DIARRHEA

Edited By

Michael Gracey

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PREFACE

Diarrhea is one of the most distressing and disabling of symptoms; it is also one of the commonest. In tropical and developing countries, diarrheal diseases cause immense morbidity and millions of deaths annually, particularly in children under five years of age. In the industrialized countries, diarrheal diseases declined in incidence and severity over recent decades but they are still major causes of illness, sometimes fatal, and can bring considerable costs to the community and the affected individual. Modern methods of mass food production, manufacture, and distribution provide a set of circumstances which can bring outbreaks of diarrhea to public attention through press, radio, and television, and can cause severe financial damage to food producers, retailers, eating houses, and others in our modern food chain, as well as causing headaches to health authorities and embarrassment to politicians. The upsurge in international travel in recent years has provided another means for diarrheal episodes to inflict the individual with "travelers' diarrhea", which can mean much more than discomfort or disruption of a vacation or international conference.

Advances in knowledge of the diarrheal diseases have been very rapid over recent years with the discovery of "newer" bacteria, viruses, and parasites that can be responsible for sporadic episodes as well as epidemics. Advances in treatment, notably oral rehydration therapy, have been dramatic and have helped reduce deaths from diarrhea, particularly among children in developing countries. There have also been encouraging developments towards the successful production of vaccines to prevent diarrheal illnesses. These advances have been accompanied by a vast and often highly technical literature which is generally out of the reach of practicing doctors. This book attempts to summarize this recent literature and present it to the reader in a practical and readily comprehensible style. It should be particularly useful for practicing doctors as well as undergraduate and postgraduate medical students. It should also prove useful for other health professionals with interests in diarrheal diseases.

Diarrhea is not always due to infections; it can be due to inborn errors of metabolism, allergies, and intolerance to dietary constituents, chronic inflammatory disorders, malignancies, and many other underlying causes.

We have attempted to bring to the reader an overview of the diarrheal disorders which affect humans, concentrating on the most important advances which have occurred in recent years. Appropriate references to recent literature are provided throughout the text. My co-authors are distinguished authorities in their various fields relevant to diarrheal disease; I thank them for their contributions made despite numerous other calls on their time. I partic-

ularly want to thank my wife, Valerie Burke, who has been my co-investigator, colleague, and loyal supporter in studying diarrhea for more than twenty years

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Epidemiology and Transmission of Diarrhea

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DEFINITIONS

It is important for the understanding of our subject and of the relevant literature to have some agreement about the definitions of diarrhea. Although universal agreement has not been achieved, the following definitions are widely accepted.

Diarrhea refers to abnormally loose or fluid stools which are passed more frequently than is normal. Normal here relates to the pattern which is usual for the individual concerned and depends to some extent on the perceptions of that person or, in the case of a young child, the perceptions of the mother. These considerations are of particular relevance in relation to the young breast-fed infant whose stools are characteristically loose and frequent compared with those of older children. A working definition of diarrhea in common use, and applicable to older subjects, is the passage of one watery or explosive stool, or three loose stools in 24 h.

Dysentery refers to diarrhea when abnormally loose or fluid stool is

admixed with blood or mucus. It is usually due to macroscopic mucosal damage resulting from intestinal infection with an invasive organism (see Chapter 2).

Acute diarrhea refers to the most common episodes of infectious diarrhea which have a rapid onset and are self-limiting and short-lived. Acute watery diarrhea typically lasts for 4 to 5 d, while acute dysentery tends to last longer, of the order of 7 to 10 d. Patients with acute diarrhea requiring treatment and investigation usually do so within 48 to 72 h of onset.

Chronic diarrhea refers to the passage of abnormally loose stools for 14 days or more, irrespective of whether they are watery, dysenteric, or simply bulky (as in malabsorption syndromes). There is less agreement about this definition, partly reflecting a wider variation of pathogenesis and clinical illness. Chronic diarrhea can be of insidious or of rapid (acute) onset. In the latter case, the term *persistent* is often used. Children in whom resumption of diet after an acute attack of diarrhea results in chronic or intermittent diarrhea are sometimes referred to as having a *postenteritis syndrome* (Manuel, 1986).

