criticisms cannot, however, be substantiated, for the scheme proposes no more specialization than exists now, but merely seeks to end the present very unsatisfactory haphazard state of affairs. But two important questions remain to be answered: will the scheme be implemented and how?

The introduction of the scheme will require financial and administrative backing with the active support of the Ministers concerned; without these it will fail. The pressure of work in the hospitals is such that no more time can be found for training programmes unless the numbers of doctors are increased. All registrar and senior registrar posts should now be regarded as training posts in which training must take priority over service and not vice versa, as has previously been the case. Senior registrar appointments should be supernumerary to service requirements, as prevails in Scotland but lamentably is not the case south of the border. Furthermore, there must be a closer correlation between the number of training posts available and the eventual number of consultant vacancies. This has almost been achieved with regard to senior registrar and consultant appointments, but the current situation in which three registrar posts exist for every senior registrar appointment available[2] is indefensible. Moreover, in 1966 of 2,217 British-born registrars in all branches of medicine and surgery in England and Wales 473 had been in this supposedly training grade for more than three years and 283 for more than four years; over 1,000 of these "young trainees" were between 30 and 34 years old and nearly 400 were 35 years or older.[3] No dictates of service can justify the perpetuation of this deplorable state of affairs. It follows that the number of registrar training posts must be substantially fewer than at present. Hard-pressed and overworked surgeons, especially those in regional hospitals, are likely to view these proposals with dread unless they receive an absolute assurance that help will be forthcoming to cope with the work load. One obvious answer, but not the only one, is to increase the number of consultant posts,[4] which would also automatically increase the number of training posts available. Inevitably the scheme will cost money, but all these problems must be realistically faced if the Health Service is to obtain the well-trained surgeons it requires on the one hand and young doctors the type of career structure they fully deserve on the other. The National Health Service can no longer afford to leave such men in anguished doubt for a dozen or more years at what should be the most formative and productive stage of their careers.

The details of how the scheme will be implemented require further discussion, but the joint committee and specialist advisory committees will clearly play a most important supervisory and correlating part. The day-to-day running of the scheme, especially in general surgery, must surely be regionally based, preferably utilizing the excellent postgraduate committees already established for this purpose. Urgent administrative action based on these imaginative recommendations would represent a substantial step towards meeting some of the recommendations of the Royal Commission on Medical Education. The scheme could also do much to restore the lost confidence and waning enthusiasm of young surgeons about their career prospects in the National Health Service. A gentle breeze is blowing through the field of postgraduate surgical education; will it be allowed to become a true wind of change?

[1] *Joint Committee for Higher Surgical Training: Report of Royal College of Surgeons of England.* London, 1968.
[2] Yellowlees, H., *Brit. med. J.*, 1966, 2, 1192.
[3] *Report of the Royal Commission on Medical Education*, 1968, Cmnd. 3569. H.M.S.O., London.
[4] *Brit. med. J.*, 1968, 3, 133.

# Tetracycline Diarrhoea

Tetracyclines are more likely than any other orally administered antibiotics to cause diarrhoea and other gastrointestinal disturbances. Reasons for this are not far to seek, and the chief of them is that tetracyclines are not completely absorbed. Indeed, the larger the dose, the larger is the proportion of it which remains unabsorbed to produce local changes in the alimentary tract.

In so far as the disturbances which result are consequent on changes in the bowel flora, it has also to be remembered that almost all the principal genera normally represented here —*Escherichia, Streptococcus, Lactobacillus, Clostridium,* and *Bacteroides*—are sensitive to tetracycline, and the degree of suppression of the bowel's normal inhabitants may therefore be profound. On the other hand, resistant strains of many of these are now common. B. Ruebner[1] and others have shown that, after initial suppression of *E. coli* and enterococci, resistant variants of these organisms sometimes proliferate during treatment, reaching or even exceeding the original population levels. Perhaps patients in whom these resistant but otherwise normal organisms grow out remain free from disturbance; we do not know. Another possible factor is the direct action of the antibiotic on the mucosa. The hydrochlorides of tetracyclines, employed for their better solubility, form strongly acid solutions, and some degree of local intolerance may reasonably be assumed.

