Current Practice

Acute Infective Diarrhoea

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Acute diarrhoea is produced by many infections, and laboratory investigations are essential for detection of the causal organisms. Nevertheless, despite careful search it is impossible in the majority of cases to isolate a bacterial pathogen or to demonstrate a virus to which there is an antibody response, though it is a fair assumption that bacteria or viruses are responsible and that the emergence of new techniques will enable us to identify them with greater accuracy. On the other hand, diarrhoea and vomiting may be the presenting feature in many conditions, notably infections of the urinary tract, pneumonia, meningitis, and septicaemia. In young children short epidemics in which there is a combination of acute respiratory and gastrointestinal upset are a by no means infrequent occurrence. Diarrhoea resulting from dietetic indiscretion must also be differentiated from diarrhoea of infective origin; this may sometimes be obvious from its transient nature and the absence of pyrexia and constitutional disturbance. In Britain chronic diarrhoea is seldom due to infection, and once giardiasis has been excluded investigation for ulcerative colitis, fibrocystic disease, coeliac disease, and genetic disorders of carbohydrate metabolism should be undertaken.

There are certain well-defined groups of infective diarrhoeas which may be discussed separately.

Gastroenteritis due to Pathogenic Strains of *Escherichia coli*

This is predominantly a disease of children under the age of 2 years; in older children and adults a very heavy dose of the organism is required to produce diarrhoea. Outbreaks are apt to occur in rest centres, children's nurseries, and hospitals, particularly when there is overcrowding. The serological strains most commonly responsible are O-111, O-55, O-26, O-119, O-125, O-126, O-127, and O-128. The last seems to have been the organism associated with the recent outbreak on Tees-side. These serotypes are not homogeneous and vary greatly in virulence. It has been estimated that 2% of healthy young children are infected with specific serotypes at any one time,¹ and Thomson *et al.*² found that approximately one-quarter of all babies were infected with types O-11, O-55, and O-26 during the first year of life. Nevertheless, the introduction of a pathogenic strain of *E. coli* into a maternity unit, children's nursery, or paediatric ward may have disastrous consequences. Unless infected babies are immediately isolated in a cell ward with skilled nursing the condition spreads rapidly. In infants and young children diarrhoea and vomiting tend to produce rapid dehydration, and if the fluid and electrolyte imbalance is not promptly corrected a fatal result may ensue. On the other hand, the illness may be trivial, with only a few loose stools and no constitutional disturbance. Characteristically the stools are watery, green in colour, and have a musty odour; very occa-

sionally they are streaked with blood. Diarrhoea may or may not be accompanied by vomiting. Persistent vomiting or signs of dehydration are indications for admission to hospital for intravenous therapy. Convulsions and neck stiffness have a particularly sinister significance, as they are indicative of hypernatraemia. The carrier of pathogenic *E. coli* may play a large part in the infection of babies and infants. In a study made by the Public Health Laboratory Service³ it was found that these organisms were carried by as many as 15-20 per 1,000 in a sample of normal children aged 0-5 years.

Typhoid and Paratyphoid Fevers

Between 100 and 200 cases of typhoid and 300 and 400 cases of paratyphoid fever are notified annually in England and Wales. A large proportion of these are sporadic infections contracted abroad, in contrast to small outbreaks where the "carrier" is a common source. In sharp distinction to the remainder of the large family of salmonellae, the typhoid bacillus originates solely in the human intestinal tract. Though *Salmonella paratyphi* "B" has on several occasions been found in lower animals, it is predominantly an infection of man. *S. paratyphi* "A" is seldom encountered in this country. These organisms are also distinctive in that when ingested they give rise to a generalized systemic infection before finally localizing in the intestinal tract. Typhoid is commonly spread by water, or food contaminated by water, whereas paratyphoid spreads after multiplication of the bacilli in food. Several serious epidemics of typhoid fever have resulted from contamination of milk or milk products such as ice-cream, while shellfish, particularly oysters, are notorious vectors of the organism. Cream, synthetic cream, ice cream, confectionery, and desiccated coconut have all been implicated in epidemics of paratyphoid fever. In recent years synthetic creams have been one of the most important sources of paratyphoid in Britain. The usual features of the illness are malaise, anorexia, headache, constipation, a simple cough, and occasionally epistaxis. Nevertheless, the mode of onset varies greatly, and, if the infecting dose of the organism is heavy (as in the first batch of cases in the Aberdeen outbreak), diarrhoea may be present at the outset. Since the illness is generally curtailed by modern therapy, only a small proportion of patients develop diarrhoea, and classical pea-soup stools are seldom seen.

