Empirical antibacterial treatment of infection with *Chlamydophila pneumoniae* in Multiple Sclerosis

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After much controversy there is now powerful evidence for the respiratory pathogen *Chlamydophila (Chlamydia) pneumoniae* being a causal factor in some variants of the neurological illness multiple sclerosis. A series of remarkable studies finds:

- **the presence of *C. pneumoniae* gene sequences in the cerebrospinal fluid of patients who have the disease, and culture of the organism when sensitive cultural methods are used** [Sriram S, Stratton CW, Yao S, Tharp A, Ding L, Bannan JD, Mitchell WM. *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. Ann Neurol. 1999 Jul;46(1):6-14.]

- **an association of new *C. pneumoniae* respiratory infections with episodes of clinical relapse** [Buljevac D, Verkooyen RP, Jacobs BC, Hop W, van der Zwaan LA, van Doorn PA, Hintzen RQ. *Chlamydia pneumoniae* and the risk for exacerbation in multiple sclerosis patients. *Ann Neurol.* 2003 Dec;54(6):828-31.]

- **a statistically significant elevation of *C. pneumoniae*-specific serum antibody levels when the disease shifts into the progressive form** [Munger KL, Peeling RW, Hernán MA, Chasan-Taber L, Olek MJ, Hankinson SE, Hunter D, Ascherio A. Infection with *Chlamydia pneumoniae* and risk of multiple sclerosis. *Epidemiology* 2003 14:2 141-147]

- **antibodies to *C. pneumoniae* in the cerebrospinal fluid of patients with the disease** [**(1.)** Yao, S., Stratton, C.W., Mitchell, W.M., Sriram, S. (2001). CSF oligoclonal bands in multiple sclerosis represent antibodies against Chlamydophila. *Neurology* 56, 1168-76. **(2.)** Fainardi, E., Castellazzi, M., Casetta, I. et al. (2004). Intrathecal production of *Chlamydia pneumoniae*-specific high-affinity antibodies is significantly associated with a subset of multiple sclerosis patients with progressive forms. *Journal of the Neurological Sciences* 217, 181-8.]

- **evidence of active *C. pneumoniae* protein synthesis in the central nervous system, with production of a bacterial protein evoking an antibody shown to cause death of oligodendrocyte precursor cells** [Cid C, Alvarez-Cermeno JC, Camafeita E, Salinas M, Alcazar A. Antibodies reactive to heat shock protein 90 induce oligodendrocyte precursor cell death in culture. Implications for demyelination in multiple sclerosis. FASEB J. 2004 Feb;18(2):409-11.]

- **a peptide specific to *C. pneumoniae* causes inflammatory CNS disease**

(with some parallels to MS) in rats [Lenz DC, Lu L, Conant SB, Wolf NA, Gerard HC, Whittum-Hudson JA, Hudson AP, Swanborg RH. A *Chlamydia pneumoniae*-specific peptide induces experimental autoimmune encephalomyelitis in rats.
J Immunol. 2001 Aug 1;167(3):1803-8.]

- ***C. pneumoniae* gene transcription in the CSF of patients with MS** [Dong-Si T, Weber J, Liu YB, Buhmann C, Bauer H, Bendl C, Schnitzler P, Grond-Ginsbach C, Grau AJ. Increased prevalence of and gene transcription by Chlamydia pneumoniae in cerebrospinal fluid of patients with relapsing-remitting multiple sclerosis. *J Neurol.* 2004 May;251(5):542-547.]

- **MRI improvement in antibiotic-treated patients with early disease in a small but fastidious double-blind trial of non-immunomodulatory antibiotics** [Sriram S, Yao SY, Stratton C, Moses H, Narayana PA, Wolinsky JS. Pilot study to examine the effect of antibiotic therapy on MRI outcomes in RRMS. J Neurol Sci. 2005 Jul 15;234(1-2):87-91.]

- **MRI improvement, with reduction of the number of Gd-enhancing lesions, in a second treatment study with minocycline** [Metz LM, Zhang Y, Yeung M, Patry DG, Bell RB, Stoian CA, et al. Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann Neurol.* 2004 May;55(5):756.]

- **An association of *C. pneumoniae* in the CNS with MS is demonstrated by immunohistochemical, molecular and ultrastructural methods.** [Sriram S, Ljunggren-Rose A, Yao SY, Whetsell WO Jr. Detection of chlamydial bodies and antigens in the central nervous system of patients with multiple sclerosis. J Infect Dis. 2005;192(7):1219-28.]

The evidence for a causal association of *C. pneumoniae* with majority subsets of MS has been garnered by a surprisingly diverse array of methods; cultural, molecular (both DNA and RNA based), immunohistological, serological (blood and CSF based), animal model, ultrastructural and therapeutic trial. It is this very diversity of methodology which makes the evidence compelling. The organism itself is difficult to detect in persistent disease; sensitive and innovative methodology is required to elucidate its presence.

