lactase, may cause fluid accumulation in the bowel lumen and severe diarrhea due to the osmotic effects of the unabsorbed disaccharide and its breakdown products in the colon (46).

**Mucosal Cell Metabolism**

The mucosal cell has many metabolic properties which, to date, are poorly defined. Estrogens are conjugated to glucuronides, cholesterol is synthesized, and striking interreactions have been demonstrated between dietary agents and intestinal metabolism of drugs. Chemicals that act as inducers of mucosal cell metabolic activity in animals and man include such agents as halogenated hydrocarbons, including polychlorinated biphenyls, metals, and cigarette smoking, as well as constituents in the diet (charcoal broiled beef). Such agents enhance metabolism and decrease absorption and bioavailability of a variety of drugs (47). The activity of the phenacetin metabolizing enzyme system in the mucosa is increased in rats by such agents. At the present time the functional role of these intestinal enzymes and
their relation to mucosal metabolism of ingested toxic agents require further definition (48).

Whereas, at least, several metabolic pathways are present in the intestinal mucosal cell, metabolic interactions in other regions of the bowel wall are poorly defined and often only by chance are local toxic effects noted. A recent example was the observation that Practolol, a beta-adrenergic blocking agent used in Europe, caused the formation of dense peritoneal thickening and adhesions which resulted in small bowel stasis and obstruction. Other beta-adrenergic blocking agents do not appear to have this effect and no cause has yet been defined for such a localized action on the peritoneal surface (49).

Likewise, very little is known of factors which may alter proliferation of the crypt cells or the underlying mesenchymal elements which surround the crypt cells and which may have an important modulating role in their proliferation. Humoral (gastrin, beta-adrenergic agents, thyroxin, serotonin, growth hormone) as well as dietary products are known to enhance epithelial cell renewal in the mucosa. Chalones — substances which may inhibit mitotic activity — are well recognized in developmental processes, but little information is available as to their role in the adult intestine and whether environmental toxins might exert their effect on the small bowel through chalones (50).

This short review provides much evidence that our concepts of the metabolism of toxic agents in the intestine are rudimentary. Nevertheless, development of methods of organ and isolated cell culture as well as rapid methods to detect mitogenicity of fecal and food materials may lead to a quickening in the rate of understanding of this complex organ in its relation to environmental chemical substances.

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