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Acute Diarrhoeal Disease in Less Developed Countries

1. An Epidemiological Basis for Control*

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Some of the acute diarrhoeas of man are specific infectious diseases Another and major proportion have no demonstrated infectious agent No characteristic clinical pattern regularly distinguishes one specific disease entity from another, nor specific from non-specific infections, nor epidemic from endemic disease Since clinical and laboratory differentiation is at present possible for only a small fraction of the diarrhoeas, an alternative in community control, especially where facilities are limited, is to regard all diarrhoeal disease as constituting a clinical syndrome, "acute undifferentiated diarrhoeal disease", and to base control measures on the epidemiological characteristics common to the group

Apart from its contributions to research, epidemiology has a major practical use as an instrument for action in the control of community disease To this end, pieces of knowledge from clinic, laboratory and field are fitted together to give a pattern of disease behaviour within populations A considered programme for control then evolves through the identifying of various features in a complex of causality that is multifactorial, with variables individually related to an agent of the disease, to the human host and to the environment which encompasses both A recent analysis of chickenpox (Gordon, 1962) illustrates the procedure Epidemiology so employed serves as the diagnostic discipline of public health (Gordon, 1954), through operational as contrasted to investigative activities (Gordon, 1953)

The present purpose is to consider the diarrhoeas and the dysenteries of man, especially those of infants and young children, from this viewpoint Our intent is to assemble recorded knowledge, to make free use of the opinions and interpretations of many colleagues, and to supplement these findings where appropriate with personal observations which have extended from the Arctic (Gordon & Babbott, 1959) to the tropics (Gordon, Chitkara & Wyon 1963), over a period of many years (Cathcart & Gordon, 1924) Research interests will be touched upon only to indicate those gaps in knowledge relating directly to control In simple terms, the aim is to state what to do now with the information at hand to examine the behaviour of diarrhoeal disease in nature and the application of that knowledge to prevention and control in human populations.

The attempt to control the acute diarrhoeal diseases involves more than a restriction of the morbidity and mortality they cause The attendant disability has important economic consequences In less developed countries, where diarrhoeal disease is highly prevalent, a recognized synergism with nutrition seriously affects general health (Scrimshaw, Taylor & Gordon, 1959) The resultant deterioration in nutritional status, frequently to the level of malnutrition, is reflected in impaired resistance to other infections and the precipitation of specific nutritional disorders, notably kwashiorkor. A community programme for the control of diarrhoeal

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disease is thus tied intimately to general health activities, and the relative emphasis it receives is of necessity a function of the broader effort. It is more than an action of itself, whether at the national, provincial or local level. As with most public health activities, any programme for control starts with the clinical aspects of the disease.

ACUTE DIARRHOEAL DISEASE: A CLINICAL SYNDROME

Whether prevailing with high or low frequency, the endemic diarrhoeas everywhere are mainly of acute evolution Chronic diarrhoeal disease is minimal; in less developed regions it is an inconsequential part of the whole and not included in this discussion Like most acute infections, diarrhoeal disease follows a biological gradient from clinically undetectable inapparent infection to severe manifestations with an appreciable fatality. By arbitrary definition, it is possible to make crude clinical separation into mild, moderate and severe forms of the disease

Acute diarrhoeal disease includes a proportion of specific enteric infections, such as shigellosis, salmonellosis and diseases caused by enteropathogenic colon bacilli, but it consists mainly of undifferentiated disease with no demonstrable specific infectious agent. The significant feature is that a similar clinical form occurs with all endemic diarrhoeas, whether of demonstrated specific etiology or otherwise There is no characteristic clinical pattern, as with measles among the acute exanthemata, to distinguish one etiological entity from another, nor the total of cases attributable to a specific pathogen from those without a known infectious agent.

It is true that in Guatemala severe cases are more likely to be related to *Shigella* than to any other infectious agent and that cases with a demonstrated agent include more than a proportionate share of severe infections However, a severe case has nothing to mark it as shigellosis, other than the greater probability of isolating an organism; and the majority of severe cases are of indeterminate microbial origin

Epidemics in a general population are usually superimposed on an endemic base. Consequently, various pathogens are isolated in the course of an outbreak. In our experience no epidemics have been encountered without the predominance of some particular infectious agent among those isolated, although never to the extent of accounting for a majority of the cases Furthermore, from a practical standpoint, diarrhoeal disease in epidemic form in less developed countries has not, in our experience, been distinguishable clinically from endemic cases.

