QUINOLONE ANTIBIOTICS TOXICITY

Have you planned to take a quinolone antibiotic (cipro, levaquin, tequin, avelox) and want to avoid permanent and long-term injuries?

→

Do you suspect that you are having an adverse reaction to a quinolone antibiotic?

↓

Do you want to know why some people take a lot of quinolones and believe that they worked fine for them?

←

Do you want to know more about this type of toxic antibiotic that causes extensive damage to everybody?

↓

Do you think that reactions to drugs are characteristic to certain persons and that you will be safe taking quinolones because you have never had any reaction or allergy before?

→

Do you want to know why the FDA has had to admit in October 2004 that quinolones may cause irreversible neurological damage, only after thousands of reports of evidence and 20 years of consumer and citizen struggle?

↓

Then, perhaps you might consider reading this non-medical research paper. It has been written by a group of formerly healthy and young athletes with no known allergies or intolerance to any drug, that suffered devastating adverse health effects caused by the toxicity of quinolones.

←

The paper is a technical summary that condenses the victims' stories of powerless struggle to overcome permanent, deep and irreversible damages that stressed their careers and family relationships to the limit, and changed their lives forever.

The Flox Report

An investigative approach to the true toxicity of quinolone antibiotics. A patient's point of view.

FLUOROQUINOLONE ANTIBIOTICS TOXICITY A SUMMARY OF CLOSELY FOLLOWED CASES

Damage and disorders caused by fluoroquinolone antibiotics (cipro, levaquin, floxin, tequin and others)

[FLUOROQUINOLONES ARE A CLASS OF ANTIBIOTICS THAT ARE VERY TOXIC FOR TENDONS, CARTILAGES, THE NERVOUS SYSTEM AND OTHER ORGANS]

Last edition: March 2007

WARNING AND MANDATORY DISCLAIMER.

This article consists of the description of the adverse toxic effects caused by the quinolone and fluoroquinolone class of antibiotics, on previously healthy people. Many of these injuries are irreversible and permanent in nature. In addition, the article contains data obtained from many individual experiences, as well as information that comes from reputed medical sources available to the public. This article does not contain medical advice or professional statements on its own.

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- *Thank you also to all the hundreds people that have indicated that the information provided here has been useful for them.*

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The report is lengthy. If you plan to print it out, take into account that is about 270 pages long. It is formatted for A4 paper size (210 x 297 mm).

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FACT SHEET

QUICK GUIDE TO FLUOROQUINOLONE ANTIBIOTICS TOXICITY

1. Cipro, levaquin, avelox, are fluoroquinolone antibiotics. There are others as well.
2. These antibiotics are not natural compounds, but chemotherapeuticals with a potent toxic profile.
3. Many people get intoxicated during their first treatment, or during a later treatment after having followed with apparent success some previous treatments.
4. Although one can start feeling symptoms of intoxication during the treatment, it is more common that many symptoms start well after completing the treatment.
5. Once intoxicated, the initial symptoms increase in intensity and new symptoms appear during, weeks or months after treatment cessation.
6. There are intoxications that heal relatively quickly, in a year or so, and others that take 10 years or more to become endurable.
7. Many injuries caused by fluoroquinolones are permanent, irreversible in nature.
8. Some of the most debilitating symptoms affect the brain, the whole nervous systems, the musculoskeletal system, and almost all organs of the body.
9. Almost all intoxications to fluoroquinolones are not linked with the antibiotic, neither by the patient nor by the doctors.
10. Intractable pain is present in the majority of intoxications.
11. Once the intoxication takes place, there is no known treatment, and only time and avoiding toxic medications as much as possible brings some healing.
12. It is very difficult to find a doctor with a knowledge about this kind of intoxications. Most medical professionals, out of ignorance, would never accept that the symptoms of a patient are a manifestation of fluoroquinolone toxicity.
13. The most likely diagnoses for a fluoroquinolone intoxication are fibromyalgia, Sjögren's, Reactive arthritis, serum sickness, multiple sclerosis, Raynaud's, chronic fatigue syndrome, lyme, and all sorts of neuropschyatric disorders.
14. Once intoxicated, you have to avoid any rechallenge with another quinolone, for the rest of your life.
15. Save for mild cases of intoxication by quinolones, the victim thas to adapt his/her way of living to the new situation, in order to speed up recovery.

<<Laboratories and doctor's sects can only attempt to create their own reality for so long. All these real adverse effects that have long been denounced by victims are now coming to become evident by the sheer humbers of people injured, and while there are still the nay-sayers, many of them on the payroll, or getting grants from laboratories, still trying to deny and confuse the issue, it has become a short of moral issue, because it has to do with the right of people to not to be maimed for life just for nothing>>.

EXCLUDED IN THIS PAPER: MENTAL ALTERATIONS CAUSED BY QUINOLONE ANTIBIOTICS

1.MENTAL ALTERATIONS CAUSED BY QUINOLONE ANTIBIOTICS

1.1. Real damage of the mental/cognitive functions

The quinolone and fluoroquinolone antibiotics cause much damage to the central nervous system, very frequently inflicting a vast number of brain injuries and dysfunctions that cause mental alterations and psychiatric states that can be debilitating and life altering, both for the patient and the persons close to him/her. The present version of this paper does not deal with those serious events. Unfortunately, by not discussing the psychological toxicity of the quinolones, the scope of this paper excludes at least half of the toxic profile of this class of antibiotics. In some passages of the report certain references are made but not discussed in detail.

Among the most common injuries of this kind are the following (all of them listed in the package insert of a typical quinolone):

- depersonalization, depression, paranoia, toxic psychosis, unresponsiveness, phobia
- restlessness, nervousness, dizziness, agitation, confusion, delirium, depression
- nightmares, hallucinations, manic reaction, irritability, anxiety, lethargy
- convulsive seizures, panic attacks, suicidal behavior
- light-headedness, vertigo, insomnia

Some persons have acquired very long lasting mental injuries after a single pill of levaquin, floxin, ciprofloxacin and other quinolones, not to mention the countless cases of tragic events caused by altered behavior after the ingestion of quinolones, nearly all of which are blamed on something else by the medical class.

1.2. Fictional diagnoses

Sooner or later, people suffering from severe quinolone reactions are referred to a psychiatrist. In many cases, these psychiatrists give the patient wrong diagnoses. The most common is paranoid delirium, according to which the victim of the intoxication from quinolones would have many physical symptoms and would worry about the injuries suffered that only exist *"in his/her mind",* simply because the psychiatrist firmly believes that an antibiotic cannot cause these long- lasting arrhythmias, insomnia, joint pains, need of a cane or wheelchair, vision problems and all the rest of health problems that you will learn through this paper.

In Part XII you can find information on the most common psychiatric diagnoses for people suffering a quinolone reaction by their doctors.

PART I: INTRODUCTION

2. INTRODUCTION

Tens of thousands of people are damaged by quinolone (Cipro, Levaquin, Floxin, Noroxin, etc.) antibiotics each year, yet nearly all those damaged remain undiagnosed or misdiagnosed. Some are diagnosed as having fibromyalgia, lupus, lyme disease, multiple sclerosis, rheumatoid diseases, myositis, diverse heart problems or neuropathies of every kind. Thousands of people become severely crippled for years, or even permanently, after taking a quinolone antibiotic for minor infections.

Quinolone antibiotics are toxic from the very first milligram of ingestion. The effects of quinolone antibiotics are cumulative. Each person has a unique threshold of tolerance for the quinolones that once surpassed releases symptoms corresponding to various disorders, with long-lasting and potentially permanent damage. People are exposed to quinolones through taking them as a drug prescription or through food (chemically treated poultry and cattle).

Only a handful of doctors are aware of this devastating problem. The rest are uninformed, at least in technical matters, by the manufacturers. The drug manufacturers conceal the real toxic profile of the fluoroquinolone antibiotics. The manufacturers know they cause extensive damage, destroy lives and impair people for life, but they manipulate the trials, especially in not conducting any long-term follow up studies and under-reporting the adverse events. It is typical for manufacturers to state as *"very rare adverse events found in less than 1% of cases"*, for adverse effects that have a real percentage above 70% for therapeutic doses.

Manufacturers have found a brilliantly disguised drug that in many cases wreaks havoc on its users some weeks or months after cessation of the drug therapy, or through food ingestion, making it almost impossible to trace back the symptoms to the real cause.

Recently (fall 2004), it has been made mandatory that the package inserts of the quinolone antibiotics must include a warning about *"rare"* adverse reactions that can cause irreversible neuropathic conditions. Up to now the possibility was simply systematically denied by the manufacturers because admitting it could harm their revenue. The Food and Drug Administration (FDA) also rejected any link between the thousands of individual reports on long-lasting and permanent damage caused by quinolones because their policy with respect to already marketed drugs is to delay as much as possible any warning that could alarm the people and show the inefficacy of the procedures and surveillance methods that they set to theoretically protect us.

Now, the overwhelming evidence has forced manufacturers and the FDA alike to admit irreversible damage. We had warned of it early in 2003, and many other groups of people and doctors are reporting such cases for at least the past 20 years. Now they try to avoid the sheer responsibility of indefinitely prolonging such a public health tragedy– rating it as *"rare"*. It is only a matter of time before they will have to admit that the extensive toxicity of quinolones is a class effect of this type of antibiotic, and that it affects everyone taking them, and that these drugs should be restricted to very special cases of antimicrobial therapy.

Of special interest for athletes is the fact that quinolone and fluoroquinolone antibiotics cause many problems concerning the musculoskeletal system, most of which resemble other ailments that are acceptably known, diagnosed and treated (epycondilitis, shin splints, plantar fascitis, overuse syndromes, trochanteric bursitis, all sorts of tendinitis, tenosynovitis and enthesitis, ulnar compression neuritis, ileotibial band syndrome, and many more). But the damage caused by quinolones does not respond to conventional treatments and leads to very disabling conditions, usually attributed to other causative factors (leg length discrepancy, worn shoes, lack of flexibility, muscle imbalance, over-pronation, supination, misalignements, wear, tear, etc...).

NEW TEXTS ON THE PACKAGE INSERTS OF FLUOROQUINOLONES:
<< Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition >>

As a result, many of these problems are improperly diagnosed and remain elusive to all the treatments of choice devised for other pathologies. When conventional treatments (corticoids, steroids or anti-inflammatory medications) are used for disorders caused by quinolone antibiotics, they can cause great additional damage that can lead to tendon ruptures and permanent disability.

That is the reason why there is an imperative need for clearer and more honest information about this class of antibiotics called quinolones and fluoroquinolones. The present report is a summary of many real cases studied over the last several years that shows a closer picture of the real toxic nature of quinolone antibiotics.

VERY IMPORTANT:
Quinolones can cause extremely serious illnesses, organs destruction, life threatening disorders, inmunological and incurable reactions, as well as fatal outcomes. The present FLOX-REPORT does not treat those really rare events, neither allergic reactions to quinolones.
The present FLOX-REPORT only treats the common, true nature, toxic side effects of quinolones that this class of antibiotics cause to everybody when taken in therapeutic doses by healthy and normal people.

The current version of the present report focuses mainly in SEVERE reactions experienced by previously healthy and young athletes. And, therefore, it is more focused on all areas relevant to physical and athletic performance. After studying dozens of cases in detail, the similarity between all of them is very striking. A few other hundred cases have been analysed in less detail to form the report.

As the report is large, some sections are repetitive, in order to facilitate and inform and they can be consulted quite separately. In the report we do not make any distinction between quinolone and fluoroquinolone antibiotics because both subfamilies share the same toxicity.

3.WHO WILL BENEFIT FROM THIS REPORT

You may find this report helpful if:

- You are looking for a connection between your recent physical problems and the drugs you have been taking lately or have taken in the past.
- You are concerned about a prolonged course of fluoroquinolones (i.e. Cipro, Levaquin, Floxin, etc.) that you have been prescribed and are about to start.
- You may have taken quinolones in the past, and are planning to take a more prolonged course of these antibiotics, so you want to obtain more information and have a clearer picture.
- You are a medical practitioner and want to learn more about the patient's point of view regarding

this dramatic health problem.

As you can learn through the paper, for the sake of simplicity we have rated the reactions to quinolones as: MILD, INTERMEDIATE and SEVERE. Severe reactions are relatively unusual and really different to all the rest. This article deals especially with the implications of SEVERE reactions to fluoroquinolone antibiotics. Nevertheless, this report is not a reference for current long-term sufferers of quinolone toxicity because it does not add new information to the wealth of it already available. When a floxed person is one year out from the initial intoxication, he/she will not probably find much information useful in this report because by then an aware and informed person will possess a more comprehensive knowledge than the one provided by this paper.

This report may help you to have a first glimpse about the toxicity of the quinolone antibiotics. From there on, what counts is what you learn on your own or with the help of your doctors.

We recommend that you read the report with a critical perspective and also read from other sources, to form the big picture that a floxed person really needs, until the medical class decides to take on the subject and acknowledge this disorder.

HOW TO USE THIS ARTICLE IF YOU ARE A PERSON THAT HAS SUFFERED A REACTION TO A QUINOLONE
This article might be useful to help you to understand where you are during the first stages when you are wondering what is happening to you, why, and who to ask for help. The article could help to overcome your disorientation. The article could save you erratic searches for answers and could contribute to facilitating a general overview of this health problem. The article does not contain much information that you cannot collect anywhere else after months of research.
This article must not be interpreted literally. It is not a manual for those intoxicated by quinolones. You should not attempt to fit your case in any of the groups or scales provided herein, because they are average experiences. Many reactions have 80% or 90% of common symptoms, especially in severe cases, but in mild and intermediate intoxications there is a varied range of personal conditions, although always within the common thread of the well-known specificity of the reactions to quinolone antibiotics.

The awareness about quinolone toxicity is in its infancy. We see this struggle as a relay race. We feel we are about to complete our final lap. We hope that new people take over the baton and soon the present report becomes superseded, rudimentary and forgotten. This is the real objective of our work, that is to say, to contribute along with other web sites to unveil and reveal this tragedy and to prompt proper research. We would be especially happy if a medical research team conducted an honest, independent, thorough, thoughtful and long- term survey of the toxicity of quinolones.

4.LIMITATIONS OF THE REPORT

This report is not a compendium about quinolones. To start with, for the technical molecular structures and pharma-dynamics, and for all the virtues of the quinolones, you can visit the websites of the drug manufacturers. We focus on the dark side of the fluoroquinolones, which is dark because no light has been shed on it until now. Take a look at a professional pharmaceutical drug monograph (drug insert from the manufacturer) about a typical quinolone to get a first notion about their use, dosage, and directions for use, along with a list of adverse effects and their prevalence (the percentages you will read there are crudely manipulated). A good site for monographs of drugs is www.rxlist.com.

This report has failed to meet some of its initial objectives, because it has not discovered any relevant details. Some very minor correlations have been postulated for the first time by some floxed persons that have collaborated with the report, like the vascular-matrix implication, and a handful of casual links between intensity of symptoms and foods (soy, omega-3 and sugar for example). Or some potentially interesting therapies like the enriched plasma treatment, which could also eventually prove itself useless for our tendons. None of them have made a difference and all of them could be proven wrong in the near future.

Sometimes, new updates are included in a given section and therefore do not reach the whole report resulting in the appearing of some small contradictions between sections. We thank you in advance for any comments with this aspect, that you can send through the contact link if it is operative.

If you are reading the English version of the flox-report, take into account that it is a translation of its original language and that many technical words have been translated from their Latin root, which in central Europe may have slightly different meanings. This is a problem with nearly all translations of medical reports from French, German, Italian or Spanish into English.

Although we have talked to hundreds of people suffering from this syndrome and we have tried to use logical methodologies to draw many conclusions, from observation, repetition and comparison alone, we cannot aim to discover the mechanism of damage, or the elusive clues for a healing protocol.

5.COMMON MISTAKES DONE READING THIS PAPER

For a person that is starting to become aware of his/her intoxication by a quinolone antibiotic, the contents of this report can be overwhelming, depressing and frustrating. So much information mixed in a lay document has two big disadvantages: Firstly it can confuse some because there is some difficulty to discern between real medical research and personal opinions, all of them from floxed persons. In second place, some people may think that this is a compendium of information and feel they do not have the need to look for information elsewhere. You have to avoid both disadvantages of the report and read it with a critical, detached attitude and look after your own information and expanding awareness.

You should NOT read this report if you are the kind of person that believes he/she has all the symptoms of any illness that you read about (hypochondria). If you do, you will end up convinced that you are suffering a far worse reaction than it really is, and that will make you suffer unnecessarily.

