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Multiple Sclerosis and Chronic Fatigue A Bacterial Etiology?

Dr. Luther E. Lindner

**General Comments: The Presence of Bacteria in the Human
Bloodstream and Their Presumed Significance.**

**Nutrition And Lifestyle Suggestions In Relation To Our Bacteria
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**Experimental Antibiotic Treatment Protocols For New Bacterium
For Physicians Investigations**

**The Presence of Bacteria in the Human Bloodstream and Their
Presumed Significance.**

Luther E. Lindner M.D., Ph.D.
Revised January 11, 2008.

This is written in response to requests for information about our research at the Lindner Research Foundation, particularly in relation to multiple sclerosis (MS) and the chronic fatigue syndrome (CFS). I am a physician (pathologist) on the faculty of Texas A&M Health Science Center, College of Medicine, the director and founding member of the Lindner Research Foundation and a research associate of The Stowe Foundation. In the latter two I have been studying several newly recognized bacteria that live in human blood and tissue that appear to be associated with chronic illness and autoimmune disorders, including the ones of interest here.

The bacteria were discovered essentially by accident in blood samples. The more abundant of these bacteria have been identified as several species of *Methylobacterium*. They are present in the



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bloodstream of all of the human population in significant numbers. They apparently are acquired prior to birth, although new strains might be acquired later. They are generally present in higher numbers in persons who are symptomatic. There is no direct proof that they cause the chronic fatigue syndrome, multiple sclerosis, or any other disease, but their presence in the bloodstream gives them the potential to be involved in a number of problems. In persons with certain conditions who were treated with appropriate regimens, a reduction in these bacteria was associated with clinical improvement and an increase corresponded with increased symptoms. It is presumed that the symptoms require not only the presence of the bacteria, but also some sort of immune or inflammatory reaction against them to produce disease that is not present in asymptomatic individuals, but this is not yet proven. Most individuals lack an effective immune reaction against them presumably because their presence prior to birth leads to immune tolerance. In addition, they coat themselves with a complex polysaccharide and with serum proteins, which help to hide them from the immune system. This polysaccharide is itself a potential cause of chronic problems. Individual strains of bacteria may be important, but this has not yet been studied. It is possible that an abnormal immune reaction is triggered by exposure to other organisms or chemicals.

I am not treating any patients with these bacteria myself, and clinical tests for them, including their level, specific strains, and immune responses to them are not currently available. My primary interest at present is in improving the culture systems, developing diagnostic tests, and understanding the characteristics of the organisms and whether and how they cause disease. Previously, the Lindner Research Foundation and a collaborator separately developed EXPERIMENTAL drug treatment regimens that have shown benefit in some patients, using standard FDA-approved antibiotics. These are NOT RECOMMENDED FOR USE UNDER CURRENT CONDITIONS!!!! We have seen good responses in about 20% of MS patients with a marked improvement in function; chronic fatigue patients are more likely to show a short-term response, but again only about 20% have achieved a long-term relatively complete response. Some CFS patients have remained asymptomatic after treatment, however, and some MS patients have sustained a clinical remission while on antibiotics that has apparently allowed major healing with a



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marked improvement in their condition; in a few of these patients the remission has been sustained.

The problem with the antibiotic treatment regimens is that we have demonstrated that with some patients, antibiotics can actually stimulate bacterial growth and produce an exacerbation of symptoms. The reason for this is partly understood, but there is currently no way of reliably testing for whether this will happen. Furthermore, although we have seen a reduction in bacterial levels in some patients, we have never successfully cleared these bacteria completely from the bloodstream.

Part of the problem is that many of the bacteria lack well-formed cell walls; some antibiotics act by destroying cell walls and therefore are ineffective. None of the available drug treatments are free of hazards and many of these drugs are expensive.

We are constantly looking at alternative treatment approaches that may work better. Assuming that the bacteria can be confirmed as the cause of these and/or other diseases, the long-term goal of the research is to study the immune response to these bacteria and to develop effective treatments. The Lindner Research Foundation is currently collaborating with The Stowe Foundation on an investigation of patient-specific transfer factors developed against these bacteria. The hope is to develop immune therapy protocols that can have long lasting effects on keeping the bacteria in check or by controlling the body's immune response to them.