Of the various side-effects which have been observed, nausea and vomiting seem inexplicable in any other way than this. They cannot result from a change in the flora of the stomach, since it has virtually none. It is possible that effects related to more distant parts of the alimentary tract may be caused in a similar way, and how abdominal pain or flatulence are produced is anybody's guess, but when diarrhoea results it is generally assumed to be due to replacement of the normal bowel flora by other organisms. These may be of three kinds. A resistant and virulent strain of staphylococcus may cause a severe necrotizing enteritis, with copious liquid stools and rapid dehydration. This fortunately rare infection, seen mainly in surgical patients, stands apart. Secondly, resistant strains of enterobacteria other than *E. coli* (including *Proteus, Klebsiella,* and *Pseudomonas*) may overgrow other species, and this change may be accompanied by diarrhoea and may perhaps justifiably be assumed to cause it. Thirdly, a species totally resistant to antibacterial antibiotics and normally present, if at all, only in small numbers also finds an opportunity for abnormal proliferation; and indeed, apart from the bacterial vacuum produced, tetracyclines are said actually to stimulate its growth. This is *Candida albicans,* which, whatever it may do in the bowel, occasionally causes severe infections elsewhere in tetracycline-treated patients.

It is commonly believed that growth of this organism is associated with the intestinal side-effects of tetracycline treatment, and this belief has been fostered by the advertising of preparations containing tetracycline and nystatin, the effect

of the latter being to prevent such growth. That it has this effect there can be no question, as many studies have shown, one of them, by B. J. Smits and his colleagues in the *B.M.J.*[2] However, in patients in this trial who were given tetracycline without nystatin the proliferation of *Candida* had no observable clinical effects. The evidence in this and other trials connecting such proliferation with symptoms is either nonexistent or conflicting, as is the evidence that the addition of nystatin prevents symptoms of disturbance in the alimentary tract.

Previous studies of this kind are reviewed and some are adversely criticized in the report of a further trial organized by the British Tuberculosis Association and published at page 411 of the *B.M.J.* this week. It was conducted at eight centres on a double-blind basis, patients being randomly allocated to two groups, receiving either 2 g. tetracycline alone daily for 10 days, or this dose together with the usual dose of nystatin. All the mycological studies were carried out in one laboratory, at the Westminster Medical School. It is claimed that the procedure for eliciting symptoms was free from fallacies entailed in methods of inquiry used in some previous trials. Many of the patients were elderly chronic bronchitics; some were having antibiotic treatment at the time of admission, and some already had gastrointestinal symptoms. The total number of such symptoms diminished slightly during the 10 days' inpatient treatment, but there was no significant difference in their frequency in the two groups. Indeed, such differences as there were, particularly in the frequency of "flatulence" or of "softer or liquid stools," appear to favour treatment with tetracycline alone. There was the usual wide and highly significant difference in the percentage of rectal swabs positive for *Candida* at the end of the treatment period, but this finding was unrelated to symptoms. In the group given only tetracycline the percentages with and without symptoms from whom *Candida* was isolated were 37 and 38%. The authors have thus failed to "show any association between candida and gastrointestinal symptoms normally attributed to chemotherapy," and conclude that "the addition of nystatin to tetracycline cannot be justified" as a measure for preventing such symptoms.

If this conclusion is accepted it will clear the air, and the routine administration of this combination, to which there are other objections,[3] will appear to be usually undesirable. This is not to say that combined treatment is never indicated. A fortunately very small minority of patients treated with tetracyclines develop overt candidiasis which may involve the throat and bronchi, the oesophagus or the bowel, operation sites, and even the blood stream. These patients are usually severely debilitated by the primary disease or by some other underlying condition. Since the source of the infection is almost certainly the alimentary tract, protection with nystatin by mouth is indicated whenever it seems possible that this complication can arise.