This is not to discount recognition by Hardy (1959) and most others who have worked in the two situations that the diarrhoeas in pre-industrial countries with poor environmental sanitation and prevailing malnutrition differ importantly in clinical form and in severity from those of more favoured areas. The infectious agents broadly encountered are much the same, suggesting that clinical variations relate mainly to host resistance and the size of the infecting dose (Sabin, 1963)

Among malnourished children, the disease is not usually an isolated episode of acute evolution Systemic manifestations are often less pronounced than in the well-nourished child, but the attack tends to persist Instead of the prompt recovery characteristic of children in better nutritional state, a low-grade indisposition often follows, sometimes for as long as three months, with irregular loose stools, a progressively depleted nutrition, and occasional recurrent acute episodes Two or three such events during a year are frequent in young children, and some have as many as eight or ten Dehydration and electrolyte imbalance are frequent, and difficult to correct Because of this, the usually deficient diet is further restricted, which contributes to maintaining the situation A bloody or mucopurulent exudate in stools is commoner than in the mild undifferentiated diarrhoeas of developed areas

Clinically considered, acute diarrhoeal disease is a syndrome, occurring universally and in different degrees of severity, with essential differences characterizing special areas and different environmental conditions In any single situation, clinical entities cannot be distinguished, although etiologically distinct diseases exist. This circumstance is neither unique among infectious diseases nor does it necessarily limit specific action. In acute sore throat or typhoid fever, for example, laboratory examinations compensate for the limitations of clinical appraisal But, as will become evident, this is not true for acute diarrhoeal disease

SPECIFIC ETIOLOGY OF ACUTE DIARRHOEAL DISEASE

The designation of a disease as a clinical syndrome in no way precludes the existence of exactly determined disease entities within the group Aseptic meningitis is an illustration of a typical clinical reaction induced by many different infectious agents, one of which is demonstrable in most instances

On the other hand, the common cold, which also is a clinical syndrome or collection of diseases, includes several recognizable specific infectious disease entities For example, those due to the syncytial viruses, parainfluenzal viruses, rhinoviruses and reoviruses and a number of others, are each irregularly represented in the total number of common colds at a particular time or place However, the syndrome includes a much greater aggregate of cases, with good reason judged infectious and communicable, and yet with no demonstrable infectious agent A considerable number are suggestively non-infectious, or at least scarcely communicable, notably those of allergic origin

Acute diarrhoeal disease at a particular time and place is similar to the common cold in that it is a clinical syndrome of characteristic behaviour, including a minority of known disease entities, a predominating bulk of undifferentiated, presumably infectious, processes and an indefinite number of non-infectious processes The proportions are by no means fixed; the pattern is dynamic, frequently changing, and with no characteristic distribution of its elements either locally or generally

The recognized specific infectious diseases—shigellosis, salmonellosis, *Escherichia coli* diarrhoea and amoebiasis—ordinarily constitute a minor part of the whole. In pre-industrial regions with a high endemicity of diarrhoea, the three bacterial agents with their multiple serotypes are often demonstrated in less than an aggregate of 20% of cases. The usual figure is slightly higher, a proportion of 40% is occasionally met, and to find 60% of diarrhoeas associated with the specific bacterial pathogens is exceptional

Observations over a period of 17 months among children under five years of age in a Guatemalan Indian village showed that one or other of the pathogens was present in 24% of 578 cases of diarrhoea (Table 1) A specimen of faeces, usually obtained by rectal swab, was cultured on three different media Subsequently, 115 cases were subjected to intensive examination, by methods beyond any practical field application. Both rectal swabs and stools were used. If necessary, five serial specimens were examined before recognizing a negative result, and duplicate augmented lines of culture media were employed The result was the isolation of a bacterial pathogen in 35 6% of cases, the gain being mainly in numbers of *Salmonella* and *Esch coli*, the less frequent members of the group The demonstration of *Shigella* was not significantly increased

TABLE 1

BACTERIAL PATHOGENS PRESENT IN 578 CASES OF ACUTE DIARRHOEAL DISEASE IN A RURAL GUATEMALAN VILLAGE, FEBRUARY 1961 TO JUNE 1962

Bacterium	Acute diarrhoeal disease	
	No of cases	% of all cases
Shigella dysenteriae 1	10	1 7
Sh dysenteriae 2	4	0 7
Sh. flexneri 1	2	0 3
Sh. flexneri 2	23	3 8
Sh. flexneri 3	32	5 5
Sh flexneri 6	36	6 2
Sh. boydi	5	0 9
Sh. sonnei	9	1 6
Salmonella	1	0 2
Escherichia coli	17	2 9
None	439	76 0

