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Marlene E. Haffner, M.D., M.P.H.,
Director, Office of Orphan Products Development,
Food and Drug Administration, HF-35
5600 Fishers Lane, Room 6A55
Rockville, MD 20857

COPY

September 20, 2005.

Dear Dr. Haffner,
The Autoimmunity Research Foundation has been involved in 'Bench Research' leading to an effective 'Bedside Intervention' for patients with the deadly Th1 disease 'Sarcoidosis.' Over the last several years we have partnered with physicians, both specialist and PCP, to effect a Phase 2 Observational, Open-label, clinical trial of this intervention. We have trialed a method of using concomitant antibacterials capable of killing the antibiotic-resistant intra-phagocytic bacteria which cause this disease. At the last formal count, we were observing the progress of over 350 patients in the trial 'cohort,' representing a wide array of Th1 disease states. We wish to continue to Phase 3 trial(s), and are therefore applying for these Orphan Designations.

The Foundation wishes to thank your Office for the many hours of time that Staff have devoted to helping the Foundation identify those elements of its Research relevant to OOPD, and particularly how OOPD can help us formalize our intervention, and make it available to those patients who were not able to participate in our early study.

There are 3 concomitant antibacterials which are at the core of our Intervention, and thus we have today filed 3 substantially similar Applications for Designation as an Orphan Product. This cover letter accompanies the first of those applications, for an antibacterial indication of the Angiotensin Receptor Blocker 'Olmesartan Medoxomil,' marketed by Sankyo as 'Benicar.'

Sincerely
/s/ Trevor G Marshall, PhD, Director

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Application for Designation as an Orphan Product

1. Statement

Autoimmunity Research Inc, a not-for-profit California Corporation, dba 'Autoimmunity Research Foundation' (SPONSOR, FOUNDATION), hereby requests that a lawfully marketed drug, the Angiotensin Receptor Blocker 'Olmesartan Medoxomil' be granted designation as an Orphan for its indication as an antibacterial agent in the 'Rare Disease,' SARCOIDOSIS.

Discussions with Staff from Office of Orphan Product Development (OOPD) during March of 2005 suggested that the Foundation would need to apply for an IND prior to filing this Application. However, because of the favorable safety profiles of the lawfully marketed drugs used in this intervention, subsequent informal discussions with CDER staff have indicated the likelihood that 21 CFR § 312.2 might well provide an exemption from the requirements for a pre-study IND. This exemption might also be facilitated based on the survival benefit identified during our Phase 2 trials. The Foundation therefore decided to file this Application for Orphan Product Designation while discussions with CDER are ongoing.

This application for designation is specific to the Th1 immune disease SARCOIDOSIS, even though our Phase 2 trials identified promising results in patients with additional orphan diseases having a similar Th1 bacterial pathogenesis. This Application is made without prejudice to any future applications which may be made for orphan designation in these other orphan diagnoses.

2. Sponsor, Drug and Contact Details

The Sponsor is Autoimmunity Research Inc, a not-for-profit California Corporation, dba 'Autoimmunity Research Foundation'

Primary Contact person: Trevor G Marshall, PhD,
Director,
Autoimmunity Research Foundation,
3423 Hill Canyon Ave, Thousand Oaks, CA 91360
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Olmesartan Medoxomil is marketed in the USA under the Tradename 'Benicar,' in the United Kingdom under the Tradename 'Olmetec,' and in Germany under the Tradename 'Votum.' These Tradenames are also used when the drug is marketed in countries other than those named above.

Further details can be found in FDA NDA 21-286
Benicar (Olmesartan Medoxomil) Tablets
Company: Sankyo Pharma, Inc.
Application No.: 21-286
Approval Date: 4/5/2002

The drug is marketed in the USA by
Forest Pharmaceuticals Inc,
909 Third Avenue,
New York, NY 10022
phone: 212-421-7850

3. Description of the Rare Disease, and Indication(s) for Therapy

"Sarcoidosis is a disease involving organ systems throughout the body in which normal tissue is invaded by pockets of inflammatory cells called granuloma .. The causes of Sarcoidosis are presently unknown, but disease development is thought to involve both a genetic predisposition and the immune system[1]."

Until quite recently Sarcoidosis was thought to spontaneously remit in a majority of cases, but the 6-year (1995 to 2001) ACCESS study, funded by the National Institutes of Health (NIH), found that during the 2-year period subsequent to diagnosis, only 22% of patients showed a measurable improvement, and that 13% got worse[5] [see Table.3 of ref.5].

Further, it was noted that "most patients with persistent disease at 2 years were unlikely to have resolution of sarcoidosis" and "end-stage pulmonary sarcoidosis usually develops over one or two decades[5]."

Please note that the Abstract of Reference 5 (Judson, et al, 2003), is misleading in that it does not adequately reflect the data collected, or the description and statistics in the Full-text. The Abstract states that "Sarcoidosis tends to improve or remain stable over two years in the majority of patients" but this is not descriptive of the data, or of the Full-text, which states (at Table 3) "FVC, FEV1, Scadding stage, and the dyspnea scale remained unchanged over the two-year period in the majority of the patients." <u>One must note that this 'stability' is at a state of clinical disease.</u>

Subsequent to our communicating this Abstract anomaly to NIH National Heart Lung and Blood Institute (NHLBI), their booklet "Facts About Sarcoidosis" was amended to

omit the previous reference to a supposed "60%" "spontaneous" rate of remission (the full text of our submission to NIH/NHLBI is not pertinent, but is available upon request).

In summary, the ACCESS study found that 65% had no measurable change in their illness at 2 years subsequent to diagnosis, 22% improved, and 13% worsened. Most patients with persistent disease at 2 years were unlikely to have resolution of sarcoidosis, and end-stage pulmonary sarcoidosis usually develops over one or two decades. This disease kills.

3.a Sarcoidosis Causes Systemic Damage

This Foundation was also successful in getting NHLBI's "Facts about Sarcoidosis" updated to emphasize both the deadly nature of this disease, and that it is a systemic disease, affecting all organs of the body. The Foundation is continuing to discuss errors still contained in the NHLBI publications on Sarcoidosis, with the aim of bringing NHLBI's publications more into line with published studies, and with the evidence. We have been slowed in this, however, as NHLBI now says it has no budget available to further correct their publications, or to improve public knowledge about the disease. Discussions with CDER are ongoing.

Additionally, collection of demographic data has not been diligently pursued in the USA. For example, sarcoidosis is not a reportable disease, and it very rarely shows up as a 'cause of death.' Yet Cardiac Sarcoidosis is often diagnosed only at autopsy. The recent death of Football Star Reggie White showed this very clearly, where the initial medical reports blamed "heart attack" or "sleep apnea" while the coroner later determined that it was Cardiac Sarcoidosis which had killed Reggie.

Historically, Sarcoidosis was believed to primarily affect the lungs, and pulmonologists have therefore often been regarded as front-line specialists in the disease. Recently, however, it has become clear that sarcoidosis affects every system of the body, and is sometimes very hard to diagnose. The 'gold standard' for diagnosis is still "biopsy verified non-caseating granuloma, consistent with the clinical presentation of sarcoidosis."

The USA lags the rest of the world in diagnosis and treatment of systemic manifestations of this disease. For example, a recent study from Japan[11] showed that systemic initial presentation of the disease was quite frequent, with ocular manifestations (26%) not lagging far behind pulmonary symptoms (42%). Yet, in the USA, the diagnosis of pulmonary manifestations usually precedes recognition of systemic damage.

The recent establishment of a multi-disciplinary "Trans-NIH" Sarcoidosis coordinating committee enshrines the shift towards recognition of Sarcoidosis as systemic, and not merely as a disease affecting the lungs.

3.b Available Sarcoidosis Therapies are Ineffective

Sarcoidosis is a Th1 immune inflammatory disease which can damage the lungs, heart, eyes, brain, liver, and kidneys. "The morbidity associated with Sarcoidosis can be severe, resulting in significant loss of function, and decrease in quality of life[1]."

Treatment has historically been based around the use of Prednisone. The ACCESS study showed that "The interaction of corticosteroid therapy with two-year outcome is complex .. More patients with improved FVC or dyspnea at follow-up were taking corticosteroids than not, and more patients with a worse FVC or dyspnea at follow-up were taking corticosteroids than not .. Patients taking corticosteroids at follow-up tended to be improved or worsened with respect to FVC and dyspnea more often than those not taking corticosteroids .. In addition, the use of corticosteroids **may promote relapse** of Sarcoidosis when the medication is discontinued or tapered that might adversely affect the clinical course[5]."

Even though this study's authors were clearly trying to find something positive to say about corticosteroid therapy in Sarcoidosis, there was nothing positive to be found in their study results. Previous studies have also not shown any long-term survival benefit from corticosteroid therapy. The NHLBI "Facts about Sarcoidosis" information booklet has recently been changed (at this Foundation's insistence) to emphasize that corticosteroids may be helpful in the short-term but are not intended for more than a few months use, showing no improvement in long-term morbidity or survival.

Side effects of corticosteroid therapy include Avascular Necrosis, weight gain, swelling, high blood pressure, cataracts, mood changes, infection and diabetes.

Gottlieb[4], et al, studied the rate of relapse subsequent to corticosteroid therapy, and found it to be around 74%.

3.c Orphan designations

Orphan designations have been made for the following drugs in the treatment of Sarcoidosis:

1. Infliximab (Treatment of chronic sarcoidosis) 5/21/2003
2. Golimumab (Treatment of chronic sarcoidosis) 11/2/2004

Infliximab is not showing promise as a treatment for Sarcoidosis. The most recent study found equivocal benefit and concluded "Given the potential for adverse effects, use of IFX in this patient population should be confined to ongoing clinical trials[12]." In a cohort of just 42 patients, serious adverse events included "decreased WBC and elevated CPK (1pt), hyperglycemia and bronchitis (1pt), pneumonia (2pt), thigh pain (1pt), URI and suicidal ideation (1pt), cellulitis, acute renal failure, pulmonary embolus and death (1pt)[12]." Another death (from Lymphoma) was reported during a separate 10pt trial of Infliximab[3].

A presentation by Dr Robert Baughman's group at the 2005 American Thoracic Society conference, "Comparison of Anti-TNF (Tumor Necrosis Factor) Agents in Treatment of Refractory Sarcoidosis[2]," reported no success with either Golimumab or Etanercept.

Clearly there is a need for an effective intervention in Sarcoidosis, especially an intervention which does not **increase** long-term patient morbidity.

4. Scientific Rationale

4.a Establishing the Bench-Model for the Sarcoidosis Disease Process

Th1 inflammation is defined as inflammation which produces an inflammatory cytokine profile which includes significant Interferon-gamma. This cytokine, when released within the cytoplasm of activated phagocytes, stimulates the cytoplasmic Mitochondria to hyper-energetically convert 25-hydroxyvitamin-D (25-D) to the active secosteroid-hormone 1,25-dihydroxyvitamin-D (1,25-D) (under the catalysis of the P450 enzyme CYP27B1).

Some years ago, Trevor G Marshall, PhD, and Frances E Marshall, RPh, two of the Directors of this Foundation, discovered that it is possible to measure the proportion of 1,25-D which leaches into the bloodstream, together with the plasma 25-D, and estimate the extent of Th1 inflammatory process in systemic tissue. One estimate of Th1 inflammation is performed by calculating the D Ratio, the ratio of 1,25-D (in pg/ml) to the 25-D (in ng/ml). The value for a healthy population is 1.25, and this ratio is elevated in Th1 immune disease. In hundreds of D-metabolite assays taken from patients with Sarcoidosis, this assay has been found to be an excellent measure of disease activity, probably the best measure currently available[A].

Many previous investigators have noted that the level of 25-D falls in patients with the Th1 immune diseases (including many of the so-called 'autoimmune' diseases), but that observation has not heretofore been recognized as a **marker** for Th1 inflammatory disease. 1,25-D has been mistakenly linked with an aberrant calcium metabolism. The calcium metabolism is, however, primarily regulated by the Para-Thyroid Hormone (PTH) and the Calcium-Sensing Receptor (CASR), and conceptually linking it to 1,25-D is a mistake.

The Marshalls also identified that the hormone Angiotensin II has profound activity in the Th1 diseases. Although other investigators have hypothesized this merely to be an anti-inflammatory effect, the paper "Putative Antibacterial Actions of Angiotensin Receptor Blockers[10]," describes additional putative Genomic and Biochemical mechanisms for the actions of Angiotensin II in Th1 immune disease.

[A] This measurement and prediction is only valid if the patient is not taking any supplements containing Vitamin D, and the value of the presenting 25 D assay therefore is between 14 ng/ml and 24 ng/ml.

Based on the knowledge of the biochemical effects of these two hormones in Th1 disease, and based on studies which have previously suggested a bacterial pathogenesis for Sarcoidosis[8], Dr Trevor Marshall developed a model for the disease process which fully described the biochemical and histological processes occurring in Sarcoidosis.

This model demonstrated that occult, very tiny, antibiotic-resistant intra-cellular bacteria could produce the disease state seen in Sarcoidosis if those bacteria were able to evade phagocytosis in the monocytes and macrophages typical of sarcoid tissue infiltration[8].

Studies detailed in reference 8, "Sarcoidosis Succumbs to Antibiotics – Implications for Autoimmune Disease" did in fact demonstrate that phagocytosis could be evaded, and the model was therefore declared viable, and ready for testing.

4.b 'Bench to Bedside' - Clinical Issues

During 2002-2003, a number of physicians and patients collaborated in Phase 1 and Phase 2 Observational, Open-label trials, leading to the paper "Antibiotics in Sarcoidosis - Reflections on the First Year[9]."

Meg Mangin, RN, (another Director of this Foundation) subsequently published "Observations of Jarisch-Herxheimer Reactions in Sarcoidosis Patients[6]."

Indeed, the invariant appearance of Jarisch-Herxheimer provided Ex-Juvantibus confirmation of the antibiotic-resistant bacterial pathogenesis of Sarcoidosis, and of the 'Bench-model' for this disease.

In early 2004 a paper[7] was invited by "Herald MKDTS," the Journal of the University of Kazan, in Russia, which was publishing a special issue on Sarcoidosis. The Foundation's initial clinical protocol was detailed in this Russian-language paper. An English translation has been provided in Exhibit 7 hereto.

Physicians have continued to enroll patients in the Phase 2 protocols, indeed, much of the recent interest has come from Sarcoidosis patients themselves, as the news begins to circulate that there appears to be an effective intervention for Sarcoidosis, furthermore, an intervention which uses some of the safest drugs in the US formulary.

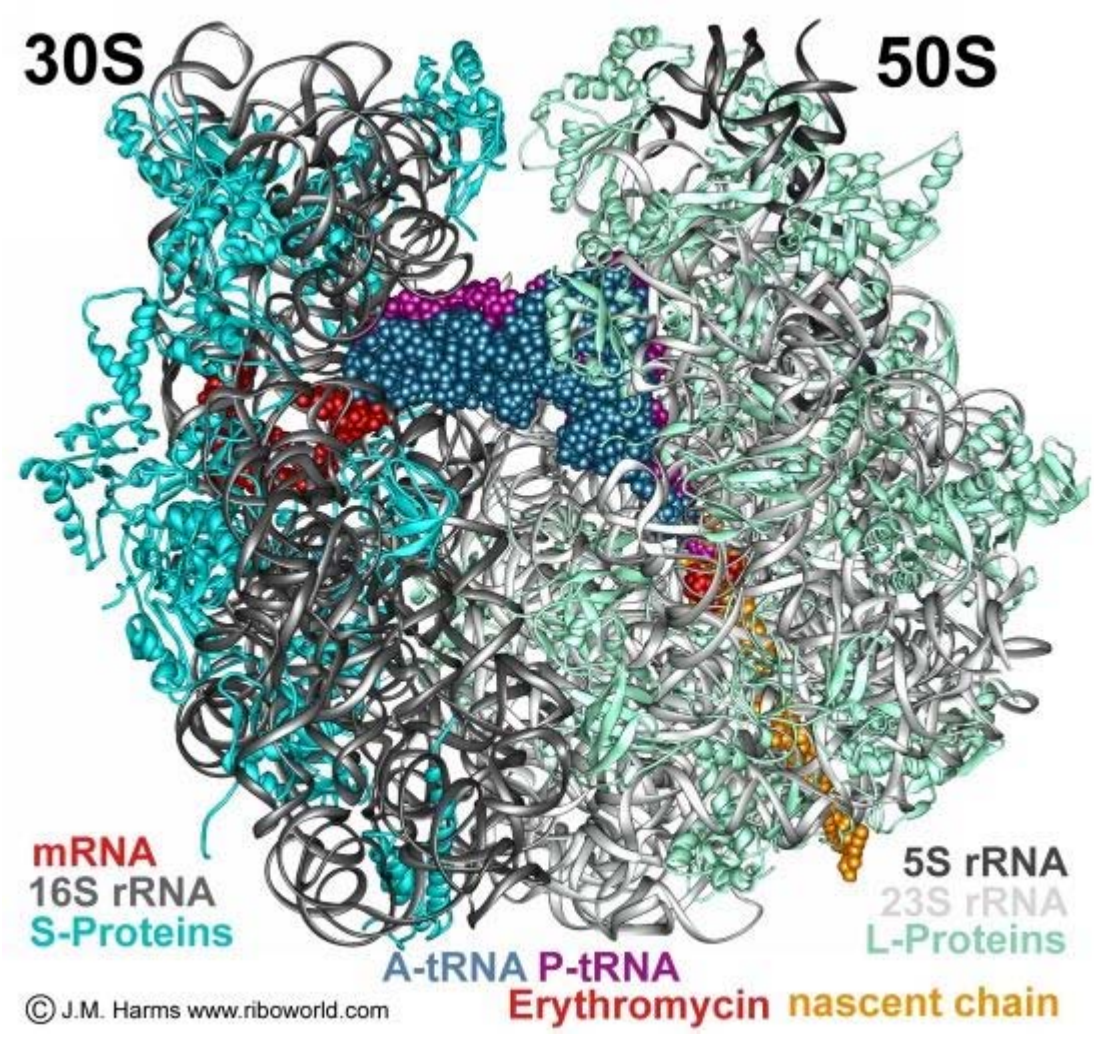
4.c Current Status and Phase 3 Trials

Slow but steady recovery of nearly 500 patients continues to validate the 'Bench' model.

Once a clamp is placed on Angiotensin II by using the Angiotensin II Receptor Blocker 'Olmesartan Medoxomil,' and once the patients have eliminated all sources of Vitamin D

accretion, the previously dysfunctional immune system of Sarcoidosis patients begins to kill the antibiotic-resistant intra-phagocytic bacteria which cause the disease.

The immune system is assisted by judicious use of bacteriostatic antibiotics designed to prevent transcription of proteins by the bacterial 70S Ribosome.
Additional 'Bench' research identified multiple symbiotic antibiotics which were capable of retarding the actions of both the 30S and 50S subunits of the 70S bacterial Ribosome, more effectively overcoming the bacterial resistance mechanisms.



This diagram shows the RNA and protein strands which make up the 70S bacterial Ribosome of *Thermus thermophilus,* and graphically separates the 30S and 50S subunits. Demeclocycline and Minocycline bind to inhibit the grayish helical structure at the top of the 30S unit, and thus obstruct mRNA advance. A molecule of Erythromycin is shown docked into the protein exit-channel on the 50S side. Azithromycin also binds at this point (so as to obstruct the assembly of proteins) and Clindamycin bonds symbiotically just above, near the t-RNA Peptidyl Transferase Center (PTC)

As of August 2005, the following bacteriostatic antibiotics have been analyzed for efficacy in the Phase 2 trial:

1. Demeclocycline (a 30S inhibitor)
2. Minocycline (a 30S inhibitor)
3. Clindamycin (inhibits the 50S unit at the PTC)
4. Azithromycin (inhibits the 50S unit below the PTC)

Additionally, the anti-bacterial anti-metabolite 'Sulfamethoxazole-Trimethoprim' has been useful in later stages of patient recovery.

The Angiotensin Receptor Blockers (ARB) 'Valsartan' and 'Irbesartan' have been shown to be of some use, but their effectiveness is totally eclipsed by 'Olmesartan medoxomil,' for the reasons cited in reference 10.

It is intended to go through to initial Phase 3 trials using the ARB Olmesartan Medoxomil, together with the antibiotics Minocycline and Clindamycin. This Application for Designation as an Orphan Product is for Olmesartan Medoxomil, and separate applications have been filed for the bacteriostatic antibiotics Clindamycin and Minocycline.

5. "Me too" Drugs

Not applicable, additionally please see discussion in section 3.b of this document.

6. Subset Applicability of the Intervention

There is no need for any sub-setting, our Phase 2 trials have shown that Sarcoidosis has a homogenous, bacterial pathogenesis.