The results of antichlamydial treatment have been very promising, particularly in early disease.

It should be stressed at the outset that this bacterium is not sexually transmitted. It causes respiratory infection and is spread by droplet infection — coughing and sneezing.

Sarah, my wife, an artist of considerable ability, was given a diagnosis of MS in July 2003. Her illness in fact stretched back to 1989, when she experienced a sudden weakness of the right arm. After a fortnight she recovered its function completely. A few years later she experienced a slight greying of vision in one eye; this resolved over a few weeks. Occasional relapses followed, all with a complete recovery. In 1999 the remissions started to become less complete. Right foot-drop began insidiously and did not resolve. Then, in 2001, shortly after a prolonged upper

respiratory infection which led to mild new-onset asthma, Sarah began to enter a new, rapidly progressive stage of the illness. Within two years she was unable able to stand unaided, had to hold furniture, was unable to hold or use a pencil or paint-brush with her right hand, and she felt giddy. She said that she seemed to live in a mental fog: indeed, in the evenings she would fall into a half-sleep from which she obtained no rest. Her speech was becoming slurred. There was a continual sense of flickering and worsening neurological deficit. She suffered tinnitus, hearing the continual sound of distant machinery. She developed L'hermitte's sign, manifested as an electric-shock-like pain down the back on bending the head forward and signifying damage to the cervical spinal cord.

An MRI scan showed many typical active lesions, visible as variably-sized bead-like hyperintensities in the white matter of the brain. The neurologist told Sarah that she had Multiple Sclerosis; the disease had entered a secondary progressive phase for which there was no treatment, and that the illness must be expected to take its course.

I'm much more interventional than he — this goes with the territory of being a medical microbiologist — and I recommended the following oral antichlamydial regimen:

doxycycline 200mg once daily
roxithromycin 300mg once daily (azithromycin 250mg three days a week is an alternative.)
Short courses of metronidazole will later be added to this regimen.

We started the doxycycline first, as it was immediately available. The results were astonishing. For five days she suffered a worsening of her symptoms; this was accompanied by a flu-like illness, with headache round the eyes, pains in the large joints (hips and shoulders) and night-sweats. This is a typical Herxheimer-like reaction; it is caused when a large bacterial load is broken up by antibiotics or other agents. After five days she lost the mental fog: indeed, she said she felt clearer than for two years. The roxithromycin was added three weeks later, when it became available.

This information has been made available at Sarah's request. It has to be said that, despite all the research which has been published in the scientific literature, the existence — let alone the therapeutics — of chronic infection with *C. pneumoniae* is barely understood by the medical community.

Updates on progress may be found here

Article in *Hospital Doctor* here (graphic - 629Kb)

Questions and Answers

What is the evidence that *Chlamydia pneumoniae* has a causal association with Multiple Sclerosis?

C pneumoniae is known to patchily parasitize the cells which line small blood-vessels, causing episodes of vasculitis. This is a local inflammatory process characterised by tiny punctures in the vessel walls and leakage of blood-components into the surrounding tissue space. It can be visualized directly in the retinal veins, where the vessels appear to be coated with a thin greyish sheath. This sheath is comprised of T lymphocytes. A very similar pathology takes place in the brain in early MS. The association between sheathing of retinal veins and MS was first made in 1944. The anatomical distribution of lesions within the brain in MS is often centred on small veins; elongated plaques may follow the sinuous curves of the vessels they surround. [Esiri MM, ed. *Oppenheimer's Diagnostic Neuropathology*, 2nd edition, 1996 Blackwell: 256-9.]

Examination of the eye reveals retinal vasculitis in about a third of persons with early MS, but it is probably present in far more. It is especially common following optic neuritis (a common precursor of MS), and is characterised by leakage of dye in a fluorescein dye test, blood cells, and cuffing of the vessel walls by inflammatory cells. Where it is seen, there is a raised likelihood that MS will follow.

MS is currently considered an autoimmune demyelinating disease. Myelin is an insulating lipoprotein; its sudden local loss causes the acute MS relapse. But this myelin loss may well be a secondary phenomenon. The very fact that retinal vasculitis is commonly associated with MS casts considerable doubt on myelinopathy being the root cause of MS; myelin, and the oligodendrocyte cells which produce it, are not found in the retina, and the earliest pathological manifestations of MS are in blood-vessels, not nerves and glial cells. Demyelination has recently been shown to be a secondary phenomenon in the acute, typical lesion of MS: the first visible event in a newly-forming fatal MS lesion is the sudden, orderly, non-inflammatory local mass death of oligodendrocytes, the cells which make and support myelin. [Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol*. 2004; 55(4): 458-68.] This casts further doubt on the notion of MS as a primary autoimmune disease. The removal of unsupported myelin by inflammatory cells may well be a secondary 'housekeeping' activity. We may be witnessing the beginning of a sea-change in thought. [Chaudhuri A, Behan PO. Multiple sclerosis: looking beyond autoimmunity. *J Roy Soc Med* 2005; 98: 303-306.] These authors cite ten important considerations about MS which cannot be explained by the concept of a myelin-specific autoimmune process.