Isolation of a pathogen from the stools of a patient does not, of course, establish an etiological relationship, and the diarrhoea in a bacterial carrier may not be caused by the pathogen isolated. Furthermore, in no less than 12% of the cases of diarrhoea, in the Guatemalan experience where a recognized pathogen was demonstrated, two or more bacterial pathogens were present concurrently, it being an open question which, if either, was the responsible agent. Enteroviruses were frequently associated with bacterial agents, and, indeed, more often than not a pathogenic bacterium, when present, was accompanied by a protozoan or other intestinal parasite High or low incidence of diarrhoea was not a determining factor in the frequency of mixed infections

In addition to this varying proportion of commonly recognized intestinal pathogens, the intestinal flora of man, in health as well as in acute diarrhoeal disease, contains a major fraction of commensal organisms, normal inhabitants of the intestinal tract, without accepted pathogenicity, most of them being coliform organisms Between these extremes is a group of infectious agents of indeterminate and irregular pathogenic power, poorly evaluated as to numbers and of diverse kinds They include certain serologically distinct *Esch coli*, other bacilli, enteroviruses in profusion, coagulase-positive staphy-

lococci, occasional fungi and ubiquitous protozoa and helminths. As a group, they are of low-grade pathogenicity, with evidence to suggest that if they attain pathogenic activity it is mainly because of favourable factors in the host or environment Conceivably this includes impaired host resistance (Taylor, 1961), specific and nonspecific. Unpublished pathological observations by G. Dammin and D. S Feldman at the Institute of Nutrition of Central America and Panama (INCAP) suggest a mechanism analogous to that in cholera, an overgrowth that produces huge numbers at all levels of the intestinal tract, with a dietary or nutritional factor presumptively important as a predisposing influence (Gangarosa et al , 1960)

Remote infections of other systems, principally of the respiratory tract and its appendages, potentially have the capacity to light up intestinal disorders Measles has a prominent place among such parenteral infectious diseases (Morley, Woodland & Martin, 1963) Experimental infection of volunteers with rhinovirus, a respiratory pathogen, has led to acute diarrhoea (Cate, Couch & Johnson, 1964).

Foods have the capacity to induce acute diarrhoea by other means than infection. A number of the nutrient deficiencies have this capacity, pellagra, beriberi and especially kwashiorkor. Some foods induce diarrhoea because of their roughage content and a few are poisonous, for example, some varieties of mushrooms and fish

Toxins formed in foods by the growth of staphylococci and other bacteria are a frequent source of epidemic diarrhoea and, to an ill-defined degree, of endemic disease The diarrhoeas induced by emotional stress are others of non-infectious origin

The impossibility of identifying, among the acute diarrhoeal diseases, clinical entities sufficiently distinct to permit an individualized programme for control has been noted Acute diarrhoeal disease can be delineated satisfactorily, but its elements, which other evidence shows to exist, cannot. The solution is to interpret the group as a clinical syndrome, acute undifferentiated diarrhoeal disease

The summary of etiological agents just given likewise discounts the possibility that modern laboratory procedures are able to compensate for clinical deficiencies, as they can with some other infectious processes Although research has been largely microbiological, an impressive effort has succeeded in distinguishing as disease entities only a relatively small number of the acute diarrhoeas of the world and, still more important, those identified lack other than microbiological characteristics separating them from the bulk of undifferentiated diarrhoeal disease. To centre control activities on specific entities is to ignore the main problem The possibility remains that the group has enough common epidemiological characteristics by which to establish principles for general control, and that recognizable epidemiological patterns exist within the complex, of sufficient importance and magnitude to warrant individualized measures in their limitation

ACUTE DIARRHOEAL DISEASE AS AN EPIDEMIOLOGICAL ENTITY

The occurrence of acute diarrhoeal disease in all populations of the world suggests innate host characteristics, physiological and biological, conducive to the disease and common to all mankind Because of this universality, it is to be expected also that fundamental features in human behaviour, with the exception of the artificial variations introduced by time and place, in cultural practices, and in the social environment of communities, all have a bearing on the propagation and presence of the condition

Such individual diseases as may be separated within the complex of acute diarrhoeal disorders show no differences from one another or in relation to the whole so far as potential effect on a general population is concerned All produce epidemics. In endemic form they are, in varying degrees, a feature of populations everywhere, and under favourable circumstances of external environment and nutrition they prevail at hyperendemic levels in many parts of the world