Every pyrexia of undetermined origin must be carefully investigated as a possible case of typhoid fever. This is most easily done in hospital, where frequent samples of blood and faeces can be obtained for culture. Diagnosis by isolation of the organism from blood or faeces should always be attempted, as interpretation of the Widal reaction is difficult, and some time may elapse before an unmistakable rise in antibody titre is obtained. The occurrence of "rose spots" and enlargement

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of the spleen are valuable clinical evidence of typhoid fever, but the rash does not occur in more than 20% of cases.

In paratyphoid fever the rash, though less common, can be very profuse and may be mistaken for measles. Though paratyphoid fever may follow a course closely resembling typhoid fever, it not infrequently presents as a gastroenteritis. The natural tendency to relapse and the development of the "carrier state" remain two problems which chemotherapy, far from providing a solution, has tended to intensify.

Salmonellae

Many salmonella serotypes give rise to acute food-poisoning; of these *S. typhimurium* is the chief. These salmonellae are commonly derived from animal sources, and outbreaks of salmonella infection in farm animals play an important role in human disease. Food stored in warehouses may be contaminated by salmonellae from rodents. Duck eggs are a notorious source of infection; the organisms are present within the shell and are difficult to kill by cooking. Dry hen eggs are safe, as the infection is generally confined to the surface and so readily destroyed. Imported liquid egg may be contaminated with several strains of salmonellae and has been an important source of human infection.

Infection with these organisms is usually confined to the intestinal tract, and therefore presents as a gastroenteritis. After an incubation period of 6 to 24 hours the onset of the illness is sudden, with fever, vomiting, and diarrhoea. The temperature may remain elevated for several days before falling by lysis, but the severity and duration of the illness vary greatly. Vomiting is the predominant feature at onset; diarrhoea may persist for some time after vomiting has ceased. The stools are watery and may contain blood and mucus. There may be a considerable amount of fluid loss with rapid dehydration. While the disease is usually mild in young infants, in debilitated patients and patients who have had a partial gastrectomy the illness may be extremely severe and septicaemic manifestations may occur, particularly with certain serotypes, notably *S. cholerae-suis*. Sickle-cell anaemia predisposes to salmonella osteomyelitis. Chronic infection of the gall bladder or bowel wall with salmonellae is by no means rare, and patients who give a history of recurrent episodes of bowel disturbance should be investigated with this possibility in mind.

Many sufferers from salmonella food-poisoning continue to harbour the organism for three to four months after an attack. Occasionally the carrier state persists for two or three years, but lifelong carriers are seldom encountered. A Public Health Laboratory Service study³ showed that the carrier rate for salmonella organisms in a sample of healthy children aged 0-5 years was 2 per 1,000.

Staphylococcal Food-poisoning

Certain phage types of *Staphylococcus aureus* produce an enterotoxin which can cause acute diarrhoea and vomiting. Manufactured meat dishes such as cold ham, pressed meat, corned beef, brawn, and pies are prone to be contaminated by staphylococci derived from the nose, throat, or skin of food handlers. Precooked foods are particularly dangerous, as the toxin is heat-stable and unaffected by subsequent reheating. In these cases the incubation period is short, usually less than four hours, and the illness starts abruptly with vomiting, quickly followed by diarrhoea. The illness is generally brief, and complete recovery takes place, but in severe attacks there may be gross loss of water and electrolytes, leading to dehydration, circulatory collapse, and cramp. Pyrexia is not a feature of the illness, and bacteriological examination of vomit and faeces proves negative if the staphylococci have been killed by subsequent cooking.

Clostridial Food-poisoning

Clostridium welchii is an anaerobic, sporing bacillus which produces various toxins. Heat-resistant type A strains may be responsible for food-poisoning. The organism is present in the bowel of many animals and has been recovered from raw meat. There is therefore ample opportunity for contamination of meat dishes in the kitchen. Moreover, spores of the food-poisoning clostridia may survive four to five hours' boiling. If cooked meat is allowed to cool slowly under suitable anaerobic conditions (such as in a rolled joint or in a stew) spores which have survived cooking or have subsequently come from dust may germinate and within a short time produce large numbers of vegetative bacilli. Anyone consuming such meat will develop acute food-poisoning. Communal outbreaks have occurred in schools and hospitals. The clinical course of the illness is less severe than staphylococcal food-poisoning, and vomiting may not occur. Pyrexia is also seldom encountered. Colicky abdominal pain and diarrhoea are the main features. Sometimes there is dehydration, but complete recovery in 12 to 24 hours is the rule. The organism can usually be recovered from the patient's stools for at least two weeks after the attack, and there should be no difficulty in isolating it from the suspected food.