The epidemiology of MS has been well studied in the Faroe Islands, where MS was unknown until the Second World War. It suggests a communicable factor acquired in early adolescence, starting at about the age of 11. [Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. *J Clin Epidemiol.* 2001 Jan;54(1):1-22.] This is the age when seroconversion to *C pneumoniae* often begins. Two other organisms posited to initiate MS - Human Herpes Virus 6 and the Epstein-Barr virus - would seem unlikely candidates when this evidence is considered. HHV-6 is acquired by almost all infants by the age of three. Seroconversion to the Epstein-Barr virus occurs in two peaks; one in very young children and the second in later adolescence and adulthood. Furthermore, Kurtzke's Faroese data suggest an agent which caused outbreaks at 13 year intervals: EBV, due to its close and personal mode of spread, rarely causes outbreaks. The agent which caused MS in the Faroese seemed to be rather ineffectively spread; this is consistent with infection caused by *C pneumoniae*,

which is known to be inefficiently transmitted and thus causes patchy outbreaks. In 2000 there were areas of the Faroes free of MS. [Kurtzke JF. Multiple sclerosis in time and space - geographic clues to cause. *J Neurovirol.* 2000;6 Suppl 2:S134-40.] Niki and Kishimoto, with regard to *C pneumoniae* outbreaks, note that 'transmission occurs only after repeated and close contact. Small outbreaks may occur in households and schools where persons have prolonged close contact. Unlike acute viral infections, it may spread slowly.' [Niki Y, Kishimoto T. Epidemiology of intracellular pathogens. *Clin Microbiol Infect.* 1996 Mar;1 Suppl 1:S11-S13.] In an urban environment the situation is different from that of island populations: *C pneumoniae* is ubiquitous; infection is endemic and outbreaks are correspondingly difficult to delineate.

C pneumoniae has been linked to relapsing-remitting forms of disease elsewhere in the body, including asthma, reactive arthritis and coronary artery disease. Causal associations have been made by isolation of the organism and by detection of diagnostically raised antibody levels which subside on treatment. MS can be considered an analogue of these conditions; it is, for instance, characterized by lipid peroxidation, elevated serum homocysteine and antioxidant depletion — a pathology characteristic of chronic chlamydial disease and one likely to be due to local endotoxin activity — but, because it represents an intracerebral infection, shielded from the general circulation, high circulating antibodies are not to be expected. Actually, *C pneumoniae* serology is notoriously difficult to interpret.

A historic study was published by workers at the Vanderbilt School of Medicine in 1999. CSF samples from 17 patients with relapsing-remitting MS, 20 patients with progressive MS, and 27 patients with other neurological diseases (OND) were examined by culture, by PCR and by antibody detection. *C pneumoniae* was isolated from CSF in 64% of MS patients against 11% of OND controls. Polymerase chain reaction assays demonstrated the presence of C pneumoniae MOMP gene in the CSF of 97% of MS patients versus 18% of OND controls. Finally, 86% of MS patients had increased CSF antibodies to *C pneumoniae* elementary body antigens as shown by enzyme-linked immunosorbent assay absorbance values that were 3 SD greater than those seen in OND controls. The specificity of this antibody response was confirmed by western blot assays of the CSF, using elementary body antigens. Moreover, CSF isoelectric focusing followed by western blot assays revealed cationic antibodies against *C pneumoniae*. [Sriram S, Stratton CW, Yao S, Tharp A, Ding L, Bannan JD, Mitchell WM. *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. *Ann Neurol.* 1999 Jul;46(1):6-14.] It should be noted that the methodology used by the Vanderbilt workers is fastidious. In tissue-culture isolation, for instance, repeated centrifugation and prolonged incubation was carried out; this is very important as in chronic infection the organism may produce few of the spore-like elementary bodies, and those that are produced may be damaged. (It is interesting to note that the discovery of *Helicobacter pylori* was made possible by extending traditional incubation times.)

Episodes of relapse in MS patients are associated with new respiratory infections with *C pneumoniae*; [Buljevac D, Verkooyen RP, Jacobs BC, Hop W, van der Zwaan LA, van Doorn PA, Hintzen RQ. *Chlamydia pneumoniae* and the risk for exacerbation in multiple sclerosis patients. *Ann Neurol.* 2003 Dec;54(6):828-31.] The relapse is evidence of host ‘collateral damage’.

At a population level antibodies to *C pneumoniae* rise as the disease becomes progressive [Munger KL, Peeling RW, Hernán MA, Chasan-Taber L, Olek MJ,

Hankinson SE, Hunter D, Ascherio A. Infection with *Chlamydia pneumoniae* and risk of multiple sclerosis. *Epidemiology* 2003 14:2 141-147.]