Although antibiotic treatment appears to be hazardous and of limited effectiveness at this point, you may still derive benefit from nutritional adjustments and transfer factors. We have learned a lot about the basic nutritional requirements of the bacteria and why their growth in the body is so limited. This information allows the growth of the bacteria to be manipulated within limits. The single most important component of that appears to be zinc supplementation and the limitation of other minerals to normal daily ranges. Supplementation with antioxidants also brings benefits to cellular respiration and helps to limit oxidative stress. It is recommended that nutritional adjustments



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be begun prior to the antibiotics if they are used. Most of what we have found to be true about the optimum nutritional regimen with regard to this bacterium is good nutrition anyway for other reasons. The Stowe Foundation provides its clients a specific immune support regimen.

Nutrition And Lifestyle Suggestions In Relation To Our Bacteria

Luther E. Lindner M.D., Ph.D.

Revised Jan. 8, 2008

Methylobacterium species are present in the bloodstream in all "normal" persons and in increased levels in persons with nonspecific symptoms or a number of active clinical disorders including the chronic fatigue and immune dysfunction syndrome (CFIDS), fibromyalgia, and several autoimmune disorders such as multiple sclerosis, lupus erythematosus, and rheumatoid arthritis. There is no direct evidence that the bacteria are the cause of these disorders, and the causation probably is complex, but individual patients with these problems who have shown a reduction in their bacterial counts on an appropriate regimen have also had a significant improvement in their symptoms. It is possible to partially control the level of the bacteria by nutritional measures. Some patients are actually made worse by antibiotic treatment. They can also be made worse by inappropriate diet and certain other factors.

Persons who are ill should attempt to maintain good nutrition in general. High dose vitamins make many patients feel better. There may be a danger to taking increased amounts of certain vitamins, however, especially nicotinic acid (niacin, vitamin B-3), which can significantly stimulate bacterial growth. Replacing other grains in the diet with corn may reduce the body's levels of nicotinic acid. Because niacin and several other components of multivitamin capsules appear to stimulate bacterial growth and to be needed by them, the use of comprehensive multivitamin preparations is strongly discouraged. Vitamin C and possibly vitamin E are desirable, however large doses of vitamin C may affect antibiotic sensitivity. Vitamins A and D do not appear to have any effect, pro or con. Very large doses of certain of the B vitamins, vitamins A, C, D and E can be toxic, so there is a limit to how much of any of the vitamins should be taken. Some patients have reported improvement in



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symptoms from vitamin B-12 injections; these are usually administered by a physician. Apparently a similar effect can be achieved with high dose oral B-12, on the order of 200-1000 micrograms per day. Experiments suggest a rationale for a B-12 effect. A specific metabolite produces some growth stimulation, and its level can be reduced by increased B-12. Folic acid appears to directly inhibit bacterial growth. B-6, B-12 and folic acid may be particularly important in persons using cysteine (cystine) supplements or with a high cysteine intake (see below).

Some CFS literature suggests that there may be improvement from injections of magnesium sulfate and oral zinc supplements. In culture increased levels of magnesium have little effect on the growth of the bacteria. Presumably the reported effects of magnesium are due to a secondary effect on symptoms. I cannot recommend these injections at this time, although they apparently do no harm. You could consider supplementation with oral magnesium, but be careful with the dose, especially if it is not taken in combination with calcium. Magnesium compounds are laxatives at oral doses over a few hundred milligrams at a time.

Our studies indicate that the growth of these bacteria is stimulated by compounds of copper, manganese, tin, iron and possibly other metals. You should avoid mineral supplements containing these minerals as well as foods that are high in them. It is likely that copper, manganese and iron are the most important of these.

We have repeatedly noted that both stress in general and inflammatory processes in particular stimulate the growth of the bacteria. Inflammation results in the release of several copper and manganese-containing enzymes from white blood cells and raises blood copper levels. Inflammation, stress, and certain hormones all elevate blood levels of copper, mostly bound to a specific protein. I suggest a reduced intake of foods high in copper, particularly shrimp, lobster, crab, crayfish, and liver. If you have copper pipes, consider bottled water for drinking and cooking. Manganese and iron may be harder to avoid. Absolute avoidance of these foods is not indicated, first because at least some of these minerals is necessary for health and second because there may be an easier way to deal with the problem. Dental amalgam could be a



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source of some of these minerals, although it is unlikely that it plays a major role with most patients.