Every patient with biopsy-verified Sarcoidosis has responded to our anti-bacterial therapeutic regime.

Patients with Neurosarcoidosis have recovered. For example, one patient who had been confined to a wheelchair, is now walking again with only the help of a cane, and one who was being prepped for a wheelchair, and confined to a spinal brace, has recovered well enough to again ride her beloved horses in competition.

Patients with Skin Sarcoidosis have recovered.
Patients with Pulmonary Sarcoidosis have seen a reduction in Dyspnea, and many have had that improvement confirmed by CT.

There has been a small drop-out incidence which is hard to estimate, but seems to be below 5%, and there have been a few non-responders, again less than 5%. There have been no reported incidents of relapse during as much as 3 years of follow-up.

7. Summary of Regulatory and IND Status

Olmesartan Medoxomil is lawfully marketed under NDA 21-286 for the indication "Hypertension."

However, in order to obtain a total blockade of all Angiotensin II receptors in the immune system, it has been found necessary to use a dosage regime differing from the dosing which was found to be efficacious in its current indication, Hypertension. The dosing is, however, still within the dosing levels which are documented in NDA 21-286.

Discussions with OOPD staff indicated that it is possible that the modified dosing may compel us to file a new IND application, but initial discussions with CDER staff have indicated that a waiver under 21 CFR § 312.2 might well be issued. Such a waiver might also be facilitated by both the 'function benefit' and the 'survival benefit' which we identified in the hundreds of patients who informally participated in the Phase 2 trials.

The first issue is that the Angiotensin II receptor blockade must remain effective as a function of time. Due to both receptor dis-association, and clearance of the ARB from the circulation, the effective half-life of the ARB in a Th1 patient is in the order of 6-8 hours.

Dr Norman Stockbridge (HFD-110) wrote, for the Clinical Review of once or twice-daily dosing in NDA 21-286, "One can expect to get some return on twice-daily dosing, and even more with dosing 3 or 4 times a day, but the amount of return on twice-daily dosing is already a poor investment." Our Phase 2 trials showed that this is not the case in the indication of Sarcoidosis (and the other Th1 diseases trialed), as the loss of total blockade cannot be tolerated at any time, and the q8h to q6h dosing mooted in the Clinical Review is essential for establishing and maintaining efficacy of the ARB's antibacterial actions.

The optimal dosing of Olmesartan Medoxomil discovered in our Phase 2 trials was, for the typical patient, 40mg every 8 hours, and for the most seriously ill patients, 40mg every 6 hours. The dosing interval had to intermittently be reduced to q4h to deal with unexpected, acute herxheimer events.

Further, there is no indication in NDA 21-286 that a "3 or 4 times a day" dosing regime might not be safe, indeed, studies which contained evidence to the contrary are documented in the NDA under the protocols numbered 866-101 and SE-866/01.

It would also seem that an IND could be avoided if we changed the dosing to 20mg q6h. Our experience in the Phase 2 trials was that this lower dose did increase pain and suffering for a Sarcoidosis patient , but that it nevertheless allowed the ARB to exert a partly effective antibacterial activity, and effect recovery, albeit a much slower recovery.

We are continuing to discuss this issue with CDER staff.

8. Incidence of the Orphan Disease

Earlier this year, in its annual report to Congress, the NIH stated that "the number of Americans with sarcoidosis range from 13,000 to 134,000, and between 2,600 and 27,000 new cases appear each year[1]."

The Foundation has no reason to question this statement, and accepts that this disease affects less than 200,000 people in the United States. Bibliography 1 contains a copy of the header and relevant pages from the cited NIH Report. It is available on the Internet at URL http://rarediseases.info.nih.gov/html/reports/fy2004/FY2004_index.html

9. Statement of Interest

The Foundation is the real party in interest of the development of this indication, and of the upcoming Phase 3 clinical trial(s), but, at this point, has no interest in the actual production and sales of the product. Olmesartan Medoxomil is already lawfully marketed for the treatment of Hypertension.

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Biennial and Annual Report on the Rare Diseases Research Activities at the National Institutes of Health

FY 2004

Office of Rare Diseases

National Institutes of Health

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

www.nih.gov

JUL 07 2005

The Honorable Michael Enzi
Chairman, Committee on Health,
Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

I am pleased to submit to you the National Institutes of Health (NIH) Biennial Report and Plan on Rare Diseases Research Activities: FY 2004. This report also meets the requirement for our annual report to Congress found in section 404F of the Public Health Service Act, Public Law 107-280, the Rare Diseases Act of 2002.

This report presents the contributions and research advances of the NIH Institutes and Centers research programs and the Office of Rare Diseases (ORD). The basic, clinical, and research training programs contribute to the development and dissemination of information on the prevention, etiology, diagnosis, and treatment of rare diseases. Many advances presented in the report are the results of years of basic research sponsored by the NIH. Patients with rare diseases and their families continue to benefit from the treatment applications realized from the diverse nature of and emphasis placed on both basic and translational research by NIH.

Should you or your staff have any questions regarding the report please feel free to contact Dr. Stephen Groft, Director of ORD, at 301-402-4336.

Sincerely,

Elias A. Zerhouni, M.D.
Director

being made in the search for a trigger or modifying condition for clinical presentation of BMPR2 mutations. The NHLBI supports a PPH Family Registry that was begun in 1994 to discover the genetic mechanism(s) of the disease. The registry currently comprises 81 families and has collected 324 samples for study. Research is determining whether variations in certain candidate genes contribute to development of the disease in genetically susceptible individuals. Current data from the registry suggest that roughly 50 percent of familial and 26 percent of nonfamilial (sporadic) PPH patients have mutations in the coding region of the BMPR2 receptor gene. As only 20 percent of individuals with a BMPR2 mutation develop PPH, other genetic factors likely play a role. Recent findings from the registry identified several possible modifier genes, including serotonin transporter, nitric oxide synthase 3, and vasoactive intestinal peptide, that may be risk factors for development of clinical disease or may in part determine the age of disease onset. Elucidating the genetic basis of PPH will enhance the ability of clinicians to inform affected family members about their risk of developing the disease. The basic research already funded by the NHLBI has enabled development of new agents that are currently being evaluated in clinical trials. So it is reasonable to expect that further basic research advances will lead to better treatments for PPH and other forms of severe pulmonary arterial hypertension.

Sarcoidosis

Sarcoidosis is a disease involving organ systems throughout the body in which normal tissue is invaded by pockets of inflammatory cells called granuloma. Most sarcoidosis patients have granuloma in their lungs. The disease can occur in a mild form that disappears spontaneously or in a severe form that results in a life-long condition. Estimates of the number of Americans with sarcoidosis range from 13,000 to 134,000, and between 2,600 and 27,000 new cases appear each year. Up to 5 percent of individuals with pulmonary sarcoidosis die of causes directly related to the disease. The morbidity associated with sarcoidosis can be severe, resulting in significant loss of function and decrease in quality of life. The causes of sarcoidosis are presently unknown, but disease development is thought to involve both a genetic predisposition and the immune system. Although corticosteroids are the mainstay of current treatment, alternative therapies could be beneficial given the multiple side effects that can arise from the use of corticosteroids.
The NHLBI supports research on sarcoidosis in both its extramural and intramural programs. Researchers in the NHLBI's intramural laboratories conduct translational studies relating to the effectiveness of cyclic nucleotide phoshodiesterase inhibitors and statins as potential new therapies for sarcoidosis. The NHLBI also funds extramural research grants to investigate the causes of sarcoidosis and the role of immune cell responses in the disease. As part of its extramural program, the NHLBI also supports a multicenter study, the U.S. Sarcoidosis Genetic Analysis Consortium (SAGA), to perform linkage analysis of 360 African-American families with affected siblings, using a 300-microsatellite marker scan. The focus is on African Americans as they are more likely to report a family history of sarcoidosis, present at an earlier age, and have more severe disease.

The NHLBI multi-center ACCESS (A Case Control Etiologic Study of Sarcoidosis) study created a repository of DNA specimens collected from more than 700 sarcoidosis patients and paired controls. A public access database for the repository is being prepared. In FY 2004, a publication by ACCESS investigators reported on social predictors of disease severity at presentation. The results showed that lower income, the absence of private or Medicare health insurance, and other

barriers to care were associated with sarcoidosis severity at presentation, as were race, sex, and age. Blacks were more likely to have severe disease by objective measures, while women were more likely than males to report subjective measures of severity. Another publication in FY 2004 focused on a 2-year follow-up study of a subset of 215 ACCESS patients. The investigators reported that about 80 percent of subjects had improved or stable pulmonary function. Patients with erythema nodosum at presentation were more likely to have improvement in the chest radiograph at 2-year follow-up. Patients with a lower annual family income were more likely to worsen with respect to dyspnea and were more likely to have new organ involvement at 2-year follow-up. The investigators concluded that in this group of sarcoidosis patients the disease tended to improve or remain stable over 2 years in the majority of patients. In a third ACCESS study, researchers interviewed participants (cases and controls) regarding occupational and nonoccupational exposures. Analysis of these data show some positive associations between sarcoidosis and specific occupations, e.g., agricultural employment, exposures to insecticides at work, environments with mold/mildew, and microbial bioaerosols. However, a history of smoking cigarettes was less frequent among cases than the controls. The study did not identify a single, predominant cause of sarcoidosis.

Blood Diseases and Resources Programs

Acquired Aplastic Anemia

Acquired aplastic anemia is an unusual hematologic disease in which the bone marrow fails to produce red cells, white cells, and platelets resulting in severe anemia, low white blood cell counts, and low platelet counts. The NHLBI Division of Intramural Research conducts clinical and laboratory research on bone marrow failure syndromes, including aplastic anemia. Intramural researchers have conducted multiple laboratory experiments directed at the pathophysiology of aplastic anemia as well as clinical programs dedicated to the treatment of the disease by immunosuppression and stem cell transplantation. Recently, the intramural program completed two clinical trials testing treatments for mild and severe aplastic anemia and a study of molecular clonotyping of the T-cell response in patients with aplastic anemia. They also described mutations in the telomere repair complex genes in patients with apparent acquired aplastic anemia.

Cooley's Anemia

Cooley's anemia (also called beta-thalassemia, thalassemia major, or Mediterranean anemia) is a genetic blood disease that results in inadequate production of hemoglobin. Individuals affected with Cooley's anemia require frequent and lifelong blood transfusions to sustain life. Because the body has no natural means to eliminate iron, the iron contained in transfused red blood cells builds up over many years and eventually becomes toxic to tissues and organ systems. Many children with Cooley's anemia have acquired other diseases such as hepatitis through years of transfusion exposure. Extramural research efforts of the NHLBI include identifying mutations in the globin gene cluster that lead to Cooley's anemia, determining the mechanism by which naturally occurring mutations significantly increase levels of fetal hemoglobin (Hb F) in adult red blood cells, developing therapeutic applications related to the naturally occurring mutations, studying iron chelation, identifying clinically useful therapies and drugs for the disorder, and developing gene therapy strategies to reduce morbidity and mortality associated with Cooley's anemia.

[A14] Comparison of Anti-TNF (Tumor Necrosis Factor) Agents in Treatment Refractory Sarcoidosis

D.A. Bradley, MD, E.E. Lower, MD, R.P. Baughman, MD, Cincinnati, OH

Introduction: Anti-tumor necrosis factor (TNF) agents have been effective in treating refractory sarcoidosis. There has been no previous comparison of efficacy of these agents for the treatment of sarcoidosis. **Methods**: A database of all patients (pts) seen in the Interstitial Lung Disease and Sarcoidosis Clinic was reviewed to identify pts treated with anti-TNF agents for at least 1 month. All pts had progressive disease or unacceptable toxicity with previous regimens. Response was graded as improved (>25% improvement in index organ), stable, or worsened. **Result**s: Forty-five pts were treated with infliximab intravenously: 35 (78%) pts improved, 6 (13%) remained stable, and 4 (9%) had worsening of disease. Sixteen pts were treated with adalimumab as a subcutaneous injection every 1-2 weeks: 4 (25%) pts improved, 5 (31%) remained stable, and 7 (44%) worsened. Twelve pts were treated with etanercept as a subcutaneous injection twice a week: 2 (16%) pts improved, 5 (42%) remained stable, and 5 (42%) worsened. Significantly more pts responded to infliximab than the other anti-TNF agents ($p<0.0001$). Infliximab was discontinued in 19 pts (42%). Reasons for discontinuation included: insurance no longer covering therapy (7 pts), toxicity (9 pts), and no further response to therapy (3 pts). Fourteen pts (74%) who had originally responded to infliximab relapsed after drug was stopped. Two pts remained clinically stable after discontinuation of therapy. **Conclusion**: Etanercept, a soluble receptor antagonist, was significantly less efficacious than the anti-TNF antibody agent infliximab. While both infliximab and adalimumab are antibodies against TNF, infliximab was significantly more effective. The difference in efficacy may be due to the higher peak levels achieved by intravenous route of administration used for infliximab. This study suggests that infliximab is the preferred anti-TNF biologic agent for treatment refractory sarcoidosis

SUNDAY, May 22, 2005 10:00 am, Room 3 (Upper Level), San Diego Convention Center

[**] Mini-Symposium (Abstract Page: A19) Session: 8:15 am-10:45 am, TREATMENT OF SARCOIDOSIS AND IPF

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Treatment of sarcoidosis with infliximab.

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BACKGROUND/OBJECTIVES: Many patients with sarcoidosis are unable to tolerate corticosteroids or alternative therapeutic agents due to side effects or have disease refractory to these agents. We report our experience using infliximab to treat such patients. METHODS: A group of patients in whom traditional sarcoidosis therapy failed, either due to drug failure or intolerable side effects, were prescribed infliximab. Their charts were retrospectively reviewed. RESULTS: Ten patients receiving infliximab were reviewed. Nine of the 10 patients reported a symptomatic improvement with therapy, and all 10 demonstrated objective evidence of improvement. A drug reaction developed in one patient after several months of therapy, oral candidiasis developed in one patient, and angioimmunoblastic lymphoma developed in another patient. The corticosteroid dose was reduced in five of the six patients who were receiving corticosteroids at the time of infliximab therapy. CONCLUSION: Infliximab appears to be an effective, safe treatment for patients with refractory sarcoidosis, including such manifestations as lupus pernio, uveitis, hepatic sarcoidosis, and neurosarcoidosis. Infliximab appears to be steroid sparing. Patients receiving the drug should be screened for latent tuberculosis and lymphoproliferative disorders.

PMID: 15764796 [PubMed - indexed for MEDLINE]

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Outcome in Sarcoidosis*

The Relationship of Relapse to Corticosteroid Therapy

Jonathan E. Gottlieb, MD, FCCP; Harold L. Israel, MD; Robert M. Steiner, MD, FCCP; Joseph Triolo; and Herbert Patrick, MD, FCCP

Study objective: **To determine the demographic, clinical, and radiographic characteristics of corticosteroid-treated patients with sarcoidosis who developed relapse following a period of clinical stability lasting longer than 1 month, and to compare these characteristics with those of a group of patients with sarcoidosis who were not treated.**
Design: **Historic, concurrent and prospective, nonrandomized, observational study.**
Setting: **Ambulatory sarcoidosis clinic in a university city hospital.**
Patients: **Over a 4-year calendar period, 337 patients with sarcoidosis were prospectively enrolled in a registry. One hundred eighteen patients were assigned to a *spontaneous remission* group when symptoms resolved without treatment, and 103 were assigned to an *induced remission* group when symptoms resolved following corticosteroid therapy and successful discontinuation. In 116 patients assigned to a *recalcitrant* group, therapy could not be stopped for 1 month or more owing to severity of symptoms or lack of compliance. We defined relapse as a recurrence of symptoms of sufficient severity to warrant treatment with corticosteroids, following a remission without treatment lasting greater than 1 month.**
Intervention: **Patients who were judged to be sufficiently symptomatic to preclude observation without treatment or who failed to respond to conservative treatment with topical or inhaled corticosteroids or nonsteroidal anti-inflammatory agents were treated with systemic corticosteroids at a target dose of 20 mg prednisone per day for 1 year.**
Measurements and results: **We observed a 74% relapse rate in the induced remission group, but only an 8% relapse rate in the spontaneous remission group ($p<0.01$). Relapse occurred with similar frequency in whites and African-Americans (20% vs 28%), despite a lower treatment rate in white patients than in African-Americans (43% vs 76%; $p<0.01$). White patients maintained a sustained remission with twice the frequency of African-Americans (58% vs 29%; $p<0.01$). During relapse, 40% of chest radiographs showed no change in type, but there was a significant increase in interstitial profusion ($p<0.05$). Initial presentation with asymptomatic chest radiographic abnormalities, erythema nodosum, or peripheral adenopathy portended a favorable prognosis, with sustained remission in 60% of such patients lasting 130±226 months from time of diagnosis. In contrast, patients who presented with musculoskeletal complaints were nine times, and those with symptoms from hepatic involvement were three times more likely to suffer relapse than to sustain remission without receiving corticosteroids. Most relapses (50%) occurred between 2 and 6 months after discontinuing steroid therapy, but late relapse was not unusual, occurring more than 12 months after discontinuing steroid therapy in 20% of patients with induced remission.**
Conclusions: **Relapse occurred frequently in patients with sarcoidosis who had been treated with corticosteroids, and rarely occurred in patients who had not been treated with corticosteroids in the past. The striking difference in relapse rate between treated and untreated patients suggests that patients with disease that would later be severe and protracted were almost unerringly identified early in their course. One explanation is that severe presenting symptoms portend a protracted and recurrent course; an alternative explanation is that corticosteroids contributed to the prolongation of the disease by delaying resolution.** ***(CHEST 1997; 111:623-31)***

Key words: corticosteroids; outcome; relapse; sarcoidosis
Abbreviations: ACE=angiotensin-converting enzyme

*From the Departments of Medicine (Drs. Gottlieb, Israel, and Patrick) and Radiology (Dr. Steiner), Jefferson Medical College, Philadelphia.
Manuscript received July 12, 1995; revision accepted October 1, 1996.

Physicians treating patients with sarcoidosis have long been aware that a reduction in dose or termination of corticosteroid therapy is often followed by recrudescence of disease, and have there-

fore recommended adequate dosage and long duration of treatment.[1,2] According to one experienced physician, "spontaneous remissions of sarcoidosis are rarely followed by clinical exacerbation. Reappearance of clinical disease, however, is common when corticosteroids are withdrawn when the patient's disease remains active."[3] Despite the fact that relapse has been recognized as one of several common clinical patterns of sarcoidosis, there are little published data to support these clinical impressions, and relapse is not listed in the indexes of standard monographs on this disease.[3-8]

Having followed a general policy of prolonged treatment with corticosteroids, we noted in a retrospective study of activity markers[9] a frequency of relapse following remission that far exceeded our clinical impressions. To examine this phenomenon concurrently, a registry of patients with sarcoidosis at Thomas Jefferson University Hospital was instituted and the appropriate data analyzed to determine whether clinical relapse was related to the following factors: demographic characteristics, initial manifestations, duration of treatment, and chest radiographic changes. The purpose of this study was to enable clinicians to identify patients at high risk of relapse or to predict a benign course.

Materials and Methods

Patients with documented sarcoidosis who were examined during a 4-year period were enrolled in the registry, and hospital and office records of these patients were used as data sources. Documentation of the disease was based in most instances on demonstration of noncaseating granulomas found in biopsy specimens of the pulmonary parenchyma, lymph nodes, skin, conjunctiva, or liver. In asymptomatic patients, a diagnosis was made without biopsy only if a gallium scan demonstrated characteristic pulmonary uptake in the hila and extrapulmonary uptake in the lacrimal and salivary glands. In no instance was corticosteroid therapy initiated without tissue diagnosis.

At each office visit, the patients were examined and clinical evaluation of the presence, nature, and severity of symptoms was recorded. Chest radiographs, pulmonary function testing, and angiotensin-converting enzyme (ACE) activity were obtained as clinically indicated, but were not routinely performed on each patient at every visit. The initial manifestations of sarcoidosis that prompted the patient to seek medical attention were recorded and categorized according to major organ system involvement. If symptoms recurred, they were again characterized according to the predominant organ system involved.

Chest radiographs were read independently by at least two of the investigators, one of whom had no knowledge of the clinical status of the patients. When differences in scoring occurred between readers, the results were averaged. Radiographs were grouped according to type: type 0, no abnormality; type 1, hilar adenopathy only; type 2, hilar adenopathy and parenchymal abnormalities; and type 3, parenchymal abnormalities only. Within types 2 and 3, an estimate of the grading of parenchymal involvement was obtained using a profusion index.[10] The radiographic lower, middle, and upper lung zones were graded on the left and right for severity of pulmonary opacities: 0 (normal), 1 (slight), 2 (moderate), and 3 (severe); the sum of the scores for both lungs (possible range, 0 to 18 per radiograph) formed the profusion index.