These three seminal papers triangulate the evidence that *C pneumoniae* plays a pathogenic role in the evolution of Multiple Sclerosis.

A review of the evidence for a causal role of C pneumoniae, together with references, is given in this paper (Adobe pdf) which can be printed out and shown to your doctor.

What is the life-cycle of *C pneumoniae*?

Simplifying slightly, *C pneumoniae* has two major phases to its life cycle. The infectious form is called the Elementary Body (EB). This spore-like form transmits the organism from person to person and, within a person, from cell to cell. The EB is metabolically inert; it has an external membrane which includes potentially unstable proteins. When it attaches to a susceptible host cell a sudden change takes place; the proteins which are embedded in its external membrane become loose and the host cell wall closes behind the entering EB. We have no method at the moment for seeing these molecular activities dynamically, and so much of this story is 'best guess'.

Once inside the host cell, the organism expands to become the Reticular Body (RB). It efficiently uses host membrane to make its own environment within a cell. Then it takes up its position around the host's mitochondria to steal the energy-rich molecules fabricated by these organelles, probably by means of small tubes. The RB then begins to control the direction of the host-cell metabolism, again probably using microscopic syringes and needles. Its own nuclear material eventually divides into many separate individuals, which then condense into EBs. The host cell bursts, scattering EBs into the extracellular milieu. This is the picture in cell-culture and is the likely picture in acute infections.

In chronic infections a different pathway is taken. Under pressure from host defences the organism enters into persistent state, where its metabolic processes are diminished. The organism in this state is called the Cryptic Body (CB). This chronic unresolved infection - which can last for several decades - can initiate the malign process of autoimmunity. To a large extent the form of the disease depends on the host's genetic inheritance. This is why many of the chronic disease forms caused by infections with *Chl pneumoniae* tend to have inherited characteristics. An excellent and readable account of how peristent unresolved infections can initiate chronic diseases with autoimmune aspects can be found in this dissertation by Tiina Sävykoski: http://herkules.oulu.fi/isbn9514269853/html

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How might *Chlamydia pneumoniae* reach the brain?

The organism settles on some part of the respiratory lining and then invades. A respiratory infection (sinusitis, bronchitis, pharyngitis or pneumonia) results. Host defence cells mop up the organism; some become parasitized. *Chl pneumoniae* can travel round the body in the blood monocytes - mobile host defence cells - when these are called to deal with a remote infection - perhaps a transient virus infection. As the monocytes pass through the blood vessel walls, *Chl pneumoniae* are shed; these infect the lining cells. Microcolonies of *Chl pneumoniae* are set up. This can happen in the brain, in joints, in the vessels which supply the great arteries themselves, and in the skin. See [Gieffers J, et al., Phagocytes transmit Chlamydia pneumoniae from the lungs to the vasculature. *Eur Respir J.* 2004 Apr;23(4):506-10.]

MS is a many-staged and complex disorder. How can a simple bacterial colonisation / infection cause such complexity?

MS has four variants: **relapsing-remitting**, where neurological deficits occur suddenly and resolve over a few weeks. Resolution is at first usually complete; later, it is less so. Although called relapsing-remitting, most patients gradually accrue deficits. The disease may change to the **secondary-progressive** form; remissions are now unusual and deterioration is the rule. The third variant is the **primary-progressive** form, where the disease worsens from the beginning. The fourth, or so-called **benign** form, describes rare cases where resolution is always complete; the deficits themselves may cease to happen. (It is unwise to use this term as MS can become aggressive twenty years after its first mild appearance.)

All these forms and stages would correspond well with an established *Chlamydia pneumoniae* infection in the brain. In the relapsing-remitting form the infection is silent until a new respiratory infection provokes a new host response. This tends to become more severe as time goes on. (Parallels are seen in the increasing severity of pneumonias caused by *Chlamydia pneumoniae* in those who suffer repeated infections after seroconversion: the severity is caused by the increasing strength of the host response.) In the progressive forms the host response is continuously firing, often against an extracerebral bacterial infection; a patient with early SPMS will often mention chronic sinusitis, chronic middle ear disease or new-onset asthma which began some time before the MS began to slide into the progressive phase. Sarah experienced a prolonged respiratory infection followed by new-onset asthma before her illness became progressive.

MS has a genetic component. It also has a marked geographical distribution. How do you account for this, given that *Chl pneumoniae is* ubiquitous?

MS has a pronounced geographical distribution. It is most common in the cooler latitudes, becoming rarer as the tropics are approached. Migration from temperate to tropical areas confers protection, provided the move is made before adolescence.

People who migrate to temperate areas are more likely to develop MS than those who have remained behind.

