Antibiotics in Sarcoidosis — Reflections on the First Year

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ABSTRACT:

A year has passed since our paper "Remission in Sarcoidosis", and, in that year, over 50 sarcoidosis patients have been early adopters of minocycline antibiotic therapy. Almost without exception, they have flourished. Additionally, a much better picture of the occult bacteria has emerged, and the mechanisms by which they assert their toxicity upon the immune system is taking form. Clinical experience has significantly clarified the precepts underpinning the use of tetracycline antibiotics to induce remission in sarcoidosis.

PRIOR ARGUMENTS SUPPORTING THE BACTERIAL PATHOGENESIS

Similarities between Tuberculosis and Sarcoidosis have caused researchers to suspect a mycobacterial pathogenesis since, at least, Guy Scadding's Bradshaw Lecture in 1949 [1]. Attempts at using anti-tuberculosis medications however, have been largely unsuccessful (for reasons that will be explained below). Du Bois, *et al.*, [2,3] have postulated an etiology where *"microbes are a likely trigger (but not as an infection) in a genetically predisposed individual"* while Eishi, *et al.*, have suggested that *"sarcoidosis may arise from a Th1 immune response to one or more antigens of propionibacteria in an individual with a hereditary or acquired abnormality of the immune system"* [4].

Bachelez *et al.*[5] administered long-term minocycline and/or doxycycline in a cohort of twelve sarcoidosis patients, achieving remissions both of cutaneous lesions and pulmonary manifestations of the disease.

"...the precepts underpinning the use of tetracycline antibiotics."

Finally, Moller and Chen presented persuasive arguments [6] based, in part, on communication of sarcoidosis during transplant surgery, both from a sarcoidosis patient to one previously without the disease, and upon infection spreading into 'clean' tissues implanted into a sarcoidosis patient.

WHAT DOES THE PATHOLOGY OF SARCOID GRANULOMA TELL US?

It is commonly believed *"the immunologic process that leads to sarcoidosis begins when an antigen is presented to a macrophage via HLA class II molecules to a T Lymphocyte. This induces a Th1 T-lymphocyte response whereby cytokines are released that result in granuloma formation"*[7].

However, a century of research has failed to definitively identify how the antigen-processes thus described could ever result in the characteristic pathology of the sarcoid granuloma. Further, while this description implies that the Th1 cytokine cascade should be associated with high levels of T-lymphocytes, the opposite is true:- advanced cases of sarcoid inflammation present with T-lymphopenia [8].

This conventional description is based on an understanding of the immune system of healthy individuals, and it fails to describe the immune system of patients with sarcoidosis because the factors at work in immune disease are different from those at work in a healthy individual.

The presence of cell-dwelling pathogens creates an entirely different immune environment, one where it is the pathogens 'calling the tune', and where the conventional sequence of antigen-to-T-lymphocyte activation is no longer the driving force.

"In 1989 Wirostko, Wirostko and Johnson published transmission electron microscopy photographs of CWD bacteria living inside each type of immune cell."

Cell-dwelling pathogens cause Th1 immune disease by utilizing an ability to mimic the T-cell Receptor alpha-beta V protein [4]. They are thus capable of directly activating the 'host' monocytes, macrophages and giant-cells which they have parasitized. A cascade of cytokines and chemokines is then continuously released, directly by the parasitized 'host' cells, without the need for any activated T-lymphocytes to be present.

The SARS Coronavirus is a pathogen with the apparent ability to virulently hyper-activate the immune system in this manner [9,10,11,12]. While the granuloma of sarcoidosis are formed by an accumulation of considerably less virulent pathogens than SARS, the anomalous T-cell Receptor alpha-beta V protein is similarly present [13].

The granuloma of sarcoidosis are formed within inflamed tissue when sufficient lymphopenia-inducing parasites have colonized the monocytes, macrophages and giant-cells in order to sustain a self-activated and non-necrotic inflammatory core [12]. The un-needed T-lymphocytes are down-regulated and expelled to the granuloma's periphery, forming the characteristic non-caseating granulomatous pathology of Sarcoidosis.

