# Lyme, Spirochetes, Flagyl and the Nitroimidazoles

by Martin Atkinson-Barr CPhys PhD
http://mab.webprovider.com/index.html
Please note that this is my first web page design, and is very much a learning experience. There will be frequent updates and what you see should be considered as a work in progress.

In late 1997 I started to investigate Lyme disease. I discovered that, contrary to the medical textbooks, Lyme disease is not easily treated and that there are many Lyme patients who are profoundly ill with this disease.

The facility for patients to disclose and discuss their problems over the Internet marks a great change in medicine. Using the newsgroup sci.med.diseases.lyme I was able to explore the problems, insights and discoveries of some remarkable people who had had their lives turned upside down by a tiny tick. To all of the contributors that helped me see further I say bless you all. My motivation at the outset was to help my relatives. I could not have done so without the input from the newsgroup. Every problem disease needs a group like this, for without the flow of information from patients it would be impossible for a scientist to see the big picture.

Thanks to some serendipity and the training I received from some great molecular biologists, I initially predicted and then confirmed, to my own satisfaction, that the nitroimidazoles would be useful in the treatment of Lyme. Flagyl is the original and best known of the nitroimidazole class of drugs.

As the details of this discovery are important to understanding what I do know - and do not - I have included a history of the work that convinced me of the benefits of using Flagyl in the treatment of Lyme patients.

Since the presentation of the results of Lyme treatment with Flagyl at the April 1999 Lyme & Spirochetal Diseases Conference, held in New York, many thousands of Lyme sufferers have been prescribed Flagyl. I am pleased to say that the early promise of that treatment has been continued. Not a day passes without an e-mail, letter or telephone call from a Lyme patient who has seen dramatic improvement in their condition.

That's the introduction, so now on to the information you came here for!

My very best wishes to you all.
Martin Atkinson-Barr

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**About Martin Atkinson-Barr**

First things first. I AM NOT AN MD. That's important to remember. I cannot, by law, give anyone any medical treatment, nor do I have any patients. That said, I do know quite a lot about certain diseases.
I attended (went up is what the British say) Cambridge University in England in the early 1970s to study science...
After Cambridge I worked at Rhone-Poulenc, the giant French pharmaceutical company...
In 1991 an Australian physician, Barry Marshall, astonished the world with his discovery, with Dr. Robin Warren, that gastric and peptic ulcers were a consequence of an infection by a bacterium, Helicobacter pylori. The first treatment was a combination of metronidazole (Flagyl), tetracycline and Pepto-Bismol,

termed "triple therapy". That such a common condition, always linked to stress in common belief, could be an infectious process was stunning. This reinvigorated the study of infectious diseases. Certainly a paradigm shift if ever there was one. I gave a few lectures on the subject locally and encouraged those with ulcers to seek out treatment in the face of a campaign of fear, uncertainty and doubt promoted by some pharmaceutical companies. I found one interesting case of chronic halitosis that responded to triple therapy which was written up here.
One of my relatives had a dramatic response to triple therapy and later investigation was the basis for the discovery of the use of Flagyl in Lyme disease. He was patient zero.
People often ask me where I do my research. My answer often confounds: mostly it is done in the shower! I think for hours about a problem until I understand it. I am pleased to say that Isaac Newton was reported to be the same way, though I am nowhere near his level it does seem to be a technique that works. It drives my wife to distraction, though in recent years she has become used to me staring out of the window for hours. The most important parts of research are done in one's head, not at the laboratory bench.

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## The History of the Flagyl Treatment

**Patient Zero**

At a New Year's Eve party in 1984 one of my family became quite ill, just after the haggis had been served. Nothing unusual in that you might say, except over the next few days he was bedridden and obviously suffering from a severe flu-like illness. Doctors were called and various diagnoses were offered: influenza, mumps, unknown viral.

After about two weeks he was out of bed but he still did not feel right. In fact he never fully recovered.