Virus Infection

It has long been suspected that some forms of gastroenteritis are due to virus infections, but proof is difficult to obtain, as standard virological techniques have been very unrewarding. Bell and Grist⁴ consider "it is unlikely that these are significant causes of uncomplicated diarrhoeal disease." In young children, however, combined acute respiratory disease and gastroenteritis is common, and gastroenteritis may be accompanied by minor respiratory disease in adults. Epidemic nausea and vomiting also behaves like a virus infection with airborne spread. E.C.H.O. viruses types 11, 20, 8, and 19 have certainly been associated with several outbreaks of acute respiratory disease with vomiting and diarrhoea.^{5,6} Gastroenteritis may be the sole manifestation of infection with the virus of infectious hepatitis and is a common feature of the catarrhal stage of measles.

Giardiasis

Infection of the gut with a flagellate organism, *Giardia lamblia*, is world-wide, and outbreaks may occur in institutions and nurseries. While the disease usually causes chronic diarrhoea with bulky, frothy, offensive stools, it may also give rise to acute attacks of gastroenteritis. A search should always be made for the parasite or its cysts in cases of recurrent diarrhoea when no bacterial pathogens have been found.

Management of Infective Diarrhoea

From the public health aspect there can be no doubt that the primary consideration in the management of infective diarrhoea is the bacteriological examination of a specimen of faeces. Except when outbreaks occur in nurseries, institutions, or paediatric wards this may well prove a counsel of perfection; nor is it of prime importance clinically, since treatment is based on correction of fluid and electrolyte balances and not on anti-biotic therapy.

Except in the case of invasive salmonella infections and the Flexner form of dysentery antibiotics have no place in treatment. These drugs should be withheld so far as possible in infections of the alimentary tract, since they may induce antibiotic resistance in normal bowel bacteria which is then by a "resistance transfer factor" transmitted to other organisms. Anderson⁷ has detected R-factor in several strains of *E. coli*

associated with the recent outbreak of infantile enteritis on Tees-side. "Sensitivity" patterns of bowel pathogens can prove very misleading, as the in-vitro reaction of the organism does not necessarily correspond with its behaviour in vivo. Furthermore, it has been shown that antibiotics, particularly chloramphenicol, prolong the carrier state,^{5,9} and antibiotics may in themselves aggravate diarrhoea.

There are very great variations in the severity of attacks of diarrhoea and vomiting, and the milder forms may be treated at home. Indeed, the great majority of patients with gastroenteritis will recover if treated with warmth and oral fluids. In institutions, nurseries, and open wards, however, all cases of diarrhoea should be immediately segregated and contacts screened until three negative stool cultures have been obtained. During the first 12 to 24 hours of an attack of gastroenteritis fluids only should be given, but the practice of giving plain glucose water cannot be too strongly condemned, since it results in a serious depletion of electrolytes. There is indeed a very strong case for inclusion in the *National Formulary* of a tablet which can be dissolved in water to give a solution suitable for the treatment of early dehydration.

Dehydration and acidosis from rapid depletion of water and salts are features of the more severe attacks of gastroenteritis. Persistent vomiting or signs of dehydration are therefore indications for immediate admission to hospital, since correction of water and electrolyte loss becomes imperative if a fatal issue is to be averted. Estimation of serum electrolyte levels is an important part of the management of such cases. This is particularly so should the condition present with convulsions, neck stiffness, and suffusion of the eyes indicative of a state of hypernatraemia, which may result in serious brain damage and be followed by severe, permanent disability. Minor neurological disturbances may also occur after these episodes.¹⁰ A buffered electrolyte solution, such as half-strength Hartmann's, is suitable for the treatment of gastroenteritis. In mild cases in which vomiting has ceased this may be given by mouth. In cases with severe dehydration or persistent vomiting it must be given intravenously. Once diarrhoea has abated and improvement has started small feeds of half-strength Hartmann's may be given by mouth, and if these are retained the intravenous infusion may be stopped. Feeds should be increased gradually until the appropriate diet for the patient's age has been reached.