The epidemiology of MS is not as simple as this, however. The disease has an increased incidence in certain groups of women in the Middle East. The common factor seems to be a seasonal or cultural reduction in exposure to sunlight; in those with a genetic predisposition a relative lack of Vitamin D develops. Vitamin D deficiency is indeed found in those with MS; it is linked to calcium and magnesium deficiency and to osteoporosis. By contrast MS has not been recorded amongst the Inuit, who, though living through arctic winters, derive ample Vitamin D from a fish-rich diet.

Vitamin D is vital for the maintenance of the blood/brain barrier. Not only may a mild Vitamin D deficiency allow ingress of *Chl pneumoniae*; it may also activate quiescent infections. The number of active white-matter lesions seen on MRI in persons with MS closely follows the seasonal fluctuation of levels of circulating Vitamin D.

Other infectious agents, notably Human Herpesvirus 6, have been put forward as causative agents in MS. How does this square with a primary Chl pneumoniae infection?

Human Herpes Virus 6 may have a secondary input into MS; read a brief note about this here.

Can a chlamydial cause for MS be proved in an individual patient by serology?

Not at the moment. This because *Chl pneumoniae* is a common organism and infections with the bacterium are common. Antibody levels tend to rise during life, even in people who are asymptomatic. Patients with extracerebral infections of some duration (particularly reactive arthritis) can show high titres in the microimmunofluorescence test; it is generally reckoned that a titre of 1:512 or above, in the presence of appropriate clinical findings, supports a diagnosis of *Chl pneumoniae* disease. MS is different; the pathology is at the blood-brain barrier. One would not expect an elevation of circulating antibodies unless an extracerebral component to the infection were also present. This may be the case in progressive disease; there is a statistical elevation of antibodies in a group of such patients. This supports the idea of a chlamydial cause for MS, but makes no prediction in an individual. That is why treatment must at the moment be empirical.

Antibiotics have been around for more than sixty years: surely they must have been tried before.

This puzzles me, too. Neurologists have speculated from the late 19th century that MS might have an infective origin. They were used to dealing with infections, particularly syphilis. I'm sure that penicillin, so effective against syphilis, would have

been tried in MS. There is new evidence that newer penicillins have some activity against chlamydiae, but they do not achieve high concentrations in the CNS in the absence of meningitis. The first generation of tetracyclines may well have been tried; whether they could be given orally in sufficient quantity to enter the brain is uncertain. By the time doxycycline was invented, neurology, and the received beliefs about the cause of MS, had changed. Neurologists now rarely saw patients with underlying infections and MS was considered a primary auto-immune disorder. And, too, there is a battle-weariness in the neurology establishment. So many hopes about finding a treatable cause for MS have been dashed over the decades. The mind-set of the neurological establishment needs to be changed. This will happen.

And, too, MS sufferers are often seen as people who are difficult to help. When I was a student it was customary to speak of the 'typical mental attitude' of those with established MS; this included an impression of blunted insight, a kind of insouciance, even euphoria. In these more politically correct days one does not speak like this any more, but there is an element of truth in it. Now that I think of MS as an infection, the answer becomes clear: this 'typical mental attitude' is a state of intoxication with bacterial metabolic products. A similar state is seen in other chronic infections. In the days before antibiotics persons with active tuberculosis were said to have a typical mental state. People who were nursing at the time still vividly remember this.

In addition to this (recalcitrant doctors and recalcitrant patients) the beginnings of recovery with antibiotics are not pleasant. The early bacteriolytic reaction can be alarming. And, as Sarah found, as-yet unorganised repair can cause function to worsen in the short term. This could easily lead to an early impression that antibiotics were unhelpful or even harmful and could have led to their discontinuance.

Why doxycycline and roxithromycin (or azithromycin)?

Both are oral, both are active against *Chlamydia pneumoniae*, both are relatively inexpensive. They are relatively risk-free. They act synergically against test strains of the organism; giving both together would be the equivalent of giving a four-fold increase of each drug were it to be given alone. The drugs work on different steps in the bacterial protein synthesis pathway. Combination therapy reduces the chance of the emergence of resistance. Both drugs pass into the brain. Both reach good levels inside cells. This is very important. Both are well tolerated. Azithromycin is an alternative to roxithromycin. They deplete the organisms slowly: this is very important, as the release of bacterial endotoxins should not be sudden.

Rifampicin may also be considered. It, too, is synergic with doxycycline, penetrates the brain and is active intracellularly. It is not suitable for intermittent use. It is highly active, and, in patients with a large bacterial load, it may give rise to intense reactions.

Why are later short courses of metronidazole to be taken together with these antimicrobials?

Chlamydiae are complex organisms. Long ago their ancestors must once have been free-living bacteria which possessed their own energy-generating pathways. The transformation from EB to RB is an active change, and an active change implies the retention of at least some of these pathways. The ones with the most utility for this purpose would be anaerobic, and thus susceptible to metronidazole.

