"THE PROPHYLAXIS OF TRAVELLER'S DIARRHOEA IN ATHLETES"

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Gordon has defined Traveller's Diarrhoea as "a notorious world-wide illness, usually lasting 1 - 3 days with precipitous onset with loose stools and variable symptoms of acute gastroenteritis such as nausea, vomiting, cramps, chills, myalgia and profound malaise".

While a causative organism may be found, the majority of cases escape clear cut pathological classification. Certain features of Traveller's Diarrhoea such as its incidence, prevalence and spread, for instance in families strongly suggest an infective causation and it is perhaps logical to think that one is dealing with an infective group of disorders for two further reasons. Firstly, changes of climate, temperature, surroundings, diet and water - as "pure drinking water", in the absence of pathogenic organisms - have not been shown to cause diarrhoea by themselves and those who propose climatic environmental change alone as a causal agent have not shown any mechanism whereby these factors directly affect the bowel.

Secondly, the more extensive the searches for causative organisms in so-called Traveller's Diarrhoea, the more rewarding these have been. For instance, Mackey (personal communication) in a series of Traveller's Diarrhoea in East Africa was able, by intensive studies and follow up, to show that the majority of these episodes were due to the various local strains of Salmonella. He was able to isolate over 100 different strains of this organism, and the clinical course of the individual cases was in some cases confined to only one or two loose stools.

It is not suggested that all episodes are similarly caused but this illustrates the scope for further investigation, especially in the large number of slight or trivial cases which are so short or mild that medical attention is not sought and no bacteriological investigations are undertaken.

General Aspects of Infective Diarrhoeas

As a background to the problem of Traveller's Diarrhoea, it may be helpful to give a simple classification of diarrhoeas, together with a brief word on their treatment. They must be divided into four broad categories:- Non-specific, Specific, Nervous and General Medical.

1. Non-specific.

By definition these would form the majority of cases of Traveller's Diarrhoea.

2. Specific:

Here a pathogenic organism is demonstrated by microscopy or culture, or confirmatory evidence from serum antibody titres is obtained. The three main categories are the specific diarrhoeas

of viral, bacterial and protozoal origin.

A. Viral

A large number of viruses have been shown to cause acute diarrhoeal symptoms of varying severity. These include over 50 types of Enteroviruses (including Polioviruses, Coxsackie and Enteric Cytopathogenic Human Orphan viruses), as well as various Reoviruses and Adenoviruses. They can cause clinical conditions similar to Traveller's Diarrhoea and often go under such names as "winter vomiting disease", "gastric flu" and so on. In one experiment, Gordon, Ingraham & Korn were able to transmit "epidemic gastroenteritis" to volunteers via bacteria-free faecal filtrates and were in fact able to differentiate 2 separate strains with different severity and incubation periods. However, all attempts to isolate the responsible infective agents on tissue-culture were unsuccessful.

B. Bacterial

These may be broadly divided into 2 causative groups -(a) pathogens and (b) pathogenic strains of common organisms. These latter include certain strains of *E. Coli*, as well as *Proteus* and *Pseudomonas*.

The main pathogens are the groups of *Salmonellae* and *Shigellae*.

Salmonellae may cause either an Enteric Fever type of illness, *Sal. typhi* being the commonest organism in some countries, *Sal. paratyphi A* in others, *Sal. paratyphi B* in Britain. Some *Salmonellae*, by contrast, cause the different clinical picture of an acute gastroenteritis. *Sal. typhimurium* is the commonest of these pathogens in Britain, but the work of Mackey mentioned previously illustrates the dimensions of this problem, with its varying severity, and large number of strains.

It should be stressed that while the Enteric fevers are of great seriousness, acute *Salmonella* gastroenteritis is usually a short, self-limiting illness and it is doubtful whether specific antibacterial therapy does any more than reduce the number of residual carriers.

The other main pathogens, also of world-wide distribution, are the *Shigellae*, which cause bacillary dysentery. Mild forms such as some *Sh. Sonnei* infections could be confused with Traveller's Diarrhoea but the more pathogenic strains such as *Sh. Shigae*, commoner in the Far East, are a different clinical problem with a severer illness.

