Woessner and colleagues [1], in their article Long-term Antibiotic Treatment with Roxithromycin in Patients with Multiple Sclerosis, report that three 6-week courses of roxithromycin over the space of a year did not ameliorate the course of MS in a group of patients. From this they conclude that Chlamydothila (Chlamydia) pneumoniae is unlikely to have any input into the disease. This conclusion is not tenable: in chronic infections C. pneumoniae enters a persistent state, becoming inaccessible to conventional antichlamydial agents. Relapse may occur even after prolonged treatment [2, 3]. Clinical observations are reinforced by in vitro studies; the organism is not cleared from monocytes [4] and continues its metabolic activities in lymphocytes [5]. Conventional agents may not kill the organism; rather, they may force it into an aberrant or cryptic state [6, 7].

Effective treatment may, however, be possible. Most bacteria possess a number of alternative metabolic pathways and are able to switch from one to another in response to alteration of redox potential, nutrient resources and other changes in their environment. Chlamydiae, which have a unique and complex life-cycle (extracellular/nonreplicating, intracellular/nonreplicating and intracellular/replicating) may use different pathways at various stages of this cycle. It is known that Chlamydia trachomatis possesses genes which code for oxidative pathways; these operate during the actively replicating intracellular phase to supplement ATP taken from host mitochondria. As the organism enters the persistent or cryptic phase it evidently becomes dependent on host mitochondrial ATP, downregulating its own glycolytic and pentose phosphate pathways (discussed by Gérard et al.) [8]. C. pneumoniae is known to have the ability to enter a similar persistent phase [2]. Chlamydial persistence may be analogous to the stringent response found in many free-living bacteria. This is a survival mechanism involving a phenotypic simplification of the metabolic economy under the onset of stress conditions. Survival in this form may depend upon a non-oxidative metabolic pathway [9]. The finding that Chlamydiae enter the cryptic form when starved of amino acids [10] lends support to the idea of persistence being a stringent response. Such a transformation may occur naturally during untreated infection as interferon-gamma (IFN-γ) is produced by the host in an attempt to curtail intracellular infection (reviewed by Rottenburg et al.) [11]. IFN-γ has been shown to induce persistence in C. pneumoniae in vitro by means of host-cell mechanisms which reduce the availability of intracellular tryptophan [12, 13]. Chlamydia psittaci (but not C. pneumoniae) possesses a pathway which by-passes host-mediated tryptophan starvation [14]. A tryptophan starvation strategy on the part of the host seems to be important in the genesis of conditions which favor chronic disease. IFN-γ acts by inducing host enzyme indoleamine 2,3-dioxygenase which converts tryptophan to formylkynurenine [15] and by the induction of host tryptophanyl-tRNA synthetase, which denies the organism access to remaining tryptophan [16]. Another host strategy against intracellular infection is the depletion of iron reserves [17]. From this it seems clear that the endurance of starvation conditions is a part of the evolutionary history of persistent infection with C. pneumoniae. Induction of hypoxia within the phagosome may be another possible component of the host-cell starvation strategy. Evidence may be gained from the behavior of a taxonomically remote organism undergoing similar stress. Schnappinger and co-workers, examining gene-expression of Mycobacterium tuberculosis in artificial media and in macrophages, found that genes expressed differentially as a consequence of intraphagosomal residence included an IFN-γ and NO induced response which intensified an iron-scavenging program, induced a dormancy regulon and forced the bacterium to convert from aerobic to anaerobic respiration [18]. Were the cryptic form of C. pneumoniae forced, by host starvation-strategies and by anti-replicating antimicrobials, to adopt an anaerobic...
survival-metabolism, metronidazole, a member of the nitroimidazole class of antibiotics and a potent anti-anaerobic agent [19], would be expected to be an efficient killer. There may be parallels once more with *M. tuberculosis*, which, though considered an aerobe, can be induced, by the gradual depletion of oxygen from the culture media, to enter a sluggishly metabolising but non-replicating state in which the organism is killed by metronidazole [20]. This action may happen *in vivo*; metronidazole has been found to assist resolution in chronic but not acute *M. tuberculosis* infection in a mouse model [21]. The bactericidal effect of metronidazole involves its reduction to create short-lived but highly reactive intermediates, which damage the DNA of the target cell. This can take place only within a strongly reducing environment where electrons will be donated preferentially to metronidazole. The direct donors of electrons in anaerobic bacteria are a family of electron transport proteins, which include ferredoxin [22]. If *C. pneumoniae* has the ability to utilize an anaerobic pathway it should have the potential to fabricate ferredoxin or a ferredoxin-like protein, and, indeed, chlamydiae do possess this ability [23]. One of us (CWS) has shown, in tissue culture and in a mouse model, that administration of metronidazole following the induction of the cryptic form with protein-synthesis inhibitors kills the intracellular organism (unpublished data).

Multiple sclerosis is undoubtedly multifactorial, but chronic infection with *C. pneumoniae* is likely a key factor in the initiation and fuelling of the pathology. We have recently reviewed the evidence for this [24]. We are successfully treating patients with MS (diagnosis being made at consultant neurologist level) by inducing the persistent state with a combination of bacterial protein synthesis inhibitors (doxycycline and azithromycin or roxithromycin or rifampicin) and then adding metronidazole to this. Caution is necessary here, as, in our experience, large numbers of organisms can be destroyed, releasing endotoxins, often causing a response reminiscent of a Jarisch-Herxheimer reaction. Some patients, as these reactions subside, develop *C. pneumoniae*-specific IF antibodies, indicative of the release of bacterial antigens specific to this species. Progression in both primary progressive (PPMS) and secondary progressive MS (SPMS) and relapses in relapsing-remitting MS have been effectively halted. One patient, a 45-year-old woman with SPMS of three years’ duration and a pre-treatment EDSS score of 2. Another patient, a 64-year-old woman with PPMS of 9 years duration and a pre-treatment EDSS score of 6.7 has, over 2 years, returned to an EDSS score of 2 also. It will be recalled that, once progression is established in MS, sustained improvement is rarely part of the natural history of the disease [25]. These and other case-reports will be submitted for publication after an extended follow-up period. Initial results, though encouraging, will need to be validated by comprehensive multicenter trials of combined antibiotic treatment aimed at all phases of the organism’s life-cycle.

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References

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