Not all acute diarrhoeal diseases are of infectious origin, but most of them are Despite definite and diverse infectious agents, the main reservoir of infection is man A few types of disease are of animal origin, notably salmonellosis as in Costa Rica (Moore & de la Cruz, 1959-61), but this disease also comes mainly from infected persons In all recognized specific diarrhoeal disease, carriers have a significant place together with cases in the community reservoir of infection In Guatemalan villages, carrier rates in the general population of children under five years of age without diarrhoea were 7 8% for *Shigella*, 0 1% for *Salmonella* and 4 2% for enteropathogenic *Esch. coli* (Table 2). Epidemiological evidence points to a similar situation for diarrhoeas of indeterminate infectious etiology The immediate source of

TABLE 2

CARRIERS OF ENTERIC BACTERIAL PATHOGENS, CHILDREN WITHOUT DIARRHOEA, BY AGE, IN THREE GUATEMALAN HIGHLAND VILLAGES, 1959-62

Age (years)	No of children	*Shigella*		*Salmonella*		*Escherichia coli*		Total	
		No of carriers	%	No of carriers	%	No of carriers	%	No. of carriers	%
Under 1	647	10	1 5	1	0 2	31	4 8	42	6 5
1	690	61	8 8	0	—	38	5 5	96	13 9
2	678	71	10 5	1	0 1	25	3 7	93	13 7
3	676	69	10 2	0	—	24	3 6	90	13 3
4	459	35	7 6	2	0 4	14	3 0	47	10 2
Total	3 150	246	7 8	4	0 1	132	4 2	368	11 7

infection, faeces, is common to all infectious diarrhoeas, whatever the method of transfer.

All these diarrhoeas, whether etiologically distinct or undifferentiated forms of enteritis, have common modes of transmission Only food poisoning has its own method of spread Noteworthy differences occur, however, in the patterns of distribution Endemic and sporadic diarrhoeal disease is transferred predominantly by direct contact, hand-to-mouth infection Indirect contact through objects freshly contaminated with faeces has minor significance Fingers other than those involved in direct contact spread infection by contaminating food and sometimes water stored in the household Flies play a variable part, far less important than that of contact dissemination.

The classical concept of epidemic diarrhoeal disease is of disease originating from a common source (water, milk or solid foods), with the outbreak rising and falling abruptly (Gordon & Babbott, 1959, Gordon, Chitkara & Wyon, 1963, Scrimshaw et al , 1962) By contrast, most of the epidemics personally observed in rural areas of less developed regions have been spread by contact. Characteristically they were of slow evolution They failed to reach the high peak of common-source outbreaks and usually followed a protracted course, occasionally as long as three years

The incubation period is among the more regular epidemiological characteristics In epidemics of *Salmonella* infections it may be an interval as short as 12 hours, but sporadic cases usually become clinically evident two or three days after exposure, this is true also for the undifferentiated group and for the remaining specifically identified infections In shigellosis, for example, the usual incubation period is less than four days

The duration of communicability in acute diarrhoeal disease is not well known Most of the evidence relates to shigellosis, where infectiousness is essentially for the duration of symptoms and briefly thereafter Chronic convalescent carriers are stated to be few and the carrier state is said to end usually within days or weeks However, existing observations relate mainly to adults and to patients in good nutritional state The longer clinical course among malnourished children and the tendency of the disease to relapse suggest that communicability may be appreciably longer under such conditions, a possibility supported by the high carrier rates in many communities—of the order of 8% The subject needs investigation Limited studies suggest that carrier rates for *Esch coli* may be greater than indicated by the infrequent cases *Salmonella* carriers in acute diarrhoeal disease have had minor attention because, again, cases are few. Serial studies of families, as in the INCAP observations, should provide information on the communicability of the undifferentiated diarrhoeas

The known facts about resistance and susceptibility to acute diarrhoeal disease are also few. In less developed regions, relatively few cases occur during the first six months of life During the second six months, few persons escape Thereafter, incidence decreases with age, so that attack rates in late childhood are much lower and the incidence in the adult population is still less