WHAT SPECIES OF MICROBES HAVE BEEN FOUND IN SARCOID GRANULOMA?

In 1982 Cantwell [14] described a special type of bacteria, called 'Cell Wall Deficient' (CWD) bacteria (synonyms: L-form, pleomorphic, mollicutes, mycoplasma, cysts), which were minute granules in the inflamed tissue, appearing as 'coccoid' or 'cyst' semi-spherical forms. He found this bacteria in a variety of tissue samples from sarcoidosis patients. Cantwell recently published some colored micrographs of this CWD pathology [15].

Mattman, *et al*., in 1996, [16] performed a careful study of blood samples from 20 sarcoidosis patients and 20 controls using an oil-immersion lens and the Intensified Kinyoun stain. Mattman also developed specialized media which were capable of culturing the CWD organisms she isolated from the CWD specimens.

Cantwell reported that the CWD forms were extremely difficult to culture, even with special media, and that the cultures sometimes took several months to produce visible results. CWD bacteria grow and propagate very much more slowly than spirochetes and other walled forms. Recognizing this extremely slow growth is crucial when choosing an optimal antibiotic therapy.

In 1989 Wirostko, Wirostko and Johnson [17] published transmission electron microscopy photographs of CWD bacteria living inside each type of immune cell:- lymphocytes, monocytes, macrophages and giant-cells. They used cells taken from the eyes of sarcoidosis patients.

Finally, in 2002, Nilsson *et al.*[18], published stunning electron microscopy of a bacterial organism replicating within the cells of a granuloma. Here was definitive evidence that not only could bacteria live within the phagocytic cells of the immune system, but also that the bacteria remained healthy, and they were able to flourish inside the hostile environment of the granuloma.

LESSONS FROM LYME DISEASE

Until the widespread availability of PCR DNA assays there was a general reluctance to even recognize that

CWD bacteria exist, and, if they did, that they might induce disease. The Lyme parasite, Borrelia burgdorferi, is one of the few bacteria that have been actively studied in both the spirochetal and mycoplasmal states. Borrelia studies can give us valuable information about the characteristics of the bacteria we are facing when treating the CWD bacteria of sarcoidosis.

Dr. Willy Burgdorfer (who first discovered Borrelia burgdorferi) observed [19] *"It's probably the answer for the difficulties we have in diagnosing Lyme and other spirochetal diseases, in that we can demonstrate these cysts by microscopy, but once they are in the tissues of the patient, we can no longer detect them. It is quite possible that this material that we cannot see by microscopy is responsible for producing prolonged and chronic disease."* Further, Burgdorfer notes that when *"the antibiotic or immune pressure is gone, and then when the conditions are right for their further development, they develop into typical spirochetes again."*

Borrelia spirochetes have been observed to revert to the CWD form when confronted with the immune components of spinal-fluid in-vitro, and then to transform back to mobile spirochetes in a less hostile environment [20].

There have also been reports that patients whose immune systems have been suppressed with Remicade (and other TNF-a agonists) often present with Tuberculosis [21]. Total elimination of the TNF-a cytokine apparently creates a less hostile immune environment, allowing the tissue-bound CWD mycobacterial organisms to transform into the mobile walled form, a form capable of propagating an active Tuberculosis infection.

Although 'Chronic-lyme' is a lymphopenic disease, chronic-lyme patients do not usually form sarcoid granuloma. Borrelia burgdorferi appears to be a pathogen with insufficient lymphopenic activity to proliferate sarcoid granulomas on its own. However, together with other pathogens, it is frequently found as a component of sarcoid inflammation.

Borrelia burgdorferi is also found as an inflammatory component of Lofgren's syndrome [22] and Lupus Erythematosus [23], presumably in combination with a different set of pathogens.

Indeed [4,24,25,26,27] it seems that sarcoid granuloma hardly ever form in response to a single species of parasitic lymphopenia-inducing pathogen. Prudent therapeutic intervention must assume the presence of multiple species of CWD pathogen.