In 1989 he developed low back pain but X-rays revealed no particular abnormalities and he was placed on a course of exercise and stretching. He was fastidious about the course, often sweating with the pain during sit-ups. After two years there was no benefit to be seen in spite of all the effort.

1991 came and we had a bereavement which upset everyone greatly. After the funeral he had an episode of anxiety which was alarming but perhaps understandable. However a few months later the anxiety recurred and was accompanied with shortness of breath. A trip to his physician revealed high blood pressure - very high blood pressure of 180/120. Now normal is 120/80 and a blood pressure that high should probably trigger a hospital visit. Of course he was given an aggressive course of antihypertensive medication with anxiolytic drugs and sent for further diagnostic tests. He complained of epigastric pain. Despite intensive and expensive tests including MRI, CAT scan, ultrasound no diagnosis was forthcoming.

During that time the discovery of ulcer-causing bacteria was made by Barry Marshall and I suggested he might be tested for an ulcer. He was given a prescription for antibiotics as a consequence, including metronidazole. Seven days after he started the ulcer medication his low back pain disappeared and when I checked his blood pressure it was normal. My first guess was that this was some undocumented set of symptoms secondary to the Helicobacter pylori infection. I even went so far as to contact Barry Marshall himself to enquire if others had seen anything similar. He had not.

Over the next three years things really deteriorated, to the point where he was having trouble remembering his telephone number and was often unable to drive a car. His wife thought him a hypochondriac. He was unable to take up employment.

March 1997 came and I decided something had to be done. The Internet had just come to our house and I thought I'd try to find out what was wrong using the search facilities and all the knowledge available through the Web and the newsgroups. I thought to make this a hobby for the summer. My first job was to get a full list of symptoms then find the least common one and search on that. A little questioning revealed that both knees were somewhat stiff. I typed knee pain into Altavista. Rather than a summer hobby I had a possible diagnosis in twenty minutes - Lyme disease.

I asked if there had ever been a tick bite. No memory of one. I asked if there had ever been a funny rash. At first, none was remembered but the following day it was revealed that there had been a circular rash on the upper thigh some time in the fall of 1984. The timing was just right.

A quick call to Igenex, when I spoke with the wonderful founder and CEO Dr. Nick Harris, and I determined the tests that had to be done. Another call and I found a local "Lyme expert physician". Off the family went - I suggested they should all be tested.

They were all three positive by CDC criteria. OK, I said, there's no problem because the books say it will just take a few weeks of antibiotics and you'll all be cured. The parents were put on doxycycline, the child on amoxicillin. A couple of weeks later they were no better, perhaps worse, so Biaxin was added. Then they really deteriorated. Its called a herxheimer I explained. Just wait and it will go away. But it didn't. August came and the family was in dire straights.

Right, my wife said, you have a new summer hobby. Find a cure. My wife thinks I can fix anything - garage door openers, appliances, computers (well I can fix them). But a disease? That's a tall order. Try, she implored. I spread everything I had out on my large desk and looked, and looked. And perhaps somewhere I remembered what Max Perutz had said: the secret's in the proteins.

There was the 41kDa protein. I knew that protein. It was in the flagella of the trichomonas that I had observed immobilized by Flagyl twenty years ago. And I thought of the experience with the triple therapy. A little research revealed that the flagellar protein in my enemy Borrelia burgdorferi was in the form of the axial filaments. The Lyme spirochete was an internally flagellated bacterium a little similar in form to Helicobacter pylori.

A trip to the Lyme newsgroup brought forth a few Lyme patients who had taken Flagyl for unrelated conditions, especially giardia, and seen improvement in their Lyme symptoms.

Things were so bad a suggestion of eye of newt would probably have elicited a volunteer. A friendly physician agreed to try the triple therapy approach again. We just added Flagyl to the doxycycline and Biaxin. Seven days later came a real breakthrough with relief of all symptoms. I had the blood pressure as an objective measurement of response too. We tried Flagyl for three weeks this time. A good result but each time the Flagyl was stopped the symptoms would come back, despite the continued doxycycline and Biaxin.