The decision to begin systemic corticosteroid therapy was made in each instance by a single investigator (the same clinician for all of the patients) based on the following clinical criteria: presence of disabling or distressing symptoms of sarcoidosis of the upper or lower respiratory tract, including dyspnea, cough, or wheezing; disfiguring cutaneous sarcoidosis unresponsive to topical steroid or chloroquine therapy; diffuse myalgia or arthralgia unresponsive to nonsteroidal anti-inflammatory drug therapy; diffuse lymphadenopathy; and ocular manifestations unresponsive to topical steroid therapy. Patients with cardiac or CNS involvement were treated for any symptoms. Confirmation of symptoms was sought from physical examination, chest radiograph, pulmonary function, or biochemical laboratory testing. However, radiographic findings, pulmonary function testing, or ACE activities were not sufficient indication for corticosteroid treatment in the absence of compelling symptoms. Indeed, angiotensin-converting enzyme activities were infrequently repeated once a diagnosis of sarcoidosis had been made. Pulmonary function studies were not repeated routinely in the absence of symptoms, so that the number of patients with regular serial pulmonary function testing was too small to make analysis meaningful.

Corticosteroid treatment was initiated with a dose equivalent to 20 mg of prednisone daily; higher doses were used infrequently, and only after lower doses were found to be inadequate. Steroid therapy usually was continued for at least 1 year, and was then decreased slowly over several months to the equivalent of 5 mg of prednisone daily. Only when symptoms were stable with this dose was steroid therapy discontinued. Five patients subsequently treated with chlorambucil are included in the recalcitrant group because of their failure to respond to corticosteroid therapy or their intolerance to the medication. Several patients were treated with oral prednisone after topical corticosteroids failed to control ocular or cutaneous sarcoidosis, or after inhaled corticosteroids failed to improve respiratory symptoms. These "alternative" approaches were not, however, used routinely.

Of the 337 patients examined over the 4-year calendar period, 90 patients had been examined twice, 126 had been examined on three occasions, 80 on four occasions, and 41 on five or more occasions (Table 1). Medical and treatment history was documented for all patients from the time of diagnosis of sarcoidosis, and encompassed a mean of 110.3 months (range, 0 to 508 months) from initial diagnosis to first registry visit. Including the 4-year calendar period of repeated observation, mean follow-up from time of diagnosis was 129.8 months. Because all patients were evaluated at multiple time points, no patients were considered "lost" to follow-up.

One hundred three patients achieved complete remission of symptoms lasting more than 1 month following discontinuation of steroid therapy; they formed the *induced remission* group. To compare this population with patients whose symptoms did not initially require corticosteroids, we identified a second group of 118 *spontaneous remission* patients. This group consisted of patients with asymptomatic radiographic abnormalities or initial symptoms that were not judged of sufficient severity to warrant treatment; the criteria for treatment are listed above. The purpose of highlighting these two groups was to explore the possible impact of corticosteroid treatment by comparing two groups of stable, asymptomatic patients with sarcoidosis, only one of which had been treated. The remaining 116 patients belonged to neither group, as became evident over the course of the study; they comprised a clinically heterogeneous group of patients who manifested recalcitrant disease that required steroid treatment

Table 1—*Patient Characteristics**

	Induced	Spontaneous	Recalcitrant	Total
Patients, No.	103	118	116	337
Relapse, No. (%)	76 (74)†	10 (8)†	0	86 (26)
Age, yr (SD)	42.4 (12.1)	40.6 (12.1)	42.5 (12.2)	41.9 (12.2)
African-Americans, No. (%)	75 (73)‡	49 (42)‡	91 (78)	215 (64)
Male, No.	20	11	23	54
Female, No.	55	38	68	161
White, No. (%)	28 (27)‡	69 (58)‡	25 (22)	122 (36)
Male, No.	9	36	12	57
Female, No.	19	33	13	65
Visits, No. (SD)	3.4 (1.0)	2.8 (0.8)	3.5 (1.0)	3.2 (0.9)
Months from dx, No. (SD)	124.1 (107.6)	92.9 (92.8)	114.5 (93.5)	110.3 (96.7)
	Relapse	**Sustained**	**Recalcitrant**	**Total**
Patients, No.	86	135	116	337
Relapse, No. (%)	86 (100)	0	0	86 (26)
Age, yr (SD)	42.8 (10.8)	40.7 (13.0)	42.5 (12.2)	41.9 (12.2)
African-Americans, No. (%)	61 (71)‡	63 (47)‡	91 (78)	215 (64)
Male, No.	14	17	23	54
Female, No.	47	46	68	161
White, No. (%)	25 (29)‡	72 (53)‡	25 (22)	122 (36)
Male, No.	8	37	12	57
Female, No.	17	35	13	65
Visits, No. (SD)	3.5 (1.1)	2.7 (0.7)	3.5 (1.0)	3.2 (0.9)
Months from dx, No. (SD)	112.9 (92.0)	101.9 (105.6)	114.5 (93.5)	110.3 (96.7)

*Upper panel: characteristics of patients among induced remission, spontaneous remission, or recalcitrant groups. There was a significantly greater proportion of relapses, and a greater proportion of African-Americans from the induced remission group compared to the spontaneous remission group. Lower panel: characteristics of patients who suffered relapse or sustained remission, or remained with recalcitrant disease. There was a significantly greater proportion of African-Americans among the group with relapse than among those who had sustained remission. Dx=diagnosis.

†$p<0.01$.

‡$p<0.05$.

throughout the study period, or whose symptoms recurred as a result of noncompliance or reduction in dosage (Fig 1).

Clinical *relapse* was defined as a return of clinical manifestations severe enough to warrant treatment, following a sustained (longer than 1 month) remission of symptoms without administration of corticosteroids. Thus, patients with relapse were identified only from the 103 *induced remission* and 118 *spontaneous remission* patients. Patients who had suffered relapse prior to or during the 4 years of the prospective study period comprised the major focus of this investigation.

Statistical Analysis

Differences in proportions between and within each group were compared using the χ^2 statistic. Mean values were compared using Student's *t* test or, where multiple comparisons were made, using a one-way analysis of variance with Bonferroni's correction factor; p values of less than 0.05 were considered significant.

Results

Three hundred thirty-seven patients were enrolled in the sarcoidosis registry over a 4-year period. One hundred three of these were judged to have had an *induced remission* lasting longer than 1 month following cessation of treatment; corticosteroid therapy had been discontinued by the treating physician. Of these, 76 developed clinical relapse, yielding a relapse rate of 74% in patients with induced remission who were examined during the 4 years of the study period. One hundred eighteen of the total group had remission of symptoms without treatment with corticosteroids; of these, only 10 suffered relapse, yielding a relapse rate of 8% ($p<0.01$, induced vs spontaneous remission). Mean age, total duration of sarcoidosis, and number of visits were similar in the induced and spontaneous remission groups; demographic differences are described in Table 1.

African-American patients comprised 64% of the entire study population and were treated significantly more frequently than whites. Eighty percent of African-American men and 75% of African-American women received corticosteroids, in contrast to only 37% of white men and 48% of white women ($p<0.01$, African-American vs white). Of the total study population, relapse occurred in 29% of African-American women, 26% of white women, and 26% of African-American men, but in only 14% of

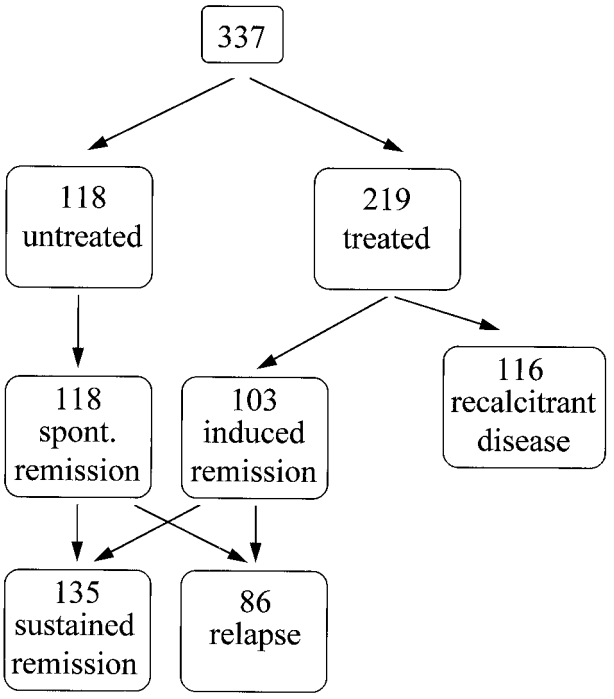

FIGURE 1. Flow chart illustrating initial categorization based on decision to treat, attainment of remission, and sustenance of remission or relapse. For details, see text.

white men ($p<0.05$, percent relapse in white men vs African-American men or women or white women).

Complaints referable to the lower respiratory tract were the most frequent initial manifestation of sarcoidosis in our patients, and were found in 97 patients on presentation. Initial manifestations for the remainder of the patients were as follows: uveitis in 65; referral for abnormal chest radiographs without symptoms in 53; cutaneous lesions in 22; erythema nodosum in 18; musculoskeletal problems including arthritis and myopathy in 10; generalized symptoms including fever and malaise in 11; and "other" comprising a diverse group of patients with peripheral adenopathy, hypercalcemia, CNS, cardiac, upper respiratory, or hepatic abnormalities in the remaining 61 patients (Table 2). Relapse was extrapulmonary in 35 of 86 patients who suffered relapse. Overall, there was "discordance" between initial manifestations and manifestations of relapse (pulmonary vs extrapulmonary) in 35% (30/86) of patients.

The distribution of presenting complaints was different in patients who suffered relapse from those who sustained remission ($p<0.05$). Patients who presented with musculoskeletal manifestations had a greater likelihood of relapse than did all other groups (Table 2), whereas patients who presented with asymptomatic radiographs were likely to have sustained remission. Other patterns of initial manifestation including peripheral adenopathy, erythema nodosum, and uveitis showed trends toward favorable outcome (sustained remission), but p values were all >0.05 and <0.10.

By dividing the likelihood of relapse by the likelihood of sustaining a remission for each initial manifestation, a likelihood ratio of relapse was calculated.[11] This ratio is analogous to a "relative risk" of relapse following remission based on each initial manifestation of sarcoidosis (Fig 2). The purpose of

Table 2—*Distribution of Initial Manifestations Among Patients With Relapse, Sustained Remission, or Recalcitrant Disease**

	Relapse No. (%) (n=86)	Sustained, No. (%) (n=135)	Recalcitrant, No. (%) (n=116)	Total, No. (%) (n=337)	p Value
Cardiac	1 (1)	0 (0)	0 (0)	1 (0)	>0.10
Upper respiratory	1 (1)	4 (3)	1 (1)	6 (2)	>0.10
Parotid/lacrimal	2 (2)	2 (1)	3 (3)	7 (2)	>0.10
Hepatic	4 (5)	2 (1)	2 (2)	8 (2)	>0.10
CNS	2 (2)	3 (2)	4 (4)	9 (3)	>0.10
Musculoskeletal	6 (7)	1 (1)	3 (3)	10 (3)	0.01
General	2 (2)	4 (3)	5 (4)	11 (3)	>0.10
Nodes	1 (1)	8 (6)	3 (3)	12 (4)	0.06
Erythema nodosum	3 (3)	11 (8)	4 (4)	18 (5)	0.06
Other	2 (2)	11 (8)	5 (4)	18 (5)	>0.10
Cutaneous	5 (6)	7 (5)	10 (9)	22 (7)	>0.10
Asymptomatic cxr	13 (15)	32 (24)	8 (7)	53 (16)	0.002
Uveitis	20 (23)	20 (15)	25 (23)	65 (19)	0.09
Lower respiratory	24 (28)	30 (22)	43 (38)	97 (29)	0.02

*Patients who presented with musculoskeletal manifestations were more likely to develop relapse than were other presentations, and patients with asymptomatic radiographic changes had a higher likelihood of sustained remission. Lower respiratory tract symptoms were associated with a high likelihood of recalcitrant disease. Peripheral (nodes), erythema nodosum, and uveitis as presenting complaints trended toward decreased likelihood of relapse, but $0.05<p<0.10$. Cxr=chest radiograph.

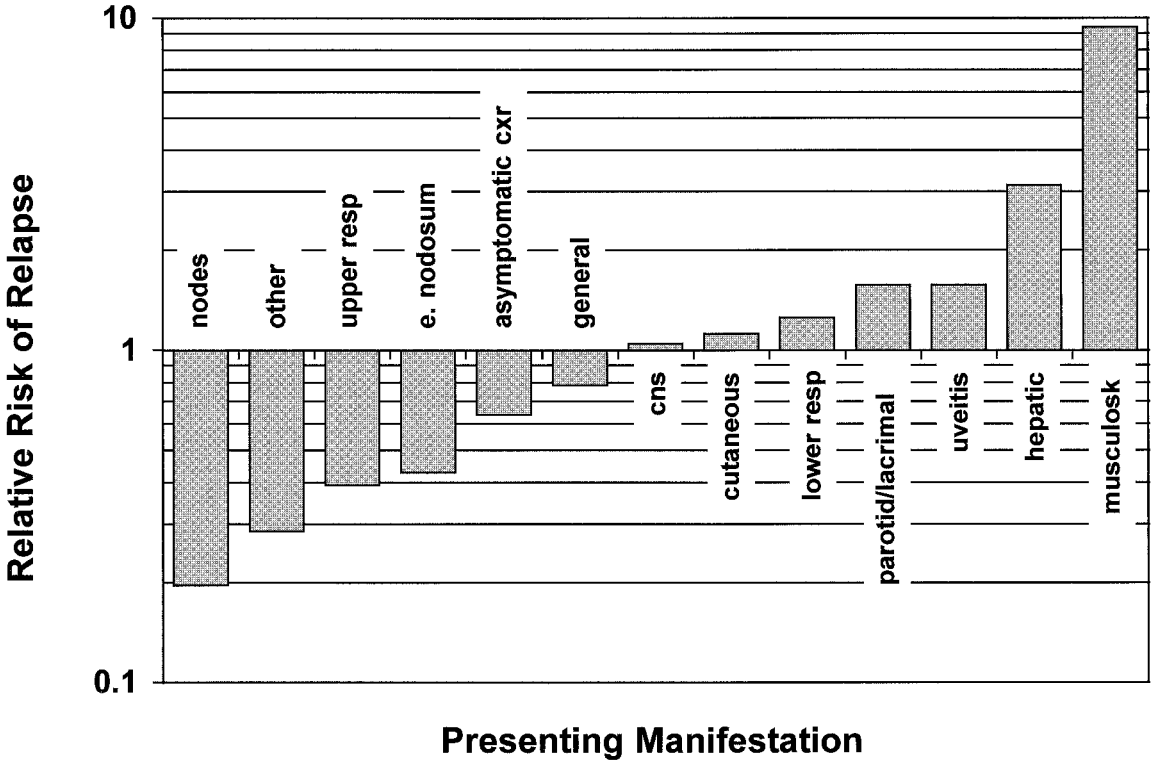

FIGURE 2. Column plot demonstrating "relative risk" of developing relapse based on initial presentation of sarcoidosis. Only increased risk associated with musculoskeletal manifestations was significant. For details, see text.

expressing the risk in this manner is to provide the clinician with a likelihood of successfully maintaining remission without steroids once the patient has had a trial of discontinuation of treatment. Only patients with musculoskeletal manifestations, as noted above, had a statistically significantly increased chance of relapse, however. For initial manifestations with a likelihood ratio near unity, such as lower respiratory complaints, cutaneous or generalized manifestations, the probability of developing relapse was similar to sustaining remission.

Chest radiographs at the time of initial diagnosis of sarcoidosis revealed that 45% presented with type 1 radiographs, in contrast to only 8% with type 0. Types 2 (29%) and 3 (17%) occurred at presentation with intermediate frequency. Sixty-six percent of patients with type 1, 80% with type 2, and 71% with type 3 chest radiographs at time of initial diagnosis received treatment with corticosteroids; these proportions were not significantly different from one another. However, only 50% of patients with type 0 radiographs had symptoms that required treatment ($p<0.05$, type 0 vs types 1, 2, or 3).

In patients who developed relapse, chest radiographs immediately before relapse were approximately evenly distributed among types 0, 1, 2, and 3 (Fig 3). During relapse, the distribution of radiographs shifted away from types 0 and 1 and toward types 2 and 3, but the change was not significant. These changes largely resolved after treatment for relapse. Within types 2 and 3 (those types associated with parenchymal abnormalities), there was a significant increase in profusion index without moving between types ($p<0.05$). Overall, 60% of patients developed increase in type or profusion index during relapse. Conversely, 40% of patients showed no change in their chest radiograph during clinical relapse.

In 15 patients, ACE activity had been measured within 2 months of relapse, during relapse, and following institution of corticosteroid treatment. Overall there was a mean increase of 9.5 ± 17.1 U during relapse. The change in ACE activity with corticosteroid treatment was more profound, with a mean decrease of 34 ± 13.7 U (Fig 4). Although these changes were significant ($p<0.05$), it should be noted that ACE activity fell during relapse in three patients (20%).

Patients who suffered relapse had been treated for an average of 47.9 ± 36.4 months, with a target regimen of 20 mg of prednisone a day. Patients with recalcitrant disease had been treated significantly

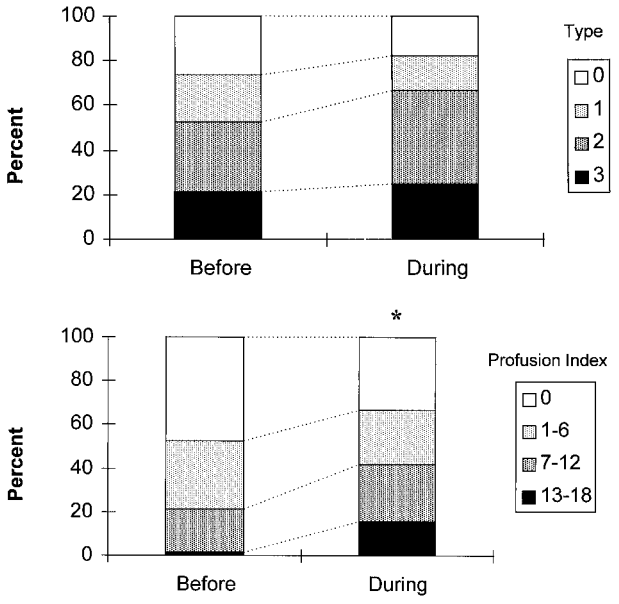

FIGURE 3. Bar graph representing change in radiographic type immediately before and during relapse. Patients were approximately equally distributed among the four types before relapse (left bar, *top*), with a trend toward increase in types 2 and 3 during relapse that did not reach significance (right bar, *top*). Profusion indexes shifted from lower scores before relapse (left bar, *bottom*) to higher scores during relapse (right bar, *bottom*, $p<0.05$, before vs during relapse). Fully 40% of patients showed no change in radiograph during relapse. For details, see text.

longer (54.9 months, $p<0.05$) at the time of their first clinic visit. Following cessation of therapy, relapse occurred within 6 months in more than one half of patients (Fig 5). However, "late" relapse was also seen, with 20% of relapses occurring more than a year after discontinuing steroid therapy and 10% after 2 years without steroid therapy. Although the duration of therapy and the interval between the cessation of steroid therapy and relapse varied widely (1 to 150 months), there was no clear relationship between the two. This suggests that longer treatment did not result in longer relapse-free interval.

DISCUSSION

Following cessation of corticosteroid therapy for longer than 1 month in patients judged to have had adequate treatment for sarcoidosis, 74% developed clinically significant relapse. In contrast, relapse was unusual in patients who had never been treated with steroids. When relapse occurred, it frequently involved organ systems other than those involved at initial presentation of sarcoidosis.

Our findings are consistent with a limited study of clinical relapse in patients with sarcoidosis during corticosteroid therapy withdrawal.[12] Although methods and definitions were different from our own, 67% of patients suffered relapse in that study, compared with our 74%. Small sample size (15 patients) and different methods preclude direct comparisons; entry criteria in their study restricted chest radiographs to types 2 and 3. Johns and coauthors[13] also calculated a 75% likelihood of one or more relapses following corticosteroid therapy withdrawal in a series of 181 patients, although details of definitions and criteria were not provided. These authors stressed a 93% concordance between initial manifestations and long-term outcome or asymptomatic outcome. We emphasized the "other side of the coin;" although the majority of all patients demonstrated such concordance, in the group of patients who met our definition of relapse, involvement of previously uninvolved organ systems was common. It should be noted that frequency of relapse of sarcoidosis also appears to be high following withdrawal of chlorambucil therapy.[14]

A more recent study of the outcome of sarcoidosis in 98 patients concluded that simple clinical criteria, including pulmonary function tests and symptoms of extrapulmonary disease, can be used effectively to guide treatment decisions.[15] Of 55 patients without prior treatment, six (11%) suffered relapse requiring corticosteroids; two additional patients unavailable for follow-up may have increased the rate to 15%. In contrast to our population, only 5 of 37 treated patients (14%) subsequently suffered relapse after discontinuation of steroid therapy. Several factors may account for these differences. First, our patients were treated only for compelling symptoms, and not for asymptomatic deterioration in results of pulmonary function testing. Using the latter criteria for treatment decisions may have selected a group with less severe illness for treatment. Second, our period of follow-up was longer (10 years vs 2), increasing our ability to detect relapse. Third, 64% of our patients were African-American, in contrast to 15% or less, suggesting greater severity in our population. Finally, our patients with relapse had been treated for an average of 55 months, in contrast to 12. This feature could also indicate greater severity of disease, in that long duration of treatment was judged to be clinically indicated by symptoms.

