Relation of Antibiotic Treatment to Natural Response to Infection

R. E. O. WILLIAMS, MD, FRCP, FRCPath, Professor of Bacteriology, Wright-Fleming Institute, St Mary's Hospital Medical School, London

The effect of antibiotics on microbes in the test-tube is often so dramatic that one cannot avoid the temptation to consider bacteria in the infected man as being in a strictly analogous position to those in the broth culture. But in reality the bacteria in infections are rarely freely exposed to the action of antibiotics. They may be buried in pus or surviving within macrophages that are impenetrable to the antibiotics; and outside the tissue cells they may be held in a 'dormant' form not susceptible to antibiotics that act on dividing cells. Also the concentration of the antibiotic around the bacteria fluctuates from time to time.

Therapeutic experience of infected patients with congenital defects in tissue defence mechanisms, as in chronic granulomatous disease, suggests that when the defence mechanisms are inadequate, antibiotic treatment of infections is more difficult. The same impression is gained from treatment of infections in patients on immunosuppressive therapy. Unfortunately, it is very difficult to proceed from impression to the quantitation; for example, we have no factual information on the extent to which more vigorous antibiotic treatment is needed in the face of any particular defect in the defence mechanisms. There is remarkably little evidence, in cellular or sub-cellular terms, on the ways in which antibiotics affect the tissue response to infecting microbes and there is a large field here for investigation by techniques compounded from experimental pathology and microbiology.

Generally, it seems possible to overcome the deficiencies in tissue defences by giving more antibiotic, or a greater variety of antibiotics. Either procedure is liable to carry some penalty in the form of direct or indirect toxicity. As with effectiveness, so with toxicity; it is far too glib to limit our consideration to the direct effect of the drug on the host: there are indirect complications of antibiotic treatment that are liable to occur with doses far below those directly toxic to the tissues.

In this article I shall touch on two situations in which the effectiveness of antibiotic action can be seen to interact with the host 'defences'. The lack

of detailed studies means that some examples have to be drawn from anti-biotics other than penicillin.

A simple example is offered by penicillin treatment of acute streptococcal sore throat: if treatment is started early in the illness (as is necessary if rheumatic fever is to be prevented) the patient fails to develop antibodies to the M antigen and, since it is M antibodies that protect against re-infection, the patient is liable to re-infection on return to a community in which there are sources of infection (Breese et al., 1960; Siegel et al., 1961). It seems that the streptococci need to infect the tissues actively for several days to provide an adequate antigenic stimulus; the M protein may be as poor an antigen in man as it is in the laboratory rabbit.

In chloramphenicol or tetracycline treatment of rickettsial infections and tularaemia, and perhaps typhoid fever, early treatment is also disadvan-tageous. Patients are very liable to relapse within a few days of the end of treatment if the drug is given during the incubation stage to suppress the clinical signs, but remain well if treatment is delayed for six days (Woodward, 1962). Chloramphenicol is, of course, a bacteriostatic drug and, presumably, the elimination of the microbes demands the initiation of an immunological response that occurs only after some period of infection. In these cases the intracellular residence of the microbes might be thought to be relevant but since treatment with streptomycin is effective from the outset this is presum-ably not the case.

Bigger (1944) drew attention, in the early days of penicillin, to the survival of small numbers of staphylococci in cultures in the presence of seemingly adequate penicillin concentrations. He named these 'persisters'. McDermott (1958, 1969) has reviewed the topic of persistence very extensively and demon-strated its clinical importance in a wide variety of infections, especially strep-tococcal infections, syphilis, and tuberculosis.

The mechanism of persistence is not known but three ideas have been advanced. It may be that the bacteria become sequestered within cells, such as macrophages, and so are inaccessible to the antibiotics (Holmes et al., 1966), and, while not killed by the cells, are prevented from multiplying. Or it may be that the bacteria are held 'dormant' in the tissues, surviving but not multiplying and so not susceptible to the action of penicillin.