After an attack of gastroenteritis many babies have reduced tolerance for glucose and fats. In cases of hypernatraemia physiological saline should not be used intravenously, since it contains too high a level of both sodium and chloride. The maximum concentration which may be safely given is a half-strength solution, and whenever possible this should be supplemented with water by mouth. Similar principles apply to the treatment of adults, although the need for intravenous therapy is less urgent. Antibiotics have no value in treatment. Neomycin is sometimes recommended and may be given by mouth in divided doses of 50 mg./kg. per day, but this is of secondary importance to fluid replacement and may only aggravate the diarrhoea. Drugs to control diarrhoea should not be used in young children. For older children and adults Lomotil, which contains diphenoxylate and atropine, and mixtures containing kaolin and pectin may be helpful. Chlorpromazine is useful in controlling nausea and vomiting.

Many children recovering from attacks of *E. coli* gastroenteritis become convalescent carriers. Such carriers are dangerous to other young children, and particular care must be taken if they are returning to a nursery or a hospital ward, when it is advisable to obtain a minimum of six consecutive negative stools before transfer. All infectious diseases units and paediatric wards should be equipped with milk kitchens.

When typhoid or paratyphoid fever is suspected it is important to withhold antibiotic therapy until sufficient material has been collected for bacteriological investigation, unless the condition of the patient is critical. Several blood cultures as well as specimens of faeces are required. Blood should be taken also

for serological tests, and in the Aberdeen outbreak it was found that the organism could be grown from the clot in many instances after the orthodox blood culture had become negative. Despite its bactericidal action and the sensitivity of the organism in vitro, ampicillin has proved disappointing and chloramphenicol therefore remains the drug of choice. For adults a daily dose of 2 to 4 g. given on a six-hourly basis should be used; for children the dose may be estimated on a basis of 100 mg./kg. body weight per day. The drug should never be given for less than 14 days, and many observers believe that the possibility of relapse is reduced if it is given for longer periods. Paratyphoid fever may be treated on similar lines, but the results are less convincing. Some patients fail to show a satisfactory response to chloramphenicol therapy. For these and for gravely ill patients it is sound practice to add corticosteroids if after 48 to 72 hours there is no clinical improvement. Prednisone 15 mg. six hourly is suitable; it should be given in full dosage for three days then gradually reduced and discontinued after a week or ten days. Chloramphenicol seems to have increased both the likelihood of relapse and the perpetuation of the carrier state. While in the past the possibility of relapse receded if the patient remained afebrile 10 days after subsidence of the acute phase, after treatment with chloramphenicol and steroids relapses have occurred as long as 21 days after the acute attack despite an intervening period of subnormal temperature.

Detection of Carriers

Detection of the carrier is the first consideration in the prevention and control of outbreaks of typhoid and paratyphoid fevers. While this may be relatively easy in the patient who is convalescent from typhoid it may prove a formidable task in the case of contact carriers, as is instanced in the record of "Typhoid Voirrey."¹¹ The person in question, an amateur cook of some renown, had probably been a carrier for 47 years before detection. The patient who is convalescent from the disease may be expected to be a carrier for seven to eight weeks, but a high proportion of those who are carrying after three months become "chronic carriers," defined as persons still carrying the organism after 12 months. Middle-aged women are particularly apt to do so. Medical officers of health are now given powers to ensure that carriers are debarred from occupations that have to do with the handling of food. Specimens of stool are examined at regular intervals and serological tests are carried out. About 85% of chronic carriers have Vi agglutinins in titres of 1:5 or more. The absence of Vi antibody does not exclude the carrier state. The test must be interpreted with caution, but if the titre is less than 1:5 it is unlikely that the person will become a chronic carrier.

Treatment of carriers is difficult. Chloramphenicol should never be used, since it is ineffective, potentially dangerous, and prolongs the carrier state. Christie¹² reported success using high dosages of ampicillin for 12 weeks, but it is only fair to say that other workers have not met with the same degree of success. If the organism can be grown from the duodenal juice the biliary tract is infected. In such cases cholecystectomy alone has been successful in 70% to 90% of chronic carriers, but it is logical to combine surgery with a course of ampicillin. There is no general agreement about what constitutes proof of clearance in a carrier. Negative cultures of faeces, urine, and duodenal juice together with a negative Vi test over a period of three months would be accepted by most, if not all, authorities as satisfactory evidence. Observation of a high standard of personal hygiene is of much greater importance than any arbitrary number of negative cultures.