"Prudent therapeutic intervention must assume the presence of multiple species of CWD pathogen."

SATISFYING KOCH'S POSTULATES

It is important to note that bacteria can cause the Th1 immune reaction without morphing to the walled form, as we have previously detailed in a response to the Brown, *et al.*, ACCESS study [28]. This walled-CWD pleomorphism is key to understanding why a bacterial pathogenesis for Sarcoidosis has not been proven to the satisfaction of Koch's Postulates. However, it is instructive to note that Leprosy has never satisfied Koch's postulates, yet it is accepted that Leprosy indisputably has a bacterial pathogenesis.

JARISCH-HERXHEIMER – INDISPUTABLE EVIDENCE OF BACTERIAL PATHOGENESIS – AND A THERAPEUTIC PROBLEM

We have been following the progress of a heterogeneous mix of over 50 neurosarcoidosis, cutaneous sarcoidosis, and pulmonary sarcoidosis patients, some chronic (wheelchair-bound), and some newly diagnosed. Of these 'early adopters', all except two have reported a lifestyle-limiting Jarisch-Herxheimer Reaction [40,42]. Many of these reactions have been severe, some with (fortunately benign) cardiac involvement [39]. Several required supplemental oxygen due to tightening of muscles in the trachea (oxygen had been unnecessary before the Herxheimer).

We found the only way to minimize the risk of cardiac and respiratory complications is to start therapy with an extremely low dose of antibiotic and let the patient increase that dose, month by month, as the degree of Herxheimer allows.

The Herxheimer reaction most commonly reported was an exacerbation of previous symptomology. Patients reported that it was just as though their sarcoidosis had become "much worse". Herxheimer usually disappears 24-48 hours after dosing, and reducing the dose also reduced the degree of discomfort experienced. Several patients reported that skin lesions became more prominent during the first few weeks of antibiotic treatment.

Most of the 'early adopter' patients report that the Herxheimer has lasted for 3 months or more, and in several cases it has not totally disappeared after 9 months of continuous therapy.

THE BIOCHEMISTRY OF THE Th1 IMMUNE REACTION

The secosteroid hormone 1,25-dihydroxyvitamin-D is responsible for differentiation of hematopoetic cells into monocytes, and then for catalyzing monocyte differentiation into macrophages and giant-cells. It is an excellent marker of the presence of sarcoid inflammation, even when the serum ACE is masked by steroids or ACE Inhibitors [29,30].

The Angiotensin II Receptor blocker, Benicar (Olmesartan Medoxomil), administered as 40mg q6h or q8h, has been very effective at reducing the suffering of patients experiencing Herxheimer. Some 'early adopters' have called it a 'miracle drug'.

ARBs suppress the release of TNF-a, apparently without disabling the immune system. When Angiotensin II binds at Type 1 receptors in the granulomas it signals the release of cytokines (including TNF-a) and chemokines via the NuclearFactor-kappaB pathway. We have previously published the detailed Th1 biochemistry [29,30] explaining why ARB therapy is so effective, and will avoid repetition in this review.

ANTIMICROBIALS

Rifampin is an antimicrobial commonly used in Tuberculosis and Leprosy. This antimicrobial does not kill CWD organisms effectively. In fact, one study showed Mycobacteria changing into a Rifampin-resistant CWD form under the action of a triple therapy of rifampin, isoniazid and ethambutol [31]. This drug is thus a poor choice for sarcoid therapy. Our aim should be to kill the CWD bacteria, not to create more of them.

Hydroxychloroquine Sulfate (HCQ) (Plaquenil) is an anti-microbial which has been partially successful in a small group of sarcoidosis patients. But like Rifampin, it does not kill CWD organisms very effectively. In fact, *"HCQ alone may be sufficient in the treatment of intracellular cystic forms .. at concentrations which are achievable in-vivo .. however, when the infection is located at the dermis .. the MBC (minimum bactericidal concentration) of HCQ is not achievable."*[32] Considering the widespread tissue distribution of CWD organisms reported by Cantwell [15], HCQ monotherapy is therefore not an optimal choice. Further, its use as a component of multiple-antibiotic therapies must also be questioned in view of the risk of serious ophthalmologic complications.