I strongly recommend an increased intake of zinc. Zinc suppresses the growth of these bacteria in culture and increased zinc intake competes with the other minerals that we have noted as a problem, resulting in less absorption, increased excretion, and less availability within the body. Zinc also has a beneficial effect on the immune system in general. The recommended amount is 25-35 mg. a day of zinc as zinc sulfate or an equivalent zinc compound for the average adult. Amounts over 50 mg. can lead to overdose. Overdosage will produce anemia and weakness because excessive reduction of available copper interferes with the body's ability to make enzymes that supply the bulk of the energy to all the cells in the body and interferes with the incorporation of iron into the hemoglobin in red blood cells that carries oxygen throughout the body. Because of the problems with possible overdose, I recommend periodically monitoring the iron levels in the blood and/or the blood counts when taking high dose zinc supplements.

I also recommend monitoring the iron level because of the possibility that iron stimulates bacterial growth. The best test for total body iron stores is the serum ferritin, but it is possible that this is not the best test for whatever the active form of iron for the bacteria is, most likely the free iron. We recommend keeping the level at the lower end of the normal range. If it is in midrange or above, I recommend donating blood periodically to reduce body iron stores. Blood donation has been proved to provide benefits to health in general.

Another trace metal that has been suggested as beneficial in the CFS literature is chromium. Our testing shows no inhibition of bacterial growth by this, and possibly stimulation with some strains, so any beneficial effect is indirect, but we have confirmed symptomatic benefit in some patients. Chromium is known to be needed for insulin activity, through mechanisms that aren't fully clear. Many CFS patients have sugar cravings and fatigue increasing several hours after eating. Chromium antagonizes this. Since increased zinc will probably antagonize absorption of chromium, some chromium supplementation along with it is probably needed. I suggest 100-200 micrograms per day.



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Chromium may also reduce the risk of arteriosclerosis. There is a risk to excessive chromium supplementation so these levels are probably maximum.

These metals are probably acting as cofactors in critical biochemical reactions needed by the bacteria. Certain metals are probably acting as oxidants, oxidizing as yet unidentified compounds. This raises the possibility that high levels of antioxidant compounds may be of help. The known major antioxidant materials in the diet are vitamin C, vitamin E, carotenoids and selenium, as well as a variety of sulfur-containing compounds and bioflavonoids, including so-called pycnogenols and proanthocyanins. We do not yet have solid data on the possible effect of these, but since they are good in the diet for other reasons, supplementation with this class of compounds is recommended.

We have encountered a few patients with elevated porphyrin levels. It is unclear whether this is common, but elevated metal levels, especially iron, can elevate porphyrins. Elevated porphyrins can be toxic.

Another mineral that may be beneficial is boron, in the form of borates. It definitely inhibits bacterial growth in culture. A recommended dosage is not yet established. High levels may be toxic.

The CFS literature suggests that certain sulfur-containing compounds may be beneficial. Garlic in particular has been mentioned. The compound that gives garlic its aroma (stink?) is one of these sulfur-containing compounds. These compounds react with several metals within the body, including copper, and therefore may be complementing zinc. This doesn't get rid of the copper, but ties it up temporarily. The garlic powders and oils that have been deodorized may lack some sulfur compounds and may be less valuable. Onions and other relatives of garlic may have some of the same benefits. I have seen two patients who apparently converted from antibiotic resistance to slight sensitivity while taking large doses of garlic.

Experiments on the effect of sulfhydryl reagents suggest other sulphur compounds may have value, but also suggest that sulfhydryl



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compounds may sometimes be bad. The best data we have is on the effect of L-cysteine (cystine), an amino acid that is one of the basic building blocks of proteins. Cysteine usually stimulates bacterial growth in culture, but this can be converted to growth inhibition in the presence of certain other compounds.

We have observed in culture that the chemical which makes peppers hot can stimulate bacterial growth. Peppers should be used in moderation.

The CFS literature suggests that taurine may be beneficial. In the testing to date, taurine has no effect on cultures. In the body cysteine is converted to taurine. Taurine could be affecting the breakdown of cysteine.