The problem of preventing gastrointestinal disturbances caused by tetracyclines remains. For any of those attributable to a direct action of the antibiotic on the gastric or intestinal mucosa it appears insoluble, unless perhaps by using newer but less well-tried tetracycline compounds, of which one at least forms a nearly neutral solution and several are said to be better absorbed. If changes in the intestinal flora are responsible for diarrhoea, these perhaps deserve further study. Another approach is bacterial replacement therapy. There is evidence[4 5] that antibiotic-resistant *Lactobacillus acidophilus* can be implanted in the bowel during broad-spectrum antibiotic therapy with beneficial results. This treatment has also been shown to suppress the growth of staphylococci in the bowel during treatment with tetracycline.[6] The place of this kind of treatment is still uncertain, and some of the claims which have been made for it in other connexions will not bear critical examination, but its use in the type of case discussed here appears to be logical and to deserve further study.

[1] Ruebner, B., *J. Path. Bact.*, 1957, **73**, 429.
[2] Smits, B. J., Prior, A. P., and Arblaster, P. G., *Brit. med. J.*, 1966, **1**, 208.
[3] *Med. Lett. Drug. Ther.*, 1961, **3**, 33.
[4] Torok, J., and Turay, P., *Kinderärztl. Prax.*, 1960, **28**, 385.
[5] Kleinhauf, I., *Arch. Kinderheilk.*, 1959, **160**, 51.
[6] Gordon, D., Macrae, J., and Wheater, D. M., *Lancet*, 1957, **1**, 899.

# Heavy Chain Disease

Seven cases have now been described[1-4] of an unusual form of lymphoma in which the malignant cells make an excess of the Fc fragment of the "heavy" chains in the immunoglobulin G molecule. This paraprotein, or "M" component, is found in the serum of the patient. On paper electrophoresis it gives rise to a narrow spike or an obliteration of the trough between the $\beta$ and $\gamma$ globulin peaks. It also appears in the urine. Unlike the Bence Jones proteins excreted in the urine in multiple myeloma, which immunochemically represent the "light" chains common to all classes of immunoglobulin, the Fc fragments in heavy chain disease do not precipitate and then redissolve on progressive heating of the urine. On electrophoresis of concentrates of urinary protein they can be shown to have the same mobility as the abnormal Fc protein found in the serum, and this is of great diagnostic significance in differentiating the new disease from multiple myeloma with reactive proteinuria.

Heavy chain disease appears to give rise to a fairly distinct clinical picture. Six of the seven patients have been middle-aged men who presented either with painful, tender, enlarged lymph nodes or with loss of weight and weakness. About half the cases ran a rapid course, with death in a few months, while in others there was temporary spontaneous regression of the lymphadenopathy and survival for several years. A special clinical feature noted in four of the cases was oedema and redness of the uvula and soft palate. None of the patients had any bone pain or the *x*-ray changes seen in multiple myeloma.

The proteinuria varied from 50 mg. to 15 g. per 24 hours in different patients and tended to increase in those who survived for several years. As in myeloma and in Waldenström's macroglobulinaemia, the amount of the abnormal $\gamma$-globulin in the serum also increased as the disease progressed, and in most cases this increase was accompanied by a reduction in the synthesis of normal IgG, with the result that the patients nearly all died of infections, especially pneumonia,

[1] Franklin, E. C., Lowenstein, J., Bigelow, B., and Meltzer, M., *Amer. J. Med.*, 1964, **37**, 332.
[2] Osserman, E. F., and Takatsuki, K., *Amer. J. Med.*, 1964, **37**, 351.
[3] Lebreton, J. P., Rivat, C., Rivat, L., Guillemot, L., and Ropartz, C., *Presse Méd.*, 1967, **75**, 2251.
[4] Ellman, L. L., and Block, K. J., *New Engl. J. Med.*, 1968, **278**, 1195.
[5] Prahl, J. W., *Nature (Lond.)*, 1967, **215**, 1386.
[6] Grey, H. M., and Kunkel, H. G., *Biochem. J.*, 1967, **6**, 2326.