"We have previously published the detailed Th1 biochemistry explaining why ARB therapy is so effective..."

The Flouroquinolones have been reported with some activity against intra-cellular pathogens, albeit at one tenth the efficacy of doxycycline [33]. One of the 'early adopter' patients was experiencing Herxheimer at only 50mg of minocycline, q48h. Minocycline was stopped, and he was placed on Ciproflaxin for 2 weeks to treat a kidney infection. There was no Herxheimer while using Cipro. As soon as the 50mg q48h minocycline was resumed, so did the Herxheimer. Neither the study nor this clinical observation bode well for the potential efficacy of Flouroquinolones against the CWD bacteria of Sarcoidosis.

Minocycline[34] has recently been recommended for the treatment of Rheumatoid Arthritis (RA). A University of Nebraska study found minocycline an effective treatment for RA, with remissions cumulative during all four years of the study [35]. With a tissue penetration twice that of doxycycline [34], and a low incidence of side-effects, **low-dose** minocycline would seem to be the ideal antibiotic for treatment of sarcoid CWD bacteria.

Many studies refer to a biochemical immunospressive property of minocycline[43]. Each cites a previous paper, yet none cite a definitive source which might describe a specific biochemical activity to which this property is due, or exactly how minocycline might actually act to 'suppress' 'the immune system'. The problem of dealing with barely-detectable mollicutes within tissue is that one is tempted to ignore that they might exist. *"Caution should therefore be exercised when interpreting Ang II-related data obtained from cells that have not been checked for mollicute contamination"* is the admonition from Whitebread, *et al*.[44]. Yet we have sifted through dozens of papers citing this ill-defined immunosuppressive property for Minocycline. Not one of them has considered the liklihood of 'mollicute contamination'. We formed the opinion that the experimental outcomes of the studies invoking such a property can all be explained solely by consideration of minocycline's antimicrobial actions against mollicute-like bacterial organisms. We do not believe Minocycline has ever been proven to possess a chemically-based immunosuppressive ability, and this belief was reinforced by numerous clinical observations during our study. We note particularly that antibiotics other than the tetracyclines have been effective at inducing remission.

Our 'early adopters' are primarily using Minocycline, with a dose determined solely by the level of

Herxheimer they can tolerate (from 25mg q48h up to a maximum dose of 200mg q48h). A few used Doxycycline initially, then changed to Minocycline. Even though the tetracyclines are bacteriostatic, they produce intense and lengthy Herxheimer reactions in sarcoid patients, further highlighting the difference between fighting CWD microbes and blood-borne bacteria[41].

We also found that Azithromycin, Clarithromycin and Sulfa/Trimeth were effective at treating neuro, eye, and sinus manifestations when they were used **at a low dosage** in combination with **low-dose** minocycline.

"... the remission induced by this Antibiotic/ARB protocol was dramatic."

INTERMITTENT DOSING

We have previously demonstrated [36,37] how intermittent dosing of a drug can radically change its properties in Cryptorchidism and Diabetes. We were thus intrigued by Thomas McPherson Brown's book "The Road Back"[38], where he chronicles half a century of antibiotic treatment in a disease that he was convinced was due to CWD bacteria (RA). Albert Sabin and he had simultaneously isolated mycoplasmas while they were both at Rockefeller Institute in the late 1930s.

Brown was convinced that the body had to be given time to clear away dead cells in between antibiotic doses, if the therapy was to be optimally effective against CWD bacteria. The 'early adopters' have proven him correct. Most are using a q48h dosing interval, slipping to q72h, or even longer, during significant Herxheimer events.

Herxheimer has, at times, made antibiotic therapy become somewhat onerous for many of the 'early adopters', and intermittent dosing has been a significant factor in improving patient tolerance and ensuring compliance.