Intractable diarrhea refers to more or less serious episodes of chronic or persistent diarrhea, not usually associated with an identifiable specific causal agent, which do not respond to normal treatment regimes and which may necessitate parenteral nutrition. Mortality is correspondingly high.

The following comments are confined to diarrheas of infectious or presumed infectious origin. We do not include inflammatory bowel disease, even though this may be caused by infectious agents.

INCIDENCE AND PREVALENCE

Diarrheal morbidity and mortality vary greatly in different populations and different parts of the world. Endemic acute watery diarrhea is most common in young children in underprivileged communities living in conditions of poor environmental hygiene in the tropics and subtropics. There, the prevalence of diarrheal disease is second only to upper respiratory tract infection, and in many communities young children may have diarrhea for around 1 d in 5, typically with seasonal fluctuations. Attack rates of acute diarrhea of eight or more episodes per child are recorded during infancy, falling to around one third of this in the second year and thereafter (Snyder and Merson, 1982).

With the intense international efforts over recent years, which have helped to substantially reduce the morbidity and mortality from acute diarrhea in children (Merson, 1985), the problems of chronic, persistent, and non-dehydrating diarrheas are gaining prominence. Less data exist with respect to chronic as distinct from acute diarrhea. In one Gambian series, some 50%

of infants suffered one or more chronic episodes during 1 year, and approximately 10% of diarrheal episodes persisted for 14 d or more (Rowland et al., 1986). In other developing countries, the latter figure varies between 3 and 20% (WHO, 1988). It is important to realize that in high prevalence situations, the documented incidence of acute and chronic diarrheal episodes will depend on the definition of the duration of the symptom-free interval between attacks, as well as of the attacks themselves (Rowland et al., 1986).

Travelers' Diarrhea

Diarrhea among international travelers is also an important problem (see Chapter 5). The incidence varies according to whether travelers are from low- or high-risk areas of the world and whether they are traveling through low-risk or diarrhea-endemic areas. At least 16 million people travel annually from industrialized countries to developing countries. Around one third of these suffer travelers' diarrhea, 30% being ill enough to be confined to bed and 40% to have to alter their scheduled activities (Gorbach and Edelman, 1986). Risk factors are discussed by DuPont in Chapter 5. Other useful reviews have been written by Steffan (1986) and Gyr and Barz (1987).

MORTALITY AND LETHALITY

Acute diarrhea has been estimated to kill upwards of 5 million children under 5 years of age each year, and diarrhea-specific death rates often exceed 20 per 1000 in the early years of life (Rohde and Northrup, 1976; Merson, 1985). Probably not more than around 3% of all acute watery diarrheal episodes produce clinically overt or life-threatening dehydration. The case fatality rate in such cases is now less than 1% when oral rehydration therapy (ORT) is vigorously instituted, but many countries have yet to achieve truly national coverage with ORT programs. It is currently estimated that just under 60% of the world's population has access to supplies and instruction in the use of oral rehydration solution (WHO, 1989a). Rehydration therapy is, in any case, of limited effectiveness in many cases of shigellosis, in whom case fatality rates of around 20% have been described in severe cases admitted for hospital treatment.

Chronic diarrhea also has a higher case fatality rate than acute watery diarrhea (Shahid et al., 1988) and, though less common, contributes substantially to diarrhea-related mortality (WHO, 1988). In association with malnutrition, diarrhea may contribute to one third or more of early childhood deaths in developing countries (Puffer and Serrano, 1973; Snyder and Merson, 1982). More than half of all such diarrhea deaths in undernourished populations have been attributed to chronic diarrhea (Ament and Barclay, 1982; Chowdhury et al., 1982).

ECONOMIC IMPACT

The heavy burden of morbidity and mortality in developing countries tends, understandably, to be regarded in predominantly clinical terms. In developed countries, with much lower rates, it is salutary to consider the economic impact.

Medical costs and lost productivity from acute infectious diarrheal diseases incur a huge financial cost to the community which amounts to at least $23 billion annually in the U.S. (Garthright et al., 1988).