Various herbs and other nutritional remedies have been recommended by various persons without a scientific basis. Limited testing done to date has not shown most herbs to be beneficial. I have, however, noted a few individuals taking complex mixtures of herbs that have shown marked improvement both in their levels of bacteria and in their symptoms, so there undoubtedly are nutritional supplements of this sort that are beneficial. Pycnogenol preparations, including Isotonix OPC-3 (see www.marketamericaUSA.com) are probably helpful. Another supplement that may be effective that is also reasonably priced is The Missing Link from Designing Health, Inc., (805) 257-1705. A complex regimen from Sunrider International (the Sunpack) is the most effective that I have seen to date, producing significant reductions in bacterial levels and symptoms, but it is expensive and it is unclear what most of the components do. A distributor in Houston, TX, who will ship, is Janet Snell at 281-870-1092. It has been suggested that turmeric root or its main active component curcumin may be beneficial. This is known to have strong anti-inflammatory effects and may also have a direct effect on the bacteria. Other herbs that reportedly have an anti-inflammatory effect include comfrey, feverfew, and fenugreek. Since herbs are very complex materials, they may contain compounds that are hazardous at high doses or in chronic use. Recommended doses are not established.

It is now possible to predict many chemicals, including drugs,



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which will stimulate or inhibit bacterial growth. Many of the herbal preparations contain large amounts of complex phenolic compounds and their conjugates which are predicted to inhibit growth.

As previously discussed, we have observed that the growth of the bacterium is somehow tied to the inflammatory process. Isolates of the bacteria from patients who have been stressed, are more ill, or who have active inflammatory processes going on show not only greater numbers of organisms, but also their organisms have a greater growth potential in culture which subsides over time. Something the bacteria have acquired in the patient is required for the growth process. I initially related this to release of metal-containing enzymes during inflammation, and that may be part of the process, but our data suggests at least one other cause. Apparently the growth of the bacteria is affected by the availability of derivatives of unsaturated fatty acids that are produced as part of inflammation. Unfortunately, at this time we aren't sure which of these derivatives is the critical one that produces most of the growth stimulation.

The critical material(s) are presumably derived from an unsaturated fatty acid known as arachidonic acid that is released as one of the primary reactions in the inflammatory process. Arachidonic acid is a normal and necessary component of the body that can be derived from the diet directly or synthesized in the body from other unsaturated omega-6 fatty acids. Many anti-inflammatory drugs such as aspirin and its relatives block the conversion of arachidonic acid to compounds that are effective mediators of inflammation. Unfortunately, these drugs block some of the possible conversions but not all, and administration of most drugs in this class to patients has not produced much effect on the bacteria or the symptoms of the patients, so presumably they are not blocking the critical pathway(s) of conversion. Nizoral blocks another pathway. Steroids partially block the release of free arachidonic acid. Steroids have been used for a long time in the treatment of various "autoimmune" disorders including lupus erythematosus, rheumatoid arthritis, and multiple sclerosis, all of which may be related to our bacterium. They are not a cure-all, since there are many complications associated with their use and they don't block the conversions completely. It is possible that the beneficial effect of the steroids in these processes is directly related to suppression of growth of the bacteria,



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rather than just their effects in suppressing inflammation.

Nonsteroidal anti-inflammatory drugs may partially block this process and their use at a moderate level should be considered, taking into consideration the risks of long-term use. Other things can be done to affect this. The first is to control any treatable inflammatory processes that exist in the body and to control infection and inflammation in general, no matter what the source. This includes a general control of stress. CFS and MS patients have known for a long time that physical or mental stress or illness makes their disease worse. They have also noted a relationship of their symptoms to dental infections, sinus infections and similar problems. If necessary, the lifestyle should be adjusted and other medical and dental problems should be cleaned up. Extreme exercise and injuries should be avoided. It is suggested by some sources that food allergies may be present and be providing an inflammatory stimulus in some patients. Testing for food allergies and elimination of offending foods is suggested.

Another dietary maneuver that can be tried is to adjust the amount of arachidonic acid that is available to be released in the body by adjusting the dietary intake of fatty acids. Fat intake in general should be reduced, and particularly the intake of many cooking oils and margarines. Completely avoiding unsaturated fatty acids will have bad consequences; they are essential nutrients. The type of unsaturated fatty acids that are consumed, however, will affect the amount of arachidonic acid available in the body. There is reason to believe that the omega-3 fatty acids that are available in marine fish and some other seafoods are desirable and they can replace much of the arachidonic acid in the body. Nuts and nut oils also tend to contain non-omega-6 fatty acids and are also a good source of fats. Reduction of meat in the diet and replacement of much of it with marine fish is recommended. This may have health benefits unrelated to our bacteria, such as reduced arteriosclerosis. Oil of primrose, flaxseed oil, borage oil and nuts are recommended sources of non-omega six fatty acids. Walnuts, almonds, and macdamia nuts appear to be particularly good nuts. Most of the available vegetable oils contain mostly omega-6 fatty acids which are the precursors of arachidonic acid. Most processed foods contain these and they should be reduced in the diet. Canola oil and olive oil may have a more neutral effect and are the recommended cooking oils.