Now following one case is difficult. People get out of bed each day feeling different. We have to watch carefully and have some idea of the average patient condition. There were many evenings when I paced my backyard trying to decide if I was right that Flagyl was effective.

Throughout 1998 we tried varying dosage, different period of treatment. By September 1998 we could all see the change. He insisted on treatment for his wife and child. By now the child was showing Lyme symptoms too. They responded equally dramatically - if not more so.

I put the information out through the Lyme newsgroup. A couple of physicians contacted me. One had good results on a tough case but felt unsure of trying it on more. Finally in October 1998 Dr. Richard Horowitz contacted me and agreed to try Flagyl on some of his intractable cases.

On December 4, 1998 Richard Horowitz called me to say that he too had had very good results on Flagyl. We agreed to publish at the forthcoming Lyme & Spirochetal Diseases conference. The paper was not accepted for full presentation, just the poster session. Who needs new treatments when the disease is readily cured? We presented on 140 patients and I was able to meet and discuss Flagyl with many of the well known Lyme physicians.

Since then things have gone from strength to strength. Tinidazole, very similar to Flagyl, has proven to be more effective in-vitro and in-vivo. I have run out of volunteers - they are all well thankyou.

Note that these three test patients repudiate the claims of certain researchers who invoke a "post-Lyme syndrome" to explain away chronic Lyme cases. These three were treated for 6 months with conventional therapy before the addition of Flagyl. Only after Flagyl treatment did they improve and then they relapsed despite ongoing conventional therapy. Clearly there is no need to conjecture a post-Lyme condition - symptoms reflect an ongoing infection.

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## Nitroimidazoles: Flagyl, Tinidazole & Others

### Metronidazole
**(Flagyl)**

**History:**
Metronidazole was introduced in the mid-1950s by Rhone-Poulenc under the brand name Flagyl. It was the first of the group of drugs we now call nitroimidazoles. In the US it was licensed to Searle. As a patent-expired drug it can be purchased inexpensively as a generic. I have no reason to doubt the quality of the generic alternative.
Flagyl was first introduced as a treatment for trichomonas vaginalis, a sexually transmitted disease, and revolutionized therapy for that condition. In 1964 a dentist, Shinn, noted that patients with gingivitis treated with Flagyl were cured and the second major indication was established. Flagyl was found useful in the treatment of the protozoans giardia lamblia and entamoeba histolytica during the late 1960s and 1970s. In the early 1970s it was found that Flagyl was very active against the obligate anaerobes of which the two best known families are Bacteroides and Clostridia. Flagyl is the gold standard for treating these infections.

**Chemistry:**
Metronidazole is quite a simple chemical, hence its low molecular weight.

**Safety**:
Unfortunately in the mid 1970s a competitor with another of the nitroimidazoles tried to attack the market share of metronidazole by promoting their drug as a safer alternative and highlighting the possible carcinogenicity of Flagyl. This backfired and physicians saw all nitroimidazoles as a cancer threat, denying their patients a very valuable medication and probably costing many lives. This was the 1970s and a similar attack was made on saccharine as the reader probably recalls. Flagyl had been used as a routine pre-operative prophylaxis for gut and gynecological surgery, post-operative infections are normally anaerobic. The cancer scare stopped routine prophylaxis. Physicians need to be aware that the long term safety of many drugs is not established and drugs they use every day do demonstrate some

carcinogenic potential. A case very much in point is doxycycline which is associated with pituitary tumors - the standard datasheet has this information yet few doctors limit their use of that drug. It is however prudent to examine all factors of safety and use appropriate caution, especially when there appears to be a safer alternative.

**Absorption and Distribution**:
Flagyl is well absorbed following oral administration and while there is an intravenous presentation available its use is intended for emergency treatment of life-threatening anaerobic infections and where oral dosing is not possible. Anaerobic infections are not fun at all! The pictures are particularly gruesome and during a lecture I was once giving at a major London Hospital on a hot summers day I actually fainted even though I had seen those pictures hundreds of times before!