LIMITATIONS IN STUDY METHODOLOGY

Ours is a Phase II observational study. Many of the patients in this cohort are Health Care workers (Physicians, Nurses and ex-Nurses), and thus are not necessarily representative of the patient population as a whole. Therapy was prescribed and monitored by the patients' personal physicians. Since the recruitment and ongoing support was provided over the Internet, all patients needed to have a level of education sufficient to operate Internet-capable Computers.

These factors are all capable of introducing bias into the study results. Further bias could be introduced by the lack of a standardized results questionnaire (it was adjudged impractical to produce a standardized questionnaire which could meaningfully evaluate a heterogeneous cohort of Cutaneous, Cardiac, Pulmonary and Neuro-sarcoidosis patients).

To compensate for these biases, extreme care was taken to document adverse events, especially adverse outcomes, and correspondence was ***publicly*** logged and reviewed by both investigators.

Despite these reservations, the remission induced by this Antibiotic/ARB protocol was dramatic, and it is unlikely that any of these methodological limitations were sufficient to have skewed the study's conclusions.

IN SUMMARY

The >50 'early adopters' are a heterogeneous mix of neurosarcoidosis, cutaneous sarcoidosis, cardiac and pulmonary sarcoidosis patients. Some cases are chronic (wheelchair-bound) and some are newly diagnosed. All but three patients report progress induced by minocycline alone, or by the combination of olmesartan medoxomil (40mg q6-8h) and minocycline (<200mg q48h). **Sarcoid inflammation is proving to have a primary, homogeneous, bacterial pathogenesis** [28,45].

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SELECTED REFERENCES:

1. Scadding JG: **Sarcoidosis, with special reference to lung changes**. BMJ 1950, 1: 745-753

2. McGrath DS, Goh N, Foley PJ, du Bois RM: **Sarcoidosis – genes and microbes—soil or seed**. Sarcoidosis Vasc Diffuse Lung Dis. 2001 Jun;18(2):149-64

3. du Bois RM, Goh N, McGrath D, Cullinan P: **Is there a role for microorganisms in the pathogenesis of sarcoidosis**. J Intern Med. 2003 Jan;253(1):4-17

4. Eishi Y, Suga M, Ishige I, Kobayashi D, Yamada T, Takemura T, Takizawa T, Koike M, Kudoh S, Costabel U, Guzman J, Rizzato G, Gambacorta M, du Bois R, Nicholson AG, Sharma OP, Ando M: **Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis**. J Clin Microbiol. 2002 Jan;40(1):198-204

5. Bachelez H, Senet P, Cadranel J, Kaoukhov A, Dubertret L: **The use of tetracyclines for the treatment of sarcoidosis. Arch Dermatol**. 2001 Jan;137(1):69-73

6. Moller DR, Chen ES: **What causes sarcoidosis**. Curr Opin Pulm Med. 2002 Sep;8(5):429-34

7. Judson MA: **The etiologic agent of sarcoidosis: what if there isn't one**. Chest. 2003 Jul;124(1):6-8

8. Bergoin C, Lamblin C, Wallaert B: **Biological manifestations of sarcoidosis**. Ann Med Interne (Paris). 2001 Feb;152(1):34-8

9. Lee RE: **SARS E2-spike Protein Contains a Superantigen Between Residues 690 through 1050**. JOIMR 2003;1(1):3

10. Yu XJ, Luo C, Lin JC, Hao P, He YY, Guo ZM, Qin L, Su J, Liu BS, Huang Y, Nan P, Li CS, Xiong B, Luo XM, Zhao GP, Pei G, Chen KX, Shen X, Shen JH, Zou JP, He WZ, Shi TL, Zhong Y, Jiang HL, Li YX: **Putative hAPN receptor binding sites in SARS-CoV spike protein**. Acta Pharmacol Sin. 2003 Jun;24(6):481-8

11. Lee RE: **SARS Coronavirus Appears to be an FcgammaR Agent, Causing an Hyperimmune Response via a CD13 pathway — Implication for Therapeutic Interventions**. JOIMR 2003;1(1):2