Doxycycline and roxithromycin block the replicating phase by inhibiting protein synthesis and may be expected to force the organism to maintain itself by using its own primitive anaerobic respiratory mechanisms. In this suspended state it would be susceptible to anti-anaerobic agents such as metronidazole.

This is borne out by clinical evidence. The administration of metronidazole after doxycycline in a patient with likely high-load *Chl pneumoniae* infection causes a bacteriolytic reaction more severe than that following the original administration of doxycycline.

However, there is a difference: in this leg of treatment there is no risk of the emergence of resistance, for the organism is unable to replicate. Metronidazole need thus be given in courses only as long as can be tolerated.

Five-day courses of metronidazole at three-week intervals, during continuous treatment with doxycycline and roxithromycin, would seem reasonable; at first, metronidazole may be limited to one or two doses on one or two days to judge the severity of reaction.

The eventual aim would be to give all three agents intermittently. This, the final leg of treatment, would entail a 14 day course of doxycycline and roxithromycin, with metronidazole given from day five for five days. (The reason for continuing doxycycline and roxithromycin for a few days after the metronidazole has been stopped is because these drugs both possess anti-inflammatory activity which may prevent a reaction to the organisms killed by metronidazole.) This course would be given once a month. After several months the intervals between the antibiotics would be cautiously extended.

Why this complex antibiotic regime?

The literature is filled with instances of treatment-failure in serologically-proven chronic *Chl pneumoniae* infections of non-CNS systems, whether macrolides, tetracyclines or rifampicin have been used. When the drug is stopped, even after months of treatment, serology rises, and the patient relapses.

The intensive cyclical regime of combined antimicrobials outlined here corrals the pathogen, initially halting replication, then eliminating stalled intracellular forms. Extracellular forms may be depleted by giving N-acetyl cysteine (see below.)

No single antimicrobial agent can be expected to achieve this effectiveness against every phase of the organism's life.

What are the expected reactions to the antibiotics?

There seems to be two components to the reactions experienced on taking the antibiotics.

The first is caused by elimination of bacterial fragments — *endotoxins* — and is characterised by shivering, influenzal symptoms and general malaise.

The second is caused by the release of metabolic toxins; waves of giddiness and feelings of unreality are quite common. They are alarming if not known about and understood. The strength and duration of these reactions depends largely on the bacterial load. In MS, particularly early relapsing-remitting MS, the bacterial load is likely to be small, and the reaction brief. In other conditions, particularly those with multi-system involvement, the bacterial load may be large and the reaction to antibiotics unpleasant and prolonged.

It may seem unlikely that doxycycline, roxithromycin and rifampicin can kill chlamydiae; they are, after all, considered to be bacteriostatic agents — normally they inhibit rather than kill bacteria. However, intracellular *Chlamydia pneumoniae* must continuously elaborate proteins to ensure its own survival within the host-cell.

The reaction to the metronidazole component of treatment is particularly severe as at this stage numerous bacteria are being killed. For this reason it may be best to give an initial course of one single day, followed by review. Prochlorperazine, 10mg orally, may be useful.

The patient can be reassured that a reaction to the antimicrobials are evidence of bacterial destruction and that they will end. And, too, the morale induced by physical improvement has to be set against them.

Isn't giving antibiotics for a long time is a bad thing?

That depends on the illness. Long-term doxycycline is used fairly routinely for certain kinds of gum disease and for acne. Doxycycline is also used long-term in malaria prophylaxis.

Long-term use of these antibiotics engenders no real risk of an increase of resistance in other bacteria within the wider community.

Does the fact that antibiotics can roll back MS tell us something about the nature of the illness itself?

I think it does. Components of MS, at some stages and in some variants, may be:

A bacterial toxaemia. This may account for the mental fog, blunting of insight, greatly increased reaction times and many other non-specific symptoms which are hard to explain by demyelination alone, including fatigue; indeed, there is evidence of abnormal cortical activity. [Leocani L et al., *Neuroimage.* 2001;13(6 Pt 1):1186-

92.] A toxaemia would be expected to resolve quickly with effective antibiotic treatment, as has happened here.

Early phenomena: local mass oligodendrocyte death and secondary demyelination. This is the sudden stripping away of the insulation of the nerve-fibres in the classical MS relapse. It is reversible, but recovery depends on the replacement of oligodendrocytes, the cells which produce and sustain myelin. Damage to the nerve fibres occurs even in early disease, but becomes more severe with time.