A patient with recurrent sarcoidosis was described by Badrinas and colleagues,[16] with three recrudescences of sarcoidosis involving different organ systems over a 9-year span. This patient presented with erythema nodosum, a manifestation we found to have a low likelihood of relapse. Unlike our study population of patients with relapse, none of these exacerbations was severe enough to require systemic corticosteroid treatment, and the patient recovered spontaneously following each episode.

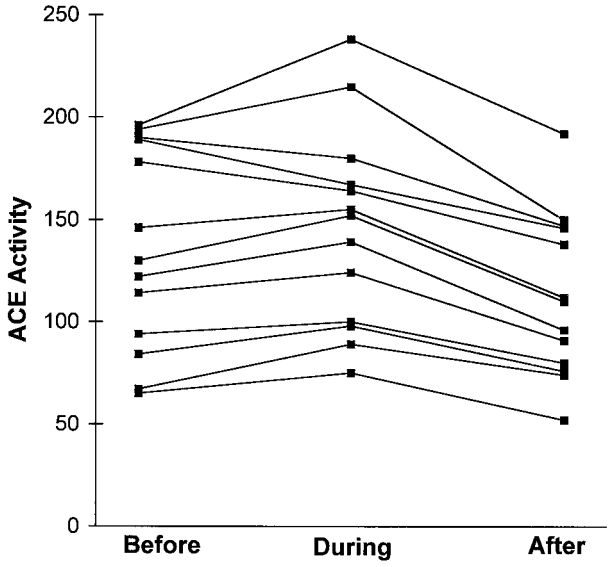

FIGURE 4. ACE activity obtained within 2 months before relapse in 15 individual patients, at time of relapse, and within 6 months following treatment with 20 mg prednisone. There is a small but significant increase in ACE activity during relapse, and a significant fall with corticosteroid treatment ($p<0.05$, before vs during and $p<0.05$, during vs after).

An obvious explanation for this high frequency of relapse in our *induced remission* patients is that we selected for treatment those patients whose course was to be chronic and severe. There are several reasons, however, to question this explanation.

For example, African-American patients were treated with twice the frequency of whites, because of greater severity of symptomatic disease; the difference in severity of sarcoidosis between African-American and white patients is well established.[10] Despite this known difference in severity, the relapse rate among adequately treated patients was similar in African-American patients and whites. Because African-American patients would be expected to have a more severe course, the similar relapse rates suggest that some other factor overshadowed racial differences.

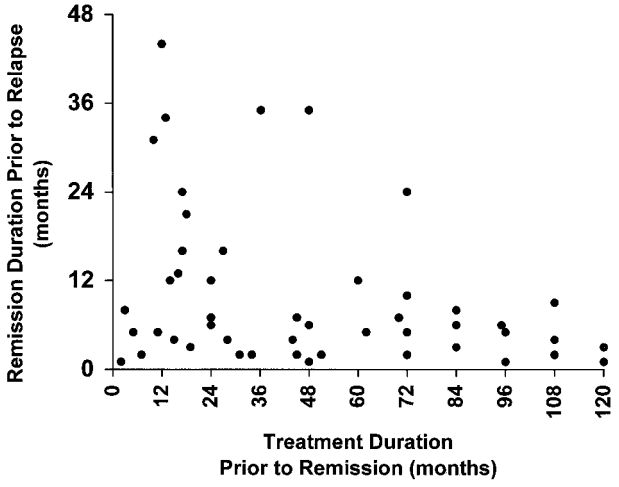

FIGURE 5. Scatter plot of duration of therapy vs interval between cessation of steroid therapy and appearance of relapse for individual patients. There was no relationship between duration of therapy and interval before relapse (p value>0.10 for Pearson's correlation coefficient). Seventeen additional patients not plotted had remission duration >48 months or treatment duration before relapse >120 months.

Could our findings have been the result of treating patients with more advanced disease, so that gradual and inexorable progression of disease was interpreted as relapse? We think not, because patients with radiographic types 1, 2, and 3 were treated with similar frequency, so that patients with more "advanced" or fibrotic disease were not treated disproportionately. Furthermore, relapse frequently involved organ systems not originally involved at presentation, indicating that relapse was not simply progression of organ dysfunction due to granulomatous inflammation or fibrosis, but was rather a recrudescence involving previously uninvolved systems.

If selection bias were the explanation for the high relapse rate in treated patients, we would have had to have been almost unerring in treating only those patients destined to have chronic relapsing pulmonary or extrapulmonary disease. In effect, our clinical assessment would have succeeded where other tests of "activity" such as BAL, ACE activity, or gallium scanning have failed.[9,15,17-19] Therefore, either our determination of symptom activity (and need for treatment) stands out as a unique and highly accurate predictor of tendency to suffer relapse, or some other factor explains the relationship between treatment and relapse.

We suggest that an alternative explanation cannot be excluded: that corticosteroid treatment itself, rather than the need for treatment, contributed to the propensity for relapse. There is indeed some support for this hypothesis from the observations of others. Eule and coauthors[20] randomized a group of 182 asymptomatic patients with sarcoidosis to receive 6 or 12 months of corticosteroid therapy, or no therapy. Following a mean observation period of 8.9 years, they found no differences in tests of lung function between the two groups. However, they noted that 22% of the treated group needed to be treated with corticosteroids for relapse once treatment with the medication was tapered, whereas only 13% of the untreated group required subsequent treatment due to relapse or disease progression. Unlike our patients, these patients were identified from screening chest radiographs and were asymptomatic, making comparison to our own study diffi-

cult. Nevertheless, it is intriguing that in this randomized group, steroid treatment may have resulted in a higher relapse rate; their sample size was too small to yield differences of statistical significance.

Similar findings were reported by Izumi[21] in 185 asymptomatic patients with sarcoidosis over a 10-year period. Of the 63 treated patients (prednisolone at least 20 mg/d for more than 3 months), 24% demonstrated persistent radiographic abnormalities 10 years later, compared with only 8% of the untreated group. These differences were even more striking in a subgroup of 101 asymptomatic patients whose sarcoidosis was diagnosed radiographically before age 30 years. Twenty-seven percent of the treated group (n=30), in contrast to only 3% of the untreated group (n=71), demonstrated persistent radiographic abnormalities at 10 years following diagnosis.

The British Thoracic Society sarcoidosis study recently reported their results in 149 patients followed up for 5 years.[22] Patients were initially classified by symptoms requiring prednisolone treatment or by radiographic findings. Thirty-three required treatment for symptoms at study entry, and 15 were still receiving treatment an average of 3 years later. Fifty-eight showed initial radiographic clearing and no compelling symptoms; these patients were observed and only one required subsequent steroid treatment. The remaining 58 patients, whose radiographs did not clear over the initial 6 months, were randomized to receive either long-term treatment to normalize radiographs, or selective treatment based on symptoms or deteriorating lung function. Five of 25 patients treated in the long-term group, and four of six patients treated in the selective group were still taking steroids at final assessment. Expressed differently, only 5 of 89 patients not initially treated subsequently required corticosteroids, in contrast to 20 of 58 patients initially treated with prednisolone ($p<0.0001$). Patients randomized to long-term treatment showed a 10.4% improvement in vital capacity, whereas patients in the selectively treated group showed only a 2.6% improvement over the 5-year period ($p<0.05$). No significant differences in FEV_1 or diffusing capacity for carbon monoxide were seen.

This patient population differs from our own in several respects. First, only 9 of the 149 (6%) were nonwhite, compared with our 64%. Second, treatment decisions were based not only on symptoms, but also on radiographic appearance, whereas we did not use radiographic findings to guide treatment. In one important respect, the two studies are in agreement: initial treatment with corticosteroids for compelling symptoms of sarcoidosis is associated with subsequent requirement for treatment, and observation without initial treatment is associated with a low subsequent need for treatment. In the British Thoracic Society study, only 5 of 25 (25%) patients randomized to receive steroids long term continued to receive treatment at 5 years, suggesting a lower relapse rate than would be predicted from our findings (74%). Differences in indications for treatment, patient populations, and definitions may explain the apparent contrast. Neither study was designed to address the question of a causal link between corticosteroids and relapse in sarcoidosis, and neither study, we believe, settles the issue.

In summary, 74% of patients who were adequately treated with systemic corticosteroids for severe symptoms of sarcoidosis appeared to be at lifetime risk for recurrence of disease. Because of the risk of relapse, we recommend at least semiannual visits for those patients who are or who have been treated with systemic corticosteroids. Prior to instituting such therapy, consideration may be given to a period of observation. Our uncontrolled experience suggests that nonsteroidal anti-inflammatory agents or inhaled or topical steroids may be effective in some instances, although there is only anecdotal evidence to support this approach. If corticosteroids predispose to clinical relapse, the implication would be to withhold treatment from patients with newly diagnosed sarcoidosis unless symptoms and disability were compelling, and a similarly conservative approach would be appropriate during relapse. Although the answer to whether corticosteroid therapy prolongs the course of disease remains uncertain, the results of the present study add to the growing body of evidence suggesting that this potential risk be considered in treatment decisions.

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Two-year prognosis of Sarcoidosis: the ACCESS experience

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Abstract. A cohort of 215 Sarcoidosis patients from the ACCESS study underwent a clinical evaluation at study enrollment and two years later. Approximately 80% of subjects had an improved or stable FVC, FEV1 chest radiograph determined by Scadding stage, and dyspnea scale. African Americans had less improvement in FVC than Caucasians (p = 0.04). Patients with erythema nodosum at presentation were more likely to have improvement in the chest radiograph at two-year follow-up (p = 0.007). Patients with a lower annual family income were more likely to worsen with respect to dyspnea (p = 0.01) and more likely to have new organ involvement at two-year follow-up (p = 0.045). The development of new organ involvement over the two-year follow-up period was more common in African Americans compared to Caucasians (p = 0.002) and more likely in those with extra-pulmonary involvement at study entry (p = 0.003). There was an excellent concordance between changes in FVC and FEV1 over the two-year period. However, changes in FVC alone were inadequate to describe the change in pulmonary status of the patients, as changes in chest radiographic findings or the level of dyspnea did often but not always move in the same direction as FVC.
In conclusion, data from this heterogeneous United States Sarcoidosis population indicate that Sarcoidosis tends to improve or remain stable over two years in the majority of patients. Several factors associated with improved or worse outcome over two years were identified. (*Sarcoidosis; Vasc Diffuse Lung Disease 2003*; 20; 204-211).

Key Words. Sarcoidosis. Prognosis. Spirometry. Chest radiograph. Dyspnea.

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Introduction

Sarcoidosis is a multi-system granulomatous disease of unknown cause. The disease has a variable clinical course from an asymptomatic state to a progressive life- threatening illness [1]. The prognosis of Sarcoidosis is affected by clinical [2-4], radiographic [5-8], genetic [9], and racial [4] factors. Corticosteroid therapy may also affect the prognosis of Sarcoidosis [6,10,11].

The National Heart, Lung, and Blood Institutes' - sponsored study entitled A Case Control Etiologic Study of Sarcoidosis (ACCESS) examined patients with Sarcoidosis at 10 centers within the United States [12]. A cohort of Sarcoidosis patients who were enrolled in ACCESS was reexamined two years after study entry to assess their clinical status. This report describes the two-year prognosis of the follow-up ACCESS cohort.

Methods

We reassessed a cohort of 215 consecutive ACCESS cases 2 years after initial enrollment. Because clinical data was collected in the ACCESS study for only 3 years, two-year follow-up data could only be obtained from subjects enrolled in the first year of ACCESS, and therefore only these subjects were eligible for enrollment. All cases enrolled were required to have had a tissue biopsy demonstrating noncaseating granulomas within six months of enrollment. We excluded known causes of granulomatous inflammation by demonstration of negative stains of the biopsy specimens for mycobacterial and fungal organisms and negative polarized light examination for particulate matter. As part of ACCESS, all cases had data collected concerning their demographic characteristics; socioeconomic status, spirometry, chest radiograph results, extent of extrapulmonary involvement with Sarcoidosis [13], and a 5 point dyspnea scale modified from Watters *et al* [14]. Chest radiographs were classified by Scadding stages: 0- normal chest radiograph, 1- bilateral hilar adenopathy with normal lung parenchyma, 2- bilateral hilar adenopathy with pulmonary infiltrates, 3- pulmonary infiltrates without hilar adenopathy, 4- pulmonary fibrosis/fibrocystic parenchymal changes [15].

For each patient in the cohort, we defined "improved" and "worse" at the follow-up measurement as listed in *Table 1*. Measurements that did not meet criteria for improvement or worsening were defined as "unchanged." The following characteristics were evaluated that might confound the prediction of outcome: ever smoked (yes, no), currently smoking (yes, no), annual family income ($5,000- $9,999, $10,000 - $19,999, $20,000 - $29,999, $30,000 - $39,999, $40,000 $49,000, >$50,000), erythema nodosum (yes, no), splenic involvement (yes, no), use of corticosteroids at ACCESS entry (yes, no), use of corticosteroids at 2 year follow-up (yes, no), health insurance limited (yes, no), could not get health care (yes, no), seen by a specialist (yes, no), missed appointments (yes, no), takes medication (all of the time, not all of the time), could not get medication (yes, no), feels medication can control Sarcoidosis (very confident, somewhat confident, not confident, not taking medication).

Statistical Methods: The statistical elements of change were categorized into a trichotomous outcome representing the patients' condition as: improved, unchanged, or worsened. These categorical outcomes were compared to categorical demographic and clinical characteristics that represented the patients' initial state. The distribution of improvement is presented using point estimates of the three percentages representing the categories of improved, unchanged, and worsened. All comparisons were accomplished using p- values from Chi Square Statistic. Critical p- values were considered 0.05 and were reported from the SAS statistical software.

Results

A total of 251 cases of the 740 ACCESS cases were enrolled in the first year of ACCESS and therefore asked to return for the two-year follow-up visit and gave their consent. Three of these cases were determined to be ineligible when the eligibility of all cases was reviewed during the second year of ACCESS enrollment. Of the remaining 248 cases, 215 completed the two-year follow-up visit and are the subject of this report. There were no significant demographic differences between the patients who returned for the two-year follow-up and those who did not (data not shown).

Table 1: ***Definitions of change in clinical status compared to enrollment***

PARAMETER	IMPROVED	WORSE	UNCHANGED
FVC	≥10% increase	≥ 10% decrease	*
FEV1	≥10% increase	≥10% decrease	*
CXR	≥1decrease in Scadding stage	≥1 increase in Scadding stage	*
Dyspnea Scale	≥1 decrease in dyspnea scale	≥1 increase in dyspnea scale	*

FVC: Forced vital capacity. FEV1: Forced expiratory volume in 1 second, CXR: Chest radiograph., *Neither improved or worse

Table II lists the demographic data concerning the cohort. Of the 215 patients, all had repeat evaluations of organ involvement and completed another dyspnea scale. One hundred and ninety-three had repeat spirometry, and 205 had follow-up chest radiographs. The mean length of time between ACCESS enrollment and the follow-up visit was 25.2 + 0.1 months with a median of 25 months.

Table II: ***Patient characteristics, N=215***

		N	%
Race			
	Caucasian	ll7	54.4
	African American	93	43.2
	Other	5	2.3
Gender			
	Male	70	32.6
	Female	145	67.4
Age	**<40 Years**	101	47.0
	>40 Years	114	53.0

Table III shows the change in the clinical parameters of FVC, FEV1, Scadding stage of chest radiograph, and dyspnea scale between ACCESS enrollment and the two-year follow-up. For each measurement, approximately twice as many patients had improvement as had worsening. **FVC, FEV1, Scadding stage, and the dyspnea scale remained unchanged over the two-year period in the majority of the patients.**
A total of 11 of 176 (6%) with Scadding stage 0, 1, or 2 chest radiographs progressed to stage 3 or 4 over the two-year follow-up period (data not shown).

Table III: ***Distributions of clinical outcomes***

	IMPROVED	UNCHANGED	WORSE
FVC	20.5% (44)	57.7% (124)	11.6% (25)
FEV1	21.9% (47)	56.7% (122)	11.2% (24)
CXR	37.7% (81)	41.4% (89)	16.3% (35)
DYSPNEA	19.5% (42)	67.0% (144)	13.5% (29)

Table IV shows the relationship of the change in FVC to the change in FEV1 over the two-year follow-up. Changes in FVC and FEV1 were discordant (better vs worse) in no patients and were concordant in 80.3% (155/193).

There was no effect of gender or age on FVC, FEV1 Scadding stage or dyspnea scale (data not shown), but African Americans had less improvement in FVC compared to Caucasians (*Table V*). Patients with worsening dyspnea over the two years were more likely to have one or more new organs involved with Sarcoidosis (p = 0.013) (*Table VI*).

Several patient characteristics (see methods section) were analyzed and some of these were associated with prognosis (*Table VII*). Patients with erythema nodosum at presentation were more likely

Table IV: ***Comparison of FEV1 outcomes to FVC outcomes***

	FVC IMPROVED	FVC UNCHANGED	FVC WORSE
FEV1 improved	17.1% (33)	7.3% (14)	0
FEV1 unchanged	5.7% (11)	53.9% (104)	3.6% (7)
FEV1 worse	0	3.1% (6)	9.2% (18)

to have improvement in the chest radiograph at follow-up (p = 0.007). Patients with a lower annual family income were more likely to worsen with respect to dyspnea (p = 0.01) and more likely to have new organ involvement at follow-up (p= 0.045).

The relationships of corticosteroid use to FVC and dyspnea were complicated. Patients taking corticosteroids at follow-up tended to be improved or worsened with respect to FVC and dyspnea more

often than those not taking corticosteroids (*Table VII*). Ninety-five out of 205 (46%) patients were not taking corticosteroids at enrollment and 75 of these 95 (79%) never received corticosteroids over the two-year follow-up. One hundred and ten of the 205 (54%) patients were receiving corticosteroids at enrollment and 52 (47%) were maintained on corticosteroids throughout the two years of follow-up.

Fifty of the 215, (23% a) of patients, developed one or more new organs involved with Sarcoidosis over the two-year follow-up period. These fifty patients developed a total of 67 new organs involved with Sarcoidosis (*Table VIII*). The skin was the most frequent new organ involved with Sarcoidosis over the two-year follow up. *Table IX* shows the development of new organ involvement in terms of race, sex, and age. No consistent patterns are observed, although African Americans may have had more frequent development of skin involvement than Caucasians.

Table V: ***Change in disease status by race***

	CAUCASIAN			**AFRICAN AMERICAN**			
	(N=17)			(N=93)			
	N	n	%	N	n	%	p-val
Dyspnea	117			93			
Improved		23	19.6		18	19.3	
Unchanged		80	68.3		62	66.6	
Worse		14	11.9		13	13.9	0.910
FEV1	107			86			
Improved		23	21.4		24	27.9	
Unchanged		75	70.0		47	54.6	
Worse		9	8.4		15	17.4	0.056
FVC	107			86			
Improved		20	18.6		24	27.9	
Unchanged		77	71.9		47	54.6	
Worse		10	9.3		15	17.4	0.040
Chest X-ray	110			90			
Improved	46	41.8			31	34.4	
Unchanged	49	44.5			39	43.3	
Worse	15	13.6			20	22.2	0.246

•p value from a Chi square or F-test statistic comparing

distributions among the 2 groups.

Table X shows that development of new organ involvement in the follow-up period was more common in African Americans compared to Caucasians and in those with extra-thoracic organ involvement at baseline. However, development of new organ involvement was not affected by gender or age.

Discussion

The prognosis of Sarcoidosis is variable and is difficult to predict in an individual patient. Several studies have found associations between various clinical, biochemical, and genetic factors and the prognosis of Sarcoidosis. Most of these studies have involved relatively homogeneous populations of one racial or ethnic group. In ACCESS, we examined a relative large population of Sarcoidosis patients in the United States with a diverse mix of socioeconomic status and ages, an adequate representation of both genders, and the Caucasian and African American races [16]. The cohort of 215 ACCESS patients who underwent two-year follow-up was similarly diverse.