The experience of previous editions of this paper shows that some floxed persons want at all costs to match and rate their reactions against the tables and graphics of this paper, in order to have an instrument to rate their reaction, have a precise time schedule of recovery, make normal plans and foresee in advance every event that is going to happen during their recovery, no matter how minute may it be. This paper cannot do that and it is not its objective. After reading the report you will only get an idea of what a floxing is (the suffering of the toxicity of a quinolone antibiotic), but no information to evaluate your reaction is provided here. The tables and graphs have been obtained from different samples of people, have not been scientifically controlled and their only aim is to provide a contrast experience -based on imperfect but real life facts- to all the mainstream official information that denies the possibility of what is really happening to thousands of people all over the world.

If you attempt to use this paper as a guide for your illness, you will become frustrated and you will devoid yourself of the necessary perspective and strength to handle your intoxication adequately. This paper is not the helping hand that can lead you to a certain sense of normalcy.

As a fellow floxed person, known for his tireless and exhaustive research once said (reproduced with permission):

> *"After researching these issues for years now and talking to tens of thousands of individuals I have found that the bottom line is that there is no bottom line. Everybody is different, everybody's experiences are different and what works for one is a disaster in the making for another. Nobody is right when everybody is wrong. Some people have died, some have been crippled for life, some have recovered to a degree and others have recovered completely. No rhyme, reason or logic is to be found within all the data. Your chances of recovery are pretty much the same as the next guy, zero to one hundred percent, or somewhere in between.*
> *We really do not understand the mechanics behind these reactions. We have theories, and just like opinions, everybody has one. We have few studies that actually explain what is going on. Mostly dealing with the tendon damage, which, by the way, has been extensively documented as to causation.*
> *Recently we have added hypo and hyperglycemia as well as heart damage as subjects that are under investigation. But for the most part nobody has done any kind of in depth study of our problems. There*

are just too many of them, which defy logic as well as the investigative tools available to the average physician. We are a Rubic's Cube without a solution. No matter how many different ways we turn the cubes the solution escapes us.
We may never know what is wrong with us during our lifetime. But what we do know is that we are far from alone and time seems to be the only reliable treatment available. Not to be measured in days, weeks or even months but years. Perhaps someday someone will take pity on us and provide us with an answer. But the hard cold fact is that we haven't a clue and that day has yet to arrive. This is what I have learned over the past six years. Myth or fact? Who the hell knows?" .

Suffering a floxing is a life altering experience, that does not resemble any normal illness process that you have experienced before in your life–like post-surgery, an infection, or post-traumatic recovery. Most likely, all health issues that you had prior to the floxing started to heal as soon as the offending agent was removed. Not with quinolones. You will feel progressively worse for months or years before some levelling off is felt. With your prior illnesses, there was something to be done: take medications, put a cast on, and perform rehabilitation exercises; Apparently nothing can be done to halt or reverse or help healing from a quinolone intoxication a few days after ending the treatment. Is very much like suffering from chronic degenerative illnesses like the toxic oil syndrome, the gulf war syndrome, lyme, lupus, multiple sclerosis and others.

If you have one or a few symptoms of a severe reaction–that does NOT mean that you have a severe reaction. It is the whole entire picture that counts. We have seen too many floxed persons enduring really mild reactions becoming hypochondriacs with the possibility of having a severe reaction and magnifying real or imaginary symptoms to match those of a severe reaction.

Another extremely common mistake is to let oneself become overcome by an overzealous search for exact answers, explanations, cures, treatments, timetables and protocols for any minor symptom that shows up-- like extremely negligible physical changes or events that take place in one's life and that would be ridiculously ignorable even in a healthy person.

Overreaction to the quinolone intoxication causes many floxed persons to become worried and look for quinolones laying in wait at every corner of their lives, or extremely afraid and obsessive about potential negative influences of normal habits, like taking a shower with tap water tainted with fluoride.

To look at life through the cipro or levaquin lens only adds anxiety and despair to the already intense impact of the intoxication.

Take into account that if one victim that has participated in the flox-report recovered from a symptom in 7 months and another in 17 months, the AVERAGE indication is about 12 months for recovering from that symptom. If after reading this flox-report you try to establish at all costs the predicted recovery date for that symptom of yours, and you are a person that let us say is going to heal from that symptom by month 18, you will surely get very anxious and depressed when you do not feel well by month 12. Above all, keep in mind that your reaction is unique, and that nobody and no report or paper can substitute for your knowledge about your symptoms, your recovery and all your health aspects.

6. TERMS THAT MAY CAUSE CONFUSION

For the sake of simplicity, we do not discern between the terms side effect, adverse reaction, adverse effect, although some doctors do. In our case we also frequently use the word "intoxication" to describe what a floxing is; that is–nothing but the predictable result of the guaranteed toxicity of the fluoroquinolone antibiotics.

We also extensively use the term "delayed" for reactions that become apparent months or years after exposure to fluoroquinolones. Most doctors only consider "delayed" a reaction to a drug that takes place 2 to 7 days after exposure and that normally shows up as a dermatologic (skin) abnormality. Accordingly, most doctors -out of sheer ignorance- think it impossible for a new symptom to happen at 6 months post-

exposure, for instance.

We use "allergic" for a sudden, extremely acute and intense reaction that can be life threatening, with or without anaphylactic reaction, and that can take place with any substance that enters a body. The flox-report does not treat those cases because they are irrelevant to our purpose.

We use the term "inhibit" accordingly with its technical and precise definition in biology; to inhibit means to decrease, limit, or block the action or function of (an enzyme or organ, for example). It does not necessarily mean that the action or function is entirely suppressed.

We have rated the reactions as mild, intermediate and severe. The ratings are average experiences. The rating itself is a fiction, because each reaction is unique and cannot be classified. But it simplifies the handling of information and the explanations. For undifferentiated reactions of a certain intensity we use the terms strong, intense, high or something similar.

Much effort has been focused on trying to introduce a lay floxed person to the basic concepts of medicine necessary to understand some principles of the floxing syndrome. Using simple terms and explanations is easier than true medical terminology, so some terms and explanations have been simplified so much that are not medically correct.

The paper is over 260 pages long and takes some time to read, especially if you go back over certain passages that request several readings before understanding them. So it is recommended to focus on the sections of the paper that you prefer.

7.WHY HAS THIS REPORT BEEN WRITTEN

There is little or no medical information publicly available via the Internet for the general population that deals with the practical side of adverse reactions to quinolone antibiotics.

The only real information available to date comes from the support groups sustained by sufferers. We strongly recommend visiting the webpages:

www.fqresearch.org
www.drugvictims.org
www.medicationsense.com

Those sites belong to their owners and do not have any relationship with the authors of this report. In particular, *www.fqresearch.org* is a very comprehensive database on fluoroquinolone and quinolone antibiotics and is a mandatory visit that will save you hundreds of hours of research if you decide to take the responsibility of doing your own research.

Nearly all the medical investigations in progress are not comprehensive. The researchers in charge have a sheer lack of knowledge about the real and true facts of this syndrome. Many investigations are very superficial, nearly anecdotal, and only look after a publishable paper, so that statistics of activity in the scientific group remain high in the annual report. There are myriad scope-limiting articles, all of which have contributed to extensive data, plus many, many instances of scientific evidence supporting the great damage that quinolones inflict upon people, but there is not a single comprehensive study about the adverse effects caused by quinolones.

No consistent clinical studies can be found that put the real figures of adverse effects where they really are. There is not a single study that shows the true extent of the damage caused by these antibiotics.
There are multiple causes for this lack of proper investigation:

- The pressure exerted by drug manufacturers, the propaganda they spread in medical circles, and the counter-studies that they promote, most of which are unscientific creations of well paid doctors

that show *"evidence according to their personal experience"* of maximum beneficial activity of the antibiotic and their *"negligible"* adverse effect profile. We can even see irresponsible and poorly educated doctors prescribing and recommending quinolones for children, when currently there is overwhelming evidence that quinolones cause cartilage and joint injuries of extreme severity in immature persons.

- The manipulation of the post marketing adverse events performed by the *"industry"* (laboratories), that make all that is in their hands and to label the most appalling severe reactions to quinolones with the assertion that *"unequivocal link of the event with the quinolone ingestion could not be proved"* and thus dismissing most of the reports of serious reactions, and keeping the statistics of toxicity intentionally low. Manufacturers only consider the possibility of toxicity before a quinolone reaction when a doctor states boldly that there was not any other concomitant agent causing the adverse event, or when the patient has been re-exposed to the quinolone and the reaction cannot be blamed on anything else.
- The delayed onset of symptoms is perhaps the most important fact that is universally ignored by doctors. Many researchers only monitor patients while they are on the medication and in some isolated cases *"up to a month later"*. The vast majority of disorders appear months or up to a year and a half later and are therefore never linked with the real cause. In most issues related with nerve toxicity, a floxing is a delayed-onset-neuropathy.
- The lack of knowledge and preparation of the doctors that prescribe them and the aspect that doctors nearly always dismiss their patient's complaints, and their refusal to admit any link between the severe and long lasting pathologies and their causal agent: the quinolones. The ignorance of doctors about the toxicity of quinolones is simply appalling, irrational and unjustifiable. Many doctors are handing out lifelong misery to their patients and destroying their lives forever.

This report will help the non-medical population know more about the true and real-life nature of quinolones. It can also be a wake-up call for the caring doctor to learn a different point of view, promote a more critical approach and perform unbiased professional research prior to prescribing quinolones.

There is a need to convince the medical class that:

- Until better antibiotics are developed, a defectively designed drug like a quinolone antibiotic should be restricted to emergency, complicated infections or life or death cases, but never used as a first line of treatment. Quinolones are not an antibiotic in the traditional sense, but a toxic chemotherapeutic agent, with very severe and long-lasting adverse effects.
- Thousands of affected people need help, and adequate research is urgently needed in order to determine the mechanisms by which these drugs cause their damage, and how to limit their effects.

It is a shame that patients and victims once again have to write reports like this, placing themselves years ahead of their doctors. In ten years time the essential information contained in this report will already be common knowledge for thousands of persons, and it will be *"discovered"* by the medical class and then become accepted knowledge. Too late for too many. Is this the medical class that we deserve?

PLEASE REMEMBER:
Half of the quinolone antibiotics marketed in the last twenty years have been withdrawn from the market because of their great toxicity. Two of them during the life of this paper.

8.HOW HAS THIS REPORT BEEN WRITTEN

Nobody that has collaborated to create this article has had any previous reaction to any drug, food or allergen. We all were healthy people. We come from different backgrounds, races, social classes, and we don't share any common physical aspect that makes us more prone to be injured by quinolone antibiotics. It only happens that we have managed to link our health problems to the exact agent that caused them. In

nearly all cases, we noticed that the drug was damaging us during the treatment, but by then most of us had already taken the entire quantity of the prescription. Others reported to their doctors that the quinolone was causing pains but the doctors dismissed any link between the symptoms and the drug and asked them to continue on with the treatment; even though the patients themselves knew their bodies well as trained athletes and there was no doubt about what was happening. Some people started to feel bad after ending the treatment.

The statistics of this report have no objective value. They are a gross attempt to illustrate some facts that are better seen through some numeric figures. The sources of information for elaborating the statistics of this report come from individuals that have collaborated, sometimes in an organized manner and other times rather spontaneously. The amount of data behind some conclusions is scarce some times, but that has not deterred us from attempting to make some deductions, all of them objective. For a few issues, the amount of data handled has been simply huge. Do not forget that one of the most important practices of clinical research is reporting individual cases ("case reports"), because they help to outline the medical issues at stake. We have not used the case-report technique much (because intoxications to fluoroquinolones can be very unique), and have attempted to study at least small groups of people for every aspect of our research.

One source of data used to write some passages of this paper comes from the experience of a group of people with the following profile:

-TABLE 1- STATISTICAL PROFILE OF A WELL STUDIED GROUP OF PEOPLE RELATED TO THIS REPORT	
Number of persons	42
People with complete recording of data and battery of tests	18
People with partial recording of data and battery of tests	24
Sex	78% male, 22% female
Age	28 to 56; mean 39 years at the onset
People without any prior major medical problem:	37
People without any prior known allergy to medications:	36
People without any prior known immunological or rheumatic disorder:	37
People that suffered a mild reaction to quinolones	6
People that suffered a mild to intermediate reaction to quinolones	11
People that suffered an intermediate to severe reaction to quinolones	16
People that suffered a severe reaction to quinolones	9
Cases that were re-exposures (with unidentified prior reactions)	6
People that had taken quinolones in the past with apparently no reactions	8

For some deductions or setting up of hypothesis we have used hundreds of testimonies; or dozens; or only a few. It depends on every aspect discussed, as the collection of data has not been uniform and does not cover all issues in all individuals. For instance, the cohort of people in table 1 has been used for some of the core suggestions and proposals of this report, but not for all. For the time being, the collection of data is ongoing and probably will be considered finished when we have detailed data of a handful of long-term floxed persons, with reactions lasting 6 years or more. Our best asset is without a doubt the close monitoring of some otherwise healthy and young people that have already been going on for more than four years in this toxic altered state.

This report is nearly useless for people with mild reactions, except the evident advice of not being re-exposed to quinolones in the future.

Our statistics have no medical value, but are useful to evidence and elucidate the kind of problem we are facing. This report is a true piece of scientific evidence. When we do not comply with an official theory embraced by doctors or complain of its lack of depth it is because it is insufficient to explain our real experiences, or enter into conflict with most of our symptoms. We are uneasy at the prospect that some doctors seem to suggest belonging to a group of coincidentally special people with idiosyncratic flawed

bodily constitutions and a peculiar inclination to being affected by antibiotics, especially because many of us took quinolones in the past without permanent injuries. Our assumptions about the floxing can be wrong. All our theories are just sparks that seek to start a fire of more medical studies.

We have spent more than six years studying the floxing syndrome (quinolone toxicity syndrome or QTS), especially from the point of view of severe neuropathies, muscular and joint disorders, with specific emphasis on the healthy, young, active and athletic population. Some doctors have contributed with their opinions or outcomes of limited research that they have done in order to help us.

We have challenged ourselves with blind trials using placebos and active agents (foods, supplements, provocative tests) but always stayed away from potent drugs or supplements. We have kept detailed diaries for years with tens of thousands of entries recording ongoing symptoms and our attempts at regaining basic movement, fitness, and athleticism. We have probed and pushed ourselves through pains, endurances, and tests of many kinds, varying as few factors as possible in each trial, so that results could be of use. We have had more than a hundred MRIs (magnetic resonance image), dozens of CATs (computerized axial tomography), plain radiographs, three phase gammagraphies, dopplers, echographies, electromyographies, nerve conductivity tests, ultrasound tests, and hundreds of blood, urine, stool, and hair tests along with many other diagnostic tests as well as a few biopsies.

We have contacted many doctors. A few very reputed doctors politely answered our questions, and some of them were very helpful and caring indeed. Most doctors, universities and research teams have ignored our begging for small bits of information not only on quinolones but on related issues as well. This report does not contain any single reference that identifies any information exchanged with floxed persons or doctors, because anonymity is part of its fundamental policy. All citations and testimonies have been reproduced with permission from the persons that produced them. When a person's name is cited, it is because we make reference to public information that pertains to that person.

As stated, we did not want to write a medical paper, and we are not entitled to. We have intentionally not bound our conclusions to scientific methods like double blind trials or the well-established protocols for testing drugs. For us, it is enough proof of a symptom being a toxicity of quinolones that literally thousands of previously healthy people link it to the antibiotic and describe it in an astounding identical manner in many groups that have no connection between them.

If we were doctors we would be afraid of shedding light on the toxic properties of the fluoroquinolone antibiotics because of many reasons. First we would be acting against well-established common beliefs about safety of quinolones. Secondly, we could face fierce counter reports stating on the contrary written in a way that would question our professional proficiency. We could also face retaliation in terms of funding and rejection from other professionals. We would also be worried to raise concerns about a powerful class of antibiotics that are very much needed medications now that resistance to bacteria is on the rise. We would feel obligated to begin all considerations with the unfounded but mandatory *"quinolones are extremely useful drugs with a low toxicity and very well tolerated...,"* and would feel compelled to end the reports saying the not less mandatory "*.. is perfectly known that all the above mentioned adverse effects might be caused by something else because the patients were very stressed*.[for instance]*"*..... We would also need to conduct very regulated trials, get the approval of magazines and journals, etcetera.