Loss of neurones. [reviewed by Minagar A et al., Pathogenesis of brain and spinal cord atrophy in multiple sclerosis. *J Neuroimaging.* 2004; 14(3 Suppl): 5S-10S.] Neurone-loss has been shown to occur in MS and may cause eventual dementia. One might speculate that appropriate antibiotic treatment would prevent further neuronal loss. (Given that neurones are very susceptible to toxins, and that the brain has evolved an elaborate defence system for keeping toxins out, it is possible to speculate that the neuronal loss seen throughout the course of MS might be a direct result of chronic toxaemia maintained from within the brain itself.) Until fairly recently it was considered that, in the adult, lost neurones could not be replaced; there is now a lot of evidence that neuronal replacement occurs throughout life: neural stem cells are known to occur at various loci, including the hippocampus, sub-pial and periventricular area. [reviewed by Taupin P. Adult neurogenesis in the mammalian central nervous system: functionality and potential clinical interest. *Med Sci Monit.* 2005l; 11(7): RA247-252.] In addition, the brain is known to have considerable functional plasticity.

Can relapses occur after starting antibiotics?

In relapsing-remitting MS the major cause of relapse, a new respiratory infection with *Chlamydia pneumoniae*, will be prevented by the antibiotics. However, for the first six months or so it is possible for a relapse to occur secondary to a virus infection. This may be particularly likely in a household with young children.

Not all new deficits which occur during treatment are relapses, though: see this page

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What might a schedule of treatment comprise?

Antimicrobials
Doxycycline 200mg once daily with plenty of water.
Roxithromycin 150mg twice daily or **Azithromycin** 250mg three times a week.
These are maintained without a break for at least six months.

N-acetyl cysteine 600mg - 1,200mg twice a day, should be taken continuously. This is a commonly-taken dietary supplement, available at health-food stores. It is an acetylated sulphur-containing amino-acid, and may be expected to cause chlamydial EBs to open prematurely, exposing them to starvation; more on this and other benefits here.

Two or three months into the treatment regimen, or when the patient is experiencing

few problems with reactions, three-weekly cycles of intermittent oral **Metronidazole** are added. During the first cycle metronidazole is given only for the first day. If problems with reactions are found, the period of administration is kept short. When metronidazole is well tolerated the period of administration in each cycle is increased to five days.

The dosage of metronidazole is 400mg three times a day. If it is suspected that a patient may have a heavy chlamydial load a smaller daily dose may be given.

The eventual aim is to give all three agents intermittently so that the patient has a respite from antibiotics. This, the final leg of treatment, may entail a 14 day course of doxycycline and roxithromycin, with a five day course of metronidazole in the middle. This course is given once a month. After several months the intervals between the antibiotics may be cautiously extended.

Rifampicin is not suitable for intermittent use, and azithromycin may be given instead.

Adjuncts

The brain has extraordinary powers of repair, but must be provided with the building-blocks by which to do it. This infection is intracellular; the organism interferes with mitochondria, the cells' powerhouses. Many of the symptoms of the disease - particularly the fatigue - may be due to mitochondrial exhaustion. Toxins known as free radicals are released as various synthetic pathways are disrupted. If this oxidative stress continues unchecked for too long irreversible mitochondrial damage may occur. A combined dietary supplementation of antioxidants is strongly recommended. (See Syburra C, Passi S. Oxidative stress in patients with multiple sclerosis. *Ukr Biokhim Zh.* 1999 May-Jun;71(3):112-5.)

Vitamin C 1G daily
E 800iu daily
Omega 3 fish oil daily
Evening primrose oil 1G daily
Acetyl L-Carnitine 500mg daily
Alpha Lipoic acid 150mg daily
Ubiquinone (Coenzyme Q10) 200mg daily
Selenium 200 micrograms daily.
N-acetyl cysteine 600mg twice daily
melatonin 1.5mg at night may be considered.

This may seem like polypharmacy, but there are good reasons to consider these agents. This is because the mitochondrial membrane is the bottle-neck for numerous key cellular reactions, and it is exactly here that chlamydiae hover as they control the host cell and steal its vital molecules via tiny projections. These agents are available at health food stores and are obtainable on-line.

More details on how antioxidants can act synergistically to enhance their effects, and to regenerate each other can be found on this page.
Apart from mitochondrial support, Vitamin D is needed. There is evidence that a

relative Vitamin D deficiency is common in MS, and may allow the disease process to begin. High dose supplementation - 4000iu is recommended. (less may be needed in infections other than MS)

In addition, B complex, Magnesium, 300mg and Calcium 500mg supplements in the evening (remote from the time of taking doxycycline) daily.

Vitamin B12 injections once weekly for 3 months, then monthly for the duration of continuous treatment; B12, (together with B6 and folate) counteracts the hyperhomocysteinaemia which accompanies chronic *Chl pneumoniae* infection and which is thought to cause connective tissue damage. (There is now evidence that oral B12 is satisfactorily absorbed, except in patients with pernicious anaemia. High dose supplementation is recommended.)

Regular *Lactobacillus acidophilus*, daily, either as a supplement or in capsules. This is to maintain bowel flora in the face of antibiotic treatment. Tablets of *Lactobacillus sporogenes* spores may be considered. These have the advantage of getting into the small bowel in large numbers.