Although end-stage pulmonary Sarcoidosis usually develops over one or two decades [17], this assessment of the clinical status of the patient at two years has important prognostic implications. In one

Table VI: ***Relationship or changes in clinical measurements***

	IMPROVED		**UNCHANGED**		**WORSE**		**P-VALUE**
A.CHANGE IN FVC	N	%	N	%	N	%	
Scadding Stage							
Improved	18	24.0	51	68.0	6	8.0	
Unchanged	17	20.7	54	65.8	11	13.4	
Worse	5	7.2	17	58.6	7	24.1	0.285
Dyspnea							
Improved	10	27.8	23	63.9	3	8.3	
Unchanged	27	20.6	86	65.6	18	13.7	
Worse	7	26.9	15	57.7	4	15.4	0.763
Number of New Organs							
None	28	19.3	97	66.9	20	13.8	
One or more	16	33.3	27	56.2	5	10.4	0.131
B. CHANGE IN							

DYSPNEA							
Scadding Stage							
Improved	14	17.3	52	64.2	15	18.5	
Unchanged	17	19.1	61	68.5	11	12.3	
Worse	**7**	20.0	25	71.4	3	8.6	0.660
Number of New Organs							
None	32	19.5	116	70.7	16	9.7	
One or more	10	19.6	28	54.9	13	25.5	0.013

cohort of 193 Sarcoidosis patients [2], only 22% had persistent disease two years after diagnosis, and only an additional 5% of this cohort had disease resolution over the subsequent three years. Therefore most patients with persistent disease at two years were unlikely to have resolution of Sarcoidosis.

We found that more than 80% of patients with Sarcoidosis have improvement or stability of spirometry, chest radiographic findings, and dyspnea over the two-year period after diagnosis.
The resolution was not statistically related to whether the patients did or did not receive therapy. These data are similar to other studies in homogeneous populations of Sarcoidosis patients. Romer [5] found that only 13% (27/210) of Danish Sarcoidosis patients had radiographic progression over a mean of 5.5 years. Other authors have noted a similar good prognosis. Chappell and coworkers [81] showed that 75% (112/150) of patients with Sarcoidosis referred to a single medical consultant in New South Wales had resolution of stage I or 11 chest radiographs over a two-year period. Nagai and colleagues [18] showed that 68% of chest radiographs of Japanese Sarcoidosis patients cleared within 3 years. Mana and coworkers [2] found that only 22%a (35/193) had persistence of Sarcoidosis at two years as assessed by clinical features, chest radiographic findings, spirometric

Table VII: Patient characteristics associated with clinical measurements

		OUTCOME			
MEASUREMENT	**PATIENT CHARACTERISTICS**	**IMPROVED**	**UNCHANGED**	**WORSE**	**P - Value**
FVC					
	Follow-up Corticosteroids				
	Yes	27 (26%)	59 (57%)	18 (17%)	0.04
	No	17 (l9%)	65(73%)	7 (8%)	

Scadding Stage					
	Erythema Nodosum				
	Yes	17 (68%)	5 (20%)	3 (12%)	0.007
	No	64 (36%)	84 (47%)	32 (18%)	
Dyspnea					
Annual Family Income					
5,000-9,999	3 (17%)	9 (50%)	6 (33%)		0.01
10,000-19,999	7 (27%)	19 (73%)	0 (0%)		
20,000-29,999	6 (29%)	11 (52%)	4 (19%)		
30.000-39,999	6 (24%)	12 (48%)	7 (28%)		
40,000-49,999	3 (11%)	20 (74%)	4 (15%)		
≥50,000	16 (17%)	70 (75%)	7 (8%)		
Follow-up Corticosteroids					
Yes	29 (25%)	67 (58%)	20 (17%)		0.007
No	13 (13%)	77 (78%)	9 (9%)		
Specialist					
Yes	18 (28%)	33 (51%)	14 (22%)		0.004
No	6 (10%)	45 (75%)	9 (15%)		
Unknown	18 (20%)	66 (75%)	6 (7%)		
Number of Organs	**None**		**1 or More**		
Family Income					
5,000-9,999	12 (67%)		6 (33%)		0.045
10,000-19,999	20 (77%)		6 (23%)		
20,000-29,999	13 (62%)		8 (38%)		
30,000-39.999	19 (76%)		6 (24%)		

40,000-49,999	16 (59%)		11 (41 %)		
> 50,000	79 (85%)		14 (15%)		
Baseline Corticosteroids					
Yes	83 (70%)		35 (30%)		0.023
No	81(84%)		16 (16%)		
Follow-up Corticosteroids					
Yes	76 (66%)		40 (34%)		0.000
No	88 (89%)		11 (11%)		

changes, gallium scanning, and serum Angiotensin Converting Enzyme levels. One limitation of this radiographic analysis is that only a small number of patients progressed to Scadding stage 3 or 4 chest radiographs that are associated with a worse symptoms and prognosis. However this was to be expected, as the length of follow-up was limited to two years. Another limitation of the ACCESS analysis of chest radiographs is that the initial and follow-up chest radiographs were not directly compared. It is possible that significant chest radiographic changes may occur without a change in Scadding stage. However, we suspect that they would have observed frank worsening of a significant number of chest radiographs by Scadding stage if the radiographic findings of this cohort truly worsened.

Data concerning the natural course of spirometry and pulmonary symptoms in Sarcoidosis is sparse. Similar to our patients, more than 70% of Japanese (18, 19), and Spanish [2] patients had resolution of pulmonary symptoms within two years. This is in contrast to a study of Finnish patients [19] in which more than 75% had persistent symptoms 2 years after diagnosis. Our data concerning spirometry are also similar to studies of more homogeneous populations. We found that 88% of our subjects had

Table VIII: ***Organ involvement for all patients who were seen at follow-up, N = 215***

Organ	Number with initial organ involvement	new organ involvement
Lung	197	3
Skin (Excluding Erythema Nodosum)	35	13
Extra Pulmonary Lymph Node	35	8

Eye	31	7
Erythema Nodosum	26	0
Salivary	16	2
Calcium	12	2
Neurological	13	5
Cardiac	8	5
Spleen	12	4
Bone Marrow	2	9
ENT	4	4
Renal	2	0
Liver	21	4
Bone/Joint	3	0
Muscle	1	1

improved or stable spirometry after two years, which is similar to the finding of 18% (29/160) Spanish Sarcoidosis patients having worsening or a persistently abnormal FVC two years after diagnosis [20].

We found that African Americans had worse outcomes in FVC over two years compared to Caucasians. There were no other racial, gender, or age (< 40 versus > 40 years) differences in terms of FEV1, chest radiographic findings, and level of dyspnea. African American patients are known to have a worse prognosis of Sarcoidosis compared to Caucasians (more frequent relapse, more extrapulmonary involvement, worse lung perfusion on chest radiograph) [21,22], although there are limited data specifically concerning the outcome of spirometry. Johns and colleagues [23] found that FVC was decreased in African American Sarcoidosis patients compared to Caucasians followed an average of 5 years after diagnosis, but no analysis of the change in spirometry was performed.

We found that African Americans were more likely to develop new organ involvement with Sarcoidosis over two years compared to Caucasians. This is consistent with a previous study [23] that found that African Americans had more extra-thoracic disease than Caucasians at 5 years, although the time of onset of extra-thoracic involvement was not reported. We also found that extra-thoracic organ involvement at baseline (within 6 months of diagnosis) was associated with an increased likelihood of new organ involvement over two years. New organ involvement was not affected by gender or age. We found no significant patterns of new organ involvement, but this may have been because of inadequate sample size. It is important to point out that organ involvement is different than severity of involvement. ACCESS did not assess the severity of organ involvement with Sarcoidosis with the exception of the lung where measurements of spirometry, chest radiographic findings, and level of dyspnea were made.

Table IX: ***Type of Organ Involvement By Age, race, and sex***

Type of Organ Involvement

ORGAN	BLACK		WHITE		MALE		FEMALE		Age<40		Age
	(N=93)		(N=117)		(N=70)		(N=145)		(N=101)		(N=
	Initial	New	Initial	New	Initial	New	Initial	New	Initial	New	Initial
Lung	84	3	108	0	65	2	132	1	96	2	101
Skin (excluding Erythema Nodosum)	18	10	17	3	9	4	26	9	I5	8	20
Extrapulmonary Lymph Node	19	4	16	4	12	1	23	7	21	8	14
Eye	15	3	16	4	8	1	23	6	14	4	17
Erythema Nodosum	10	0	13	0	4	0	22	0	12	0	14
Salivary	7	1	9	1	4	1	12	1	8	2	8
Calcium	1	1	11	1	8	0	4	2	2	0	10
Neurological	8	3	5	2	1	2	12	3	3	2	10
Cardiac	3	3	5	2	5	1	3	4	3	3	5
Spleen	3	1	9	2	5	1	7	3	4	2	8
Bone Marrow	2	7	0	2	0	4	2	5	1	3	1
ENT	3	4	1	0	0	1	4	3	1	3	3
Renal	0	0	2	0	2	0	0	0	0	0	2
Liver	15	4	5	0	7	1	14	3	11	2	10
Bone/Joint	2	0	1	0	2	0	1	0	2	0	1
Muscle	0	1	1	0	0	0	1	1	0	0	1

Table X: Number of patients with and without new organ involvement at two-year follow-up for specified demographic subgroups

A. Males Versus			

Females			
	Males (N=70)	**Females (N=145)**	**p-value**
New Organs Involved	N %	**N %**	
None	55 78.6	110 75.9	
One or More	15 21.4	35 24.1	0.66
B. < 40 Yrs. vs > 40 Years			
	<40 Years(N=101)	**≥40 Years (N=114)**	**p-Value**
	N %	N %	
None	75 74.3	90 78.9	
One or more	106 25.7	24 21.1	0.42
C. African Americans vs Caucasians			
	African Americans (N=93)	**Caucasians (N=117)**	**p-value**
	N %	**N %**	
None	62 66.7	99 84.6	
One or more	31 33.3	18 15.4	0.002
D. Extra-thoracic Organ Involvement at Baseline			
	Present (N=118)	**Absent (N = 97)**	
	N %	N %	**p-value**
None	81 68.6	83 85.6	
One or more	37 31.4	14 14.4	0.003

We found that there was an excellent concordance between changes in FVC and FEV1. FVC and FEV1 were discordant (worse versus better) in none (0/l93) of the patients. This suggests that using FVC alone is unlikely to result in a misclassification in or change in pulmonary function over two years. However, changes in FVC alone were inadequate to describe the change in pulmonary status of our patients, as changes in chest radiographic findings or the level of dyspnea often but did not always move in the same direction as FVC (*Table VI*).

Erythema nodosum at presentation was associated with greater improvement in Scadding radiographic stage than the absence of erythema nodosum at presentation. This has been observed in other studies

[2, 3, 19, 24].

Lower annual family income was associated with less improvement in dyspnea and more organ involvement over the two-year follow-up. This may suggest that socioeconomic factors play a role in the clinical outcome of Sarcoidosis.

More patients with improved FVC or dyspnea at follow-up were taking corticosteroids than not, and more patients with a worse FVC or dyspnea at follow-up were taking corticosteroids than not. Similarly more patients with improved dyspnea were seeing a sub-specialist than not, and more patients with worse dyspnea were seeing a sub-specialist at follow-up than not.

The use of corticosteroids may improve acute pulmonary Sarcoidosis in the short-term [25,26], resulting in a steroid-responsive group with an improved clinical status. However, patients with relatively refractory disease (a steroid unresponsive group or frequent relapse group) usually receive corticosteroids for a prolonged period and may be a group with a worse clinical outcome. We did identify a subgroup of 52/205 (25%) subjects from this cohort who were maintained on corticosteroids for the duration of the two-year follow-up, and we suspect that most of these individuals represent the refractory cases.
In addition, the use of corticosteroids may promote relapse of Sarcoidosis when the medication is discontinued or tapered that might adversely affect the clinical course [6,10]. This may also explain our findings concerning sub-specialists in that the expertise of sub-specialists may lessen patients' dyspnea, but sub-specialists might also be referred patients with refractory disease who develop worsening dyspnea. ACCESS did not obtain data concerning the dose of corticosteroids that was used by patients, which may also affect the rate of relapse [11] Some data was obtained in ACCESS concerning the discontinuation or addition of corticosteroid therapy during the two-year follow-up, but this will be the subject of a subsequent report focusing specifically on therapy.

In conclusion, data from this heterogeneous United States Sarcoidosis population indicate that Sarcoidosis tends to improve or remain stable in the majority of patients. African Americans tend to have a worse prognosis by spirometry and organ involvement than Caucasians. Erythema nodosum at presentation is associated with a good outcome. Lower annual family income is associated with a worse outcome. The presence of extra-pulmonary organ involvement at presentation is a risk factor for developing new organ involvement over two years. FVC and FEVI had a similar trend over 2 years. Changes in chest radiographs and dyspnea usually, but not always, parallel spirometric changes. Therefore assessment of change in pulmonary status at two years requires an independent assessment of spirometry, chest radiographic changes, and degree of dyspnea. The interaction of corticosteroid therapy with two-year outcome is complex.

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Observations of Jarisch-Herxheimer Reaction in Sarcoidosis Patients

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ABSTRACT
"You have to get worse, before you get better" is a common medical folklore proverb. A new, novel protocol for treating Sarcoidosis is proving that adage true, while showing the promise of a medication-induced remission and the potential for a cure. The Marshall Protocol (MP)[1,2] uses specific combinations of antibiotics in a pulsed regimen along with an angiotensin receptor blockade and avoidance of Vitamin D. Without exception, the improving patients are reporting periodic aggravation of their symptoms as an apparent direct response to the antibiotics. In other words, these patients say that their treatment makes them feel much worse before they experience

symptom-relief.

DISCUSSION

This phenomenon is known as the Jarisch-Herxheimer Reaction (JHR) and is often referred to informally as Herx. JHR is believed to be caused when injured or dead bacteria release their endotoxins into blood and tissues faster than the body can comfortably handle it.[3,4,5,6,7} This provokes a sudden and exaggerated inflammatory response and is associated with the systemic appearance of cytokines. "The JHR is an elegant model of the human cytokine cascade in events resembling sepsis…"[8]

JHR was originally observed in patients with syphilis who received mercury treatment.[9] It has been reported that Rheumatiod Arthritis, Lyme and Louse-borne relapsing fever (B recurrentis) patients have also experienced this effect when treated with the appropriate antibiotics. JHR, however, is not reported in normal, healthy individuals who are treated with antibiotics for sepsis. In Sarcoidosis patients, the Herxheimer reaction seems to be a valuable indication that an antibiotic is reaching its target.

It is normal for the body to generate an immune response when challenged by foreign matter such as microbes and allergens. Sarcoidosis, however, is a run-away, hyper-inflammatory immune system response. Research has lead to a strong suspicion that this reaction is triggered by Cell Wall Deficient (CWD) or polymorphic L-forms microbes. [10,11,12,13] Evidently, these CWD bacteria have learned to live inside the actual macrophages (phagocytes) of the immune system.[14] Apparently, they fail to be destroyed by the very immune system cells (phagocytes) which are supposed to kill them because they have learned to live in the caustic 'cytokine soup' of a Sarcoidosis granuloma. A similar adaptive cell behavior has been seen by the H. pylori bacterium which has learned to live in the hostile environment of the stomach, causing gastric ulcers.

It is difficult (and maybe unnecessary) to determine which of the many species of CWD mycoplasma might be responsible for the granulomatous reaction of Sarcoidosis. The CWD bacteria are reportedly difficult to see even with an electron microsope, very slow growing and tedious to culture. This makes it impractical to cross-match species to find the appropriate antibiotics. Thus, the elicitation of a Herxheimer reaction is a key component of the Marshall Protocol to determine, by therapeutic probe, which antibiotics are effective. Renowned scientist, Dr. Friedrich Flachsbart, MD, Göttingen, Germany, states that "Jarisch-Herxheimer is in fact the maximum of evidence possible in search of occult microbes".

The Marshalls have noted that Sarcoidosis patients have a high level of circulating 1,25-dihydroxyvitamin-D(1,25-D) and that many Sarcoidosis patients complain of symptoms similar to that of hypervitaminosis-D. One study has shown that Lipopolysaccharide is capable of stimulating sarcoid macrophages from BAL in-vitro to generate 1,25-D.[15] Since Lipopolysaccharide is known to come from gram-negative bacteria, they conclude that the high levels of 1,25-D generated in Sarcoidosis by macrophages are most probably coming from a bacterial source.

The Marshalls use 1,25-D levels as an indicator of both systemic inflammation and Herxheimer activity. They associate the JHR reaction with bacteriocidal actions AND the abnormal immune system response in Sarcoidosis patients. During the JHR, MP patients 1,25-D levels are noted to temporarily surge even higher, correlating with their reported exacerbation of symptoms. This would seem to provide further evidence that as the bacteria are killed by antibiotics, endotoxins are released, provoking a Th1 (bacterial) reaction.

The elicitation of a Herxheimer reaction is thought to be a key component in evaluating the efficacy of each MP antibiotic, antibiotic combination or dosing schedule. Indeed, the Marshalls advise that the lack of a Herxheimer reaction when Sarcoidosis symptoms are still present signals a need for a change in dosing schedule or antibiotic. Consequently the MP Sarcoidosis patient is expected to experience episodic JHRs as long as antibiotic therapy is needed. The gradual resolution of

symptoms has been noted to require months or years depending on the extent of Sarcoidosis involvement and/or disease location. Remission of Sarcoidosis is determined by absence of symptoms, both objective and subjective.

Sarcoidosis patients report that a Herxheimer reaction makes them feel as though their disease symptoms have suddenly gotten worse. They report reactivation of previous symptoms and/or the exacerbation of presenting symptoms. Depending on the extent of the Sarcoidosis inflammation and the effectiveness of the antibiotic [16,17], the onset of JHR is from 1-2 hrs to10 days after the antibiotic/s are administered. The intensity of the reaction is dependent on many factors; location of the inflammation, appropriateness of the antibiotic/s, the antibiotic dosage, the presence of immunosuppressants, the level of dihydroxyvitamin-D [18] and the prophylactic dosing schedule of the Angiotensin Receptor Blocker (ARB) used to interrupt the inflammatory cascade [19].

Herxheimer symptoms wax and wane with antibiotic administration and MP patients report that they continue to experience this phenomenon as long as effective antibiotic therapy continues. Trial and error with carefully selected antibiotic combinations has reportedly provoked a resumption of the JHR when symptoms have subsided. Since Sarcoidosis patients are believed to have acquired many different species of mycobacteria over a long period of time, the effectiveness of an antibiotic probe with a positive JHR seems to demonstrate the presence of another species or of bacteria previously hidden within poorly perfused tissues.

Herxheimer symptoms may be subjective or objective, or both. The most common symptoms reported by Sarcoidosis patients include increased fatigue, joint or muscle pain, headaches, skin rashes, photosensitivity, irritability, paresthesia, dizziness, sleep disturbances, asthenia, muscle cramps, night sweats, hypertension, hypotension, headaches (especially migraines) and swollen glands. Also reported are heavy perspiration, metallic taste in mouth, chills, nausea, bloating, constipation or diarrhea, low grade fever, chills, heart palpitations, tachycardia, facial palsy, tinnitus, mental confusion, uncoordinated movement, pruritus, bone pain, flu-like syndrome, conjunctivitis and throat swelling. Physicians have managed these JHR symptoms in MP Sarcoidosis patients with the use of an ARB and by decreasing the dosage or frequency of the antibiotics.

Physicians may note hypercalcemia, calcium deposits in the lungs, lymphopenia, anemia and renal calculi, elevation of ESR, gamma globulin and total globulin or a fall in serum albumin and hematocrit during a JHR. Unexpectedly severe Herxheimer reactions needing Emergency Room treatment have occurred. Especially worrisome is the possibility of eliciting severe respiratory symptoms or cardiac symptoms. Cardiac Sarcoidosis is sometimes unsuspected and diagnosed only when the JHR elicits chest pain or arrhythmia. If physicians are aware of the possibility of a JHR, they can avoid unnecessary testing or medications. Discontinuing the antibiotics and increasing the ARB dosage is reportedly the most effective treatment for severe JHR. The Marshalls caution that the JHR should be given the utmost respect. Since these life-threatening JHRs are most likely to occur at the start of antibiotic treatment, they advise establishing an ARB blockade to lower the level of 1,25-D before initiation of antibiotic therapy and that the initial antibiotic doses be very low.