Flagyl is lipophilic (fat loving) and low molecular weight, an almost ideal combination for good tissue distribution. It passes into the brain readily and one indication for use is anaerobic brain abscess. In neuro-Lyme this is a great advantage for the neurological complications of late stage Lyme are both the most troubling for the patient and hitherto the most difficult to treat.

There are limitations to our knowledge of the extent of tissue penetration. The extent to which a drug is concentrated in various tissues is visualized by an autoradiogram. A test animal, often a rat, is fed for several days with a radioactively labeled form of metronidazole. The rat is then killed, split in half and placed on a photographic plate. Areas of high radioactivity expose the plate. However the results may not scale well to humans. Consider the following: suppose a nerve in the rat is 1mm in diameter and the corresponding nerve in the human is 1cm, ten times as large. Diffusion time scales as the fourth power of the length. If the rat nerve attains an adequate concentration in one day then the same diffusion process in the human will take 10x10x10x10 days - 25 years! Of course we don't expect diffusion to be the rate limiting state. In living tissue there is active transport of many molecules.

**Mechanism of Action**:
When I was at Rhone-Poulenc two researchers, Jim McFadzean and Sidney Squires, were the experts on Flagyl. Then there were at least five proposed mechanisms of action, not all of which were mutually exclusive. As far as I can see this question has not been satisfactorily settled since that time though review papers often gloss over the details.

One important observation comes from an experiment I observed. T. vaginalis can be readily watched under a microscope, the twirling external flagellum is readily seen. When a low concentration (a few mcg/ml) of metronidazole is added to the culture the flagella quickly cease to function - in a matter of a few minutes. It is the time scale and the outcome which is important. Time scales of a few minutes do not equate to protein synthesis inhibition or accumulated cytotoxicity but rather this observation strongly suggests that metronidazole blocks some late part of a metabolic pathway and a pathway involved in the proton motor function which drives the flagellum.

The protozoal flagellum is structurally different from that of the bacterium but both are comprised of flagellar protein. Note that Flagyl is effective against both bacterial forms and protozoa.

**The most widely quoted mechanism of action is as follows**:

1. Passive diffusion into the microorganism
2. Intracellular reduction of the 5-nitro group by the pyruvate-ferredoxin oxidoreductase complex
3. Enhanced diffusion into cell via concentration gradient
4. Interruption of normal electron flow due to greater electron affinity of the nitroimidazole.
5. Reduction product attacks DNA with loss in helical structure and impared template function (DNA->RNA->protein synthesis)

While I think the first part of this mechanism is probably correct - stages 1, 2 & 3 - the activity at the DNA level does not square with my observations as noted above.
Instead I propose the following mode of action:
1. Same as above
2. Same as above
3. Same as above
4. Electron flow in the proton motor function (drives the flagella or axial filaments) is blocked by the greater electron affinity of the nitroimidazole, denying the potential gradient at the junction of the cell wall and the flagellum or axial filament. Consequent loss in potential gradient along the flagellum or axial filament.
5. Motility ceases, with possible permanent damage to the motor structure.
6. Accumulation of cytotoxic products interferes with protein synthesis, as above.

An online textbook describing the relevant structures can be found here.
http://www.bact.wisc.edu/microtextbook/BacterialStructure/Flagella.html

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## Tinidazole
**(Tindamax, Fasigyn)**

**Chemistry:**
Tinidazole is similar to metronidazole however tinidazole contains a larger chain. The slightly larger chain attached to the top nitrogen atom accounts for the higher molecular weight.

**General**:
Tinidazole is the generic name. It was developed and marketed by Pfizer as Fasigyn throughout the world, with the exception of the US (for presumably marketing reasons).
A datasheet can be found here. http://home.intekom.com/pharm/pfizer/fasigyn.html#SIDE-EFFECTS
Tinidazole in the US can be supplied by a compounding pharmacy. One I know that does is the Hopewell Pharmacy in NJ. Their phone number is (800) 792-6670.