An analysis of community-based data from various parts of the U.S. showed that, in 1985, intestinal infections (bacterial, viral, and protozoal) resulted in 8.2 million consultations with medical practitioners and 250,000 hospital admissions. In 1985, these hospitalizations involved the expenditure of $560 million in medical costs and $200 million in lost productivity. Nonhospitalized episodes (7.9 million) for which doctors were consulted incurred $690 million in medical costs and $2.06 billion in lost productivity. These financial estimates exclude costs such as deaths, pain and suffering, lost leisure time, financial losses to food establishments, legal expenses, and other substantial social costs.

An attempt was made to describe the dimensions of these hidden costs in a study of a single outbreak of food poisoning in 1982 in the U.K. Chocolate contaminated with *Salmonella napoli* produced 245 reported cases and no recorded deaths. Health care costs were estimated to exceed £32,000, public sector costs for investigation and testing £71,000, and direct family costs and loss of productivity £16,000. Recalled and destroyed product cost £92,000, and a value in excess of £292,000 was put on pain, suffering, and submerged morbidity, the latter based on an estimate of the impact on unreported cases (Roberts et al., 1989). The overall cost was estimated to exceed £0.5 million.

Travelers' diarrhea also has serious economic implications. This is dealt with in detail in Chapter 5.

AGE

Acute infectious diarrhea is predominantly a disease of the 0- to 2-year-old age group, mainly in developing countries, but not exclusively so.

In the neonatal period, enteropathogenic *Escherichia coli* (EPEC) are important causes of common-source outbreaks, in neonatal nurseries for example, and were among the first recognized bacterial causes of childhood diarrhea (Bray, 1945; Rogers, 1951; see Robins-Browne, 1987, for review). Rotavirus infection is usually mild or silent in neonates, but has been suspected of causing hemorrhagic gastroenteritis or necrotizing enterocolitis (NEC) in some (Dearlove et al., 1983).

A wide range of infecting microorganisms can cause acute diarrhea in older infants, children, and adults. These pathogens include viruses, enteric bacteria, and intestinal parasites.

Rotavirus diarrhea is the major cause of severe dehydrating diarrhea in young children worldwide (see Chapter 3), being most common in the age group 6 to 24 months. It is responsible for around one half of the diarrhea cases requiring hospitalization in developed countries. In the developing world, it accounts for around one third of severe diarrheal episodes in children and up to 1 million childhood deaths annually (WHO, 1989b).

In most parts of the world, rotavirus is not an important agent in acute infectious diarrhea in adults, but an important exception is China, where a novel strain has been described in association with epidemics of adult disease (Hung et al., 1984).

Enterotoxigenic *Escherichia coli* (ETEC) is also an important cause of dehydrating diarrhea in childhood, with its highest incidence in those under 2 years of age. In addition, ETEC diarrhea and shigellosis contribute substantially to another aspect of diarrheal morbidity, that of diarrhea-induced growth impairment in childhood. The role of ETEC in adult disease seems to be largely in the context of travelers' diarrhea.

Epidemic cholera, by contrast, has its highest incidence in children aged 2 to 15 years, although younger children are more likely to be affected in endemic areas, particularly if not protected by breast-feeding. Adults, too, have lower attack rates than children in epidemic cholera, although women of child-bearing age are relatively more susceptible than other adults.

In developing countries, *Campylobacter* spp. are found relatively commonly in the stools of young children, both in association with diarrhea and in controls (Glass et al., 1983). The pattern is different in developed countries, where there is less evidence of asymptomatic infections, although the spectrum of severity of illness associated with infection varies widely.

Giardia lamblia and *Cryptosporidium* spp. are important enteric pathogens, again producing more illness in young children than in older children, and less still in adults, although the latter can certainly be affected.

INFECTIOUS DOSE

It is useful to think of the epidemiology of infectious diarrhea in relation to the characteristics of the infecting microorganism, as well as the host involved, and the pathogenesis of diarrhea which their interaction produces (see Chapter 2). Some examples are given in Table 1.