Repeated attacks in the course of the first and second years are the rule in developing countries. Almost every child can be certain of a bout of

diarrhoea during each of the first three years of life, and this frequency of attack may extend through the fifth year. In the Guatemalan experience, more than one attack occurred in about half of the children during the second year, and in one child out of three in each of the pre-school years It is evident that one attack gives no general immunity, and yet it is equally certain that resistance increases with age; older children and adults have far less diarrhoea. The suggestion is of a pattern of resistance comparable to that in influenza, where a matrix of resistance is filled in with age, the elements being to some degree specific and enduring, and the final pattern being effective because it accounts for most of the prevailing agents A particular pattern holds for a particular place. Transfer to another area and the resultant contact with a new set of infectious agents brings a fresh need to accommodate, as is evidenced by the well-known " traveller's diarrhoea "

The results of long-term prospective field studies in Guatemala, to be presented in another paper (Gordon, Guzmán et al , 1964) [1], illustrate the epidemiological characteristics of acute diarrhoeal disease in a representative developing area of Latin America where malnutrition prevails at a high level.

[1]See the article on page 9 of this issue.

CONCLUSIONS

Acute diarrhoeal disease is a clinical syndrome, a collection of diseases, for the most part of infectious origin, some of specific etiology and some not. Most of them are undifferentiated, either clinically or microbiologically.

In less developed areas, signs and symptoms have an individuality sufficient to distinguish the disease from that occurring in economically and technically advanced areas. This characteristic does not extend in a particular region to differentiation of one disease of the syndrome from another. Attempted microbiological distinction leaves the bulk of cases unexplained, despite qualitatively similar findings in both circumstances

The reactions of populations to the complex of acute diarrhoeal disease usually have common characteristics, which correspond to accepted ecological principle and which permit recognition of the disease syndrome as an epidemiological entity. Measures for practical prevention and control based on epidemiological behaviour are desirable and feasible

RÉSUMÉ

Certaines formes de diarrhée aigue de l'homme sont parmi les symptômes de maladies infectieuses spécifiques La plupart des autres n'ont pas d'agent causal connu Dans les régions du monde les moins développées, la diarrhée aigue est, en moyenne, plus grave, son évolution clinique plus longue et plus irrégulière que dans les zones favorisées En général, on trouve les mêmes agents pathogènes dans les deux cas, bien qu'ils different par leur fréquence absolue et relative Les différences cliniques, surtout chez les enfants, semblent être en relation d'abord avec l'état nutritionnel de l'hôte, ainsi qu'avec l'insalubrité du milieu, qui entraîne la prolifération des germes Dans chaque situation particulière, qu'elle soit endémique ou épidémique, les entités cliniques ne peuvent être distinguées à coup sûr, bien que l'on puisse reconnaître des maladies étiologiquement distinctes. On observe fréquemment plusieurs maladies concomitantes, et les infections multiples chez un même sujet ne sont pas rares Les différences cliniques ne peuvent servir de base à une lutte sur le plan de la collectivité

Dans les régions peu développées, on peut démontrer, dans 20% environ des cas de diarrhée, la présence de *Shigella* (germe le plus fréquent), de *Salmonella*, d'*Escherichia coli* entéropathogènes, ou d'*Entamoeba histolytica*. Cette proportion peut s'élever à 40%, il est exceptionnel qu'elle atteigne 60% De nombreux cas semblent être en relation avec des germes intestinaux, considérés en général comme non pathogènes L'infection parentérale joue un rôle, la nourriture aussi, ainsi que les toxines provenant de la contamination bactérienne des aliments.

La plupart des diarrhées — mais non toutes — sont d'origine infectieuse Des mesures de lutte dirigées contre des infections spécifiques reconnues n'atteindraient manifestement qu'une fraction relativement faible de l'ensemble de ces maladies L'attitude pratique devant une telle situation est de considérer comme syndrome les maladies diarrhéiques aigues indifférenciées. Des caractères épidémiologiques communs sont évidents

Les maladies diarrhéiques peuvent être endémiques, hyperendémiques ou épidémiques L'homme est le réservoir habituel de l'infection, les animaux peuvent l'être, mais dans une moindre mesure, les porteurs de germes et les infections inapparentes sont des sources d'infection plus fréquentes que les animaux. La maladie est transmise, à des degrés divers, par le contact personnel direct, par des véhicules tels que l'eau, les aliments

solides et le lait, par les mouches et autres arthropodes. La durée de l'incubation et celle de la période contagieuse sont généralement courtes La mortalité est maximum chez les nourrissons et les jeunes enfants; la résistance se développe avec l'âge C'est pour toutes ces raisons que l'on a jugé plus efficace de diriger les mesures de lutte contre l'ensemble des maladies diarrhéiques indifférenciées.

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