We feel free to comment on the real life facts. We have only needed a group of some hundred healthy people with a good knowledge of their histories, where the only external factor entering their lives is cipro or levaquin, just to cause extreme injuries that last for many years, in many cases without any foreseeable end.

Finally, unlike the FDA regulators and general doctors, we do not feel the need to soothe our consciences after causing so many hundred of thousands of injuries–(to us, the victims) telling ourselves that that is the price to pay to save millions of lives, because that is a monumental lie. To save those lives that are in need of quinolones is compatible with sparing the lives of those of us that would not have taken any

quinolone (because they were completely mis-prescribed) had we (or our doctors) known the toxic profile that they really have.

But we are not doctors, and looking to the low profile of the published research on the toxicity of quinolones and our own compilation of information, we believe that the real value of our conclusions is worthy of being taken into account.

Even though this text is preliminary and rudimentary, it is a legitimate form of scientific evidence. In total, we, as many others, have demonstrated once more and beyond any doubt, the extensive and devastating effects of quinolone antibiotics and the unethical behaviour of the FDA and other western agencies that are dominated by the manufacturer's lobbies who routinely do not protect the people's health as they should, resulting in the increase of financial profit for the laboratories and pharmaceutical companies.

PART II: QUINOLONE AND FLUOROQUINOLONE ANTIBIOTICS

9. QUINOLONE AND FLUOROQUINOLONE ANTIBIOTICS

The main quinolone and fluoroquinolone antibiotics and their full pharmaceutical names are as follows:

TABLE 2. MAIN QUINOLONES MARKETED (with their USA names)

GROUP	Generation	Generic name	Brand name (manufacturer)	Year of FDA approval
QUINOLONES	First	Cinoxacin Nalidixic acid	 NegGram (Sanofi)	
FLUORO QUINOLONES	Second	Norfloxacin Ciprofloxacin Ofloxacin Enoxacin Lomefloxacin	Noroxin (MSD) Cipro (Bayer) Floxin (Ortho) Penetrex (Aventis) Maxaquin (Searle)	1986 1987 1990 1991 1992
	Third	Levofloxacin ~~Sparfloxacin~~ ~~Gatifloxacin~~	Levaquin (Ortho) ~~Zagam (Aventis)~~ ~~Tequin (BMS)~~	1996 1996 1999
	Fourth	~~Trovafloxacin~~ Moxifloxacin Gemifloxacin	~~Trovan (Pfizer)~~ Avelox (Bayer) Factive	1997 1999
UNDERGOING CLINICAL INVESTIGATION	many more quinolones are expected to become available in the years to come			

The antimicrobials quinolones and fluoroquinolones are bactericidal and inhibit the activity of DNA gyrase, so the bacteria cannot replicate properly. Most likely they also injure the human cells on the light of the devastating secondary effects they have. The older quinolones, **nalidixic acid** and **cinoxacin,** are active only against Enterobacteriaceae with no activity against gram-positive organisms, *Pseudomonas aeruginosa,* or anaerobes. Furthermore, bacteria tend to become rapidly resistant to these older drugs; they are used only for UTIs.

The fluoroquinolones have much greater activity against Enterobacteriaceae and are also active against staphylococci, *P. aeruginosa, Mycoplasma, Chlamydia,* and some streptococci, but with the exception of trovafloxacin, are not reliably active against anaerobes. Ofloxacin, levofloxacin, grepafloxacin, trovafloxacin, and sparfloxacin have the best activity against gram-positive cocci. Resistance has been noted, particularly with *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus.* Resistance to one fluoroquinolone generally means resistance to all. Norfloxacin is poorly absorbed orally; the other fluoroquinolones are better absorbed orally, resulting in blood levels adequate for treating systemic infection.

Tequin is being pulled out of the market (year 2006) because a class effect of quinolones like hyperglycemia and hypoglycemia has been linked to this particular fluoroquinolone with very serious and fatal results. It seems that this side effect is more evident in tequin than in the rest of quinolones, but in fact, it is of the same order of magnitude in all fluoroquinolones.

Other banned or withdrawn quinolone antibiotics are temafloxacin (OMNIFLOX), which caused low blood sugar, kidney failure, and a certain rare form of anemia; grepafloxacin (RAXAR) and sparfloxacin (ZAGAM), which caused QT-interval prolongation and increased risk of heart arrhythmias. Trovafloxacin (TROVAN) causes liver toxicity and is no longer prescribed although has not been banned in order to have it in reserve for very special and critical cases.

In other European countries, the number and names of quinolones marketed is very different. Check the best and most updated list that applies in your country, just looking in the databases of your local health

authorities.

10.THE MARKET OF QUINOLONES

The market of quinolones is growing. There are many reasons for that. Doctors have become increasingly wary of the adverse reactions of other well-known antibiotics (deafness, kidney injuries, others) and are deprived of some of the old arsenal (penicillins) due to the increasing resistance to antibiotics.

Therefore doctors do welcome fluoroquinolones for every use because their toxicity is well hidden and they do not cause the classic damage that has been concerning the medical class during the last years, like the severe pathologies mentioned.

> LEADDISCOVERY LTD IS ON THE UNITED KINGDOM:
> The quinolones are the fastest growing antibacterial class in terms of global revenue, increasingly being used in both the hospital and community sectors to treat a broad range of infections. However, the forthcoming US patent expiry of Bayer's blockbuster Cipro, is set to change the dynamics of this sector while novel compounds are increasingly favored in the light of drug resistance.
> Fluoroquinolone sales are expected to remain relatively constant to 2011 despite the expiry of US patents for Cipro and Levaquin in 2003 and 2010, respectively. Growth during this period will be driven by **increased use of quinolones in the treatment of less severe respiratory tract infections** in the community sector and aggressive life-cycle management of Levaquin and Avelox.
> Despite the large number and variety of products available, the fluoroquinolone market is heavily dominated by ciprofloxacin and levofloxacin, which together command 65% ($3.3 billion) of global sales.
> Although ciprofloxacin's key strengths lie in the treatment of urinary tract infections (UTIs), the majority (>60%) of its sales are derived from the treatment of infections of the respiratory tract (RTIs), primarily because these are the most common bacterial diseases treated across the US and EU.

As a consequence, in the years to come, if the practice of prescribing fluoroquinolones is not adjusted to the real toxicity of the anti-microbials, we are going to suffer a very big increase in people affected. All floxed persons start to ask their relatives and co-workers about their experiences with quinolones, and each one discover a handful of close people that has been hit by the antibiotic, without linking it with the cause.

For us is very paradoxical that many of us know of one or more doctors that have suffered a reaction to a fluoroquinolone (crutches for ankle pains, tendon ruptures, strong heart abnormalities, and others) and those doctors do not engage in active acknowledgement of the problem.

11.QUINOLONE FIRST FACTS

The fluoroquinolones are a class of synthetic anti-microbial agents that were modelled after nalidixic acid, a non-fluorinated quinolone antibiotic. The Food and Drug Administration (FDA) approved nalidixic acid in 1963 for the treatment of urinary tract infections. It is rapidly absorbed after oral administration and is excreted into the urine in bactericidal concentrations. This compound has several limitations, which prevents its use in other types of infections. Specifically, nalidixic acid has a narrow spectrum of activity and microorganisms easily developed resistance to this drug.

During the 1980s, modifications of this drug were made. It had been discovered that a fluorine atom on the number 6 carbon and a piperazine ring at the number 7 carbon greatly enhance the spectrum of activity. These revisions to nalidixic acid's structure were responsible for improving the activity of these agents for Gram-positive organisms and expanding the Gram-negative spectrum to Pseudomonas aeruginosa, Haemophilus influenzae, and Neisseria gonorrhoea.

Much like other antibiotics, the 6-fluoroquinolones work to inhibit bacterial DNA synthesis and exhibit concentration-dependent killing of micro organisms. However, their mechanism of action is somewhat unique in that they inhibit the bacterial DNA gyrase (the enzyme responsible for DNA replication) in such a

way that irreversible breakages occur in the DNA strand.

Overall, with the exception of sparfloxacin, the fluoroquinolone antibiotics are rapidly absorbed after oral administration and reach their maximum concentrations in one to two hours. Food may decrease the rate, but not the extent of absorption.

All fluoroquinolones are eliminated by a combination of the kidney and the liver. Good renal function is important in the elimination of all of these antibiotics, even when only small amounts of unchanged drug are detectable in the urine.

Quinolones belong to the current arsenal of antibiotics developed to treat various infections and are useful to fight bacteria resistant to other antibiotics and for people allergic to more benign anti-microbial organisms. They are also preferred for urinary tract infections because some of the antibiotics used in the past were so toxic to the kidneys or the auditory system, for instance, thus creating thousands of dialysis patients and tens of thousands of deaf people.

12.THE WAY QUINOLONES ARE INVENTED

After the development of the core quinolones, -the ones on which all the rest are based- all pharmaceutical companies want to have one or several of them in their portfolio. For that purpose, they manipulate the original molecule, shifting positions of atoms and links around. The new chemical thus made has slightly different properties, many times impossible to discern, and they try to patent it and mass produce the stuff and sell it at high prices.

Some of these new quinolones frequently have extreme toxicity, that manufacturers make their best to conceal or to not disclose during the pre-marketing trials, and they finally enter the market, causing many deaths and fulminant damage until they are withdrawn, as we have seen above.

Other quinolones are equally toxic as the parent ones, or have modified toxicities but still bear the delayed toxicity properties that are so convenient for not blaming the quinolones on the damages and injuries that they cause.

Up to now, all the quinolones marketed or in advanced stages of development possess as a class effect the wide range toxicity reported in this paper: central and peripheral nervous system damage, heart, liver, kidney and other systems, vision, cartilage and tendons and all the rest that you can consult hereafter.

PART III: TOXICITY OF QUINOLONE ANTIBIOTICS

13. TOXICITY OF QUINOLONE ANTIBIOTICS

Quinolones are very toxic antibiotics. They are not biological products but purely man-made chemical toxic compounds for killing bacteria, and ultimately, your body and its many structures and systems. High doses or prolonged courses cause a disproportionate percentage of adverse effects. Although most laboratories and manufacturers rate the number of adverse reactions as being very low, the real figures are much higher. These drugs are distinctive for one thing: for the vast majority of people, damage remains unnoticed for many weeks or months, which does not prompt the patient to stop the treatment, and then severe disorders develop with many clinical symptoms.

The mainstream medical class ignores this fact and is reluctant to learn that an antibiotic can inflict such severe, disabling and long-lasting damage. Consequently, nearly all victims of this drug toxicity are wrongly diagnosed as suffering from overuse injuries, neurological illnesses, immune reactions, osteoarthritis, cardiopathies, vision problems, etc.

Many quinolones are routinely withdrawn from the market. Recent examples are tequin (extremely serious hypoglycemia and hyperglycemia) or trovafloxacin, which has been forbidden in Europe after *"discovering"* that it caused many liver failures requiring fulminant transplants and deaths due to liver failure, along with other extremely severe damage, never associated before with the 'innocuous' trovafloxacin. For health agencies to *"discover"* these kind of toxic profiles means that they are so overwhelmed by the evidence of many tragedies gathered through the years that they can no longer please the requests of manufacturers to keep the drug on the market and increase the range of use, ultimately having to ban the drug.

TO THINK ABOUT:
Quinolones are very toxic antibiotics. As it has happened with many other drugs before, the medical class still ignores it all.

Normally, manufacturers are very keen at manipulating the results of the final phases of drug trials, and concealing the risks to patients. The *industry* is also very proficient at pursuing and discrediting any independent report on adverse effects of their medications. As the manufacturers are the almost sole providers of information to the health agencies, the health agencies normally only act after years of having proof that people were dying and being severely injured due to toxic drugs. You can learn more about the subject through many investigative and authoritative reports that have been published over the past several years. More on this issue is briefly discussed later in this paper.

Many quinolones are in the process of entering the market, both as generic forms and as new brands (all the manufacturers want to have a *"me-too"* compound that sells at high prices, so always find out to which class of antibiotics the drug you have been prescribed belongs.

For the purpose of this report we will call FLOXING SYNDROME the set of disorders caused by quinolone antibiotics. In medical terms it would be called QUINOLONE TOXICITY SYNDROME (QTS).

There is very little -if any- clinical knowledge about this syndrome, as it is not yet recognized as a major health problem, and no protocol for healing has been developed so far. There is not a single scientific study performed in order to better understand the true nature of the toxicity or to make a treatment available. Unfortunately, there are no specific tests or markers that can objectively diagnose the syndrome

or the extent of its severity at any given moment. The vast array of symptoms that usually accompany a severe QTS (QUINOLONE TOXICITY SYNDROME) makes the task of establishing a reliable diagnostic procedure difficult and complicates the search for a cure.

This syndrome is so widespread, yet unrecognised, that it could constitute in and of itself, a specific kind of neuromuscular, systemic disorder that affects all body systems, and as a result deserves to be studied and treated separately as a branch of the drug-induced generalized disorders.

14.WHAT CAN I EXPECT FROM TAKING A QUINOLONE ANTIBIOTIC

NOTE:
Everybody can have an allergic or hypersensitive reaction to any drug. Also, some people are good metabolizers (their livers for instance can process the drugs easily) but others are poor metabolizers (their livers cannot break down drugs properly so they build up in the body up to toxic concentrations).
All the statistical and research data provided in this paper is based on experiences of people who are non- allergic, not hypersensitive and considered as normal metabolizers of quinolones (quinolones have to be broken down by liver enzymes).

Like many other drugs, quinolones are highly toxic medications. A special feature and the worst problem posed by quinolones is the severity and irreversibility of many of the injuries that they cause, some of which emerge long after finishing the treatment, when there is no possibility of stopping the ingestion of the drug.

In general, you should ask your doctor to prescribe another -less toxic- antibiotic, if there is an alternative, because all doctors with proper knowledge on quinolones (including FDA officials) share the opinion that quinolones should be a carefully administered, second or third line of defense, antibiotics.

In any case, the toxicity does not show up with significant symptoms if you take short courses and low doses. Used in low doses (250 to 500 mg of the equivalent to ciprofloxacin potency daily) for short courses (up to one week) these antimicrobials have a low toxic profile.

The whole problem with the quinolones comes from their very narrow safety profile, which is rarely respected.

Although it is difficult to objectively establish the limits of what could be called "safe" or "unsafe", it is very clear that the clinical practice for prescribing quinolones is generally far beyond the safe margins. The inadequate and risky practices are:

- prescribing doses much larger than necessary
- prescribing courses much longer than necessary
- not adjusting doses for weight and build
- not testing the liver and renal functions prior and during long treatments
- not taking into account prior ingestion of quinolones and the cumulative effect
- not looking for adverse effects up to several months after completing the treatment
- dismissing or not identifying the first symptoms of the intoxications
- prescribing the quinolones to people under age of 18
- not checking the interactions with other drugs and foods (caffeine, theophylline, grapefruit and many others)

FLUOROQUINOLONE UTILIZATION IN THE EMERGENCY DEPARTMENTS OF

ACADEMIC MEDICAL CENTERS. Prevalence of, and Risk Factors for, Inappropriate Use. Arch Intern Med.2003
We studied 100 consecutive ED patients who received an FQ and were subsequently discharged. Appropriateness of the indication for use was judged according to existing institutional guidelines. A case- control study was conducted to identify the prevalence of, and risk factors for, inappropriate FQ use.
Results: Of 100 total patients, 81 received an FQ for an inappropriate indication. Of these cases, 43 (53%) were judged inappropriate because another agent was considered first line, 27 (33%) because there was no evidence of infection based on the documented evaluation, and 11 (14%) because of inability to assess the need for antimicrobial therapy. Although the prevalence of inappropriate use was similar across various clinical scenarios, there was a borderline significant association between the hospital in which the ED was located and inappropriate FQ use. Of the 19 patients who received an FQ for an appropriate indication, only 1 received both the correct dose and duration of therapy.
Conclusions: Inappropriate FQ use in EDs is extremely common.

The result is a very high incidence of adverse reactions, some of which impair people for life.

15.THE EPIDEMIC OF TOXICITIES OF QUINOLONES

15.1. The epidemic of sick people directly treated with quinolones

Those safety principles stated above should only be overruled in critical cases, after properly assessing the risk-benefit ratio. However, less than 15% of all the quinolone prescriptions meet the safety criteria, hence the epidemic of intoxications that plagues people in all countries. In other words, being antibiotics with an extraordinary toxic potential, they are prescribed carelessly, randomly, and indiscriminately.