In salmonella infections the illness is more prolonged than in the toxin food-poisonings. Although in-vitro tests show salmonellae to be sensitive to a number of antibiotics, the results in vivo are so disappointing it can be said that these drugs have no place in the treatment of salmonella gastroenteritis. In

septicaemic conditions they are more effective, and in life-threatening infections either chloramphenicol or ampicillin should be tried, although, as in gastroenteritis due to coliforms, intravenous infusions of fluid and electrolytes are of prime importance as a basis for successful therapy.

Antibiotics are useless in the treatment of the carrier state, and it has already been pointed out that chloramphenicol should on no account be used. Chronic carriers can be debarred from occupations which have to do with food handling, and no food handler should be allowed to resume work until six consecutive negative stool cultures have been obtained over a period of three weeks. Education of the carrier in personal hygiene is the only sound method of solving the problem. Control of salmonella food-poisoning is a complex matter involving the prevention of infection in farm animals, the treatment of animal foodstuffs to prevent epizootics, prevention of spread in slaughterhouses and butcher's shops, adequate refrigeration storage for meat, and detection and control of the human carrier. Virulent strains of salmonellae may spread rapidly in a hospital ward, and the strictest possible methods for isolation of individual cases should be enforced.

Antibiotics have no place in the treatment of gastroenteritis of virus origin, in which the principles of conservation of fluid and electrolyte are once again of fundamental importance. Giardiasis responds to treatment with mepacrine 0.1 g. t.d.s. for ten days.

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Drug Treatment of Epilepsy

Epilepsy presents one of the great challenges in comprehensive medical care, and the selection of appropriate drugs is complementary to more general and equally important measures. The epileptic may be frightened by his seizures and should have his disorder fully explained. Management must embrace the education of relatives, teachers, and employers, the provision of suitable employment, advice as to the patient's eligibility to drive a car or work with machinery or at heights, and provision of information about the genetic aspects of the disorder. School and industrial medical officers make an invaluable contribution to the management of these patients and should always be kept fully informed. The facilities of voluntary organizations and local authorities should be made known to patients. The treatment of epilepsy therefore involves more than the treatment of epileptic fits, but it is this aspect which dictates the choice of anticonvulsant drugs and the routine of their administration.

Though the majority of epileptic seizures occur without any recognizable endogenous or exogenous provocative factors several such factors are clinically recognized. These include febrile illness, natural sleep and the "half awake" state of consciousness, hypoglycaemia, overtiredness, the upset which follows alcohol excess, alcohol and barbiturate withdrawal, respiratory alkalosis, emotional stress, menstruation in women, and even excessive sunburn. An upset in routine such as a Continental holiday with long hours and irregular meals may be responsible. The subject's epileptic tendency may be such that seizures occur only under one or more of the above circumstances, the commonest being nocturnal seizures. However, in the majority seizures seem unrelated to such factors in the present state of knowledge. Social and emotional factors can have a profound influence on seizure frequency, and this point must be appreciated before any logical management of the patient's drug regimen can be undertaken.

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Certain broad principles of anticonvulsant medication require emphasis, not least the problem of whether or not to use drugs in a patient who presents with one episode. It is often best to withhold therapy if the attack occurred under clearly provocative conditions, and merely to warn the patient of situations to avoid. A single episode in an adult may be left untreated, provided a symptomatic cause has been excluded. In a young person further seizures so often follow that treatment should probably be instituted after a single episode. If there is doubt as to the nature of a single episode, diagnostic and therapeutic restraint should be exercised.

Principles of Drug Therapy

Once anticonvulsant therapy has been instituted certain other principles emerge. It is seldom of benefit to prescribe more than two drugs concurrently. Moreover, any increase in the dosage of drugs already being taken and any addition of new drugs to the regimen may lead to a state of socially unacceptable retardation in which the seizure frequency may paradoxically increase. Moderation of therapeutic enthusiasm is often followed by a reduction in the number of seizures and a brighter patient. Any change in anticonvulsant regimen, even the simple addition of another drug, should be done gradually; the smallest practical increase in dose should be made at an interval of some days. Even then the period of change may be marked by an increase in the frequency of seizures. The efficacy of the change should not be judged prematurely, since a stable blood level may not be achieved until several weeks have elapsed on a constant dose.

There is an understandable tendency for doctors to change or increase anticonvulsant therapy in patients with fluctuations in their seizure frequency. This temptation should be resisted, for frequent adjustments of this sort seldom provide the answer, which should rather be sought in the patients' social and emotional environment or accepted as part of the natural history of the disorder.

A stage is reached in the management of some patients when satisfactory control of seizures can be obtained only at the