Tinidazole is very similar to metronidazole. Originally I suggested that tinidazole might be more suitable for the long term treatment of Lyme disease on the basis of safety and better tolerance by the patient. Long term safety data is not available on any of the nitroimidazoles but an educated guess is that tinidazole is probably better than metronidazole.

Suprisingly when an in-vitro test was done by Brorson et al, who had done in-vitro studies of metronidazole, they reported to me, as unpublished data, that tinidazole was 10x as effective as metronidazole in killing Lyme cysts. This seems to be supported by clinical results reported from a number of physicians and patients.

**Tinidazole is currently the nitroimidazole of choice in treating Lyme**.

## Ornidazole
**(Madelen, Ornidal, Tiberal)**

Molecular weight = 215
Similar to metronidazole and tinidazole. Not available in the US but is sold in most european countries.

## Secnidazole
**(Flagentyl**, **Sindose**, **Secnil**)

**Chemistry:**
Again the molecule is very similar to metronidazole, differing only in the topmost chain.

I have had one report of the successful use of secnidazole in the treatment of Lyme disease. it appears similar to Flagyl.

## Hypotheses on What Nitroimidazoles do to the Lyme Spirochete

McFadzean & Squires studied the effect of metronidazole on the syphilis treponeme, the motile spirochetal form, and reported that it did impair the motility. Brorson & Brorson reported that metronidazole had no effect on the motile Lyme spirochete. How does one explain the difference in these observations on similar microorganisms? Spirochetal movement demands a viscous medium, one that can support shear (try spinning a corkscrew in water - there's just no resistance). In a low viscosity medium, like water, the spirochete will not be able to generate sufficient shear to effect motion, therefore any effect of metronidazole on motility will not be visible. This will require further investigation but, for the present, I do not subscribe to the notion that metronidazole is inactive against the classic spirochetal form.

Dorward et. al. also demonstrated that the Lyme spirochete can invade host cells. It seems likely that metronidazole will interfere with this process if it affects the motility of the axial filaments. Similar observations on T. denticola support the hypothesis that metroidazole prevents cell invasion. Note that Dorward's fine paper claimed that cell invasion had not been observed in other spirochetes - this is incorrect as the T denticola work from McGill University shows. I believe that cell invasion is common to spirochetal bacteria.

Brorson & Brorson did observe a bactericidal effect of metronidazole on the cyst form of Lyme.
Some words of explanation are necessary at this point. It has been observed for many years that spirochetes are able to exist in a variety of forms. Of course the spirochete, resembling a corkscrew, is the classic and recognizable configuration. Some of these forms have been given names: cysts; granules; blebs; string of pearls; L-forms. The importance of these morphologies in pathogenesis is not known but the classic spirochete is rarely seen in host tissue. These observations are not limited to Lyme disease. Perhaps the most widely studied spirochetal infection is syphilis, which demonstrates all of these phases.

It has commented that the severity of Lyme disease to the human host is out of all proportion to the quantity of spirochetes found. One explanation is that most of the Lyme organsisms are in the other forms. Brorson & Brorson were able to show that the spirochete rapidly converted to the cyst for when incubated in cerebrospinal fluid. We may therefore infer that cysts are present in the human infection. It should not be thought that the cysts are a kind of vegetative spore, or seed. The cysts are active and produce toxins. On reversion to the spirochetal form each cyst gives rise to multiple spirochetes.
It is my hypothesis that perhaps as much as 90+% of the Lyme organism present in the human body is in non-spirochetal forms.

When the Lyme spirochete invades a host cell it forms a vacuole within the host cell. As a consequence of the invasion the exterior form of the host cell changes dramatically. It is inconceivable that such a dramatic shape change has no effect on the host cell's function. As a vacuole, there is less need for a strong cell wall and the bacterium may well be cell wall deficient, rendering it invulnerable to antimicrobials, like the penicillins, which target bacterial cell wall formation.