This epidemic is one of the least recognized for now and one of the easiest to avoid. The only thing at stake is the revenue of the manufacturers of these antibiotics, which not surprisingly are among the most expensive on the market. But that does not mean that they are expensive to produce and it is known that the initial development costs were recovered years ago.

This epidemic affects both people that are very resistant to quinolones (whose bodies, especially their livers, metabolize the quinolones properly), but specially people that are hypersensitive to quinolones, poor metabolizers or intolerant to those medicines because of other reasons.

15.2. The epidemic of sick people that take quinolones through food

The *"industry"* (the manufacturers) produces quinolones massively for veterinary use. Some developing countries sell quinolones internationally for fish and cattle, literally by the ton. Much of the poultry on the market in Asia, America and Europe has been raised and fed with antibiotics (quinolones included) from the first day of their lives to the last, and then directly to our dinner plates. In 2005, quinolones have been forbidden in the United States for poultry raising.

Oddly enough, the medical associations and citizen groups are concerned only with the effectiviness of the antibiotics in the long run and not with the adverse health effects of antibiotics in our foods. They correctly advocate that new bacteria resistant to quinolones are housed by the birds, that can pass on to people and for which one day there could be no effective treatment available. For that reason they theorize that quinolones should be banned for meat and fish production, to which the manufacturers of quinolones exert a strong opposition, putting their lobbyists into action at all political levels.

Although these worries are justified and seem appropriate, equally important is the fact that the content of quinolones in some food is far beyond reasonable amounts and cause sickness in people sensitive to them and in normal people by accumulation, not to mention to people that are recovering from a quinolone intoxication. Thus, there is another silent, low grade epidemic, the one caused by the

intoxication caused via ingestion of quinolones in food, which manifests as fibromyalgia, neurological problems of every kind, insomnia, psychological disorders, osteoarthritis, and others.

16.WHAT ELSE SHOULD BE INCLUDED IN THE PACKAGE INSERT?

The pharmaceutical package inserts for prescription quinolone antibiotics contain gross underestimations of severe adverse effects. These adverse events are presented as rare or very rare, when in fact they are very common or even unavoidable, that is to say, predictable, as it has been shown by some epidemiological studies.

In order to help you to get an idea of the real toxicity profile of quinolone antibiotics, take into account that had it not been for the manufacturer's manipulation and FDA consent, the package insert would read:

- This drug is neurotoxic. The effects of this drug are cumulative, so ask your doctor to keep a record of the total amount ingested by you, so that currently supposed safe levels are not surpassed. The neuropathies associated with this drug (with sensory as well as motor and autonomic involvement) are often severe, lasting for many years or permanent.
- The therapeutic effects of this drug disappear with drug cessation, but the adverse reactions can manifest weeks, months or for up to two years later, so report to your doctor any abnormal bouts of neuropathies, central nervous system disorder like insomnia, nervousness, tendinitis, joint pains, muscle pains, twitching, fasciculations and/or body trembling, visual disturbances such as decreased visual acuity, dry eyes, blurred vision, double vision or other dry mucous symptoms (mouth, nose, skin, ears, etc…) as well as all the rest of symptoms listed in the package. In many cases the resolution of symptoms takes several years.
- This drug will deteriorate the cartilage all over the body as it kills the chondrocytes, the root cells of cartilage. The damage depends on the previous state of you cartilage, plus the dose and length of quinolone treatment. Do not take this drug if you suffer from early osteoarthritis, if you frequently play sports or perform strenuous tasks or exercises. Usually, the damage inflicted is irreversible.
- During the post marketing surveillance of this medicine, unexpected tendinitis and ruptures of major and minor tendons have been reported in all kinds of people. Ruptures reach 50% and more in persons that take this antibiotic with corticosteroids. In young, healthy and active people tendinitis becomes symptomatic in 5% of persons for low dose and short treatments, and in 100% of people with the highest doses approved and/or long treatments. The injuries of the tendons tend to heal very slowly, and in many cases they become chronic or permanent. The injuries of the tendons are cumulative; so keep a record of the total amount of quinolones ingested in your life.

> ***TAKE NOTICE:***
> ***Quinolones cause permanent injuries, especially degeneration of cartilages in knees, hips, spine, and shoulders, plus irreversible damage in the eye, fatal arrythmias and irreversible neurological disorders.***

- This drug is not recommended for those who have been diagnosed with autoimmune disorders, *or if there is a suspicion about one being present. It can cause conditions similar to, as well as* worsen or release, autoimmune disorders like multiple sclerosis, lupus erithematosus, rheumatoid arthritis, small vessel vasculitis, dermatomyositis, polymyositis and others.
- Quinolones can cause fatal arrythmias and other heart injuries. Do not take them if you suffer from any heart condition or a history of palpitations or irregular heartbeats.
- Elderly people, diabetics, patients with impaired renal function, persons under 18 (whose bones and cartilage are still growing) and people taking corticoids are at great risk of suffering very disabling reactions.
- In order to avoid skin cancer and eye lesions,you should protect your skin and eyes against strong sunlight and refrain from sunbathing for at least one year after taking a fluoroquinolone.Consult *your doctor to adjust this period according to the dose you are planning to take.*

All of these statements will be acknowledged by the medical community in the years to come, only too late for thousands of people whose lives will have already been meaninglessly ruined.

Keep in mind that half of the quinolone antibiotics marketed in the last twenty years have been withdrawn from the market because of their great toxicity. The quinolones currently available are just slight variations (shifting the position of one atom or molecule) of the openly toxic quinolones, and are still very toxic. The magic of the new position of the atom is that the toxicity is more concealed, cumulative, delayed, internal, and mimics better other serious illnesses.

17.REAL RATES OF ADVERSE REACTIONS

There are enough published reports and Rx lists about these drugs. You can find them on the Internet. The list of adverse effects for each quinolone drug is extensive, and many of the adverse reactions will manifest in normal people with long treatments or high doses, or just with one pill in extreme cases of intolerance.

Remember that the "rare" frequency of adverse reactions stated in the pharmaceutical package inserts is usually grossly underrated. The statistics provided by the manufacturers are a gross manipulation of biased clinical trials, and are totally unreliable. For a better assessment of your chances of getting seriously ill, consider the table 3 instead. We do not understand either why the package inserts do not discern among probabilities of having adverse reactions for different lengths of treatments or why they do not adjust the doses for body weight, age, or liver and renal impairments.

Let us suppose that you are a healthy, young person, you are not taking any other medications and that you are the perfect patient- not allergic to anything and able to metabolise most commonly marketed drugs without experiencing adverse effects; then your chances of developing clinical symptoms of serious disorders caused by a quinolone antibiotic are:

TABLE 3. ADVERSE EFFECTS OCCURRENCE FOR QUINOLONE ANTIBIOTICS (Using ciprofloxacin potency as reference). (People of up to 160 lb of body weight)

THERAPEUTIC REGIME / DOSAGE	PERCENTAGE OF ADVERSE EFFECTS			DURATION OF THE ADVERSE EFFECTS
	SEVERE	INTERMEDIATE	MILD	
up to one week of up to 1,000 mg daily	*7%*	*18%*	*25%*	*Several weeks to months*
6 weeks of 1.000 mg daily	*58%*	*86%*	*100%*	*Months to years*
more than 6 weeks on a 1,000 mg/day basis	*76%*	*91%*	*100%*	*Mean duration of severe limitations and pains for 2.5 years, but can be 6 years more - and in some cases the damage and destruction is permanent or ends in death.*
1,500 mg/day for a week or more	*92%*	*100%*	*100%*	*Many years or permanent*

For the interpretation of what is a SEVERE, INTERMEDIATE or MILD reaction, consult further in the report.

This table has been prepared with the input of more than 40 individuals, the majority of them, but not all, belonging to the cohort of table 1. It is updated periodically with the data rendered by the passing of time and new incorporation of people.

For people that weight much more than 160 lb or much less than that, different tables should be prepared. That is beyond the possibilities of this victim's account.

Please, read table 3 correctly. If you weigh around 160 pounds and have taken 1.000 mg /day of ciprofloxacin for more than 6 weeks, your probabilities of having a mild reaction are not 100% as there is not a 91% chances of you having an intermediate reaction. The table only says that 100% of the people studied had a mild reaction and that 91% of those studied had intermediate reactions. But YOU can fair quite differently because each individual reacts in a different way and because there is a lot of subjectivity when rating the severity of one's toxicity. So, if after that dose you don't have any reaction

and you would have been included in the study, the percentages would have been affected low-wise.

TABLE 4 RELATIVE POTENCY OF QUINOLONES USED IN THIS REPORT		
DRUG	MAXIMUM DAILY DOSE	RELATIVE POTENCY ADOPTED
Ciprofloxacin (Cipro)	1500 mg/day	1,00
Enoxacin (Penetrex)	800 mg/day	1,50
~~Gatifloxacin (Tequin)~~	400 mg/day	exceptionnally toxic
Levofloxacin (Levaquin)	500 mg/day	2,00
Lomefloxacin (Maxaquin)	400 mg/day	--
Moxifloxacin (Avelox)	400 mg/day	2,00
Norfloxacin (Noroxin)	800 mg/day	--
Ofloxacin (Floxin)	800 mg/day	1,50
~~Sparfloxacin (Zagam)~~	200 mg/day	extremely toxic
~~Trovafloxacin (Trovan)~~	200 mg/day	extremely toxic

We have used as the potency of ciprofloxacin as a reference. There is not a correlation between the relative potency of the different formulations of quinolones. In other words, there is not a formula that tells us for example how much ciprofloxacin is equivalent to 500 mg of levaquin in terms of the likelihood of side effects.

The relative potency of the quinolones is normally linked to their effectiveness against different bacteria, so potencies can be rated differently depending on the bacteria used as reference. Sometimes a simple comparison between potency of quinolones is based on their pharmacological dynamics (peak concentrations in serum-blood; half life, excretion, clearance, etc).

But floxed persons have been exposed to different quinolones and different dosages. For that reason, we have had to adopt a way to compare quinolones in terms of potency. For this purpose we have set up a scale to help floxed persons to get a first impression on "how much" quinolones they have ingested. We believe that an option to use as relative potency is the maximum daily dose, based on AVERAGE risks of toxicity posed by each quinolone.

The fact that each quinolone has subtle but unique toxic profiles does not help to establish that scale of relative potency. In any case, studying average situations, and leaving aside all uniqueness, and peculiarities, levaquin for instance has approximately double potency than ciprofloxacin. This means that 500 mg of levaquin treats most (not all) infections that 1000 mg of cipro does. Similarly, 500 mg of levaquin tend to cause as much damage as 1000 mg of ciprofloxacin.

Our tables of adverse reactions are based on that calculation. Some 60% of the floxed persons that reported their experiences had taken cipro, and the rest mostly levaquin. We adjusted all the data as explained. For the main tables all reactions corresponding to people older or younger than a certain age were left aside. Also those people whose weight differed more than a percentage than the mean value of 150 pounds.

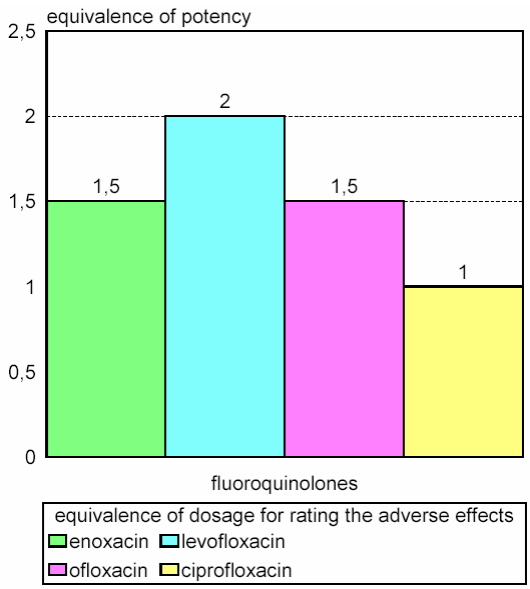


Figure 1. Relative potency of quinolones, used in this report

Not all the tables have been elaborated with such scrupulosity, because of the scarce results or information or the wild range of individual conditions.

This has to be understood clearly. We are not saying that the potency of quinolones in any case are those stated in these tables, but that they are the algorithm, the calculation that we have use to homogenize the data provided by different people.

We have talked with nearly 50 other people (not related with the report) who thought that their quinolone treatment had been successful and without any adverse effects who reported having had

their first experience of severe bouts of tendinitis or neurological problems a few weeks or months after the quinolone treatment and therefore had not linked them with the drug. The same can be said about neurological disorders. Taking into consideration all the facts, nearly all of them now believe that the cipro or levaquin they took is the cause of their insomnia, peripheral neuropathies and musculoskeletal problems. There are also many medical papers confirming that much of this damage becomes symptomatic months after finishing the treatment.

The recent experience with the U.S. postal workers (some thousands treated with up to 60 days of ciprofloxacin and/or doxycycline) presents figures very similar to those in table 3. It is the first time in history that a large group of people is treated with quinolones for an extended period of time. For instance, in a survey study of adherence (to see if people obeyed the recommendations) to the prophylaxis of that population, conducted by the Center for Disease Control, the federal agency based in Georgia, USA, only one month after the therapy, 77% of patients had one or more adverse effects after the first half of the treatment (30 days); 25% of patients had joint problems after the 30 day mark; 23% of people experienced fainting, dizziness, or seizures in that month (see the tables of the survey in this address: www.cdc.gov/ncidod/EID/vol8no10/02-0349.htm) Below you can see some excerpts:

> ANTIMICROBIAL POSTEXPOSURE PROPHYLAXIS FOR ANTHRAX: ADVERSE EVENTS AND ADHERENCE
> Shepard CW, Soriano-Gabarro-Soriano M, Zell ER, Hayslett J, Lukacs S, Goldstein S, et al. Centers for Disease Control and Prevention, Atlanta, Georgia, USA; and New York Academy of Medicine, New York, New York, USA
> We collected data during postexposure antimicrobial prophylaxis campaigns and from a prophylaxis program evaluation 60 days after start of antimicrobial prophylaxis involving persons from six U.S. sites where Bacillus anthracis exposures occurred. Adverse events associated with antimicrobial prophylaxis to prevent anthrax were commonly reported, but hospitalizations and serious adverse events as defined by Food and Drug Administration criteria were rare. Overall adherence during 60 days of antimicrobial prophylaxis was poor (44%), ranging from 21% of persons exposed in the Morgan postal facility in New York City to 64% of persons exposed at the Brentwood postal facility in Washington, D.C. ../.... Adherence of <60 days was not consistently associated with adverse events. ../... approximately 10,000 persons across the eastern United States were offered >60 days of postexposure antimicrobial prophylaxis to prevent inhalational anthrax. .../...
> Potentially serious adverse events were identified based on adverse event data collected at 10- and 30-day follow-up. Persons who reported seeking medical attention because of adverse events associated with antimicrobial prophylaxis were further investigated. The definition of a serious adverse event, based on the Code of Federal Regulations, was applied to any of the following events associated with antimicrobial prophylaxis: death, life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, persistent or substantial disability/incapacity, congenital anomaly/birth defect, or an important medical event that requires medical or surgical intervention to avert one of these outcomes. A clinician interviewed health-care providers and reviewed medical charts to assess the severity of the adverse events and determine whether they met the case definition. The relationship of the adverse event to the antimicrobial agent used was categorized as definite, probable, possible, remote, not related, and cannot assess.
> .../.. Respondents indicating the presence of adverse events were asked to identify their most severe or "single most serious" symptom, then identify other associated symptoms from a list of potential adverse events.
> Most of the respondents were 40–64 years of age, and 60% were men. Of 2,444 women, 2% reported being pregnant or having been pregnant while taking antimicrobial prophylaxis. ..... Approximately 150 persons were <18 years of age at the start of the antimicrobial prophylaxis campaign..... Persons <18 years were not interviewed as part of the program evaluation after 60 days.
> Persons who took at least one dose of antimicrobial prophylaxis numbered 5,343 (86%); fewer than half of these respondents took only one agent as antimicrobial prophylaxis. Fifty-nine percent of respondents taking at least one dose of antimicrobial prophylaxis (n=3,156) took two antimicrobial agents as prophylaxis; 56% (n=2,984) took ciprofloxacin for one part of their course and doxycycline for the rest. Data from 10, 30, and post-60 days show an overall shift in the most recent antimicrobial agent used from ciprofloxacin (84% at day 10) to doxycycline (61% at day 60).
> Of the 5,343 persons who reported taking at least one dose of antimicrobial prophylaxis, 57% (n=3,032) reported adverse events during the first 60 days of antimicrobial prophylaxis use..... Thirty-two percent of respondents with adverse events reported diarrhea or stomach pain with their most recent antibiotic, 27% nausea or vomiting, 25% headache, and 22% dizziness. The most commonly reported categories of symptoms were gastrointestinal (44%, including nausea or vomiting, diarrhea or stomach pain, heartburn, and pain with swallowing) and neurologic (33%, including headache,