More recently, opinion has veered towards the idea that bacteria persist in the tissues as cell-wall deficient L-forms, which can revert to bacterial forms after removal of the provoking antibiotic. There are many reports, of greatly varying value, claiming that wall-deficient forms occur in patients and animals treated with antibiotics that act on the cell wall (Guze, 1968), but it has been very difficult to obtain utterly convincing evidence that the forma-

tion of L-forms is responsible for the persistence of infection. In culture, L-forms need a hypertonic environment for their survival; such osmotic support is difficult to envisage in living tissues though it may occur in a few situations, particularly the renal papilla. However, it may be that, in the tissues, L-forms have less osmotic instability, for Mortimer (1965) has shown that L-forms of haemolytic streptococci may be produced in the course of a peritoneal infection, even in the absence of antibiotics. Since lysozyme is certainly present in phagocytic cells and probably concerned with the intra-cellular digestion of bacteria, and since the enzyme target in the cells is the mucopeptide of the wall, the hypothesis is a reasonable one.

It is now well recognised that the normal bacterial flora of the body con-stitutes an important element in protection against invaders and must be considered an integral part of the normal body defences. Important adverse effects of antibiotic treatment are certainly due to some inadvertent alteration in the numbers of the normal bacteria of the mouth or gut, and, perhaps, of the skin.

In experimental animals, a reduction in the gut flora by streptomycin leads to a profound reduction in the minimal infecting dose of salmonella, apparently because the normal bacteroides and coliforms produce volatile fatty acids that inhibit the growth of salmonellae (Miller and Bohnhoff, 1962; Bohnhoff et al., 1964). Perhaps for the same reason the neomycin treatment of patients with salmonella infection tends to prolong carriage rather than control it (Report, 1970).

The lethal damage that chloramphenicol can do to bone marrow is well-known; I think it could be shown that the widespread use of broad spectrum antibiotics in patients having bowel surgery led to far more deaths through predisposing the patients to a fatal staphylococcal enterocolitis. In the survey of causes of death of patients dying in hospital conducted by the Public Health Laboratory Service (1966), there were five deaths attributed to staphylococcal enterocolitis among 470 patients coming to necropsy.

The extent to which broad spectrum antibiotics, and penicillin used in doses high enough to have a broad spectrum effect, predispose to secondary infection is now well-documented. The prophylactic use of antibiotics has often been followed by an increase, rather than the hoped-for decrease, in the incidence of post-operative infection. How this happens is not fully under-stood, although it is, in part, a consequence of some replacement of sensitive commensal bacteria in carrier sites by resistant and more invasive bacteria from the environment. However, it is worth seriously considering whether antibiotics may not interfere in a more direct way with the tissue defence mechanisms. There are some indications that tetracycline may depress

phagocytosis (Seelig, 1966) and antibody production; if any antibiotic kills large numbers of bacteria, the liberation of toxic substances from them may act on defence cells.

The remarkable lack of acute toxicity of many of the antibiotics in general use means that we can commonly administer doses such that reliance on help from tissue defences is unnecessary. The facility to use large doses often has to be paid for by accepting a profound disturbance of normal flora, and perhaps by some further interference with the defences. The balance of advantages and hazards still requires much further elucidation.

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More about Jebb

Sir Richard Jebb, Harveian Orator in 1774, must have been a physician of character rather than of manners. 'That is my way,' he said to a patient astonished at his rudeness. Then said the sick man, pointing to the door, 'I'll beg you to make that your way.' He told a lady that muffins were the best thing she could eat, but she reminded him that a week before he had forbidden her to touch them. He replied, 'Good madam, I said so last Tuesday. Today is not a Tuesday'. Diet was not his favourite subject as he had little use for fads. When another patient enquired what she should eat, he said 'boiled turnips'. She replied that he had forgotten her expressed dislike of turnips. 'Then madam,' he said sternly, 'you have a damned vitiated appetite.'

It is said that his income fluctuated wildly according to the whims of his fashionable patients, but he knew how to handle them. On being given three golden guineas by a patient from whom he expected five, he dropped the coins on the floor. The footman recovered the three coins but Sir Richard continued to search the carpet. 'Are all the guineas found?' said the patient. 'No' said the physician, 'there must still be two on the floor as I have only three.'