Keusch (1982) has shown how shigellas are highly adapted to humans and some other primates and do not occur in domestic animals; human infections are always traceable to another human (or other primate), although transmission may involve food, water, or milk (Keusch, 1983). *Shigella* spp.

TABLE 1. Epidemiological Characteristics of Invasive Bacterial Enteric Pathogens

Infecting Organism	Host Range	Infectious Dose	Survival in Environment
Shigella	Restricted	Low	Poor
Salmonella			
Gastroenteritis strains	Wide	Moderate	Excellent
Enteric fever strains	Restricted	Moderate	Poor
Yersinia enterocolitica	Narrow	Uncertain	?
Campylobacter jejuni	Wide	Probably moderate	Good

From G.T. Keusch: Shigellosis, In: *Diarrhea and Malnutrition*. Eds., L.C. Chen and N.S. Scrimshaw, Plenum Press, New York. 45–72 (1983). Used by permission.

have been shown in adult volunteers to have a far lower infectious dose than other diarrheagenic bacteria, an inoculum of 10 to 100 organisms being sufficient to cause illness. This is easily acquired from infected stools which carry 10^2 to 10^3 bacteria per gram (Dale and Mata, 1968).

In the case of salmonellosis, the picture varies according to the strain. While salmonella infection is usually foodborne, enteric fever strains (*S. typhi* and *S. paratyphi* A, B, and C) are also highly adapted to humans. A relatively large inoculum of 10^7 to 10^9 *S. typhi* organisms will almost always produce clinical illness, whereas a lower dose of 10^5 or less has a much more variable result, ranging from subclinical to clinical infection.

On the other hand, gastroenteritis strains of *Salmonella* spp. are quite different; the 2000 serotypes of *S. enteritidis* are mostly nonhost adapted and can often be traced to poultry, eggs, milk, or water, as well as to other infected humans or other animals (Turnbull, 1979).

In the case of cholera produced by the epidemic strain *Vibrio cholerae* O1, there is evidence that the number of vibrios required to cause symptomatic infection is lower than previously believed. A dose of 10^2 to 10^3 viable vibrios is probably enough to cause symptomatic illness under natural conditions (WHO, 1980). Volunteer studies with the El Tor biotype have established that the infective dose is lower when the organism is administered with food than when given in small amounts of water. Possible mechanisms relate to the neutralizing of gastric acid, known to be an important factor in host resistance, or to protection from acid by adhesion of vibrios to food particles. Any condition which reduces gastric acidity, such as severe malnutrition or hypochlorhydria, further reduces the infectious dose (Gracey et al., 1977; Cash et al., 1974; Nalin et al., 1978).

The infectious dose of *V. parahaemolyticus*, an organism usually producing an illness of mild to moderate severity, is substantially higher, being

about 10^5 to 10^7 organisms in volunteers given antacids (WHO, 1980; see above).

Volunteer studies with enteropathogenic and enteroinvasive *E. coli* have shown that a relatively large inoculum is required to cause illness; this may also be reduced in conditions which decrease gastric acidity.

MECHANISMS OF TRANSMISSION

The mode of transmission of diarrhea helps determine the epidemiological patterns which occur. The main route is fecal excretion followed by oral ingestion, which can involve spread by fingers, feces, flies, fluids, foods, and fomites. Now a further "f" can be involved—fornication—with homosexual activities being involved in transmission (Keusch, 1982, 1983). Because of the overwhelming importance of fecal-oral transmission in the infectious diarrheas, such factors as overcrowding, inadequate personal and community hygiene practices, inadequate sanitation and sewage disposal, and environmental contamination (e.g., of food, water, and utensils) are major determinants of infection. These conditions typically occur in poor communities in developing countries, where undernutrition is prevalent, commonly affecting young children in the tropics. Such individuals are particularly susceptible to gastrointestinal infections (Scrimshaw et al., 1959; Mata, 1978, 1985). The problem is exacerbated in unhygienic environments if breast-feeding practices are inadequate (Rowland, 1985a) and children are exposed from an early age to contaminated fluids and weaning foods (Rowland, 1985b).