dizziness, lightheadedness, fainting, and seizure). Of the 3,032 persons reporting at least one adverse event, 23% identified “diarrhea or stomach pain” and 19% “nausea or vomiting” as their “most serious” symptom. Among persons reporting adverse events, 14% graded them as severe, 45% as moderate, and 41% as none/mild. Twenty-six percent of persons with adverse events reported missing at least 1 day of work because of symptoms.
At 10 days, the rate of one or more adverse events among persons taking ciprofloxacin most recently (45%) did not differ significantly from that of persons taking doxycycline most recently (49%). At day 30, this rate was slightly higher (77%) among persons taking ciprofloxacin most recently than persons taking doxycycline most recently (71%, p<0.01).
Of 2,907 persons participating in 10-day follow-up, 7% reported seeking medical attention. .../.... Of 3,374 persons participating in 30-day follow-up, 13% reported seeking medical attention. Of 2,135 persons with follow-up information available at 30 days ..., seven persons (0.3%) were found to have had a serious adverse event, including three persons hospitalized. .../..Four persons had reactions in which the relationship to antimicrobial prophylaxis was judged to be definite or probable, while the remaining three were classified as not related or could not assess. Two of four serious adverse events with a definite or probable relationship to antimicrobial prophylaxis were characterized by diffuse rash and systemic symptoms; the remaining two involved swelling of the face and neck. Two persons were treated as outpatients, one was treated in the emergency department, and the remaining patient was briefly hospitalized. All four recovered without sequelae.
At the post 60-day evaluation, 16% of respondents who took at least one dose of antimicrobial prophylaxis (n=842) reported seeking medical care for adverse events caused by prophylaxis at some time during their 60-day course. Nine percent (n=493) reported that their physician or other health-care provider advised them to stop taking antibiotics; 54% of these persons (n=267) reported that the presence of adverse events was the only reason for the recommendation to discontinue. Medical follow-up of persons reporting potentially serious adverse events after 60 days is ongoing.
The overall rate of reported adverse events during this campaign was higher than the rate (16.5%) listed on the usage information provided with ciprofloxacin. ..../.... Published adverse event rates among patients taking ciprofloxacin or doxycycline in clinical settings where a similar definition of adverse event is used provide a closer comparison of adverse event rates to antimicrobial prophylaxis. A recent published review of adverse events among patients taking long-term (>30 days) ciprofloxacin in clinical trials found an overall rate of 32% and a rate of gastrointestinal adverse events of 22%.
Regardless of their relation to antimicrobial prophylaxis or fulfillment of criteria for serious adverse events, high rates of reported adverse events during this event suggest the need for a management strategy in addition to monitoring efforts for future antimicrobial prophylaxis campaigns. While overall adverse events rates were high, differences in rates of adverse events associated with ciprofloxacin compared with those associated with doxycycline were not substantial.

The report on the postal workers has not included the rates of adverse events after 60 days of treatment, but surely they would have neared 100%, even more if the workers had been re-questioned some months after cessation of the therapy.

So here we see clearly exposed one of the key problems of all the literature about adverse events concerning quinolones and on which much of the firm beliefs of doctors is based:

- Manufacturers boast about ridiculously low figures of 1% or 2% for joint problems because of four reasons:
  - They have historically concealed all surveys with negative results to avoid difficulties in getting the drugs into the market (this practice has been recently banned).
  - They predominantly report the outcomes of experiments with low doses and short treatments, and not with the real doses used in clinical practice.
  - They refuse to include reports of adverse events in the statistics, that -according to them- cannot fully be attributable to their quinolone, even though it is crystal clear for practitioners, not to mention for the victims.
  - They try to be as low and inactive as possible in everything related to post marketing surveillance, because they firmly believe that a good surveillance can only bring detrimental results for their revenues, and never a boost in sales
- When an official survey like the one of the postal workers discloses that 25% of them had joint problems after one month of treatment (and surely a much higher percentage after 2 months), the survey is denied any medical value because its main objective was to study "adherence" to the program established by the federal government, not the adverse effects because there was

not a parallel control group taking placebos of candy. And that is it, nobody becomes alarmed or concerned by the appalling results.

Why hasn't the FDA drawn any conclusions from this experience already several years after the survey was done? There is a strong opposition from the drug manufacturers and the FDA to study this field experience in detail; once again to avoid responsibilities and/or liabilities with respect to the workers. With this irresponsible attitude, many more thousands will keep enlarging the group of the quinolone-damaged persons.

OBSERVATION:
For long-term or high dose treatments, the adverse reaction rate reaches 100% of patients. Many people are unaware that their illness is a manifestation of quinolone toxicity.

Nothing has changed 4 years after the experience of the postal workers (and all the overwhelming evidence). Still today the official figure of joint injuries is 1 to 2% of all people treated.

There are persons that develop a very acute reaction after one single pill that normally matures into an intermediate reaction (see later) that lasts for 1 year on average. This aspect needs to be studied by scientific groups because perhaps it would give some clues in the search for an understanding of this disorder:

> JEREMY NORMINGTON, DPT, DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
> Le Huec et al. examined two human tendon injuries that were induced by fluoroquinolones and noted the presence of giant cells. This usually indicates a reaction to a foreign body. Le Huec speculated that fluoroquinolones may be toxic to tendons because of the sudden onset of symptoms after a single dose.

18.PERMANENT AND IRREVERSIBLE INJURIES CAUSED BY QUINOLONES

In this report we have extensively used the terms "permanent" and "irreversible" to refer to the injuries caused by quinolones.

Normally, by permanent we mean damage that has not healed after 5, 6 or 7 years. By irreversible we mean those injuries that due to their nature cannot be reversed or returned to their previous healthy status, like cartilage destruction, for instance.

Some times both terms are used interchangeably, but irreversible means probably not fixable, and permanent means it lasts indefinitely.

19.THE RULE OF THUMB ON ANTIBIOTICS

Most doctors only have slight notions about pharmacology and base their knowledge on brief and solid clichés, which they tend to house as succinct and unchangeable medical principles. We have met very few doctors that prescribe quinolones that know barely a thing about their pharmacological dynamics, or their side effects. None knew a thing about the investigative reports on adverse effects, although many had heard about very rare cases of tendinitis (a very good, listening and caring doctor that prescribes a lot of quinolones, commented to us that up to then he thought that achilles tendinitis caused by quinolones was a sort of science fiction rumour; he also admitted that he had never questioned his patients about side effects, not to mention about delayed side effects). Almost all doctors consulted work on unproven axioms and common beliefs that have not been validated by research and that do not stand a minimum scrutiny. Of the doctors that sustained a conversation about the subject with their victim floxed persons, none had ever made a simple independent search on the basics of adverse effects of quinolones, thinking that they had none worth to taking into account.

Those deceitful principles of unlimited efficacy and flawless safety have been etched on them by the

propaganda of the drug laboratories, be it through wonder tales of the pharmaceutical salespeople or by biased and paid articles that praise the drugs in the medical publications. Therefore, reports and warnings about toxicity of certain drugs, raised by researchers, are not paid attention to for years; only until a massive epidemic of extremely severe or fatal events to thousands of people is revealed.

With the quinolones antibiotics, we are at the phase in which the toxicity has been identified, where it has been demonstrated that it is a direct class effect (not very dependent on personal conditions), and that it is almost a guaranteed result of every quinolone treatment for some approved dosages and lengths of treatments; but mainstream doctors are still considering it a perfect antibiotic with a broad spectrum of activity and negligible adverse effects.

Many years ago all antibiotics were considered wonder medications with no important side effects and only the risk of an allergic reaction. Millions of lives have been saved since their discovery. Later on the approach was broader and doctors started weighting all the pros and cons of prescribing antibiotics at the same time that medical research disclosed that there were some severe health risks linked to some classes of antibiotics. For instance, today it is fully acknowledged that aminoglycosides have an extraordinarily high incidence of renal damage and irreversible hearing loss.

Quinolones have a very high potential to cause permanent neurological, vision and joint damage, glucose problems, skin cancer and it is a matter of time that quinolones are linked widespread to high toxicity, and irreversible injuries. So, the current protocol when doctors prescribe antibiotics should be updated accordingly.

TABLE 5. THE RULE OF THE THUMB OF THE USE OF ANTIBIOTICS	
Antimicrobial	**Antimicrobial**
The list as it is now (in abbreviated form)...	
Aminoglycosides	Nephrotoxicity, ototoxicity, mostly irreversible
Clindamycin (Cleocin)	Diarrhea or colitis, morbilliform skin eruption
Metronidazole	Neurologic toxicity
Tetracyclines	GI intolerance, candidal vaginitis
Etcetera....	(this table is not a complete one)
And with this adding that it should contain.....	
Fluoroquinolones	Irreversible neurological damage. Permanent vision abnormalities Joint destruction

What would the medical community think about macrolides if half the macrolides invented had been withdrawn from the market due to their toxic effects?

And if the withdrawals took place almost every year; so it is not a matter of the past, but a reality constantly present?

Would they think that they are safe antibiotics? Surely not. What explains then the reputation of harmlessness that quinolones enjoy ?

20. CHARACTERISTIC TOXICITY OF FLUOROQUINOLONES

Unlike other antibiotics, that have very little toxicity (penicillins) or a very defined toxic profile (i.e. deafness and nephrotoxicity for aminoglycosides), quinolones and fluoroquinolones have a vast toxicity that affects the whole body. Although it is treated with more detail later in the report, the main toxic actions of quinolones and fluoroquinolones are:

TOXICITY TO TENDONS (TENOTOXICITY).

Quinolones are very toxic on the tendons, to everybody. They are the only frequently prescribed drug on the market that is directly tenotoxic and cause rupture of tendons, not only during treatment but months later. It is a very distinctive feature of quinolones. They damage the cartilage and tendons all over the body in a permanent nature, although symptoms only become noticeable in some 30% of the treatments. Doctors only acknowledge a less than 5% incidence of tendon disorders because usually the person that has been intoxicated by the quinolone, goes to his/her orthopedist some months after the ingestion of the quinolone, complaining of a chronic tendinitis when playing his/her favourite sport. Nobody links the tendinitis to the quinolone.

TOXICITY TO THE NERVES
This toxicity affects the whole body, because the quinolones have been invented in a way so that they have a very big penetrating capacity in all the tissues, especially the brain. The nerves of the brain, muscles, intestines, heart, lungs, tendons, eyes, and other organs, are lightly, moderately or irreversibly damaged, and their recovery can take from a few years to never, leaving a trail of pains, injuries, abnormalities and hundreds of disorders that you can see in the following sections of this report.

CHEMICAL TOXICITY
The extreme toxicity of the quinolone and fluoroquinolone antibiotics destroys the correct functioning of all types of cells in the body, causing extensive damage and abnormalities in all body functions and systems.

So, to take a quinolone or fluoroquinolone antibiotic means to take a potent toxic compound. There is no reason to prescribe or take them unless it is absolutely necessary. Do not be so naïve as to believe that the medical system, and the FDA have assessed properly the safety of these antibiotics, because they have clearly not done so, as you can learn through this report or doing your own research.

21.THE QUINOLONES STORED IN THE BODY

For months or years after their intoxication, many floxed persons tend to believe that they have to get rid of the "poisons" that have caused their syndromes. That would make sense during the first hours after exposure, but has not yet been attempted, or at least we have not detected it in the medical literature. During the acute hypersensitivity reactions (first hours) all scientific reports talk about cortico-steroid treatments, administered in order to counteract the immune-like reaction, most with “complete success” according to the doctors in charge.

However, later on, after the first days have passed, the concentration of quinolones in the body is small enough to make it impractical to attempt any flushing, cleansing, or removing of those traces of quinolones.

Many floxed persons tend to believe that massage, detoxifications, saunas and other practices liberate or disengage fair quantities of quinolones from some storage points of their bodies, and put them in circulation, causing a cascade of relapses, symptoms and events. That seems not to be the case.

The only mainstream theory that could be consistent with reality is the binding of quinolones to the GABA receptors (and other neuro receptors and tissues as well). [See the neurology section of this report]. Perhaps the quinolones, like other compounds known to doctors, bind semi-irreversibly to some neuro-receptors, causing very long term sequela. But the amounts of them, while they would be finally metabolized and liberated from their GABA positions, do not seem capable to add a substantial quinolone load to the body as to justify the strong bouts of relapses along the years of evolution of a normal quinolone syndrome. It is even possible that the quinolones do not actually bind to GABA receptors, but that they destroy them. In that case, the contents of quinolones in our bodies some years after exposure, would never justify the symptoms that we have.

However, the concentration of quinolones reached in the blood during exposure, can be measured in hair samples months or years after exposure, depending on the leg of the hair strand, and therefore help with the determination of the severity of recently floxed persons. This test should be instated routinely but it is not performed at all.

KAZUHIRO KOSUGE, ET AL . DEPARTMENTS OF CLINICAL PHARMACOLOGY AND PHARMACOLOGY, HAMAMATSU UNIVERSITY SCHOOL OF MEDICINE, JAPAN

> The distribution of ofloxacin (OFLX) along the shaft of each of three hair types, i.e., head, axillary and pubic, was investigated and compared among five healthy male volunteers 1 to 4 months after ingestion of ofloxacin for 1 or 2 days (total dose, 200 or 600 mg). Five strands of each hair type were sectioned together into successive 0.5-cm lengths starting from the dermal end, over a length of <6 cm, and the OFLX concentration in each hair section was measured by high-pressure liquid chromatography with fluorescence detection. The distribution of OFLX along the head hair shaft was narrow, having a single peak even 3 to 4 months after administration, suggesting a rather uniform growth rate among hair strands...../... head hair is the most suitable for analysis of individual drug use and the larger growth rate and cycle stage variabilities of strands of the other types of hair should be taken into account.
> We have so far shown that human head hair is a very useful and suitable biopsy material for tracing back individual drug use from the date of hair sampling for several months, even years, depending on the length of the hair analyzed. Head hair incorporates drugs within its structure in proportion to their doses or, to be exact, to their mean concentrations in blood, retaining them at the portion which is formed when the drugs are used. Thus, it can be said that head hair serves as "tape recording" that stores along its length all information about individual drug use. ..../.... Since potential drug-drug interactions relevant to adverse reactions have been reported, for example, for antimicrobial fluoroquinolones coadministered with anti-inflammatory agents, i.e., theophylline and so forth, knowledge of the past drug use of a study subject is needed for safe and effective application of drugs.

From the same Japanese report, we learn that the affinity of quinolones for melanin, make them very dangerous for the eye structures. Again, it seems that nobody in the medical practice knows this fact but only the authors of this report and people experiencing vision damage from the quinolones.

> Fluoroquinolone derivatives, including ofloxacin, norfloxacin, ciprofloxacin, and the other newly developed ones, such as AM-1155, OPC-17116, and Q-35, have also been shown to be detectable in head hair. In addition, their time-sequential use by a subject over the past several months was exactly recorded by their axial distribution along the hair shaft. It should however, be noted that these favorable characteristics of hair as a tape recording depend greatly on its melanin content. For example, ofloxacin, one of the most widely used fluoroquinolones in the world, can be detected in a 2-mm length of a single pigmented hair, even after ingestion of the usual therapeutic dose for only a day. This finding could be explained exclusively by its high affinity for melanin in hair. In fact, ofloxacin could hardly be detected in white hair samples collected from persons with grey hair who had previously taken ofloxacin, whereas it was sufficiently quantifiable in black hair samples from the same subjects. Due to this high affinity for melanin, however, potential ocular toxicity has been one of the main clinical concerns regarding fluoroquinolones, just as with the anti-inflammatory agent chloroquine. It has been reported that chloroquine was detectable in nail clippings even 1 year after the cessation of its ingestion. This phenomenon may be attributed to its high affinity for and very slow dissociation from the binding sites in the body, presumably from melanin-containing structures, including melanocytes in the skin. Therefore, analysis of fluoroquinolones in human hair seems worthwhile from the viewpoints of both therapeutic monitoring and the clinical toxicology of antimicrobial agents.