Therefore, there are a large number of viruses and bacteria able to cause diarrhoea, but as these are widely spread through the world's populations, one is left to conclude that the individual acquires an immunity to those bacteria in his own environment. Outbreaks of diarrhoea follow the introduction of new strains into the Community, and vice versa, the removal of the individual into a new community. Here, obviously, the crucial factors determining events in any individual instance are the immune status of the individual and the community, and the public health environmental factors encouraging or inhibiting the spread of pathogenic organisms.

To summarise thus far: there is fair presumptive evidence of considerable overlap between Traveller's Diarrhoea and these specific diarrhoeas, and that Traveller's Diarrhoea may represent a low grade self-limiting infective process.

C. Protozoal

Amoebiasis should be mentioned at this time as it is relevant to the setting of the forthcoming Olympics in Mexico, a country where amoebiasis is extremely widespread, and where therefore, the casual traveller is at some risk of infection, especially if he stays a few weeks and becomes careless about matters of food and hygiene.

Amoebic dysentery may be serious: its severity is unpredictable, and stringent precautions must be taken against infection - this means exercising the greatest discipline in refusing local foods, salads, drinks, fruits, ice-creams, etc.

While Amoebiasis is not strictly relevant in a discussion of Traveller's Diarrhoea, it may be considered because of its prevalence in Mexico, and in the light of the drugs to be discussed

3. Nervous Diarrhoea and General Medical Causes

These are mentioned in passing to complete the picture. More than one team doctor has correlated the incidence of "Traveller's Diarrhoea" with the approach of the individual athlete's event!

INCIDENCE OF TRAVELLER'S DIARRHOEA

What is the incidence of Traveller's diarrhoea? There is very little work available in controlled series. The latest paper, by Turner⁶ in a group of 385 unselected air travellers to all parts of the world, gave an incidence of about 17½% or about 1 in 6, which may represent a fair average, there being considerable world regional differences, ranging from about 8% in travellers to North America, to about 26% to Africa. Kean²⁵ had earlier given figures of about 30% for American students visiting Mexico.

Treatment of Diarrhoeas

This is divisible into Symptomatic and Specific.

A characteristic of Traveller's Diarrhoea, many acute gastroenteritides and "gastric flu" type illnesses is their rapid self-limiting course and response to symptomatic and supportive therapy alone, such as Kaolin or Codeine Phosphate.

Of the drugs used for specific diarrhoeas, the Sulphonamides have a place in Shigella infections, though many strains have now become Sulphonamide resistant, and Antibiotics, including Tetracycline, Streptomycin and especially Neomycin may be the best choice²⁴. Combinations of an antibiotic and a Sulphonamide have been more effective than a Sulphonamide alone in Shigellosis in some trials⁷ but not in others⁸.

The management of the Salmonella group of Enteric Fevers, of course, present a different problem, which is not relevant to this discussion, and as mentioned earlier, the acute Salmonella gastroenteritis probably

does not need specific antibiotic therapy, except perhaps to eliminate the carrier state.

In amoebiasis the mainstays of treatment are Emetine and Chloroquine. Gholz^{9,10,11} and his associates in a large scale study of over 4000 in-patients from a Californian mental hospital showed that other amoebicidal drugs, especially Enterovioform (Iodochlorhydroxyquinoline) are effective both in prophylaxis and treatment of amoebiasis. Earlier evidence of Enterovioform's amoebicidal effect was published by David et al¹², and Reed and Johnstone¹³ as far back as 1933 and 1934. All these authors reported Enterovioform doses of 750 mg daily optimum.

A further important result of Gholz's work was the finding of a dramatic fall in the incidence of Shigella infections, *pari passu* with the drop in incidence of Amoebiasis.

To summarise, there is no drug that effectively prevents or treats all the diarrhoeas, including Traveller's Diarrhoea and a compromise has to be made in prophylaxis, and an inspired guess in treatment, before any bacteriological results may be available, or the clinical course of the illness becomes more apparent.

USE OF PROPHYLACTICS

In considering the drugs commonly used in the prophylaxis of Traveller's Diarrhoea, the two main questions are, first of all, are they harmless? Secondly, are they effective?