12. Marshall TG, Marshall FE: **A Mechanism to Explain the T lymphopenia**. BMJ Rapid Response 20 June 2003; #33479

13. Silver RF, Crystal RG, Moller DR: **Limited heterogeneity of biased T-cell receptor V beta gene usage in lung but not blood T cells in active pulmonary sarcoidosis**. Immunology. 1996 Aug;88(4):516-23

14. Cantwell AR Jr: **Histologic observations of variably acid-fast pleomorphic bacteria in systemic sarcoidosis — a report of 3 cases**. Growth. 1982 Summer;46(2):113-25

15.Cantwell AR: **The Eccrine Sweat Gland as a possible Focus of Infection with Acid-Fast Cell Wall Deficient Bacteria**. JOIMR 2003;1(1):1

16. Almenoff PL, Johnson A, Lesser M, Mattman LH: **Growth of acid fast L forms from the blood of patients with sarcoidosis**. Thorax. 1996 May;51(5):530-3

17. Wirostko E, Johnson L, Wirostko B: **Sarcoidosis associated uveitis. Parasitization of vitreous leucocytes by mollicute-like organisms**. Acta Ophthalmol (Copenh). 1989 Aug;67(4):415-24

18. Nilsson K, Pahlson C, Lukinius A, Eriksson L, Nilsson L, Lindquist O: **Presence of Rickettsia helvetica in granulomatous tissue from patients with sarcoidosis**. J Infect Dis. 2002 Apr 15;185(8):1128-38. Epub 2002 Mar 21

19. Canadian Broadcasting Commission Radio One: **THE BACTERIA REVOLUTION**. June 4 1999, available from URL **http://www.radio.cbc.ca/programs/ideas/shows/bacteria/bacteria.html** Last Acessed 31 Jul 2003.

20. Brorson O, Brorson SH: **In vitro conversion of Borrelia burgdorferi to cystic forms in spinal fluid, and transformation to mobile spirochetes by incubation in BSK-H medium**. Infection. 1998 May-Jun;26(3)144-50

21. Arend SM, Breedveld FC, van Dissel JT: **TNF-alpha blockade and tuberculosis — better look before you leap**. Neth J Med. 2003 Apr;61(4):111-9

22. Klint H, Siboni AH: **Borreliosis associated with Lofgren's syndrome**. Ugeskr Laeger. 2000 Jul 31;162(31):4154-5

23. Federlin K, Becker H: **Borrelia infection and systemic lupus erythematosus**. Immun Infekt. 1989 Dec;17(6):195-8

24. Ishihara M, Ohno S, Ono H, Isogai E, Kimura K, Isogai H, Aoki K, Ishida T, Suzuki K, Kotake S, Hiraga: **Seroprevalence of anti-Borrelia antibodies among patients with confirmed sarcoidosis in a region of Japan where Lyme borreliosis is endemic**. Graefes Arch Clin Exp Ophthalmol. 1998 Apr;236(4):280-4

25. Ishihara M, Ishida T, Isogai E, Kimura K, Oritsu M, Matsui Y, Isogai H, Ohno S: **Detection of antibodies to Borrelia species among patients with confirmed sarcoidosis in a region where Lyme disease is nonendemic**. Graefes Arch Clin Exp Ophthalmol. 1996 Dec;234(12):770-3

26. Hua B, Li QD, Wang FM, Ai CX, Luo WC: **Borrelia burgdorferi infection may be the cause of sarcoidosis**. Chin Med J (Engl). 1992 Jul;105(7):560-3

27. Drake WP, Pei Z, Pride DT, Collins RD, Cover TL, Blaser MJ: **Molecular analysis of sarcoidosis tissues for mycobacterium species DNA**. Emerg Infect Dis. 2002 Nov;8(11):1334-41

28. Marshall TG: **Brown, et al, ACCESS Study finds Bacterial Pathogens in Sarcoidosis Patients**. JOIMR 2003;1(2):2

29. Marshall TG, Marshall FE: **The Science Points to Angiotensin II and 1,25-dihydroxyvitamin D**. [Electronic letter] Chest 2003; 6 Feb

30. Marshall TG, Marshall FE: **New Treatments Emerge as Sarcoidosis Yields Up its Secrets**. Clinmed 2003 Jan 27;2003010001