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We have not studied the effects of this kind of competition in the laboratory, so I have no direct evidence that it will work, but it does seem to help some patients. This requires a major adjustment in the diet. Simple supplementation with commercial fish oil capsules, for instance, without removing the dietary omega-6 fatty acids, requires very large intakes (20-40 g./day) to significantly alter the overall body composition of unsaturated fatty acids, and the high fat intake is not good. With a carefully controlled diet, however, there is reason to believe that practical intakes (5-6000 mg./day) may be helpful.

Several physicians have reported that supplementation with lecithin (soy is the recommended source), which contains certain fatty acids and other components, may be beneficial. The mechanism suggested for this benefit is probably not correct, but we have seen that a component of lecithin known as choline is inhibitory to the bacteria. Recommended doses are not yet available.

The CFS literature suggests that supplementation with carnitine helps some patients. It has no direct effect in our cultures. Carnitine plays a role in the metabolism of fatty acids, so it may affect the availability of arachidonic acid. I do not recommend carnitine supplements until we have studied this, although it is a normal and harmless dietary component in reasonable levels. The CFS literature also suggests that covitamin Q₁₀ (ubiquinone) may have some value. This also doesn't have a direct effect on the bacteria, but may again be helpful in lowering the production of active arachidonate derivatives.

Some data suggests that a component of milk promotes the growth of the bacteria. We don't know what that component might be or whether the effect we see in culture also happens in the patient. It is prudent to limit the intake of milk and milk products until more is known.

We have observed that some currently unidentified component present in fruit juices stimulates bacterial growth in culture. Since juices are digested prior to absorption, it is unclear at this time whether fruit juices will also stimulate levels in the patient. Until data is obtained, it is suggested that fruits and fruit juices be consumed in limited amounts. Citrus fruit may be less of a problem.



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Excessive light exposure may promote growth of the bacteria, so sun exposure should be controlled.

SUMMARY: At this time a large portion of the patients tested are resistant to the available antibiotics. In general, these patients have higher levels of bacteria and their bacteria show greater growth potential in culture. Nutritional manipulation to slow the growth of bacteria based on selective vitamin supplementation, zinc 25-50 mg/day, chromium 100-200 mcg/day, garlic (?), appropriate sources of non- omega-6 unsaturated fatty acids (at least 5g (5000mg) per day), elimination of undesirable foods, particularly those containing high levels of copper and omega-6 unsaturated fatty acids, a reduction of iron levels and possibly herbal supplements may convert some of these untreatable patients into responders or at least reduce the severity of their clinical problems. We are currently experimenting with a supplement regimen based on these recommendations, which appears to produce symptomatic improvement in at least some patients. If the regimen proves to be generally helpful, we will try to find someone who will make it available commercially.

Antibiotic Treatment and the New Bacteria

Luther E. Lindner M.D., Ph. D.

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The following is information on the effects of antibiotics on these bacteria, derived in part from patient data and in part from culture. Note that I DO NOT RECOMMEND ANTIBIOTIC TREATMENT FOR THESE BACTERIA, due to the problems I have noted above. We have seen patients who have actually been made sicker when treated with an antibiotic to which their isolate was resistant; the antibiotics sometimes can actually stimulate bacterial growth. Currently we cannot test reliably for antibiotic sensitivity or resistance.

Several treatment regimens have been tested and have shown value in culture and in trials on patients. These regimens produced actual cure of CFS patients or remission in MS patients in a minority of patients. Some more experienced a significant improvement in symptoms but were not cured, at least over a period of a few months.



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There is longer-term data with a few patients that suggests that either long-term cure or improvement may occur even though bacteria remain. Many patients will definitely be antibiotic resistant initially or will develop antibiotic resistance with time and will not respond or will be made worse.

With MS patients less than 50% have had some response. A complete recovery is not necessarily expected since some nervous system damage may be permanent. About 20% of patients have had a strong response that has allowed a significant improvement in function. We do not know yet whether the responders will remain relatively well indefinitely after cessation of therapy.

With this organism, true bacteriologic cure, i. e. complete elimination of all bacteria, is not possible with available antibiotics. What can be accomplished at this time is control of the bacteria long enough to allow some healing to occur, and possibly for the immune system to recover. We are working with The Stowe Foundation to try to develop appropriate immune therapy protocols.