Most effective drugs have side-effects, sometimes even fatal, but these must be weighed against any benefit gained.

The Sulphonamides are well known to cause a number of side-effects. These vary from serious blood dyscrasias and renal complications to drug reactions and sensitivity rashes. Although the incidence of severe side-effects is not great, Sulphonamide rashes are fairly commonly seen in normal clinical practice and have appeared in athletes on prophylactic tablets. Streptomycin and Neomycin have negligible dangers given orally but Streptomycin is well known to give rise to skin sensitivity in handlers, and these drugs, like the Sulphonamides may occasionally, like all anti-infective agents, actually cause diarrhoea by altering the normal bacterial flora in the gut.

Enterovioform is said theoretically to give rise to Iodism but an actual case report of this could not be found. Gholz in his monumental study made the most extensive haematological and biochemical investigations looking specifically for side-effects but was unable to detect any.

Furthermore, detailed and prolonged bacteriological studies failed to show any change in the normal bowel flora even though he used 750 mg daily, compared with our current 500 mg. daily in Traveller's Diarrhoea prophylaxis.

So, to summarise the dangers: in the small doses used there is very little chance of mishap but there is a clear risk of eventual Sulphonamide sensitisation with prolonged usage, and it must be remembered that we are considering athletes who may, on short competitive trips abroad, have a dozen or more short exposures to these drugs in a 5 year span in top level sport. There is no evidence that athletic performance is actually impaired while these drugs are being taken.

SHOULD ONE USE PROPHYLACTIC DRUGS AT ALL?

There is considerable controversy in medical circles as to whether it is desirable, or even necessary, to use these drugs prophylactically.

Such authorities as Avery Jones ¹⁴ and Woodruff ¹⁵ stress the importance of meticulous hygiene and also the lack of detailed aetiological findings in Traveller's Diarrhoea and the lack of controlled trials in travellers.

Turner ⁶ has recently published a series of 1100 air travellers, in roughly equal groups, travelling to unselected parts of the world, and taking respectively 1. An inert tablet, 2. A Neomycin/TriSulphonamide tablet and 3. Streptotriad (Streptomycin plus trisulphonamide). He was able to demonstrate the significant beneficial effects of Streptotriad in reducing both the overall incidence of Diarrhoea as well as its severity and associated symptoms. There were two surprising results in his paper that illustrate the difficulties in dealing with this topic.

Firstly, the Neomycin/TriSulphonamide group did very much worse than Streptotriad, though one might perhaps have expected Neomycin to have had much the same bacteriological effects as Streptomycin. Secondly, while the Neomycin/TriSulphonamide mixture was clearly effective in reducing the distressing symptoms associated with the diarrhoea, it did not reduce the overall incidence of diarrhoea; in fact, there was more diarrhoea than in the placebo group. As some of these cleared promptly on stopping this mixture, it is inferred that the Neomycin was itself causing the diarrhoea by altering the gut flora.

It must be admitted that much of the evidence in support of prophylaxis is circumstantial and anecdotal but the impression of good effect from personal observation by so many athletes, travellers and doctors cannot easily be dismissed.

Earlier papers from Kean & Waters ^{25,26,27} studying American students in Mexico City showed significant benefit from the use of Phthalylsulphathiazole, an insoluble Sulphonamide compared with placebos, with Neomycin giving intermediate results. They also showed that Enterovioform was significantly less effective than Neomycin, but figures varied at different institutions within the trial, some figures showing Enterovioform to be associated with more Traveller's Diarrhoea than placebo controls. There was no direct Enterovioform: Streptotriad trial.

In Rome, 1960, Dr. Denis Cussen, who looked after the British Team, used Streptotriad, 2 a day, and found that our team avoided diarrhoea whereas a number of the other teams suffered from an appreciable amount of it.

In Tokyo, 1964, Drs. Owen and Massey ¹⁶ had a party of about 275, for the period of the Olympics but seem to have been lucky in having to report only 3 cases of diarrhoea using Streptotriad, 2 tablets taken together each night. There was good evidence that not all the team took the tablets regularly.