31. Wang H, Chen Z: **Observations of properties of the L-form of M. tuberculosis induced by the antituberculosis drugs**. Zhonghua Jie He He Hu Xi Za Zhi. 2001 Jan;24(1):52-5

32. Brorson O, Brorson SH: **An in vitro study of the susceptibility of mobile and cystic forms of Borrelia burgdorferi to hydroxychloroquine**. Int Microbiol. 2002 Mar;5(1):25-31

33. Rolain JM, Stuhl L, Maurin M, Raoult D: **Evaluation of antibiotic susceptibilities of three rickettsial species including Rickettsia felis by a quantitative PCR DNA assay**. Antimicrob Agents Chemother. 2002 Sep;46(9):2747-51

34. Burke A. Cunha, MD: **New uses for older antibiotics**. Postgrad. Med. 1997; 101(4)http://www.postgradmed.com/issues/1997/04_97/cunha_1.htm Last Accessed 31 July 2003

35. O'Dell JR, Paulsen G, Haire CE, Blakely K, Palmer W, Wees S, Eckhoff PJ, Klassen LW, Churchill M, Doud D, Weaver A, Moore GF: **Treatment of early seropositive rheumatoid arthritis with minocycline — four-year followup of a double-blind, placebo-controlled trial**. Arthritis Rheum. 1999 Aug;42(8):1691-5

36. Keogh EJ, MacKellar A, Mallal SA, Dunn AG, McColm SC, Somerville CP, Glatthaar C, Marshall T, Attikiouzel J: **Treatment of cryptorchidism with pulsatile luteinizing hormone-releasing hormone (LH-RH)**. J Pediatr Surg. 1983 Jun;18(3):282-3

37. Marshall TG, Mekhiel N, Jackman WS, Perlman K, Albisser AM: **New microprocessor-based insulin controller**. IEEE Trans Biomed Eng. 1983 Nov;30(11):689-95

38. Brown TMcP, Scammell H: **The Road Back — Rheumatoid Arthritis — its Cause and Treatment**. ISBN 0-87131-543-2, M Evans and Co Inc, New York, 1988.

39. Marshall TG, Marshall FE: **The Science Points to Angiotensin II and 1,25-dihydroxyvitamin D**. JOIMR 2003;1(2):3

40. Negussie Y, Remick DG, DeForge LE, Kunkel SL, Eynon A, Griffin GE: **Detection of plasma tumor necrosis factor, interleukins 6, and 8 during the Jarisch-Herxheimer Reaction of relapsing fever**. J Exp Med. 1992 May 1;175(5):1207-12

41. Mardh PA: **Human respiratory tract infections with mycoplasmas and their in vitro susceptibility to tetracyclines and some other antibiotics**. Chemotherapy. 1975;21 Suppl 1:47-57

42. Griffin GE: **Cytokines involved in human septic shock—the model of the Jarisch-Herxheimer reaction**. J Antimicrob Chemother. 1998 Jan;41 Suppl A:25-9

43. Labro MT: **Interference of antibacterial agents with phagocyte functions: immunomodulation or "immuno-fairy tales"?** Clin Microbiol Rev. 2000 Oct;13(4):615-50

44. Whitebread S, Pfeilschifter J, Ramjoue H, de Gasparo M: **Angiotensin II binding sites on micro-organisms contaminating cell cultures**. Regul Pept. 1993 Mar 19;44(2):233-8

45. Marshall TG, Marshall FE: **Remission in Sarcoidosis**. Clinmed 2002 Aug 22;2002080004

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Doxycycline
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acid-fast bacteria
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large bodies
lupus erythematosus

MESH CLASSIFICATION

Sarcoidosis
Sarcoidosis, Cardiac
Rheumatology
Minocycline
Minocycline, Adverse effects
Azithromycin
Azithromycin, Adverse Effects
Respiratory Medicine
Atypical Bacterial Forms
Transformation, Bacterial
Lupus Erythematosus

COMPETING INTERESTS:

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