Mention has already been made of the importance of nurseries in the spread of infection among babies. In recent years, day-care centers also have been increasingly recognized as reservoirs of infectious agents of the respiratory tract and of enteric pathogens (discussed later in this chapter). The possibility of droplet spread and transmission via the respiratory tract can be considered in relation to rotavirus infection (discussed later in this chapter).

ETIOLOGY

The above are only some of a wide range of microorganisms which can cause infectious diarrhea with an equally wide range of epidemiological features. Before reviewing these organisms individually, it is worth considering some of the substantial advances in knowledge which have occurred in the last quarter of a century and some of our persisting areas of ignorance.

Earlier investigators were able to identify recognized bacterial pathogens, such as *Salmonella* spp. and *Shigella* spp., in less than 20% of stools

from children with diarrhea (Gordon et al., 1964; Feldman et al., 1970), and little was known about viral etiology. Progress has come from improvements in a number of different fields, including methods of handling and transporting specimens (Wells and Morris, 1981); knowledge of zoonoses which can affect man, such as campylobacter infections (Butzler et al., 1973) and cryptosporidiosis (Fletcher et al., 1982); taxonomy, for example, of the genus *Vibrio* (Huq, 1986); and methods of detecting organisms (Bishop et al., 1973).

Today we expect to identify causal pathogens in most patients hospitalized with acute infectious diarrhea. In community studies, however, when many of the attacks investigated are presumably less severe, our success is substantially less. This is particularly true in endemic as opposed to epidemic situations, and in the youngest children. Thus, Black et al. (1983), studying a rural community in Bangladesh, identified pathogens in 70% of diarrheal episodes seen in a diarrhea treatment center, but in less than half of those children under 2 years of age treated in their homes. In a community-based study of suburban Gambian children in the same age range, recognized pathogens were rarely isolated (less than 10%) in young infants outside of the two main seasonal peaks of diarrhea, compared with around 40% in older infants at other times (Goh Rowland et al., 1985). This study also raised the issue of control data. Many etiological studies still do not include control data, and pathogens identified in the stools during an acute attack of diarrhea are assumed to be the causal agent. This may not be the case, a clear example being the presence of *Campylobacter* spp. in developing countries, where the organism has been found in some studies, including the Gambian example above, to be as common in controls as in patients with diarrhea.

Other epidemiological aspects will now be considered in relation to specific etiologic agents.

Vibrio cholerae O-Group 1

Cholera has affected humans throughout recorded history and has devastated populations in various parts of the world. The disease can cause rapid, profound, and, indeed, life-threatening dehydration which, if left untreated, carries a case-fatality rate of around 40%. It is still a disease of major importance and is currently reported to the World Health Organization (WHO) by some 35 countries. In Asia and Africa, there may be as many as 8 million episodes annually and 124,000 deaths (Wanke et al., 1987). About one third of the deaths are in children under 5 years of age, one fourth in children 5 to 14 years, and the remainder in adults.

The present pandemic is the seventh and commenced in 1961; it is caused by the El Tor biotype. Classical cholera has reappeared in Bangladesh since 1982 (Samadi et al., 1983).

Man is the only known natural host for *V. cholerae*, which is usually acquired from contaminated water (Hughes et al., 1982) or food, especially seafood (Dutt et al., 1971). Less often, person-to-person spread occurs. *V. cholerae* O1, the epidemic strain, can survive and multiply in various foods and water, and in some instances epidemics have been aborted by chlorination of water supplies.

In nonimmune populations, adults and children are affected equally and epidemics are often associated with a single mode of spread. In this situation, asymptomatic infection is relatively uncommon and there is usually no environmental reservoir of infection (unpublished WHO:CDD document, 1989c).