JHR is sometimes mistaken for a “hypersentivitiy reaction” or even the cause of a related, (probably preexisting) disease such as lupus.[20] Pruritus, hives and rash induced by JHR can be misdiagnosed as an allergic (Th2) reaction to the antibiotic. MP patients, however, have reported safely taking sulfa, although eliciting a JHR, despite a history of ‘allergy’ to sulfa. JHR might linger for weeks, rather than the hours that would be expected from an allergic reaction. Laboratory tests can help differentiate between a Herxheimer reaction to microbial toxins and an allergic reaction to medication. WBCs and 1,25-dihydroxyvitamin-D will be elevated in a Herxheimer reaction. But a marked increase in eosinophils (about 30%) or the presence of specific antibodies is an indication of an allergic reaction.

The Marshalls report that as the number of dying bacteria is reduced with subsequent antibiotic

doses, effective treatment requires increasing doses and changing antibiotic combinations to continue eliciting a Herxheimer response. The presence of a JHR is seen as evidence of continuing elimination of these very persistant bacteria. Although the JHR is often unpredictable, they report that it can be managed with the judicious choice of antibiotic combinations, careful dosing schedule, tapering of dosing and use of an ARB to establish an anti-inflammatory blockade. The Marshall Protocol does not advocate eliciting a more severe JRH than a patient can tolerate in order to eliminate the bacteria and the antibiotic dosing is individualized to each Sarcoidosis patient.

CONCLUSION

In my work with Sarcoidosis patients, it is my experience that recovering MP patients understand and welcome the Herxheimer reactions even when they must endure temporary increased suffering. They accept it as the price that they must pay in order to get well and they even seem to find it gratifying to experience tangible evidence of bacterial elimination. The gradual resolution of their Sarcoidosis symptoms as the treatment progresses seems to be ample reward to persist with this sometimes uncomfortable treatment. Many MP Sarcoidosis patients say that their doctors were initially unaware of the JHR phenomenon. An increased awareness of the Herxheimer reaction by those who treat Sarcoidosis would seem to be of benefit to patients. Antibiotics then might be seen as the ally they are proving to be in fighting this often fatal disease.

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пична, данные электронной микроскопии свидетельствовали о присутствии полиморфных бактерий, остающихся живыми внутри фагоцитов. Когда эти бактерии оказываются убитыми, их эндотоксин высвобождается непосредственно в инфицированный фагоцит. Развивающаяся шоковая реакция Яриша-Герксгеймера истощает пациента, а для некоторых пациентов — угрожает жизни. Она персистирует в течение всего времени, пока гибнут паразиты, часто в течение года или больше. Два гормона опосредуют вызванный эндотоксином Th1-клеточный иммунный ответ — ангиотензин II и 1,25-дигидроксивитамин-D. Блокада ангиотензиновых рецепторов типа AT1 быстро приводит к облегчению симптомов и минимизирует риск угрожающих жизни кардиальных событий, особенно брадикардии. Комбинация бактериостатических антибиотиков азитромицина, миноциклина и сульфаметоксазол/триметроприма отчасти эффективны в отношении внутриклеточно расположенных бактерий. Критичным является то, что доза антибиотиков должна быть минимальной, чтобы количество высвобождающегося эндотоксина не превысило возможность пациента перенести шок Яриша-Герксгеймера.

Ключевые слова: саркоидоз, миноциклин, азитромицин, атипичные формы бактерий.

ANTIBACTERIAL THERAPY INDUCES REMISSION IN SARCOIDOSIS

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Summary

At least five studies have identified a special kind of antibiotic-resistant bacteria in the biopsy specimens from sarcoid patients, yet, until recently, an effective therapy has remained elusive. The nature of the infestation is atypical, with electron-microscopy showing polymorphic bacteria actually living within the phagocytic cells of the immune system itself. When the bacteria are killed, their endotoxin is therefore released directly into the infected phagocytes. The resulting Jarisch-Herxheimer Shock is debilitating, and, for some patients, life-threatening. It persists as long as the parasites are being killed, often for a year or more. Two hormones mediate the body's endotoxin-induced Th1 immune response — Angiotensin II and 1,25-dihydroxyvitamin-D. Blockade of type AT1 Angiotensin receptors can rapidly relieve the patients' symptomatic suffering and minimize the risk of life-threatening cardiac events, especially bradycardia. Combinations of the bacteriostatic antibiotics Azithromycin, Minocycline and Sulfamethoxazole/ Trimethoprim have been particularly effective at killing these cell-dwelling bacteria. It is critical that the dose of antibiotic is kept to a minimum, so that the amount of endotoxin release does not overwhelm the ability of the patient to tolerate the resulting Jarisch-Herxheimer Shock.

Keywords: Sarcoidosis. Minocycline. Azithromycin. Atypical Bacterial Forms.

Введение

Cantwell [1] недавно проанализовал исследования последних трёх десятилетий, в которых сообщалось о наличии плеоморфных, кислотоупорных бактерий с дефицитом клеточной стенки (ДКС) в биоптатах, полученных от больных саркоидозом. Moscovic первым идентифицировал эти плеоморфные бактерии в саркоидных тканях в 1978 году [2,3], за ним Cantwell [4,5,6], Mattman [7], и Nilsson et al. [8].

Wirostko и соавторы. [9] использовали трансмиссионную электронную микроскопию для получения ошеломляющих фотографий кокковидных бактерий с дефицитом клеточной стенки в иммунных клетках из стекловидного тела глаз 4 больных саркоидозом с хроническим увеитом. Фотографии доказывали паразитирование в моноцитах, лимфоцитах и полиморфоноклеточных лимфоцитах.

Паразитирование в моноцитах и полиморфноядерных лейкоцитах.

Протеин-димер ядерный фактор каппа Б (NuclearFactor-kappaB, NF-kB) находится в центре Th1 иммунного ответа при саркоидозе. В норме

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Antibacterial Therapy Induces Remission in Sarcoidosis

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ABSTRACT
At least five studies have identified a special kind of antibiotic-resistant bacteria in the biopsy specimens from sarcoid patients, yet, until recently, an effective therapy has remained elusive. The nature of the infestation is atypical, with electron-microscopy showing polymorphic bacteria actually living within the phagocytic cells of the immune system itself. When the bacteria are killed, their endotoxin is therefore released directly into the infected phagocytes. The resulting Jarisch-Herxheimer Shock is debilitating, and, for some patients, life-threatening. It persists as long as the parasites are being killed, often for a year or more. Two hormones mediate the body's endotoxin-induced Th1 immune response - Angiotensin II and 1,25-dihydroxyvitamin-D. Blockade of type AT1 Angiotensin receptors can rapidly relieve the patients' symptomatic suffering and minimize the risk of life-threatening cardiac events, especially bradycardia. Combinations of the bacteriostatic antibiotics Azithromycin, Minocycline and Sulfamethoxazole/Trimethoprim have been particularly effective at killing these cell-dwelling bacteria. It is critical that the dose of antibiotic is kept to a minimum, so that the amount of endotoxin release does not overwhelm the ability of the patient to tolerate the resulting Jarisch-Herxheimer Shock.

Conflicts of Interest:
This study was fully funded by the authors. There are no conflicts of interest to declare.

Keywords:
Sarcoidosis
Sarcoidosis, Cardiac
Minocycline
Minocycline, Adverse effects
Doxycycline
Azithromycin
Azithromycin, Adverse Effects
acid-fast bacteria
cell wall deficient bacteria
Atypical Bacterial Forms
Transformation, Bacterial
Rheumatology
Respiratory Medicine
Lupus Erythematosus
L-forms

Introduction

Cantwell [1] recently reviewed three decades of studies which reported the isolation of pleomorphic, acid-fast, Cell Wall Deficient (CWD) bacteria in the biopsy specimens from sarcoidosis patients. Moscovic first identified these pleomorphic bacteria in sarcoid tissue in 1978 [2,3] followed by Cantwell [4,5,6], Mattman [7] and Nilsson, et al, [8].

Wirostko, et al, [9] used a transmission electron microscope to produce stunning photographs of CWD coccoid bacterial forms in the immune cells from the vitreous of the eyes of 4 sarcoidosis patients with chronic uveitis. Their photographs documented parasitized monocytes, lymphocytes, and polymorphonuclear leucocytes.

Parasitized monocytes and polymorphonuclear leucocytes

The dimer protein NuclearFactor-kappaB (NF-kB) is at the heart of the Th1 immune response of Sarcoidosis. Normally NF-kB is stabilized in the cytoplasm of the monocytes, macrophages, dendritic cells, and polymorphonuclear leucocytes which form the central region of a sarcoid granuloma. When NF-kB is activated to move to the nucleus of these cells, a messenger RNA is released which initiates the cytokine cascade, including release of the cytokine 'TNF-alpha'. Glucocorticoids (such as prednisone) exert their immunomodulatory effect by blocking this activation of NF-kappaB [10].

NF-kB is normally activated to move to the nucleus in response to a variety of receptors located on the cell periphery. In a healthy individual the NF-kB activation is typically triggered by activated lymphocytes. However, if there are bacteria living within the cytoplasm of the cell, then these bacteria can render the lymphocytes redundant, and trigger the NF-kB to initiate a cytokine release based solely upon proteins released by the bacteria itself [11,12].

Once there are bacteria living within the cells of the immune system, then one is not dealing with an immune system which is subject to the same mechanisms of pathogen identification and reaction which occur in a healthy individual. One is dealing with a run-away immune reaction totally dominated by the parasitic bacteria. The consequent run-away inflammation forms the granuloma of sarcoidosis [16].

What Species of Bacteria are Involved?

There are many (>60) species of bacteria which have been isolated in a CWD or mycoplasmal form. Species already identified in sarcoidosis patients include Borrelia [13], Mycobacterium [14], Rickettsia [8] and Propionibacterium [15].

We believe that no one lymphopenic pathogen is solely responsible for sarcoid inflammation, but that a variety of species are typically present in any given patient. We note that our antibacterial therapy usually progresses in steps. As the antimicrobial cocktails and concentrations are varied throughout a therapy, patients experience pain due to JHS in different organs, in different regions of the body. It is rare for the same antibiotic combination to be effective both against inflammation in the eyes, for example, and inflammation in the lungs [16].

The CWD bacteria are present in the bloodstream of both healthy individuals and sarcoidosis patients [18,19], but they do not parasitize the phagocytes of healthy individuals. Genetic predisposition causes

some to become sick with the autoimmune disorders [17], while the majority of the population remains healthy [20,21].

Where do these CWD bacteria come from?

The initial pathway for infection with these bacteria is most probably from mother to child. McPherson Brown noted their presence in the birth canal [20], and Sanchez confirmed a high rate of mother-to-child infection with at least one species of mycoplasma [21].

These bacteria can survive the temperatures used in commercial pasteurization of milk [22]. So it is clear that they can pass through the food chain. They have been shown only partly susceptible to the typical sterilization processes used in the commercial water supply [23].

Many of the CWD coccoid forms are so small that they pass through the 0.2 micron filters typically used in pharmaceutical production. It can be expected that CWD contaminants are present in pharmaceuticals, especially in biologic preparations and vaccines.

CWD coccoid bacteria are also ubiquitously formed by bacterial organisms as a protective response to antibiotics whose mode of action is to attack the bacterial cell wall.

For example, the antibiotic Rifampin is used to combat Tuberculosis. Although it is well known that mycobacteria quickly develop resistance to Rifampin (this is the reason it is almost always combined with Isoniazid), it is not so well known that at least one mechanism for resistance to Rifampin is for the mycobacteria to morph into these tiny CWD L-forms. There is no longer any cell wall for the Rifampin to attack. This adaptation has been confirmed in-vitro [24].

The ubiquitous use of Penicillins also creates these antibiotic-resistant CWD bacteria. Penicillins attack bacterial cell walls, and these CWD pleomorphs have been observed forming in-vitro, under the action of Penicillins [25].

Finally, the immune system itself creates some of these resistant bacteria whenever it fights active infections. Borrelia burgdorferi have been observed morphing to these tiny cystic forms in spinal fluid, and then changing back to active spirochetes in less hostile environments [26].

Bacterial antibodies and cultures

The characteristic of sarcoid granuloma is that they are non-caseating, non-necrotic. A granuloma is a healthy collection of living cells. There is little apoptosis, and thus little necrosis. The lifetime of infected macrophages is in excess of 40 days, and turnover is low. Consequently very few bacteria die and enter the bloodstream. That low concentration is detectable with PCR technology [14], but PCR requires specific primers for each species to be detected. The wide variety of species makes it very difficult to perform a definite diagnosis using PCR alone.

Cantwell and Mattman successfully cultured the CWD species they isolated from their patients [27,7]. Cantwell has privately communicated the difficulties he experienced while culturing these CWD bacteria. He reported that they are very slow-growing. The typical minimum time to culture was 3 months, with 6-9 months not unusual [27]. There was always the risk of contamination, especially when incubating for such

lengthy periods. Based on his observations, we do not expect that cultures will become useful diagnostic tools when dealing with CWD bacteria.

Jarisch-Herxheimer Shock

Antibacterial therapies aimed at killing these intra-cellular microbes have to contend with Jarisch-Herxheimer Shock (JHS) [28,29]. Mangin writes "patients are reporting periodic aggravation of their symptoms as an apparent direct response to the antibiotics .. these patients say that their treatment makes them feel much worse before they experience symptom-relief" [31].

Thus, JHS is at once a bad thing, because it exacerbates the suffering of the patient, and also a good thing, because it indicates that the bacteria are being effectively killed. In fact, it is our observation that those patients who do not experience significant JHS are not killing the bacteria at a rate fast enough to induce remission of their sarcoid inflammation. Out of our current subject cohort (n>100) only 5 patients have had significant difficulty finding an effective antibiotic regimen, and all have eventually been 'privileged' to suffer the effects of JHS.

Indeed, the greatest danger is that too powerful an antibiotic regimen will be put in place too soon, precipitating life-threatening JHS. Even while exercising great care, we have had two patients with life-threatening bradycardia and several with (temporary) debilitating pulmonary insufficiency. The two bradycardia events each lasted about two months and disappeared as the JHS subsided. In both cases the bradycardia was controlled with high doses of the Angiotensin Receptor Blocker, Olmesartan Medoxomil (Benicar/Olmetec).

A number of cases of skin rash have developed in subjects upon commencing the antibiotic therapy. For example, one subject reported that a skin rash was exacerbated when commencing the initial (minocycline) phase of the therapy. It cleared after 4 months but returned again (in a milder presentation) when Azithromycin was added. It disappeared again after another 3 months, and has not subsequently returned.

The hormones Angiotensin II and 1,25-dihydroxyvitamin-D

We have previously proposed "the Angiotensin Hypothesis", describing the endocrine biochemistry of the Th1 immune reaction as being dependent upon the hormone Angiotensin II and the secosteroid hormone 1,25-dihydroxyvitamin-D (1,25-D) [32,33]

Nearly all (>80%) of our sarcoidosis cohort initially exhibited a 1,25-D level in excess of the Merck Maximum of (45 pg/ml) [34]. Their levels were also higher than the plus-two-sigma point of the distribution derived from the Danish population study [35]. 1,25-D has proven by far the best indicator of systemic sarcoid inflammation, and the best advance indication of the degree of JHS that a patient will exhibit when starting antibiotic therapy. Anecdotally, we take values of 1,25-D over 60 pg/ml to indicate that extra caution will be necessary, and values over 80 pg/ml warn of likely cardiac involvement.

A low value of 1,25-D indicates an invalid assay result (most frequently because the serum was not frozen before being sent to the lab) or the presence of a comorbid condition that shifts the body's Th1 response towards a Th2 immune condition. Typical diseases which significantly lower the 1,25-D value include fungal infections and cancers, especially Breast Cancer[36] and Malignant Melanoma [37], as well as viral diseases such as Hepatitis-C and AIDS [38].

Blockade of Type AT1 Angiotensin Receptors has been critical in reducing the additional inflammation and potential fibrosis caused by the endotoxin release [33]. Surprisingly, there is a large difference in efficacy between the available Angiotensin Receptor Antagonists. We have found only Olmesartan Medoxomil (Benicar/Olmetec) to be totally effective, while Valsartan and Irbesartan are much less effective. Commencing Olmesartan at the therapeutic minimum of 40mg every 8 hours significantly reduces the value of serum 1,25-D, in some cases halving the value within 14 days. The ARB also seems to make the bacteria more susceptible to the antibiotics.

As we hypothesized in an earlier paper [17] we believe that the inability of sarcoidosis patients to properly control surges in their paracrine 1,25-D production is one of the predisposing factors which allows the bacteria to initially parasitize the phagocytes.

Antibiotic and Dosing Guidelines

It is clear that the bacteria causing sarcoid inflammation do not succumb to the antibiotics that are in common usage. If this were the case, then the bacterial pathogenesis of sarcoidosis would have become obvious long ago, based on unexpected 'spontaneous remission' concurrent with antibiotic therapies for other conditions.

Partly this is because many of the species do not succumb to any one antibiotic (they are 'antibiotic-resistant') and partly it is because the dosing regimes in common usage do not work well when treating the bacteria populating the immune system of sarcoid patients.

Minocycline is the only antibiotic monotherapy that can usually be relied upon to start reducing a sarcoid patient's bacterial load. But Minocycline's action against the intra-cellular bacteria is not achieved with normal dosing regimens. As noted by Brown [20], Minocycline is most effective when its concentration in the bloodstream is allowed to decay between successive doses. With a pharmacokinetic half-life around 17 hours, the dosing schedule proposed by Brown (of Monday, Wednesday and Friday) meets that criteria. We have also used a 48 hour interval in our own dosing guidelines, depending on the preferences of the individual patient. The starting dose of Minocycline should be no greater than 25mg every 48 hours. Even this low dosage has caused significant breathing difficulties for some of the most severely ill patients. We suggest increasing the dose based on the patient's ability to tolerate the JHS, and we try to maintain the patients on Minocycline (alone) for the first three months of therapy. It is important to note that Doxycycline is not effective on as wide a spectrum of bacteria as Minocycline. In particular, Doxycycline seems ineffective against the aerobic bacteria that populate the lungs. It is our opinion that Doxycycline should not be used in any therapy for Sarcoidosis.

When the patient can tolerate the JHS resulting from 100mg of Minocycline every 48 hours, we add ***one quarter of*** a 250mg Azithromycin tablet (=62mg), once a week. We find it generally takes several months before the average patient is able to gradually increase the Azithromycin dosage to a full 250mg weekly, while maintaining 100mg of minocycline every 48 hours. At this point a little Sulfamethoxazole/Trimethoprim can be added to the 48 hour Minocycline to potentiate activity against additional resistant species [39].

Typical Timelines

Based on our observation of the progress of our initial cohort [16], at about 3 months into therapy, most subjects have achieved sufficient symptomatic relief to guarantee their compliance with the remainder of the antibiotic regimens. At about 6 months, most subjects report relief from fatigue, somnolence and insomnia, and report that their memory is returning. Useful bloodwork markers are 1,25-D, Alkaline Phosphatase, Triglycerides, and C-Reactive Protein. All should have started to improve by month 6. By the end of the first year, Imaging should show reduced adenopathy, and most bloodwork will have returned to within normal range. Even though most subjects have achieved 'remission' at around 18 months, we currently anticipate that antibiotic therapy will need to be continued well beyond that, until all species have succumbed to the antimicrobials. Peripheral neuropathy seems to have the slowest resolution, with little progress within the first 6 months.

Overview

Bachelez, et al, [40] were the first to show that Tetracyclines were capable of inducing remission in sarcoidosis. When we discussed the Bachelez study with Alan Cantwell [1] he contributed valuable insights into the bacteria he had seen under his microscope. Barbara Wirostko [9] suggested trying Azithromycin. We added our Angiotensin Hypothesis, along with a heterogeneous group of 50 sarcoidosis patients (presenting pulmonary, neurological and cutaneous involvement) and put together the study [16,17] that formed the basis for the observations in this paper.

The subjects in our initial cohort variously reported regaining cognitive focus, stamina, and stable gait, and resolving chronic pain, paresthesias and visual disturbances. Some were able to discard wheelchairs, braces and supplementary oxygen.