Does this mean that quinolones stay in the body for many years in a relentless destructive activity? We do not think so. It seems that the residual quinolones are just traces that could not justify the very big injuries caused by quinolones to those that have reached the toxic threshold.

In this sense, we believe that there are two different things to take into consideration:

RESIDUAL QUINOLONES IN THE BODY

As said, there is a lot of controversy about this issue. According to the best doctors in the USA we consulted, some of them with the highest knowledge about quinolones among the medical community, quinolones would be not detectable in body tissues after a few weeks, in amounts higher than negligible. These same doctors believe that quinolones may remain for years attached to the brain GABA neuro-receptors and some other tissues of the body. Both aspects are not contradictory because the amount of quinolones needed to collapse the GABA neuroreceptors is extremely low, and in any case, would be released little by little over the years.

DELAYED TOXICITY

Once exposed, the toxicity starts to cause its damage. Some of the damage takes its time to become evident, depending on many well-known factors discussed many times

in other sections of the flox report. We have never found reports linking quinolones to delayed effects (because the manufacturers have managed to spread the false belief that quinolones are completely safe), except for the rupture of tendons, that is acknowledged as a serious event that can take place up to more than a year after exposure. If doctors accept that tendons rupture months or years after the ingestion of the quinolones, why can't it be the same with all the neuropathies and the rest of injuries as we all floxed persons know? It would be so easily demonstrated that it is shocking to see all this idle and indolent thinking on the part of doctors.

However, there is plenty of literature reporting the delayed effects of other drugs, from weeks to months after exposure. There are a group of drugs with similarities to quinolones, like the anti-malarials chloroquine and hydroxychloroquine, whose mechanistic way of causing injuries, are very similar to quinolones, which the following data indicates:

FROM emedicine.com

Chloroquine and hydroxychloroquine belong to the quinolone family. They are related drugs with different therapeutic and toxic doses with similar clinical indications for use and manifestations of retinal toxicity.

Initially, chloroquine was given for malaria prophylaxis and treatment, and, later, it was used by rheumatologists for treating rheumatoid arthritis, systemic/discoid lupus erythematosus, and other connective tissue disorders. Chloroquine has an affinity for pigmented (melanin-containing) structures, which may explain its toxic properties in the eye. Melanin serves as a free-radical stabilizer and as an agent that can bind toxins. Although it binds potentially retinotoxic drugs, it is unclear whether the effect is beneficial or harmful. Chloroquine and its principal metabolite have been found in the pigmented ocular structures at concentrations much greater than in any other tissue in the body. With more prolonged exposure, the drug accumulates in the retina. The drug is retained in the pigmented structures long after its use is stopped. The kinetics of chloroquine metabolism are complicated, with the half-life increasing as the dosage is increased. In patients with retinopathy, 5 years or more after discontinuation, traces of chloroquine have been found in plasma, erythrocytes, and urine.

Or look to this other report:

PROGRESSION OF HYDROXYCHLOROQUINE RETINOPATHY AFTER DISCONTINUATION OF THERAPY: CASE REPORT.

Wei LC, et al. Department of Ophthalmology, Chang Gung Memorial Hospital, Taipei, Taiwan, R.O.C.

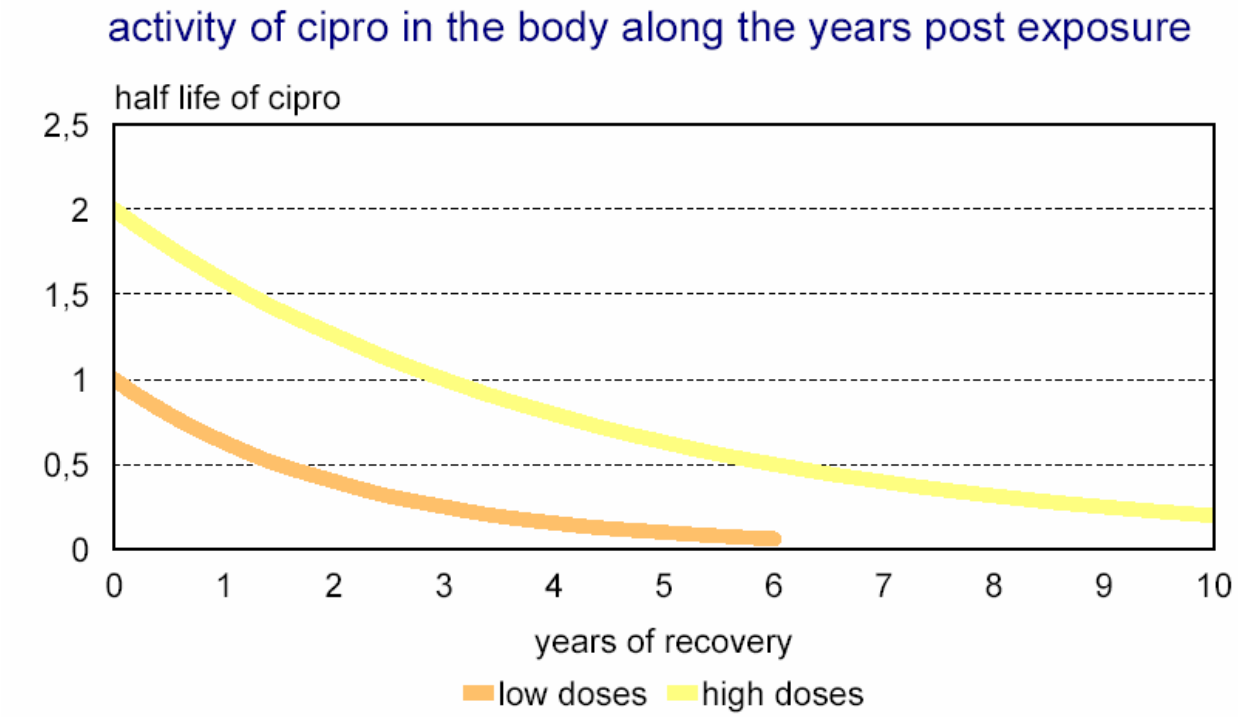
Chloroquine and its derivative, hydroxychloroquine sulfate, have been used in treating malaria, dermatitides of systemic lupus erythematosus and rheumatoid arthritis. Here we report a patient with hydroxychloroquine retinopathy which progressed even after discontinuation of hydroxychloroquine. A 42-year-old woman had systemic lupus erythematosus for twenty years. She had been treated with 200 to 400 mg of hydroxychloroquine per day (4 to 8 mg/kg of body weight/day) with a cumulative dose of 657 g. After bull's-eye maculopathy was found, hydroxychloroquine was discontinued. Her medical history revealed no chloroquine administration and no other systemic disease. **Five years after cessation of the therapy, her visual acuity and visual fields continued to deteriorate**. Ophthalmoscopic examination revealed the hydroxychloroquine retinopathy had advanced. To the best of our knowledge, the progression of hydroxychloroquine retinopathy after discontinuation of medications is a rare phenomenon. Regular ophthalmologic examinations should be performed for patients on hydroxychloroquine regimens because there is no satisfactory treatment for hydroxychloroquine retinal toxicity. Ophthalmologists, dermatologists and rheumatologists should monitor for ocular toxicity of hydroxychloroquine carefully.

In Britain there is a special request to doctors to watch out for adverse effects of drugs that appear "months or even years" after exposure. But for the moment, the most disgusting comment you can make during a conversation with your doctor is that your symptoms have been increasing or becoming apparent some months after discontinuation of the quinolone treatment. Virtually no doctor consulted by floxed persons has accepted this to occur, just out of sheer ignorance. Most have turned quite violently on their patients as if they had been insulted gravely.

The worst thing of all is that this kind of delayed onset reaction is the hallmark of the quinolone's toxicity.

Please note that the term DELAYED REACTION is commonly used by doctors for side effects that take place normally between 2 and 7 days after exposure to a drug. We assign DELAYED REACTION to the real event by which damage starts to take place during the ingestion of the drug, but that is really perceived by the victim months (a long time) after discontinuation, once the accumulated injuries make them symptomatic.

Once said all that, according to the most knowledgeable doctors consulted, cipro would have a half life of 1,5 years in the body of a floxed person. The biological half-life of a substance is the time required for half of that substance to be removed from an organism. According to us, and in line with what research indicates for antimalarials, the half life of fluoroquinolones is higher for higher doses. This figure summarizes much of our conclusions after studying floxings for almost 7 years:



The figure 2 (above) tries to illustrate that for "low doses", after 1,5 years the presence of cipro in injured tissues would be halved, and after another 1,5 years, it would be halved again, resulting in a 25% activity after 3 years. So, after 6 years a floxed person would normally have a 6,25% presence of cipro, with respect to the maximum at the onset of the reaction and he/she would feel almost fine. According to our experience, this can fit well with what we call intermediate reactions (see later in the report), but does not represent the reality for severe reactions.

Severe reactions seem to be associated with high blood concentrations of fluoroquinolones during the treatment, either because the given doses are high or because the metabolism of the drug is impaired by previous treatments or due to personal conditions. For these high doses, the initial reaction seems to be at least double than for an intermediate reaction, and very much like in the case of antimalarials commented above, the half life is increased to about 3 years. Then after 3 years, the activity of cipro in a severely floxed person would be more or less the same than that of a person with an intermediate reaction at the onset. After 6 years, still a lot of cipro presence (the same than after 1,5 years of an intermediate reaction) would still be present. And after 10 years about 20% of the activity of cipro would still be causing problems. This prediction fits well with most cases of severe reactions studied along this report. In other words, recovery seems to last four times longer, and leave a trail of permanent injuries.

We do not use this graphic for any predictions of your recovery, because recovery is a far more complex issue. This curves are useful only for discussing the half-life of the fluoroquinolones and their elimination from the neurotransmitters and other tissues, in intermediate and severely affected people.

22. CUMULATIVE TOXICITY OF QUINOLONES

Another very important thing to remember is that the toxicity of fluoroquinolones is cumulative. For people who tolerate quinolones well, and feel quinolones are a good antibiotic–it is typical to of them have successful courses. The first treatment usually goes without any noticeable event. Subsequent treatments do not develop symptoms that are noticeable by the patient, but the first hidden and subtle symptoms may start to develop (see list given in paragraph 29 "Hints and clues that could save your life").

Additional ingestion of prescriptions of quinolones can cause the patient to end up crippled forever, sustaining permanent damage. The following summary corresponds to a floxed person whose history is extremely well recorded:

TABLE 6. CUMULATIVE TOXICITY OF CIPROFLOXACIN IN YOUNG PERSONS
CUMULATIVE TOXICITY EXPERIENCED BY A HEALTHY, ATHLETIC FLOXED PERSON WITH NO KNOWN ALLERGIES, SENSITIVITIES OR REACTIONS TO ANY FOOD, DRUG OR ALLERGEN

Age	Drug	Daily dose (mg)	Length	Symptoms (*)	Medical tests / diagnosis by doctors	Patient's valoration at its time
34	cipro	2x500	8 days	none	---	Great antibiotic
34	cipro	2x500	8 days	bad sleep little less tolerance to coffee	overnight sleep study	great antibiotic a lot of stress causes bad sleep
35	cipro	2x500	8 days	bad sleep little less tolerance to coffee		good antibiotic not linked to the events
36	cipro	2x500	8 days	bad sleep little less tolerance to coffee	second sleep study	good antibiotic not linked to the events
36	cipro	2x500	8 days	bad sleep trochanteric bursitis	stress, coffee tighten belt	good antibiotic not linked to the disorders
38	cipro	2x500	40 days	Resilient, intractable tendinitis in elbows, feet. Strong neuropathy in hamstring. Bad sleep. Bladder urgencies, some other mild neuropathies	MRI's SCANs Radiographs Echographies, blood tests, electromyographies, etc Everything attributed to overuse and excess of stress at work.	No relationship with the antibiotic.
41	cipro	3x500	5 days	Too many to list. All the mild and intermediate symptoms of the previous treatments, were increased enormously, plus many other symptoms.	SEVERE neuropathies. Very severe floxing with all the classical signs (eyes, nerves, organs, joints,)	Total life destruction caused by cipro. The reaction is lasting 7 years with little remittance, according to the 2006 update.

(*) Some of the symptoms were not interpreted correctly at its time by the floxed person or his doctors, but now are very clear for them all.

23. THE VIRTUES OF QUINOLONES

You can visit the web sites of the manufacturers to check all the properties, benefits, low toxic profile, safety assurances, and extraordinarily good and positive records and surveillances that they have recorded, many published by reputed doctors or universities, and all with some kind of financing from the drug companies.

24. SHOULD FLUOROQUINOLONES BE BANNED?

No. Physicians must have the broadest arsenal of drugs to fight infections. Quinolones are extremely toxic antibiotics that have to be available for those cases that are resistant to other medicines. Then quinolones can be administered evaluating the benefit/risk ratio.

The benefit/risk ratio will be high for those infections very sensitive to quinolones that require low doses for short periods--and administered to young and healthy people.

The benefit/risk ratio will be low for suspected unspecific infections (not diagnosed by means of a culture), those that request large doses or long treatments and those administered to the eldest or pediatric population.

The benefit/risk ratio will be null for weakened people with impaired livers or kidneys, neurological disorders and people well over 70, especially if there are other therapeutic options available or unless they are in a life or death situation in regards to needing an antibiotic.

25. I DO WANT TO TAKE A FLUOROQUINOLONE. ANY ADVICE?

If for whatever reason you have decided to take a fluoroquinolone, you are not doomed to having a destructive reaction and subsequently ruin your life forever.

Perhaps your personal conditions make you unlikely to have a reaction because you are a good metabolizer of chemicals, for instance. The doses and length or the treatment that you need to take might be tolerable for your body, too.

In any case, you might consider adopting some supplementary measures to diminish the risk of suffering one of the most devastating experiences that a person can encounter. These are the following:

DODECALOGUE OF SAFETY MEASURES
(Twelve safety measures that can be adopted DURING a treatment with quinolones to lower the risk of a reaction). These measures are useless after completing the treatment.

1. ADJUST THE TREATMENT
According to your weight. For instance, if you weigh some 120 pounds, then take 2x400 mg cipro instead of 2x500 mg, (assuming that this is the dose that they have prescribed you).

2. TAKE MAGNESIUM
Magnesium interferes with the absortion of quinolones. Therefore, if you take your two-cipro pills along with your breakfast and dinner, take some magnesium with your lunch, so it does not impair cipro absorption but keeps your blood magnesium levels high. It has some protective role over many tissues.

3. DRINK A LOT OF SPRING WATER DURING THE TREATMENT
It helps to maintain an adequate hydration of the tissues and facilitate the elimination of the drug and the metabolites through the kidneys.

4. AVOID STEROIDS
Do not take any steroids during the treatment with quinolones, unless completely necessary. They dramatically increase the risk of severe injuries. Take into account that certain treatments do request the combined therapy, so disregard this advice if you cannot avoid steroids.

5. AVOID NON STEROIDAL ANTIINFLAMMATORIES (NSAIDs)
They amplify the negative effects of fluoroquinolones, specially the risk of central nervous system occurrences, and neuropathies.

6. BE CAREFUL WITH INTERACTIONS
Some drugs cause dangerous interactions with quinolones. All are included in the package insert, so read the drug insert because there is quite a great chance that your doctor does not or has not read it.

7. AVOID GRAPEFRUIT

This fruit inhibits the actions of the liver enzymes that degrade the fluoroquinolones, so these antibiotics can reach very high concentrations in the blood. As a good preventive measure, eliminate grapefruit from your life (forever).

8. WATCH OUT FOR THE EFFECTS OF COFFEE.

If caffeine starts to cause problems to you (restlessness, nervousness, disturbed sleep), then it is time to consider that your liver is becoming overwhelmed by the fluoroquinolone. Test the status of your liver drinking some coffee and watching out for changes, supposing that you drank coffee before the treatment.

9. ASK FOR SOME TESTS DURING LONG TREATMENTS

Long treatments could be considered, in this instance, those that last more than two weeks. You could ask for the normal tests plus the following:

Liver panel, especially bilirrubin.
Pancreas panel.
Muscular enzymes (CPK, aldolase).
Immunological markers (sedimentation rate and ANA specially, and also IgE to the drug).
Cholesterol and triglycerides.
Coenzyme Q10.
Thyroid panel, TSH, free T3, free T4, PTH.

10. AVOID STRONG SUNLIGHT (ULTRAVIOLET RADIATION)

Wear clothes and sunglasses to protect yourself against skin cancer and irreversible eye injuries, both caused by the photocarcinogenic action of flouoroquinolones.