In areas where cholera is endemic, the disease is rare in the first year of life, when breast-feeding appears to be protective. The incidence is highest in children 2 to 15 years of age, with a peak from 2 to 4 years (Glass et al., 1982), and declines thereafter, as partially protective immunity is acquired. This decline is less marked in women of child-bearing age, perhaps reflecting relatively high continuing levels of exposure. Acquired immunity seems to be associated with the presence of vibriocidal antibodies, which probably remains at protective levels for at least 9 months after an attack (Khan et al., 1987) and which, in Bangladesh, increase in prevalence from 40% at 5 years to 80% at 20 years of age. Immunity appears to be boosted by successive infections, regardless of whether they are symptomatic. In endemic areas, there are characteristically consistent seasonal patterns in infection, which may be symptomatic or otherwise. These probably reflect seasonal variations in environmental factors, including contaminated water, there being some evidence for an aquatic reservoir.

Man is the major source of infection and spread is by the fecal-oral route, food or water being contaminated with excreta from infected persons, whether symptomatic or not. The presence and survival of vibrios in coastal waters and shellfish, and the plant life in freshwater ponds, has raised the question of whether these also may sometimes be reservoirs of infection.

Non-O-Group 1 *Vibrio cholerae*

Strains of *V. cholerae* which have biochemical characteristics of *V. cholerae*, but which do not agglutinate in O-group 1 antisera, are known as non-O1 *V. cholerae*. These so-called nonepidemic strains do not appear to be responsible for epidemics of severe diarrhea. They are found widely in the environment, particularly in estuarine waters with and without sewage contamination, and are concentrated in molluscan shellfish, like oysters, which feed through a filter mechanism. Animals and seafood can be sources of the organism (Blake et al., 1980), and outbreaks of diarrhea have often been linked to the consumption of inadequately cooked or raw shellfish, particularly oysters, within 48 h preceding the onset of symptoms.

Noncholera Vibrios

V. parahaemolyticus is a halophilic marine vibrio which was first recognized as a cause of foodborne gastroenteritis in Japan in the early 1950s (Fujino, 1974). It is an important cause of diarrhea in India, Thailand, Indonesia, and Vietnam, as well as Japan (Blake et al., 1980), and has been linked with outbreaks in the U.S. (Barker, 1974). It appears to be an exclusively foodborne infection, with seafood being the usual vehicle. Diarrhea due to this organism is more common in adults than in children (Sircar et al., 1976) and occurs mainly in the warmer summer months; this may be related to enhanced multiplication in food or to proliferation in estuarine and other coastal waters, where it has been found worldwide.

V. fluvialis is also found in saltwater and shellfish and has been associated with outbreaks of diarrhea in the Middle East and the U.S.

Aeromonas spp. belong to the family Vibrionaceae, occur widely in nature, and require moisture for their survival (Slotnik, 1970). They are found in surface waters, either fresh or saltwater, and in estuarine and riverine sediments. They are found in greatest numbers in warm and hot weather and can also be found in chlorinated and unchlorinated drinking water (Burke and Gracey, 1986).

Aeromonas-associated diarrhea has a sharp summer peak which correlates with counts of *Aeromonas* in drinking water (Burke et al., 1984a and 1984b) and occurs predominantly in the 0- to 2-year-old age group. *Aeromonas* infections have another age peak in the over-60 age group and tend to occur in individuals who are debilitated, immunosuppressed, or have hepatobiliary disease (Freij, 1984; Burke and Gracey, 1986).

Plesiomonas shigelloides has been associated with diarrhea in Japan (Tsukamoto et al., 1978), India (Sanyal et al., 1975), and other tropical areas. Infections tend to occur in epidemics and cause watery diarrhea; the infection is thought to be waterborne.

Escherichia coli

E. coli is a very important cause of diarrhea, particularly in children in developing countries and in international travelers. There are several mechanisms by which *E. coli* cause diarrhea, including the production of toxins and other virulence mechanisms, which are discussed in more detail in Chapter 2. Important reviews about *E. coli* diarrhea have been published in recent years (Gross and Rowe, 1985; Robins-Browne, 1987; Levine, 1987).

Enteropathogenic *E. coli* (EPEC)

Common-source outbreaks of diarrhea in nurseries for neonates helped lead to the development of serotyping to identify responsible strains of *E. coli* (Bray, 1945; Kauffman, 1947; Rogers, 1951). With the discovery of the