The following information is provided as a guide to suggest antibiotics that can be used for treating other infections or that perhaps should be avoided.

The following antibiotics have shown value so far:

1. Penicillins with probenecid. We have limited comparative data on sensitivity to various penicillins. Clinical responses suggest that the response is best to the penicillin G/penicillin V spectrum. Clinical responses and failures suggest that the bacteria make a penicillinase or general beta-lactamase, probably slowly inducible. Thus penicillin alone will not be effective for a sustained response in most patients, although it will give a short-term response in many. The penicillinase can be inhibited by simultaneous administration of Augmentin (Clavulin; amoxicillin+clavulanic acid) or a penicillinase-resistant penicillin. Minimum doses are not known. The current suggestion for adults is a combination of oral penicillin V 500-1000 mg., Augmentin 500 mg., and probenecid 500 mg. all taken four times a day. A few



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patients have done better with dicloxacillin instead, but the majority of bacterial isolates show poorer sensitivity to this group of penicillins. Augmentin at these doses is expensive.

2. Ciprofloxacin in divided doses of 1-2 grams/day. The suggested dose for most adult patients is 500 mg. three times a day. Not yet tested is the effect of adding probenecid to the regimen, to reduce excretion and increase penetration of the CNS. If probenecid is given, it should be 500 mg. three or four times daily. Since probenecid slightly raises the blood and probably the CSF levels of ciprofloxacin, the dosage could perhaps be reduced if it is used, perhaps to 250 mg. three or four times daily. Also not tested is giving higher doses less often, e. g. 750 mg. twice a day. In theory, with these bacteria, it is better to give smaller, more frequent doses to maintain continuous blood levels. At a minimum, ciprofloxacin should be given for at least two months, following the clinical response. This treatment is expensive and it is contraindicated in children. In patients who don't tolerate Cipro another quinolone drug may be a viable alternative, but data on other quinolones is very limited. Quinolones have some significant toxicities, especially with long-term use, that should be considered.

3. Isoniazid, given as 100 mg. three times a day. It is unclear why the bacteria are sensitive to this, as they are not related to *Mycobacterium* at all. This is cheap and usually well-tolerated by younger patients with a wealth of data on long-term toxicity. It must be given with supplementary vitamin B-6 (pyridoxine) as it binds the vitamin and can lead to vitamin deficiency with peripheral neuropathy. It is dangerous in the elderly and liver functions must be monitored

4. Third generation cephalosporins. The bacteria are usually resistant to first and second generation cephalosporins. We have no direct data on treatment with these yet, so dosage is not established. Cefixime sometimes stimulates bacterial growth. I suggest the normal maximum sustainable dosage. CNS penetration may be unreliable. On the whole, these have been disappointing.

5. Azithromycin and clarithromycin. The bacteria are resistant to



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erythromycin. Clarithromycin appears more effective in culture, but it also sometimes stimulates bacterial growth. The tissue penetration capabilities of azithromycin suggest it might be of value, but we haven't observed much benefit. There appears to be a synergistic effect with a few isolates with chloroquin and hydroxychloroquin. The latter have major toxicities and should be used with great care, but they also sometimes are effective against bacteria by themselves.

6. Minocycline or doxycycline. These do not kill the bacteria so much as slow their growth. Only some isolates appear to be sensitive. Doses are not established, but the usual doses are suggested.

The following antibiotics have not shown any effectiveness:

7. All aminoglycosides and sulfa-trimethoprim have no effect on these bacteria in culture.

Sporadic sensitivity has been seen to some other drugs, but not consistently enough to recommend any for general use. There are several recently-developed antibiotics that have not been tested, and not all possible antibiotics within the main classes have been tested. Due to the requirement for long-term treatment, we have not looked as thoroughly at drugs that cannot be given orally. Use of nutritional adjustments in combination with the antibiotics may improve results, but this has not yet been thoroughly tested. See separate information on nutrition.

If therapy is attempted, it should be for a minimum of two months, following the clinical response. Longer treatment will be needed in the majority of patients. The treatment is complicated by the fact that the organism has so-called "resting forms" and also makes cell wall defective-forms and hence resists antibiotics in normal treatment schedules, requiring continuous high-dose antibiotics over a long period of time to have a reasonable hope of eventually catching these forms. I recommend a cautious withdrawal of drugs after several months free of symptoms. The choice of treatment regimen should be controlled by known drug risks, in vitro sensitivities when that becomes available, clinical tolerance and economic considerations. A



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combination of two antibiotic regimens at once may reduce the likelihood of development of antibiotic resistance and possibly get some synergy.