A wonderful book, replete with references, on non-classical forms of all kinds of bacteria is Prof. Lida Mattman's "Cell Wall Deficient Forms: Stealth Pathogens", published by CRC Press. Prof. Mattman is currently actively involved in Lyme research.

It is possible therefore that the nitroimidazoles act in-vivo in several ways:

*Reduction in motility of the spirochete, limiting disease progression and rendering the spirochete susceptible to immune system attack.

*Inhibition of host cell invasion, especially host immune cells.

*Bactericidal activity against cyst forms.

*Bactericidal effects on intracellular vacuole forms of Lyme (and other spirochetal diseases).

The use of the nitroimidazoles is not limited to Lyme and syphilis. There can be little doubt that these drugs will be found useful in a wide range of spirochetal diseases, including relapsing fever, late-stage syphilis and perhaps leptospira. Of considerable interest are those common diseases where spirochetes have been conjectured: multiple sclerosis and rheumatoid arthritis. Lyme disease is in a sense a model of a disease that resists elimination by popular antibiotics.

## What To Expect When Taking A Nitroimidazole

The Lyme patient's response to taking Flagyl, or similar, is rather complex. On the basis of talking with about 100 chronic Lyme patients who have taken Flagyl and closely observing three Lyme patients on Flagyl/tinidazole I think there is a general pattern.

**Days 1-6** Mild worsening of symptoms - aches, pains and general malaise. There are often palpitations and some difficulty breathing.

**Days 7-10** The honeymoon. Patients feel dramatically better, often with all pain gone, energy returns.

**Days 11-21** Unfortunately the honeymoon does not last. While the joint and low back pain may go away, malaise and neurological problems come on with vengeance. Profound lack of energy and motivation.

**Days 21-33** Depression. For no known reason deep, deep depression starts about now. It may lead to suicidal thoughts and be very stressful for family members. Being forewarned helps greatly so Lyme patients should warn all those around them before it happens. Depression typically lasts about 10 days. Some Lyme patients react badly to anti-depressants so there should probably be avoided.

**Warning! Days 40-60.** A number of patients have experienced shortness of breath and palpitations at about 6 weeks. These events may require an ER visit. This may be due to a sudden die off of the bacteria.

**Days 34-60** Gradual improvement, especially in neurological status, manifest as "good days". Eventually the "good days" become seven days per week. Profound fatigue remains however and will not abate perhaps for six months.

At **60-90 days** there should be no symptoms other than fatigue. Time to take a vacation!
Remember individual cases will differ from this average roadmap. Some patients have responded beautifully in a short time and seemingly have stayed well. One lady wrote that a low dose of Flagyl enabled her to escape from her home for the first time in 4 years and was now mountain biking.

## Elevated Liver Enzymes

One of the classic signs of Lyme disease is alcohol intolerance. This suggests that the liver is an important site in the progression of Lyme disease.

Some patients have experienced elevated liver enzymes while taking Flagyl. This could be due to a side effect of the drug or a consequence of killing the Lyme spirochete within the liver: we just don't know as yet. If it is a side effect then perhaps an alternative nitroimidazole would be an option. If it is a consequence of killing Lyme in the liver the elevated enzyme level may be part and parcel of effective treatment. More work needs to be done.

## Peripheral Neuropathy

In a similar way the nitroimidazoles may affect the peripheral nervous system. Peripheral neuropathy, typically manifest as numbness of the feet, has been recorded as a side effect of Flagyl treatment. It may be so, but equally it may be a consequence of treating Lyme-infected nerves.
The reports of Flagyl-induced peripheral neuropathy came only in recent years. Did those cases perhaps have Lyme disease? Why wasn't this side effect noted years before? Do the other nitroimidazoles have the same effect as Flagyl? It seems, just seems, that tinidazole is not so likely to cause peripheral neuropathy. That may be because tinidazole is a slightly larger molecule and may not penetrate dense

nervous system tissue so readily. On the other hand is peripheral neuropathy just a side effect confined to Flagyl. We don't know.