11. PERFORM A DAILY PROVOKING TEST

For example, do some repetitions of raising a weight like a box with the tips of your toes (resting the heels on the floor), or raising a bottle of water with the arm extended. If in a few days a strong tendinitis develops, it is time to stop the quinolone treatment.

12. TAKE A FLUID PROMOTER WITH LOW TOXIC PROFILE

And, not strongly recommended, there is an additional option that you could discuss with your doctor: taking a sialoge (fluid promoter, saliva increaser) along with your treatment (for example, 3x25 mg daily of anetholtrithione for a person of 150 lb of body weight).

The justifications behind all these recommendations that we make, are explained along the report, so you can judge by yourself and discard some or all of them.

PART IV: SYMPTOMS OF BEING INTOXICATED BY QUINOLONES

26. ARE YOU POISONED BY A QUINOLONE ANTIBIOTIC?

If you have taken a course of any quinolone or fluoroquinolone antibiotic (Cipro, Levaquin, Floxin, etc…) you have been chemically poisoned. Depending on individual conditions, and the dosage and length of the treatment, the intoxication will range from very mild and asymptomatic to very severe and disabling.

In a minority of cases, the patient notices the reaction immediately. In a vast number of cases, most symptoms, or at least the most severe ones, emerge during the last stages of the treatment, or weeks or months after the completion of the quinolone treatment.

Sedentary people tend to notice less adverse reactions because they do not use their body to full active capacity. Taking into account that at least one third of QTS presentations are predominately tendon-related or musculoskeletal, damage to their tendons, cartilages and muscles remains unnoticed.

Almost everybody can take low doses of quinolones without developing any symptoms of an adverse reaction (for instance, 250 mg daily of cipro for two weeks). Many people can take a 7-day course of a medium dosage of quinolone antibiotics (for instance, 750 mg daily of cipro) without perceiving any adverse effects. For higher doses (for instance two weeks of 1.000 mg of cipro), most people are also asymptomatic during their first treatments (remember that the damage is cumulative). For these latter doses, their cartilage, tendons, nerves and small veins and arteries have been directly damaged but not enough to make them symptomatic. That is the case of many sedentary people who deeply damage their joints as a result of repeated but short courses of quinolones. But the fact remains unknown to them since they are asymptomatic, and they do not use their joints beyond the pain threshold. Later in life, it manifests as early osteoarthritis, collagenous deterioration, or nervous system failures. In any case, this paper is not intended for these people.

Look to the following medical paper that seems to support the generalized toxicity caused by quinolones that we have been postulating since long ago:

> JEREMY NORMINGTON, DPT, IS DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
> Another study by Koeger et al. looked at tendons of asymptomatic fluoroquinolone users. Researchers observed hypersignals that indicated common increased cellular activity (4-out-of-10) in tendons of **asymptomatic** patients. **This suggests that tendon metabolism is altered in the absence of clinical signs**.

Many of us were healthy young athletes in perfect health with rock solid knees and hips prior to taking quinolones, but now have become crippled persons, with our cartilages half destroyed, our eyes barely functional, our bodies aching since several years ago and our whole lives stolen from us by a medical class that now turns its back on us.

For those that have developed symptoms like the ones described later, first of all, they have to check if they have ingested any quinolone antibiotics during the last three or four years. The damage caused by the quinolone antibiotics becomes evident at a point in time that ranges between the moment of the treatment itself from up to eighteen months later. If your symptoms fit with any of the categories listed

later in this article, and you have taken fluoroquinolones in the past, then a quinolone induced intoxication might well be the reason for all of your recent physical problems. This report could help assist you in reaching a diagnosis.

27. SOME MEDICAL TERMS AND INFORMATION

This paper intentionally has a non-medical quality. However, it is necessary that you become familiar with a few technical facts regarding the floxing syndrome. Some are explained throughout the report, when they are needed. A brief introduction to the general aspects of an adverse drug reaction is included here.

The terms drug allergy, drug reaction and some euphemisms (hypersensitivity, intolerance) are often used interchangeably. If we take into account the immune response of the patient, a drug allergy can be restricted to the reaction in which special antibodies of the IgE type are massively released. This report does not cover allergic reactions.

Drug reactions can be classified as follows:

TABLE 7. TYPES OF DRUG REACTIONS

TYPE	Specific	Key feature	Caused by quinolones
IMMUNOLOGIC			
Type I reaction	IgE mediated	Allergy	Yes, rare
Type II reaction	Cytotoxic		Yes, common
Type III reaction	Immune complex		Yes, typical
Type IV reaction	Cell mediated, delayed		Yes, frequent
Specific T-cell activation			?
Other	Chemical	Unknown	Yes, common
NON-IMMUNOLOGIC			
Primary pharmacological side effect	Direct problem associated with the drug		Yes
Secondary pharmacological side effect	Opportunistic health problem		Yes
Drug toxicity	Toxicity to organs and systems		Yes
Interactions between drugs	Like with all drugs		Yes

Some classifications have been established in order to help discern among drug IMMUNE reactions:

TABLE 7-cont'd. TYPES OF IMMUNE REACTIONS

Immune reaction	Action	Clinical symptoms	Timing of reactions
Type I reaction	Allergy (not covered by this report)		
Type II reaction	Specific IgG or IgM antibodies directed to some cells	Blood abnormalities (neutropenia, anemia)	Variable
Type III reaction	Deposition of drug antibody complexes in several tissues, with complement activation and inflammation	Arthralgias, vasculitis, rash, serum sickness	1 to 3 weeks after drug exposure or even many months later
Type IV reaction	Cytokine and inflammatory mediator release	Rash, contact dermatitis	2 to 7 days

Like many other drugs, quinolones can cause an immunologic type I reaction, plus many non-immunologic primary pharmacological side effects (insomnia, restlessness, caffeine intolerance) and secondary pharmacological side effects (thrush, leaky gut). They can also interact negatively with many drugs. But

their distinctive actions are probably due to their direct toxicity and the subsequent immunologic reaction.

In most cases, there are not any markers that can confirm a diagnosis, so all serum (blood) parameters can be normal and one can still be suffering from a very severe and incapacitating reaction. Only a very specialized and often inaccessible (in most healthcare systems) tissue biopsy can confirm the problem and even then the probable denervation and cell degeneration shown will be classified according to standard methods and fit partially into already known diseases. Therefore, without a biopsy, most diagnostics are established upon clinical symptoms. In principle, the fluoroquinolone syndrome can be classified as a TYPE III immunological reaction, with an added non-immunologic TOXICITY.

One thing is clear: re-exposure to quinolones, after having been floxed previously, poses very high health risks for the patient. Persons that become floxed twice have the worst prognosis (expected outcome). Many people with moderate reactions to quinolones are later re-exposed to another round of the same antibiotics by their doctors that dismiss their complaints about pains and disorders associated to the antibiotic. The outcome is frequently a severe reaction that lasts 3 to 6 years and ends up with permanent injuries.

The following study demonstrates that more than half of 55 patients with immediate adverse reactions (taken place during the treatment), had immunologic IgE specific for quinolones, circulating in their blood, up to 4 years after the treatment. The report also concludes that if you have suffered a reaction to a quinolone, you have to avoid all quinolones, as we know. In our opinion, this test should be considered standard practice to detect many cases of reactions to quinolones, to provide ignorant doctors with a tool for diagnosis, and to check the evolution of the reaction, by measuring the concentration of those specific IgE markers. Nevertheless, most floxed persons seem to have a response more founded on IgG than on IgE. Very likely, more studies like this one could focus on the problem with minimal effort.

DETECTION OF SPECIFIC IGE TO QUINOLONES.

Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, Campi P.
Allergy Clinic and Laboratory, Nuovo Ospedale San Giovanni di Dio, Florence.

BACKGROUND: In the last years, immediate reactions to quinolone antibiotics have been observed with increasing frequency, mainly urticaria, angioedema, and shock.
OBJECTIVE: We sought to assess whether these reactions are IgE mediated and whether an in vitro test for quinolone-specific IgE is useful in the diagnosis and understanding of cross-reactivity.
METHODS: We assayed specific serum IgE to quinolones using epoxy-activated sepharose 6B as the solid phase in 55 patients with immediate adverse reactions; specificity of IgE binding was demonstrated by inhibition tests.
RESULTS: The test yielded positive results in 30 (54.5%) patients who were tested 1 to 48 months after the reaction had occurred. The quinolone-specific IgE seems to disappear more slowly in atopic patients. The cross-reactivity between various quinolones allowed us to identify a common structural motif within quinolones that might be responsible for clinical and serologic cross-reactivity.
CONCLUSION: A substantial portion of **immediate** reactions to quinolones appear to be IgE mediated. Cross-reactivity of IgE among different quinolones is frequent and suggests that a common avoidance of quinolones should be attempted in all patients with respective symptoms.

28. WHAT KIND OF DAMAGE DO QUINOLONE ANTIBIOTICS CAUSE?

This class of antibiotics has very characteristic ways of causing injuries:

- quinolones damage the central and peripheral nervous systems
- quinolones damage small veins and arteries (vascular disorder of the vasa vasorum and vasa nervorum) and the surrounding matter of all organ cells (extra-cellular matrix)
- quinolones impair the rebuilding and repairing capacity of tissues, specially connective-collagenous

IMPORTANT FACT:
Pain and disability caused by quinolones is very long lasting and affects many parts of the body. In favorable cases recovery takes several months to years. In severe reactions pain and injuries can last for life.

- quinolones chemically destroy important structures, like cartilage

There are many other mechanisms of quinolone assault on the human body (for instance, liver, kidney, pancreas and heart reactions, all of which can be serious or even fatal), but they are not the focus of the present report.

29. HINTS AND CLUES THAT MIGHT SAVE YOUR LIFE

Perhaps you have taken quinolones in the past and you think that they worked well and that you did not react negatively to them. Check the following subtle symptoms of the beginning stages of a quinolone intoxication from an earlier treatment and the normal interpretations that people make of them.

- You had a strange bout of tendinitis, for instance in the outer tip of the hip, normally diagnosed as trochanteric bursitis caused by tight belts or resting on you side at night. The same applies to other areas of the body, like the elbow (epicondylitis) diagnosed as an overuse of your tennis racquet or gardening practices, but you remember that you had never had it before.
- It takes you longer to recover after exercise. It is not alarming and you have not paid much attention to it.
- You sleep worse than before; it seems normal as you have a lot of pressure at work.
- From time to time you have some small throbbing pains in different parts of the body. They last only for a few seconds, so there is nothing to worry about it.
- It is strange- but you have occasional twitching in an eyelid, or any other part of the body. It is not painful.
- Some nights you feel some mild itching migrating along your body. One brief itch here and another there. It is more intense in the scrotum or groin. Instead of identifying it as a peripheral neuropathy, you conclude that your clothes, your perspiration or the new brand of soap that is more irritating must be causing it.
- You feel some stiffness, and your range of movement is not as full as before, especially in one or both legs, but it is normal because you are getting older.
- You do not tolerate coffee as well as before. Now you have to reduce the amount of coffee that you used to drink.
- Your memory is not as good as it used to be. The cause may be too many things to think about and too much stress. And you are no longer a young person.
- There is an urge to urinate when the bladder is partially full. When you feel the need to urinate you have to rush for the toilet. Most urologists think that it is due to a dysfunction associated with a benign enlarged prostate but in reality it is a neurological deficit caused by the prescriptions of quinolones that they gave you.
- You cannot flex fully, or strongly, your big toe (one or both), or sustain the flexion for more than a few seconds. This is an indication that your large nerves (anterior tibialis) have started to fail due to the toxicity. This sign is a strong warning that your body will not tolerate more quinolones.
- Some times, you have nightmares while falling asleep that scare you. How strange you think. They are toxic panic attacks that reflect toxic damage to your brain.

If you have experienced some of these symptoms since you took your first quinolone, perhaps you have reached your first threshold of tolerance, that -once surpassed- can result in the destruction of your life soon thereafter if you take more quinolones.

30. WHAT ARE THE MAIN SYMPTOMS OF BEING POISONED BY A QUINOLONE?

Getting floxed is just getting intoxicated, or poisoned. The toxic agent (the quinolone compound) enters the blood stream and spreads throughout the body. The defenders of the quinolones are even proud of the big penetrative power of the drug, that reaches delicate organs like the brain that are very well shielded against most chemical compounds. Therefore, it is not surprising that symptoms of the toxicity arise over all body areas and systems.

For a complete list of symptoms, see later in the report. A strong reaction generates some 30 to 50 symptoms. In some cases adverse reactions appear right after the ingestion of the antibiotic. In intermediate and severe reactions you may start with a few symptoms and as time passes new and debilitating symptoms arise, especially around the second, sixth and ninth months mark post-floxing. And in many cases of young, very healthy and active people, the worst injuries emerge progressively up to eighteen months or more after the cessation of the drug (we have deducted it beyond any doubt from various crystal-clear cases plus several unwilling re-exposures with quinolones). There are many medical articles as well, that state that a lot of the drug induced symptoms start some weeks to months after completing the treatment.

Here we include the most easily recognizable and common symptoms in three groups. Please take into account that the heading of the three groups is only for orientation purposes and to make the text more intuitive. Some of the disorders are cyto-toxic or vascular, for instance, and the headings do reflect that fact. Some injuries have a multiple root like eye damage that can be muscular, neurological, vascular and toxic but are included just in one group for the sake of simplification.

Joints and muscles:

- Arthralgias (pain in joints) especially the tendons of the feet, ankles, knees, hips, elbows, shoulders, wrists, neck. Pain of different kinds, very frequently migrating around a joint and then moving to other joints over time. Pains are bearable sometimes but they often are very debilitating, requiring almost absolute rest for months because patients cannot walk at all or more than a few paces or stand up for long. Even if the patient is functional, pains have a neurological root and can be very intense and interfere with normal activities and prevent sleep. These arthralgias evolve to osteoarthritis in many cases with cartilage erosions. The arthralgias start as early as during the antibiotic treatment. In other cases arthralgias show mildly at the beginning and their intensity increases to its maximum intensity up to a year and a half later. For athletes with this type of delayed reaction, a medium level of pain can be constant but some six hours after exercise the symptoms may be present as acute pains that can be excruciating if the limit of tolerance is reached. This limit consists of the maximum exercise that a given body can tolerate before its impaired repairing capacity is overwhelmed by the physical demands. For the average floxed athlete, this limit is much lower than it was before the quinolone intoxication. The joints, fingers or toes can also become inflamed and appear red and feel hot.

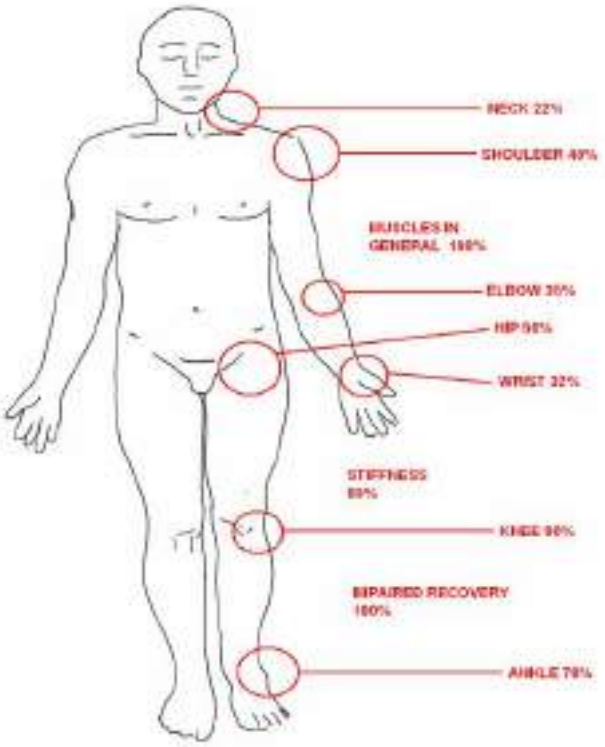
- Pains in different areas of the body not considered main joints. Pains tend to be generalized and migrating. Can be mild or very intense. Common areas affected are the back, neck, head (jaw, skull zones), chest (breastbone), groin, testes, plantar fascia (sole of feet) and others. They can be very debilitating. Pains in many muscles over the body (myalgias), that cause a lot of stiffness and soreness. These pains are of every kind, like diffuse, acute, throbbing, pulsating, vibrating, burning, shooting, stabbing, dull, deep, tremors, and many times they increase at night. A floxed person can feel pains at all times, even while resting and walking, changing positions when sitting, being unable to cross legs or make some body movements. In severe cases the pain lasts for five to six years on average.