Part of the long term effects may have to do with the patient gradually restoring his/her immune system. We feel that the symptoms are the result of an immune reaction directed against the bacterium or a bacterial product. If normal immunity is restored the patient may be able to live with the bacteria without problem.

These regimens are likely to produce Candida overgrowth. The yeasts can usually be controlled with oral nystatin 500,000U three or four times a day, Nizoral 200 mg. once a day, or Diflucan 100 mg. once a day. Nystatin only treats the GI tract; it is appropriate for most men, and for them may not need to be prescribed for more than a few weeks, as the intestinal population will adjust to where Candida is not a problem. Nizoral produces a general effect and is suggested for women. Diflucan is one alternative to Nizoral and is safer and possibly more effective but is more expensive.

Responding patients may have a pronounced Jarisch-Herxheimer-like reaction for the first few days or weeks. In theory, the Jarisch-Herxheimer reaction is due to the rapid death of organisms releasing internal contents that stimulates a short-term hypersensitivity response, and is presumably a sign of antibiotic sensitivity. The reaction should not be mistaken for a drug reaction or for an adverse response to therapy. The patients are much more comfortable when covered with a steroid for a few days. Steroids may have an additional benefit, as they may inhibit production of compounds that may stimulate growth of the bacteria. During the initial phase of treatment depression may be a problem. A few patients have complained of muscle cramping. Short term benzodiazepams or other antidepressive drugs may help these symptoms. It is our current impression that the J-H reaction is considerably less marked with isoniazid, so I suggest starting patients with this (when appropriate) and then adding the second antibiotic after the J-H reaction has passed (at least one week).



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Drug reactions are possible with any of these regimens and should be watched for. All of these drugs may produce allergic reactions. Certain patients have a much higher than usual incidence of drug allergies. Ciprofloxacin has had rare very severe reactions such as liver or marrow failure and can be a problem to the kidney with dehydration. It also produces photosensitivities and other minor problems. It produces necrosis of cartilage in children and is contraindicated for that reason; there is a potential risk of damage to cartilage and tendons with long-term use in adults as well. Probenecid is a problem for the kidney with dehydration. Isoniazid produces rare severe hepatitis or very rare marrow failure, more often in older patients. GI complaints are sometimes seen with any of these and are sometimes severe enough to require a change of therapy. Pseudomembranous enterocolitis is a remote possibility. It is recommended that the CBC and liver, hepatic and renal functions be monitored periodically, initially every 3-4 weeks and whenever there are adverse symptoms. A few patients have shown unpredictable symptoms such as chest pain and tachycardia. It is likely that there is a low-grade myocarditis present in a few patients that is exacerbated with the antibiotics. Propranolol may help these symptoms as well as help the headaches that some patients have. Some patients who had problems tolerating drugs have been successfully gotten into therapy by starting with low doses and working up. When multiple drugs are being given, it may help to sort out drug reactions if they are started sequentially. If the patient is not responding after a reasonable trial (1-2 months) or if the patient is actually getting worse, the antibiotics should be withdrawn. We have seen rare patients in which a response did not begin until over a month, but most responding patients improved within weeks.

We do not presently have an alternative drug therapy if there is no response of the organisms to these antibiotics. Some patients show an initial response and then develop resistance (documented by culture in some patients). Switching to a different antibiotic at this point may lead to further improvement.

Ongoing inflammation and/or stress promote the growth of the bacterium, related in part to release of arachidonate derivatives. NSAIDs may have a limited role here, especially ibuprofen which has been noted to produce symptomatic improvement and possibly some



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reduction in bacterial levels. 200 mg 2-3 times a day is recommended. Control of stress and other infections is an important adjunct to treatment. Related to this, it is likely that a major site of infection with this bacterium is the mouth, especially the gingiva. Many patients give a history of symptoms beginning shortly after dental problems, especially abscesses and root canals, or of flareups when dental problems developed. It is important that the patient be surveyed to be sure that there are no lurking dental infections and that any problems that are present be corrected.

Nutritional adjustments are also important. See separate discussion. Dr. Larry Stowe of The Stowe Foundation is also available to discuss his Nutritional BioTherapy program.

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