It would be wise to avoid foods containing artificial trans-fats. These are hard fats made from unsaturated oils which, after heating under pressure, are hydrogenated in the presence of a catalyst. They are widely used because they have a long shelf life and are inexpensive. With certain exceptions hydrogenated fats are not found in nature, and are metabolized with difficulty in the body. They alter cell and mitochondrial membrane functions. Two studies in animal models have found that artificial trans-fats affect mitochondrial efficiency as measured by a reduction of ATP synthesis. [Blomstrand R, Svensson L. The effects of partially hydrogenated marine oils on the mitochondrial function and membrane phospholipid fatty acids in rat heart. *Lipids*. 1983 Mar;18(3):151-70; De Schrijver R, Privett OS. Energetic efficiency and mitochondrial function in rats fed trans fatty acids. *J Nutr*. 1984 Jul;114(7):1183-91.] Dietary intake of trans-fats increases systemic inflammatory markers in humans. [Mozaffarian D, Pischon T, Hankinson SE, et al. Dietary intake of trans-fatty acids and systemic inflammation in women. *Am J Clin Nutr.* 2004;79:606–12.; Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. *Am J Clin Nutr.* 2004;79:969–73.] If the words 'hydrogenated oil' or 'partially hydrogenated oil' appear in a list of ingredients then trans-fats are likely to be present. (It may be noted that dairy products and animal fats also contain a small proportion of trans-fats, but these naturally occurring trans-fats are digestible and were beneficial in animal studies; evidence is less clear-cut in humans. [reviewed by Wang Y, Jones PJ. Dietary conjugated linoleic acid and body composition. *Am J Clin Nutr.* 2004 Jun; 79(6 Suppl): 1153S - 1158S.])

Turmeric, the yellow spice used in Indian cooking, may be very useful. The active ingredient, curcumin, moderates the pro-inflammatory effects of bacterial endotoxin, probably by restraining the activation of nuclear factor-kappa B. 'Nuclear factor kappa B has been implicated in autoimmune and inflammatory diseases, infection, cell survival, and cell transformation with subsequent promotion of cancer.' [Reviewed by Holmes-McNary M. Nuclear factor kappa B signaling in catabolic disorders. *Curr Opin Clin Nutr Metab Care.* 2002 May;5(3):255-63.]

A cautionary note must be sounded. All this is very new and much of it is speculative. It is linking up the work of others. But an empirical trial of antibiotic treatment is surely worthwhile: it would be attempted in any other disease were there even indirect evidence of a treatable pathogen. As an example, one might consider culture-negative endocarditis, where long-term antibiotics are given (often successfully) in the absence of a demonstrable pathogen. MS, as it progresses, can be just as devastating and antibiotics are very cheap by the standards of conventional treatment. In comparison with other drugs they are relatively (but not completely) risk-free.

In treating the disease, it makes sense to use antimicrobial agents which are effective against other potential pathogens of the CNS including *Borrelia garini* and *B burgdorferi.* These have been known to cause a serologically negative MS-like illness. It would also make sense to cover for *Rickettsiae* and *Mycoplasma sp*. and cell-wall deficient forms. MS and other initially relapsing-remitting but ultimately progressive diseases may have a polymicrobial phase: the punctured vasculitis caused by *Chl pneumoniae* would provide an easy portal of tissue-entry for blood-borne organisms. Microbiologists are beginning to recognise that, in many chronic infections, an altered host physiology provides a niche for a host of secondary organisms: an obvious example is chronic HIV disease, where the pathogen which initiates the disease is rarely the pathogen which causes the final event which results in death.

My own experience from treating several people with MS is that those with relapsing-remitting disease and early progressive disease can do well. Patients with later progressive disease respond less well. Generally speaking, the earlier that treatment is begun the better the result is likely to be. When treatment is started late in the course of the disease, a true auto-immune process may have begun; if this has happened, one would expect progression to continue despite antibiotic treatment.

People with dense neurological deficits which have been in place for many years and which are situated in confined anatomical bottlenecks such as the cord or cerebellum may recover little function, but treatment may halt disease progression.

In considering treatment, one must make an analysis of risk versus benefit. I believe that a trial of six - twelve months' doxycycline plus roxithromycin / azithromycin is worthwhile even in late disease; if benefits occur and / or progression is halted, the rest of the treatment can be added. If no benefit is found then the trial can be stopped. It is important to go into the trial without undue expectation. Nothing at all can be guaranteed.

A more detailed discussion of the pathology caused by *Chl pneumoniae* can be found here.

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An abbreviated version of this page in pdf format for printing may be found here.

Jim Kepner's site on *Chlamydia pneumoniae* infection can be found here. It contains much valuable information, including personal accounts of illness and its treatment. Now that this infection is at last becoming more widely recognized you learn that you are not alone.

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