There still is so much to learn about the idiopathic inflammatory diseases, but at last we are making progress…

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Sarcoidosis succumbs to antibiotics—implications for autoimmune disease

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Abstract

From time to time there have been reports of autoimmune disease succumbing to tetracycline antibiotics, but many have assumed this was due to coincidence, or to some ill-defined 'anti-inflammatory property' of the tetracyclines. But now the inflammation of sarcoidosis has succumbed to antibiotics in two independent studies. This review examines the cell wall deficient (antibiotic resistant) bacteria which have been found in tissue from patients with sarcoidosis. It examines how such bacteria can infect the phagocytes of the immune system, and how they may therefore be responsible for not only sarcoid inflammation, but also for other autoimmune disease. Proof positive of a bacterial pathogenesis for Sarcoidosis includes not only the demonstrated ability of these studies to put the disease into remission, but also the severity of Jarisch-Herxheimer shock resulting from endotoxin release as the microbes are killed. Studies delineating the hormone responsible for phagocyte differentiation in the Th1 immune response, 1,25-dihydroxyvitamin D, are discussed, and its utility as a marker of Th1 immune inflammation is reviewed. Finally, data showing that the behavior of this hormone is also aberrant in rheumatoid arthritis, systemic lupus erythematosus, and Parkinson's, raise the possibility that these diseases may also have a CWD bacterial pathogenesis.
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Keywords: Sarcoidosis; Cell-wall-deficient bacteria; Lupus erythematosus; 1,25-dihydroxyvitamin D; Anti-infective agents/adverse effects

1. Sarcoidosis and autoimmune disease

For more than a century, the pathogenesis of sarcoidosis has remained a mystery. Scadding [1] reported that the '1949 US NRC Conference on Sarcoid' identified 'the plasma globulins' as often being elevated in sarcoidosis, yet its classification as an autoimmune disease has remained a matter of conjecture. Later definitions tended to portend an antigenic etiology rather than emphasize the autoimmune aspects of the disease. Indeed, the 1999 ATS/ERS/WASOG 'Statement on Sarcoidosis' [2] does not even mention the word 'autoimmune'.

One reason for this confusion is that although sarcoidosis is a systemic inflammatory disease,

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diagnosis is most frequently made on the basis of radiographic pulmonary manifestation. However, during the course of a lifetime, sarcoidosis patients present with a variety of maladies. These do not reside uniquely within any one medical specialty. A patient with advanced sarcoid inflammation might present with disease in the lungs, as pulmonary sarcoidosis, in the cardiac muscle as 'cardiac sarcoidosis', and in the brain as 'neurosarcoidosis'. These manifestations have often been viewed, and treated, as different diseases, even though they almost certainly resulted from the same systemic inflammatory process.

Nevertheless, there is currently no doubt that sarcoidosis is a Th1 immune disease [3] and that it shares genetic susceptibility alleles on the HLA-DRB1 gene at loci *1501 with multiple sclerosis (MS) [4] and systemic lupus erythematosus (SLE) [5]. Both of these factors indicate that sarcoidosis has more in common with autoimmune disease than with any antigenic etiology.

2. Occult bacteria in sarcoid tissue

For several decades there have been consistent reports of occult bacteria being found in tissue taken from sarcoidosis patients. Cantwell [6], Mattman [7], Wirostko [8] and Moskovic [9] have all documented the appearance of a special type of tiny microbe, coccoid forms known as cell wall deficient (CWD) bacteria. Cantwell recently summarized the historical perspective in an excellent review 'Bacteria in sarcoidosis and a rationale for antibiotic therapy in this disease' [10], which contains numerous color micrographs of these bacterial forms.

Cantwell also reported similar bacteria in tissue from SLE patients [11].

3. Cell wall deficient bacteria

CWD bacteria are resistant to most antibiotics, being pleomorphic forms of active spirochetal and blood-borne species. They proliferate very slowly, and are very difficult to culture. They have adapted to a hostile environment by shedding their cell walls. The pleomorphism from blood-borne to the CWD state can be triggered by antibiotics, but it can also be a protective response to attack by the immune system itself [12]. The bactericidal action of the penicillins is upon the bacterial cell walls, and penicillin-induced morphing of spirochetal bacteria to their CWD form has been observed in-vitro [13].

Some of these CWD bacterial species have adapted to live within the phagocytes of the immune system. The very cells, which are supposed to kill the invading bacteria, actually provide them refuge.

These CWD bacteria are so tiny that 10 (or more) can live in the cytoplasm of the same phagocyte. Wirostko et al. [8], photographed CWD bacteria living within several cells of the immune system: monocytes, lymphocytes and polymorphonuclear leucocytes.

A stunning micrograph from Nilsson et al. [14], shows a (presumed) Rickettsia bacterium replicating within the cytoplasm of a phagocyte from a sarcoidosis patient. Here was evidence that not only could bacteria adapt to live in this harsh environment, but that they could also flourish.

These CWD species have evolved the ultimate survival mechanism. When the harsh environment is removed they are able to morph back into the active blood-borne state [12] and quickly propagate an active blood-borne infection. In the CWD state they are extremely hard to kill, and as they die they dump their toxic load into the cytoplasm of the phagocytes they have infected [15]—the resulting endotoxin creating a Th1 cytokine cascade, which can be life-threatening.

4. Jarisch-Herxheimer shock

We have previously reported [17] that Jarisch-Herxheimer shock (JHS) presents as a worsening of the manifestations of the sarcoidosis disease process itself. As the bacteria are killed there is a massive release of the same cytokines as are gradually released during normal disease activity. Unless the antibiotic dosage is carefully controlled, adverse events may include both life-threatening pulmonary insufficiency and life-threatening cardiac events.

Even though JHS presents a major problem with patient management and antibiotic dosing, its pres-

ence is also proof-positive of a bacterial disease process, and that bacteria are being killed by the antibiotic therapy.

In many ways sarcoidosis is the ideal test-bed to develop antibiotic therapies against these occult bacteria. The JHS symptoms allow therapy to be optimized in ways that would not be possible in inflammatory disease exhibiting a lesser degree of JHS.

5. Minocycline and doxycycline in sarcoidosis

Bachelez et al. [18], described how minocycline effectively treated skin lesions in 10 patients from a cohort of 12. Two patients also exhibited pulmonary manifestations of the disease, and these were also put into remission by a 12-month course of minocycline.

In sarcoidosis the current aim of therapy is 'to delay the disease progression'. In that context the results achieved by this team were stunning and revolutionary. However, their achievements were marginalized within the sarcoidosis clinical community, which characterized the minocycline treatment as maybe being useful for skin lesions, but overlooked the improvement in pulmonary manifestations.

Further criticism is voiced at the observational nature of the Bachelez study, and its lack of controls. We feel this criticism is totally unwarranted, as clinical trials of sarcoidosis therapies are customarily unblinded, with the ethics of withholding a potentially useful drug from chronically ill patients being traditionally cited as justification for omission of the placebo group.

Unfortunately, Bachelez only used minocycline and doxycycline in their study. There have been persistent reports incorrectly attributing an anti-inflammatory property to these tetracyclines. The resulting confusion about whether the study was killing microbes, or merely administering an anti-inflammatory, also diluted the landmark nature of this study.

6. Antibiotics in sarcoidosis

While discussing the Bachelez study with Cantwell it became clear to us that the CWD bacteria he had seen in the inflamed tissue most probably were the pathologic agent in sarcoidosis. We had previously identified the secosteroid 1,25-dihydroxyvitamin-D (1,25-D) and Angiotensin II as the key hormones driving the systemic inflammatory process [16] and had noted that this biochemistry was consistent with a bacterial pathogenesis, but not with an antigenic etiology.

A study was initiated to try and determine just which antibiotics would be effective against cell-dwelling pathogens, and not just focus on the tetracyclines.

We managed to recruit a larger cohort of 50 sarcoidosis patients for the study described in our JOIMR paper [17]. Our methodology did create some biases, but they turned out to be insignificant when weighed against the almost universal effectiveness of the antibiotic therapy.

JHS was the major problem within our own heterogeneous cohort. Before we developed suitable low-dose antibiotic protocols, we had one patient who needed emergency oxygen, and many patients complaining of worrying cardiac 'flutters' and 'arrhythmia'.

Bachelez also encountered adverse affects (presumably JHS) but took the approach that antibiotic therapy should be selective, with a focus on treating those patients from whom a favorable outcome might be expected.

We took the opposite approach. We tried to fashion a treatment protocol, which would help patients with any degree of disease dysfunction. We took the approach that sarcoidosis had a primary homogenous pathogenesis, and that any patient exhibiting biopsy verified non-caseating granuloma ought to respond to the same therapy. Our results attest to the accuracy of this hypothesis.

7. The secosteroid hormone 1,25-dihydroxyvitamin D

In 1989, Reichel et al. [19] noted that 1,25-dihydroxyvitamin D (1,25-D) appeared to be exhibiting a key immunomodulatory role. This hormone had long been thought to be associated solely with calcium homeostasis in man, but molecular medicine has revealed that it is actually the parathyroid hormone

(PTH), which regulates calcium, not 1,25-D. Although 1,25-D exerts an action upon PTH, it has only a secondary calcemic effect, and this is far less important than the other functions that 1,25-D performs in the body. Casteels et al. confirmed the immunomodulatory role in 1995 [20], as did Lemire in 1998 [21].

By the time that Hewison et al. published 'Vitamin D as a cytokine and hematopoetic factor' in 2001 [22], molecular medicine had pretty well determined exactly how this hormone controls the differentiation of hematopoetic mast cells into monocytes, and then catalyzes the differentiation of monocytes into mature macrophages. In other words, molecular science had figured out exactly how this hormone controls the Th1 immune response in man.

Unfortunately, clinical science has been a little slow to respond to this new knowledge. This hormone exists in serum at very low concentrations (typically 75 pmol/l) and it is usually ignored in clinical profiles.

However, Mawer et al. reported that 1,25-D is such a sensitive indicator of the Th1 immune response that it can even be used to determine prognosis in breast cancer [23]. As the level of 1,25-D falls, the level of the body's ability to mount a Th1 response is also falling, and the prognosis becomes less favorable.

Huag et al. noted that in AIDS the disappearance of 1,25-D is coincident with the disappearance of the body's ability to react to infection [24]. Further they confirmed that these changes in 1,25-D were not closely coupled to changes in calcium homeostasis.

We reported a study of the levels of this hormone in sarcoidosis [25], and noted that 1,25-D was almost always elevated in this Th1 immune disease. The severity of the systemic inflammation was roughly proportional to the amount of excess 1,25-D being measured by the assay.

The measurement of 1,25-D, and the D-Ratio [25] (a factor representing the energy with which Th1 inflammation generates 1,25-D), can be performed with a draw of just 8 ml of whole blood. We believe this is the single most useful test to assess the status of the immune system of any patient, with or without a formal disease diagnosis.

8. 1,25-D metabolism is aberrant in rheumatoid arthritis, Parkinson's and SLE

Even though 1,25-D is such a sensitive measure of Th1 immune activity there is very little data available about its behavior in autoimmune diseases other than sarcoidosis.

Mawer et al. [26] documented aberrant 1,25-D metabolism in Rheumatoid Arthritis (RA). They challenged a controlled cohort of 19 RA patients with the precursor, 25-D. Eight of the 19 RA patients generated levels of 1,25-D above the 'upper limit of normal'. Mawer concluded that the study provided strong evidence for the non-renal synthesis of 1,25-D in patients with RA. This situation exactly parallels the non-renal synthesis of 1,25-D by inflammatory macrophages in sarcoid inflammation.

Sato et al. [27] meticulously collected data on osteopenia in elderly patients with Parkinson's disease. Their data (Table 2 of [27]) show an inability for the Parkinson's patients to regulate 1,25-D in response to oral supplementation, with a marked increase in the generation of 1,25-D and/or a corresponding decrease in the value of the observed precursor, 25-D. Using our own nomenclature [25] this is equivalent to saying that the D-Ratio is rising away from the nominal 1.3 of a healthy person [16]. Although this study was not structured to test non-renal synthesis of 1,25-D in elderly Parkinson's patients, we interpret their data as indicating such an aberrant metabolism exists, indicative of active Th1 inflammation in Parkinson's.

Similar, but less exhaustive, data have been logged during studies with SLE patients. Huisman et al. [28], and Muller et al. [29], both noting anomalies in the D metabolism associated with SLE.

Since it is our own personal hypothesis that this aberrant D metabolism is associated with one of the primary genetic factors predisposing to autoimmune disease, we note with interest the tantalizing data from Chong et al. [30], who found that patients with active SLE respond differently to exogenous 1,25-D and IL-2 than do controls, or patients with inactive SLE.

9. Future directions

We are currently on the threshold of a revolution in our understanding of autoimmune disease. We are

able to examine similarities between each autoimmune disease by characterizing the genetic haplotypes. We have assays to measure the raw cytokine profiles, and we know enough about the healthy body so that we can accurately elucidate what triggers and sustains both the Th1 and Th2 immune responses.

We now need to explore what happens when the cells of the immune system become host to bacterial and viral parasites. These parasites are capable of activating the immune phagocytes from within, triggering a cytokine cascade without any Lymphocytic intervention. That is the dilemma we have introduced with this review. What happens when the immune system doesn't operate as it would in a healthy individual? What steps can we take to help it return to normal? With the answers to these questions will come the cure for so much disease…

Take-home messages

- Sarcoid inflammation has now succumbed to antibiotics in two independent trials, demonstrating, ex juvantibus, a primary, homogenous, bacterial pathogenesis.
- Low-dose minocycline is the antibiotic capable of inducing remission in sarcoidosis. A dual regimen of low-dose azithromycin + minocycline is especially effective.
- Jarisch-Herxheimer shock is a major problem. Unless the antibiotic dosage is carefully controlled, adverse events may include both life-threatening pulmonary insufficiency and life-threatening cardiac events.
- The pathogens appear to be multiple species of tiny, slow growing, cell-wall-deficient (CWD) bacteria living within the cytoplasm of phagocytes.
- The secosteroid hormone 1,25-dihydroxyvitamin-D is elevated in patients with Th1 immune inflammation, while the precursor, 25-hydroxy-vitamin-D, is depressed.
- 1,25-dihydroxyvitamin-D metabolism is similarly disturbed in (at least) rheumatoid arthritis, SLE, and Parkinson's, and it is likely that these diseases also have a bacterial Th1 pathogenesis.

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The World of Autoimmunity; Literature Synopsis

IgM anti-oxLDL antibody and carotid artery atherosclerosis

The role of autoantibodies directed against oxidized low-density lipoprotein (oxLDL) in atherosclerosis is not yet understood. In most human studies, elevated levels of anti-oxLDL antibodies predict future cardiovascular events. Karvonen et al. (Circulation 2003;108:2107) report an inverse association between intima-media thickness of the carotid artery and IgM anti-oxLDL in 1,022 middle-aged men. This inverse association remained statistically significant after adjusting for age, gender, LDL cholesterol, CRP and smoking. Several explanations exist for this finding. It is possible that IgM autoantibodies aid in removal of oxLDL, while IgG isotypes do not.

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Antibiotics in Sarcoidosis - Reflections on the First Year

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Antibiotics in Sarcoidosis - Reflections on the First Year

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2. Mangin M: **Observations of Jarisch-Herxheimer Reaction in Sarcoidosis Patients.** JOIMR 2004;2(1):1

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.

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.

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-α agonists) often present with Tuberculosis [21]. Total elimination of the TNF-α 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.

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-α, 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-α) 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

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.

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 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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Putative Antibacterial Mechanisms for Angiotensin II Receptor Blockers

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ABSTRACT

Angiotensin II has profound actions in Th1 immune disease. It directly modulates Nuclear Factor-kappaB (NF-kappaB), an essential precursor to the generation of inflammatory cytokines and chemokines, including TNF-alpha. Corticosteroids exert their anti-inflammatory action by totally shutting down activation of NF-kappaB, while Angiotensin Receptor Blockers (ARBs) inhibit excessive NF-kappaB activation, allowing the phagocytes to respond to immune challenge in a less aggressive manner. The two anti-inflammatory mechanisms are fundamentally different. The new ARB, Olmesartan Medoxomil, has been identified as useful in treating Th1 inflammatory disease sarcoidosis, and the suggestion has been made that ARBs might also directly affect bacterial pathogens. Receptor proteins actively binding angiotensin II have been found on several species of bacteria. We found no match between the human angiotensin receptor and any similar protein in the 294 bacterial genomes currently sequenced, lending credence to the suggestion that bacteria may be using this host hormone in such a manner as to evade the host's immune system. Clearly, if an ARB was capable of actually inhibiting the supply of A-II, thus denying a microbe the ability to protect itself from destruction by phagocytosis, then that ARB could most definitely be classed as an 'antimicrobial'. The dosing of Olmesartan reported as most useful in immunomodulation, 40mg q8h, is well above the level needed to produce maximal hypotensive activity. It would thus seem likely that Olmesartan is acting on atypical receptors, perhaps directly upon pathogens, or upon some yet-to-be-defined human angiotensin-binding-protein(s).

Abbreviations:
IL-1beta, IL-6, IL-8 are Interleukins, inflammatory cytokines

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CAM-1 is the 'intercellular adhesion molecule'
MCP-1 is 'monocyte chemoattractant protein 1'
TNF-alpha is 'Tumor Necrosis Factor alpha'
IFN-gamma is 'Interferon-gamma'
AT1, AY2 are Angiotensin Type 1 (and 2) receptors subtypes
CS-866 was the developmental name for Olmesartan (Benicar/Olmetec)
Th1, Th2 are two distinct immune responses, distinguished by their cytokine profile

Introduction

Angiotensin II (A-II) has profound actions in Th1 immune disease. Angiotensin II directly modulates the production of Nuclear Factor-kappaB (NF-kappaB) in the cytoplasm of mature phagocytes, causing nuclear release of messenger RNA (mRNA) to begin the transcription for many of the inflammatory chemokines and cytokines, including IL-1beta, IL-6, and IL-8, MCP-1, CAM-1, IFN-gamma and TNF-alpha [1,2,3,4,5,6,7,8]. The blockade of the A-II modulation pathway with Angiotensin II Type 1 Receptor Blockers (ARBs) reduces the generation of these cytokines, including TNF-alpha [5,6], and inhibits the inflammatory process [2,3,5,6].

In the light of new knowledge that Th1 inflammatory disease can be caused by bacterial pathogens [9,10], we need to determine whether ARBs might also be exerting any direct antibacterial action upon the pathogenic bacteria.

Angiotensin Receptor Blockade is Anti-Inflammatory

Marta Ruiz-Ortega has been researching the actions of angiotensin in immune diseases for some time. One of the first to identify A-II's direct stimulatory actions on NF-kappaB [1], Ruiz-Ortgea has since gone on to identify A-II as a key factor in inflammatory nephropathy, especially diabetic nephropathy [2,6], and to confirm the role of ARBs in controlling that inflammation.

Belline, et al, have also confirmed the observations of Iwai, et al, [7}, that phagocyctosis in a murine model of peritoneal inflammation is directly modulated by angiotensin [3]. Belline, et al, were further able to show that phagocytosis in murine peritoneal macrophages was attenuated by the ARB, Losartan, demonstrating that AT1 receptors were involved in "modifying the host resistance to infection".

The release of the inflammatory cytokines and chemokines in 'autoimmune' Th1 inflammation begins whenNF-kappaB is activated in the cytoplasm of monocytes, macrophages and dendritic cells (collectively, 'phagocytes'). NF-kappaB causes the phagocyte nucleus to emit a messenger RNA (mRNA) which contains the genetic code dictating transciption of the cytokines and chemokines in the cytoplasm [1,3,4,6].

Corticosteroids exert their anti-inflammatory action by totally inhibiting the activation of NF-kappaB [11] (in a dose-dependent manner).

Nevertheless, the two anti-inflammatory mechanisms are fundamentally different. Angiotensin II receptors on the phagocyte membrane are just one of the methods by which the immune system can be activated to deal with an invader. Besides the A-II receptor, there are Toll-like, and other receptors, each of which can activate NF-kappaB in order to help the phagocyte deal with the immune challenge. Angiotensin receptor blockade shuts down just one of the channels by which NF-kappaB can be activated to signal the inflammatory cascade. The phagocyte can still react to immune challenges sensed through the other receptors. Corticosteroids shut down NF-kappaB itself, and

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totally suppress any attempt by the phagocyte to prevent the body from harm, whatever the source of immune challenge.

Unusual Clinical Observations

The authors have been observing beneficial effects of ARBs in a cohort of subjects recovering from Sarcoidosis. Sarcoidosis is a chronic inflammatory disease caused by an out-of-control Th1 immune response. These clinical observations seem to reveal a number of idiosynchrasies, perhaps indicating that the ARBs are having an effect on something other than just the Angiotensin II Type 1 Receptor (AGTR1).

Firstly, dosing requirements seem anomalous. Patients report that ARBs continued to give incremental symptomatic improvement at doses well above the levels giving maximal hypertensive activity. For example, Olmesartan (from Benicar/Olmetec) (CS-866) continues to incrementally suppress disease symptoms up to a dose of 40mg every 4 hours, with 40mg every 6-8 hours being the consensus optimum dosing. Yet this ARB achieves maximal hypotensive activity at a dose of 10-20mg qd [12]. Why would a dosage of ARB higher than that make any difference?

Secondly, different ARBs were not equally effective at suppression of disease symptoms. Olmesartan was reported as 'excellent', while Valsartan was a distant 'second best', Irbesartan 'useful'. Yet these ARBs all provide an 'insurmountable' blockade of AGTR1. How could one 'insurmountable' blockade differ from another 'insurmountable' blockade?