In the British Olympic Association's ¹⁷ medical research project in Mexico in 1965, the party of 12 took Streptotriad, 4 daily for the first week, 3 daily for the second week and 2 daily thereafter. In addition, strict dietary precautions were followed. Two people had diarrhoea, but both had stopped their tablets several days previously.

In the Jamaica Commonwealth Games ¹⁸ of 1966 a team of about 250 using Streptotriad, 2 a day, in a very demanding climate, provided only 7 cases of mild diarrhoea and, for the record, 8 cases of constipation coming to the medical clinic.

Turning to other Games, there is a brief note in the Journal of the American Medical Association ¹⁹ thus: "Dr. McPhee, from Princetown, had good luck with our athletes at the (1955) Pan-American Games with 2 Enterovioform tablets daily". I should mention that this represents a dose of 500 mg daily, the same as our own current dosage.

In the last 4 University Games, we have tried to build up some sort of statistical evidence but have little to show despite our efforts.

In Bulgaria in 1961 ²⁰, Trisulphonamide, B.P., alone was used and there was a considerable amount of diarrhoea in the team, 3 athletes being unable to perform their events effectively.

In Brazil in 1963 ²¹, good records were kept of $\frac{3}{4}$ of the team who took Streptotriad, twice a day. A clear correlation was found between the incidence of severity of diarrhoea in 12 sufferers and their failure to take the pills either regularly or at all at the relevant times.

In my own experience (with the British Team) at the last two World Student Games, I have been able to demonstrate that in Hungary (1965) ²² and Japan (1967) ²³ reasonable care in food hygiene in a civilised environment makes prophylactic tablets unnecessary.

In Hungary, I split a team of 108 into 3 groups; diarrhoea occurred in 5 out of 72 Streptotriads, but only 1 out of 30 Enterovioforms and not at all in the small control group of 6. However, one person developed a typical drug rash after starting Streptotriad, which she had previously taken in similar circumstances: and, to prove everything or nothing, one young lady on Streptotriad collapsed at 8 o'clock one morning, with vomiting and diarrhoea, had a morning's rest and symptomatic treatment and won a gold swimming medal after lunch.

In Tokyo in 1967 with a team of 80, there was only one severe attack out of 16 non-tablet controls, and a couple of very mild bouts of looseness in the other 65 (32 on Streptotriad, 33 Enterovioform). I know that these were irregularly taken; in fact, the hygiene arrangements in the Olympic Village were so obviously good that most of the team used their common sense and realised that tablets were unnecessary.

To conclude, therefore: I have outlined the rationale of treating the various diarrhoeas and tried to extend these principles into the nebulous field of Traveller's Diarrhoea in athletes. On the practical level, I have suggested that there is little or nothing to choose between Streptotriad and Enterovioform as prophylactic agents, at a dosage of 2 tablets daily. Apart from the small chance of trouble with Sulphonamides, they are safe and should not impair athletic performance.

Bearing in mind that no drug can absolutely prevent Traveller's Diarrhoea, or cure all the likely causes of it, it may be that greatest danger of these medicines is that they may engender a false sense of security which may lead to laxity in the strict hygiene requirements in places like Mexico.

I would, finally, suggest that until we know a great deal more about the subject, we must treat all claims with critical reserve, realising fully the empiricism of many of our clinical habits. I would suggest an impartial consideration of available alternative drugs in different geographical situations. For instance; while the matter of dosage may be open to discussion, is there not an argument for using Enterovioform in Maxico, where theoretically its amoebicidal properties may be of practical use, instead of Streptotriad, which does not share these? Is there not a bigger question still, if some of the team are to spend upwards of 6 to 8 weeks there, faithfully swallowing Sulpha drugs and inviting sensitisation, of whether or not it would be better just to go early, eat cleanly, and build up one's own antibodies in good time before the competitions?

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Footnote: ENTEROVIOFORM (CIBA Ltd) contains 250 mg. of iodochlorhydroxy-quinoline.

STREPTOTRIAD (Pharmaceutical Specialties (May & Baker Ltd) contains

Streptomycin sulphate	65 mg.
Sulphadimidine	100 mg.
Sulphadiazine	100 mg.
Sulphathiazole	100 mg.