Finally, Valsartan did not seem to suppress 'sinus' symptoms. Even though it had adequate palliative effect on muscle pain, psychotic events [13] and dyspnea, it left some subjects with swollen and painful sinuses. After they changed to Olmesartan the 'sinus' problems disappeared. Since there is only one type of AGTR1 receptor in the body, how could any ARB not be active in the sinuses?

The *homo sapiens* Angiotensin II Type 1 Receptor

AGTR1 is a G-protein-coupled receptor (GPCR), a large family of cell-surface receptors which facilitate hormonal signalling through the phagocyte membrane [14]. Other GPCRs include the Toll-like Receptors, which also mediate the body's immune response [15,16]. An increased number of Angiotensin-II receptors are expressed in tissue inflamed by a Th1 disease compared with healthy tissue [17], due to up-regulation of AGTR1 receptors [18].

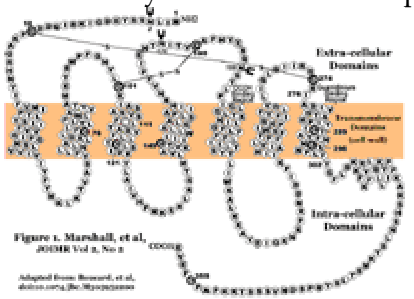

Figure 1. Schematic of the AGTR1 *homo sapiens* angiotensin type 1 receptor protein.

Figure 1 is a schematic diagram of AGTR1 (P30556) [14]. It consists of four extra-cellular domains, seven trans-membrane regions, and four intra-cellular domains. Signalling the presence of the extra-cellular homone Angiotensin-II seems to be accomplished by the structural changes which occur in transmembrane region 7 when Angiotensin II binds near the junctions of the extra-cellular domains and transmembrane regions 5 and 7. The

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carboxyl terminus (O=C-OH) binds to the Lys-199 region of transmembrane 5, and the guanidinium group of Arg2 [$(NH_2)_2$-C-NH-C] binds to Asp-281 in transmembrane 7 [14,19].

Designing and manufacturing ARBs is a multi-billion dollar business, and very few ARB molecular models have been deposited into the Protein Data Bank (PDB), or any other publicly available repositories. The model of olmesartan (shown in figure 2) was constructed from sources including its package insert and Sankyo Ltd brochures. A minimum energy conformation for the molecule (without regard for pH) was optimized using iterated Newtonian mechanics. This optimization was performed using Ghemical, a workstation-based molecular modeling package. Irbesartan was constructed similarly, while candesartan_cilexetil and valsartan were retrieved from the Department of Pharmaceutical Information Science, Tokyo University. Angiotensin II is available from the PDB, accession number 1N9V.

The carboxyl terminus of the insurmountable antagonists (including Candesartan, Irbesartan, Olmesartan and Valsartan) bind to the Lys-199 region of AGTR1. Transmembrane 7 is not affected at all. Despite this, the insurmountable antagonists effectively block the actions of angiotensin II (in man) by occluding this key region of the AGTR1 binding pocket.

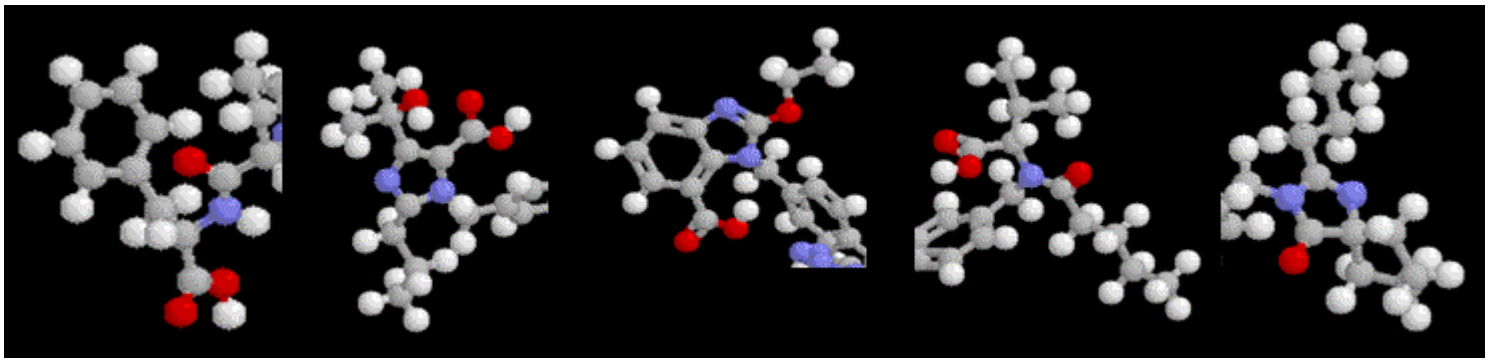

Figure 2. The carboxyl terminus of Angiotensin II and (resp.) Olmesartan, Candesartan, Valsartan and Irbesartan (note that Irbesartan has an O2, not a OCOH terminus).
[**Editor's Note: The authors supplied 3-D models of each of the ARBs.** JOIMR has created a special page where they
can be examined, interactively, in 3-Dimensions. Click here to access those models.
The images above have been supplied for those who cannot access the 3-D models]

The structure of the subject ARBs, and of Angiotensin II itself, are shown in figure 2 (angiotensin II is an octapeptide with the amino acid sequence: Asp-Arg-Val-Tyr-Ile-His-Pro-Phe).

There is significant variation between these ARB structures, and all are different from the carboxyl terminal region of A-II. Although they are extremely effective at binding the transmembrane-6 pocket of AGTR1 it is clear that small changes in the structure or conformation of the receptor might well render one, or more, of the antagonists ineffective. Perhaps if there were genetic mutations in the receptor, then those mutations might affect each ARB's ability to bind into the Lys-199 pocket. In fact, the AGTR1 gene does in fact have 5 reported mutations, but they are all in the transmembrane 7 region, and not adjacent to the Lys-199 pocket. Consequently, genetic mutations alone do not seem adequate to account for the differing ARB blockade effectiveness observed in the clinical studies. It must be inferred that we may be dealing with receptors other than the AGTR1**...**

Bacterial Receptors with affinity for Angiotensin II

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Nickenig, et al, [20] were examining tissue cultured from a human skin biopsy specimen when they noticed something strange. Their tissue sample contained "angiotensin AT1 receptors and a putatively new angiotensin receptor activated by angiotensin(1-6), both coupled to signaling pathways involved in DNA synthesis". They noted the existence of this new receptor in their paper, but were at a loss to explain where it might have come from.

Earlier, in 1993, Whitebread, at al, had warned of "mollicute contamination" in rat tissue, documenting an atypical Angiotensin-II receptor site which disappeared after application of the 'antibiotic mixture BM-Cyclin' [21]. They had noted that it was not possible to study the rat A-II receptor in the presence of A-II receptors on contaminating mollicutes ('Mollicute' is a synonym for 'mycoplasma', tiny 'L-form' or 'Cell Wall Deficient' bacteria). The culprit bacterial species was identified as *Acholeplasma laidlawii*. Finally, they noted that the bacterial receptor could not be blocked with the ARB Losartan (Cozaar).

Bergwitz, et al,{22] accurately characterized an A-II receptor they found on *Mycoplasma hyorhinis*, and noted that the bacterium adheres tightly to the membrane of mammalian cells. They noted that the atypical A-II receptors might be due to host-parasite interactions, as the receptor's affinity for A-II was 7 times higher when the bacterium had infected a cell rather than when the bacterium was in isolated culture.They carefully confirmed that the bacterial A-II receptor was specific for A-II and Angiotensin I (A-I). The antibiotic bacitracin and aprotinin (a natural protease inhibitor) were both potent inhibitors of A-II binding to the receptor on M. hyorhinis. Neither bacitracin or aprotinin affected the sensitivity of the human A-II receptor, AGTR1.

Servant, et al, [23] isolated an atypical A-II receptor in rat pheochromocytoma cells. Bacitracin potently inhibited the actions of this atypical receptor, and enzyme immunoassay confirmed that the cells were contaminated with Mycoplasma hyorhynis. The A-II binding sites were eliminated by treating the tissue with 'BM-cycline'.

Using an A-II analog they estimated that the bacterial receptor was sized at 95kDa, significantly different in size from the mammlian AGTR1 receptor. Losartan was ineffective blocking Angiotensin-II from the bacterial receptor.

Smith [24] found that the bacterial receptor on M. hyorhinis has a marked affinity for A-I as well as A-II and that the affinities were related to PH. He therefore hypothesized that the microbe might be able to tell the PH of its environment by balancing the respective magnitudes of A-I and A-I binding to its receptor.

Bergwitz [22] concluded (in 1991) "**Although the biological significance of these binding sites is unknown, they .. may have implications for the involvement of mycoplasma in the pathogenesis of autoimmune disorders.**" It is hard to disagree.

From 1991 to 2004, and the Genome

The genomes of 294 bacterial species are now available in the NCBI Genebank, most of them completed. When one takes the gene for AGTR1 and runs a comparison between the human gene and all species in the Genebank (2,199,823 DNA sequences), it becomes obvious that only the mammalian species possess AGTR1 similar to *homo sapiens*. Takanayagi [25] observed "The deduced amino acid sequence of the human angiotensin II (Ang II) receptor was 95.3% and 94.2% identical to those of bovine and rat". As you traverse the mammalian phylogeny, the differences from AGTR1 of *homo sapiens* become more and more pronounced.

The genebank further confirms that there are no DNA sequences in any microbial species capable of transcribing a protein even vaguely similar to the human AGTR1.

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We therefore took a small fragment of the transcribed AGTR1 gene, just the 30 amino acid sequence from position 181 to 210, covering the region where the key carboxyl terminus of A-II binds to the human AGTR1.

P30556 DEFINITION Type-1 angiotensin II receptor, *homo sapiens*
181-210: afhyesqnst lpiglgltkn ilgflfpfli

This region is labelled the "OCOH Binding Region" in figure 1. Comparing this sequence against the entire translated genome database (tblastn) revealed a perfect match with homo sapiens, an almost perfect match with the genomes of beef cattle, pigs and rats, but zero correlation with any of the microbial genomes. Thus one can now say, definitively, that no microbial A-II receptor is identical with AGTR1, indeed, none are even structurally similar.

It can therefore be inferred that the microbial receptor has evolved to perform a totally different function from that of AGTR1 in man. Indeed, McLaren, et al, suggested that **the binding of host proteins by microorganisms may help them avoid recognition by the host immune system** [26].

Clearly, if an ARB was capable of actually inhibiting the supply of A-II to a microbe, thus denying it the ability to protect itself from destruction by phagocytosis, then that ARB could most definitely be classed as an 'antimicrobial'.

The Alternate Hypothesis - Unknown Human Genes sensitive to A-II

Several human genes have been reported to have angiotensin type II (AT2) receptor activity. The MAS Proto-oncogene, the angiotensin/vasopressin receptor (LOC171390), the melanocortin 2 receptor (adrenocorticotropic hormone)(MC2R), and AK007383, a mouse AT1 receptor-related protein, have all been reported to have receptor sites for A-II. With the exception of the latter, it is unlikely that any of the subject ARBs could be exerting a noticeable clinical effect on this predominantly AT2 receptor activity. Unlikley, but not impossible. Additionally, if angiotensin were binding to other, yet unidentified, receptors or proteins in *homo sapiens* then this would supply an alternate hypothesis - that the subject ARBs are affecting yet-to-be-determined metabolism in the human genome itself, and not in the bacterial genomes. More research needs to be done to totally preclude this possibility.

Some ARBs Cannot Blockade Microbial A-II Receptors

Losartan (DuP 753), the earliest of the ARBs, did not stop A-II from binding at the microbial angiotensin receptors [20,22, 23]. But Losartan was an earlier ARB, and binds competitively with angiotensin, not insurmountably like the more modern ARBs. Its structure is radically different. It cannot be inferred that just because Losartan failed to inhibit the bacteria from metabolizing angiotensin, that the modern ARBs would not do a better job. This is especially true at the higher doses which the clinical studies have indicated seem to be necessary.

Variations in the AT1 Receptor Structure

Fierens, et al, [27] explored the effect of variations in the structure of an angiotensin receptor, variations which the genebank confirms must exist between any bacterial angiotensin receptor and that of man. They susbtituted the Lysine near the carboxyl binding pocket near position 199 with Glutamine, and found that just this single substitution decreased the affinity 45-fold for candesartan (95% insurmountable), 10-fold for irbesartan (40% insurmountable) and 5-fold for losartan (surmountable). It is noteworthy that when this study was undertaken, olmesartan was not yet available.

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Candesartan, irbesartan and losartan are all equally effective in the human AGTR1, yet offer widely different blockade effectiveness on atypical receptors. It could be expected that differences in activity would be also observable when blockading the (atypical) bacterial receptors.

Summary and Authors' Perspective

While there is little doubt that Angiotensin II contributes significantly to inflammatory disease, there have been surprisingly few studies performed to identify and confirm exactly how Angiotensin Receptor Blockade may ameliorate the damage and suffering from these diseases. The Angiotensin II receptor site(s) already identified on bacterial species must have some biological function. Clearly, if an ARB was capable of actually inhibiting the supply of A-II to a microbe, thus denying it the ability to protect itself from destruction by phagocytosis, then that ARB could most definitely be classed as an 'antimicrobial'. It was 1991 when Bergwitz [22] concluded "Although the biological significance of these binding sites is unknown, they .. may have implications for the involvement of mycoplasma in the pathogenesis of autoimmune disorders". It is evident that more needs to be done to identify exactly why bacteria metabolize angiotensin, whether they use fragments of this human hormone to enhance their ability to hide from the immune system [26], or whether they use them to directly pervert the very process of phagocytosis itself [28,29].

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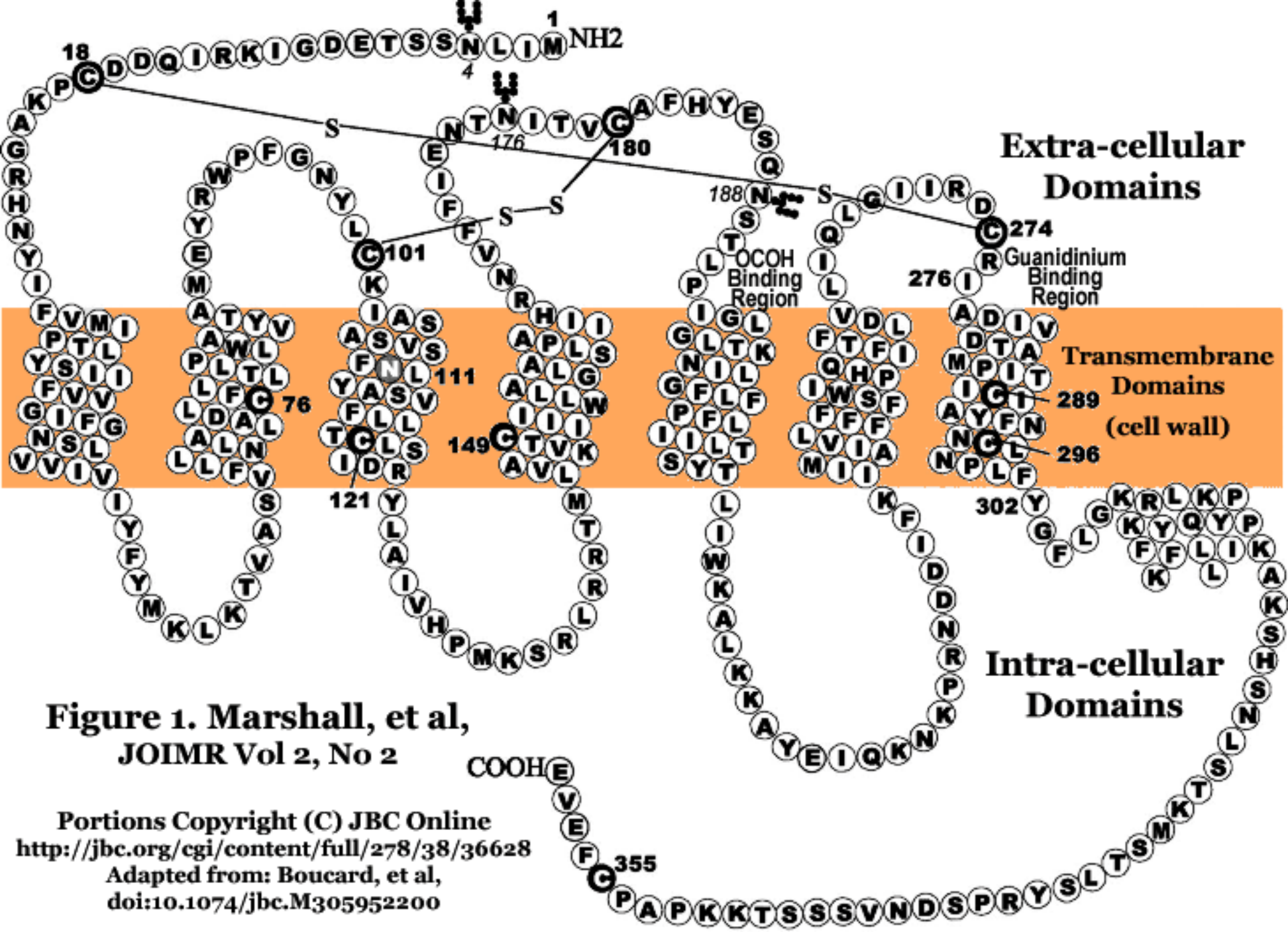

Figure 1. Marshall, et al,
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First presenting signs or symptoms of sarcoidosis in a Japanese population.

Matsuo T, Fujiwara N, Nakata Y.

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PURPOSE: To determine the first presenting signs or symptoms or other reasons leading to the diagnosis of sarcoidosis. METHODS: A retrospective review was made of the records of 123 consecutive Japanese patients with histopathological diagnosis of sarcoidosis seen at a referral-based university hospital. RESULTS: At the first presentation, eye symptoms in 32 patients, abnormal chest X-ray findings in 52 patients, common cold-like symptoms in 12 patients, lymphadenopathy in 6 patients, skin lesions in 14 patients, and examinations for other diseases in 4 patients led to the final diagnosis. Overall, uveitis was detected in 60 patients (50%) during the follow-up. CONCLUSIONS: Mass screening programs of chest X-rays are the major way sarcoidosis is detected in Japan. Uveitis is seen in about half the patients during the course of sarcoidosis, and eye symptoms are frequent first presentations of sarcoidosis. These facts emphasize the role of ophthalmologists in the diagnosis and management of sarcoidosis.

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Sep 14 2005 04:34:46

[A14] A Double-Blinded, Randomized, Placebo-Controlled Trial of Infliximab in Active Pulmonary Sarcoidosis

M.D. Rossman, MD, L.S. Newman, MD, R.P. Baughman, MD, A. Teirstein, MD, S.E. Weinberger, MD, G.F. Keenan, MD, B.E. Sands, MD, Denver, CO, Boston, MA, NY, NY, Cincinnati, OH, Phila., Malvern, PA

Background: Tumor necrosis factor (TNF) is overexpressed by alveolar macrophages in active pulmonary sarcoidosis (APS) and is essential for granuloma formation. Infliximab (IFX) is an anti-TNF antibody that binds soluble and cell-bound TNF. We performed a pilot study of the safety and efficacy of IFX in the treatment of APS. **Methods:** Subjects were included if they had APS at Scadding stage II,III or IV and vital capacity (VC) ⩾50% and ⩽80% predicted despite prednisone use. Subjects were randomized (2:1) at 5 locations to group I (IFX 5mg/kg) or group II (placebo) at weeks 0 and 2 (phase I). During phase II all subjects received IFX at wks 6 and 14. Lung volumes and spirometry were measured at weeks 0,6,12,14,22 and 38. The primary endpoint was percent change in VC (VCwk6–VCwk0 / VCwk0) between groups I and II during phase I. Forty-two subjects were planned for the study; 19 were enrolled. **Results:** Mean VC at wk 0 was 2.63 (group I) and 2.37 (group II). Preliminary analysis demonstrated the mean ± SD relative change in VC to be 0.13 ± 0.34 for group I (n=13) and 0.08 ± 0.09 for group II (n=6) (p=0.74). Seven patients had serious adverse events, including decreased WBC and elevated CPK (1pt), hyperglycemia and bronchitis (1pt), pneumonia (2pt), thigh pain (1pt), URI and suicidal ideation (1pt), cellulitis, acute renal failure, pulmonary embolus and death (1pt). **Conclusions:** IFX may improve VC in patients with APS resistant to steroids. Given the potential for adverse effects, use of IFX in this patient population should be confined to ongoing clinical trials.

SUNDAY, May 22, 2005 9:45 am, Room 3 (Upper Level), San Diego Convention Center

[**] Mini-Symposium (Abstract Page: A19) Session: 8:15 am-10:45 am, TREATMENT OF SARCOIDOSIS AND IPF

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