- Acute tendinitis over different parts of the body very similar to normal types of tendinitis but different in its persistence and unresponsiveness to conventional treatments. This type of tendinitis is very acute at times, requiring immobilization, and is nearly always triggered by a level of use that was normal in the pre-floxed state, or normal daily use. The tendinitis does not respond to anti-

inflammatory medication, which in fact, can make the symptoms worse. Sometimes the tendinitis 'migrates' within a joint and from one joint to others, which merely reflects that all tendons are equally affected and that the ones used most are the ones that fail and experience pain and damage. In the first stages of the floxing, the tendinitis is predominantly enthesitis, which is inflammation of the insertions of muscles and tendons into the joints. In many cases they end up in partially or fully ruptured tendons (achilles, shoulder rotators, wrists flexors). It is a class effect of all quinolones, in other words, all these antibiotics are very toxic for all the tendons in the body, for everybody. For every one the quinolones cause small and multiple injuries in the tendons, that eventually rupture in those people unlucky enough having weak tendons, having taken corticoids, having pre-existing vascular problems (pre-diabetics) or being magnesium deficient. Long- term floxed persons, usually affected by a severe reaction still have tendinitis in critical areas of the body 4 or 6 years post-floxing. Very typical long term tendinitis are: plantar fascia, achilles tendon, posterior tibialis complex, toe flexors, insertions of knee's tendons, both ends of the ileotibial band, iliopsoas area, shoulder rotators, elbow epicondyle, forearm and wrists.

- Arthritis-like symptoms. Many symptoms resemble those of rheumatoid arthritis and other autoimmune diseases, but are always sero-negative and with a different pattern of clinical symptoms. Reiter's is a common diagnosis for many floxed persons, even if they do not have the HLA-B27 antigen.

- Osteoarthritis-like symptoms. Joints usually start to make a lot of noise. After the intoxication, and with time, healthy cartilage becomes softened and erosion takes place, and the illness presents itself as a true clinical osteoarthritis. Knee cartilages are specially targeted by quinolones, with a very high incidence of torn menisci (inside the knee). There are many cases of complete destruction of previously healthy joints and the patient has to be submitted to very invasive surgical procedures and or total joint replacement. The most damaged cartilages are the most weight bearing ones: knees, hips and low spine. Cartilages of people that have taken several short-term quinolone treatments, as well as cartilages of those that have taken prolonged courses or high doses, have a very decreased bearing capacity. Fluoroquinolones rarely can cause osteonecrosis of the femoral heads and other areas, requiring total joint replacements.



disorders in severe reactions-

- Permanent stiffness that exhibits a clear loss in range of movements, especially with legs and arms, but that can affect the whole body. The most affected joints are the hips (adduction, abduction, flexion and extension), knees (flexion, adduction), and shoulders (extension). Increased stiffness after exercise. It takes longer to recover from exercise, and there is a clear loss of flexibility. Soreness in many muscles, especially legs and shoulders, and also a predilection for the neck. Weird sensations in the muscles and joints. Clear feeling that something is going very wrong.

- Shallow breathing that causes a deficit of oxygenation that complicates insomnia, recovery and other reactions and metabolisms in the body. During the acute phase the floxed persons can have a sense of not grasping enough air and subsequent sense of dying.

- Very slow recovery from impacts and blows. Whenever the affected person is hit in athletic or daily activities, the flesh takes much longer to recover from the pain, along with increased haemorrhaging and inflammation. Dark veins, haemorrhage-like patches under the skin.

- The skin (and other collagenous tissues) loses nearly all capacity of recovery. A cut on the skin near an affected joint leaves a pink scar for many months afterward whereas it would have become unnoticed in a pre-floxing state.

- Cold feet and hands. The presentation resembles Raynaud's syndrome. In many severe cases several phalanges of fingers turn numb or become close to frozen with cold conditions that did not cause any trouble before the floxing. Loss of sensitivity in hands and feet. Increase in the shape or depth of vertical ridges in fingernails. Pains in the nails of the big toes that feel as if they were about to fall apart.

- Chest pain. Heartburn. Tight chest.

- Weight loss, probably due to muscle destruction and atrophy and alterations in intestinal function. The weight loss reaches 15% of total weight in many cases, which is very hard to put back on again. Typically, people loss up to 15% of their weight at the start of the bottom line of their reactions, and then recover some 8 or 9% of it during the beginning of the recovery phase. The last 6 or 7% of the weight is difficult to get back and only happens when the healing is almost complete. Originally, thin people also lose the same amount of weight. This loss is muscle mass mainly.

Central and peripheral nervous system and systemic:

- Brain fog, depression, depersonalization, short-term memory loss, and lethargy. Slurred speech. Inability to speak fluently. Forgetting words, getting stuck in the middle of a sentence. Some are caused by the insomnia but it is mainly a neurological injury of the brain. Headaches, especially unilateral, or affecting one side only. Foggy mind, drowsiness, lethargy, loss of drive and power. Need to sleep. Tiredness and intense fatigue. Crying episodes. Loss of balance, strong feeling of being rocked back and forth and that everything is moving.

- Twitching, numbness, sensory disturbances, burning on the skin, trembling, throbbing, pins and needles sensations, and pulsating pains in muscles and joints are the hallmark of this disease; especially in the lower legs (ankles, Achilles, calves, thighs and knees) arms and hands, but can manifest all over the body. Fasciculations (visible crawling under the skin) of muscles, due to denervation, a very serious neurological symptom. Twitching is manifested earlier in eyelids and the triangle on the back of the hand placed between the thumb and index finger before it can affect the whole body but later spreads all over the body. Some days a floxed person can have hundreds of series of twitching all over the body.

- Burning skin, very common, burning lips, buzzing and all sort or weird feelings over the whole body. Gum numbness.

- Insomnia, very acute and difficult to deal with. Restlessness, great loss of sleep quality. Intolerance (great nervousness or increasing symptoms) to concentrated coffee (espresso) and tea. Intolerance to coffee can be present for more than 7 years (probably forever, but we only have abundant data of people up to 7 years out). Insomnia can last more than 4 years during which is difficult to get more than a few hours of disrupted and bad quality sleep. Anguish, depression, pre-seizure state. During some part of the floxing most people experience anxiety and panic attacks (awakening amidst strange nightmares with fear and a feeling of dying), especially at night or when falling asleep, but also while being awake.

- Vision problems. Diplopia (double vision) and other focusing problems. Over-scanning eyesight (swirling focusing). Large amount of floaters (dark worm, cobweb, string or spot like) that seem to float in the vitreous area of the eyes. Also ziggies (brilliant minute lights that move in a zig-zag or wavy, wandering manner in your field of vision). Sparks (flashing lights). Halos and curtains of watery sight in the upper part of the field of vision that move sideways along with your eye. Waves-like in the outer margins of the sight. Acute photophobia or intolerance to strong sunlight or artificial light. Complete or partial loss of vision (transitory, but lasting up to 6 minutes as absolute blindness seeing only solid white). In extreme cases, complete irreversible blindness has been documented in medical papers. Eye pain, ocular pressure, blurred vision. Loss of vitreous acuity. Cataracts, macular degeneration. Quinolones cause degeneration of the retina, especially the outer margins. In many cases, some very worrisome implications such as dry eye syndrome are also experienced. Dry eye can render zero mm of tear absorption in the Schirmer's test. Vision damage reaches its peak about two to six months post-floxing and lasts for years or becomes a permanent injury, being a marker of the likelihood of recovery (i.e. the drier the eye and longer lasting, the lesser are the chances of overall recovery). Vision damage caused by quinolones has a high ratio of irreversibility. Severe reactions have nearly always associated some degree of damage on the vision that is invariably assessed by the patients as very disabling. We have seen so many, really a great many, cases of irreversible damage of vision, or injuries not cured by the 5th year mark, and the distress inflicted on the sufferers, that this alone would be enough cause to withdraw all the quinolones from the market for primary care treatments.

- Diminished erectile function (semi-impotence). Difficulty to reach hard erections. Decreased sex drive (libido) both for men and women. Can last more than three years in severe reactions for young people that were very healthy and active sexually pre-floxing.

- Digestive problems. The quinolones damage the entire nervous network governing the intestines. Alteration of intestinal movements. Intolerance to foods and many compounds. Bad reactions from defectively digested foods. Inability to absorb some nutrients, especially minerals. Weight loss. Destruction all of the flora and proliferation of bad fungi like candida.

- Violent rectal (anus) pain and spasms that may cause fainting. Spasmic pains of every sort and intensity in every part of the body: skull, lower head, neck, jaw, shoulders, arms, back, hips, legs, ankles, fingers and toes.

- Trembling of a limb after sustaining tension with the muscular groups of that limb. For instance, trembling of the leg after toe raising for a while, or an inability to write steadily after holding a heavy load with that hand.

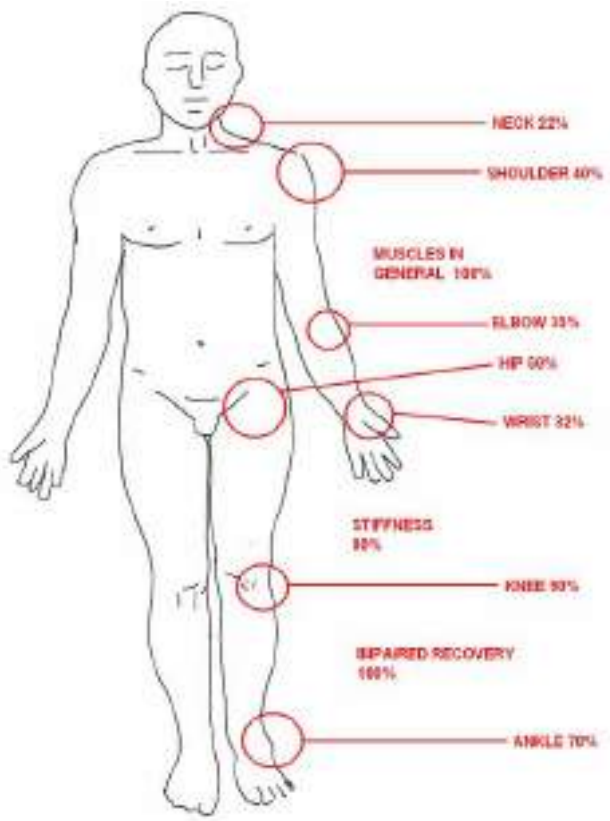


fig.4. -frequency of systemic disorders in intermediate and severe reactions-

- Tinnitus, or ringing in the ears. Ear pressure, usually in waves of pressure. Hypersensitivity to normal sound. Headaches, head pressure, mainly asymmetric. Hearing loss that can be permanent.

- Heart palpitations and strange pounding and throbbing. Skipped heart beats. Alterations of heartbeat. Irregular heartbeats are usually more common after eating. The heart palpitations and arrythmias are some times life threatening. A serious heart condition called prolongation of the QT-interval is a class

effect of all the quinolones, showing once more that they are very defective drugs. Some times floxed persons require the implantation of pacemakers. Many thousands of people die from heart attacks that are not of an infarction kind but cardiopathical, caused by deffective nerve signals. Most all of them are caused by toxic compounds, like environmental hazards or medications, among them the quinolones (none of them are attributed to the real cause).

- Neuropathies in limbs, with a lot of pain with muscle wasting and nerve involvement. In many cases they resemble muscular injuries. For instance, a femoral (upper leg) nerve neuropathy can be considered a pull in the hamstring; a peroneal nerve neuropathy can be disguised as an ankle strain, or an overuse syndrome and so on. These neuropathies have a rapid onset and grow in intensity for many months. In many cases it takes several years to get a remission of these neuropathies.

- Alterations of liver, kidney and pancreas enzymes and parameters. While taking quinolones the cholesterol and tryglicerides skyrocket up to three times their normal values, to return to normal range in a few weeks. Quinolones also provoke hypo- and hyperglycemias as a class effect. The quinolones accelerate the progression towards full diabetes of those individuals with an unrecognized pre-condition.

Autoimmune like responses:

The main symptoms of a quinolone poisoning resemble those of some autoimmune disorders because in acute intoxications they cause a type of small vessel vasculitis with neurological dysfunction:

- Dry eye, dry mouth, dry sinuses, dry ear and a shift towards dry skin. Dry eye can be measured with moisturizing stripes rendering null values in severe reactions. Sticky, gritty eyes. Dry eye can have serious consequences if not treated. Dry mouth, especially at night or when taking any vasodilator. Dry sinuses cause many infections that are also opportunistic due to the compromised immune system of the severely floxed persons. Dry ear turns the protective earwax into a sort of useless sand dust. Decreased semen production. Many doctors insist on diagnosing floxed persons with Sjögren's.

- Problems with foods and drinks. Your intestines are also altered and their permeability and ability to process foods is impaired. Abnormal intestinal function, food intolerances, chemical disturbances, cycling of symptoms and general malaise. Increased sensitivity to chemicals, especially to quinolone-tainted foods (poultry, beef). Sensitivity to perfumes, health care products and chemicals. Taste and smell perversions. Lack of sense of smell.

- Cycling or relapsing of symptoms. After the acute phase, nearly all recoveries experience cycles of improvement and relapses.

- Endocrine alterations (hormones basically), with skewed ranges for cortisol, thyroid hormones and others, causing all the associated symptoms.

- Symptoms of hypo and hyperglycemia, due to deregulation of the sugar metabolism.

- Many symptoms that resemble fibromyalgia, multiple sclerosis, lupus erythematosus, lyme, rheumatoid arthritis, reactive arthritis, vasculitis, AIDS and other diseases.

- Skin rashes, especially in distal areas (hands, ankles). Itching, all over the body, with little intensity, plus more intense in some specific areas (hips, for instance) when taking a hot shower, plus itching in the groin and scrotum at night when hot. Reddish or red-blue upper eyelids. Increase in vertical ridges in nails of toes and fingers.

31.TYPICAL ADVERSE REACTION LIST OF A QUINOLONE ANTIBIOTIC

While the above listings reflect the most typical symptoms of a fluoroquinolone intoxication, nearly all floxed persons do exhibit a wide range of abnormalities, many of which are included in the official list of potential side effects of any fluoroquinolone.

The following is the list of typical reactions observed during fluoroquinolone therapy. The list is an official one. It is comprehensive, but does not mention the severity of the reactions, and also, the percentage of people affected has been manipulated to appear as very low, when indeed it is much higher. Underlined are the reactions experienced by people related with this report.

Pregnancy Risk Factor and Implications: Category C, is excreted in human milk, potential for serious adverse reactions in nursing infants.
Contraindications: Do not use if you have a known allergy to ciprofloxacin or to any member of the quinolone class of antimicrobial agents.
Warnings/Precautions: The safety of this drug in pediatric patients, people less than 18 years old, pregnant and lactating women has not been established. This drug may cause cartilage erosion of weight-bearing joints. This drug may also cause convulsion, intracranial pressure, toxic psychosis, and it may cause central nervous system events. Use with caution in patients with CNS disorders or in patients with risk factors such as certain drug therapies and renal dysfunction that may predispose them to seizure or lower their seizure threshold. Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline. Serious and occasionally fatal hypersensitivity reactions have been reported in patients receiving quinolone therapy. Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. Pseudomembranous colitis has been reported with nearly all antibacterial agents including ciprofloxacin, and may range in severity from mild to life-threatening. Treatment with antibacterial agents alters the normal flora of the colon. Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Avoid excessive sunlight as moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in some patients while on the quinolone class of drugs.
Adverse Reactions: At least 5% experienced: Nausea
Adverse Reactions: Less than 5% experienced: Diarrhea, vomiting, abdominal pain/discomfort, headache, restlessness, rash, palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thromobosis, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, painful oral mucous, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout, interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, memophysis, bronchospase, pumonary embolism, pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjuctivae or hands, cutaneous candidiasis, hyperpigmentation, erythera nodosum, blurred vision, disturbed vision, decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, vaginitis, headache, vaginal pruritus, abdominal discomfort, lymphadenopathy, foot pain, dizziness, breast pain, nausea, diarrhea, central nervous system disturbance, abnormalities of liver associated enzymes, eosinophila, restlessness, rash, cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, ileus, jaundice, gastrointestinal bleeding, C. difficle associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric or abdominal pain, vomiting, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, thrombophlebitis, burning, pain, pruritus, paresthesia, erythema, swelling, arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, renal failure, intarstitial nephritis, hemorrhagic cystitis, renal calcuti, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis. Crystalluria, cylindruria, hematuria, and albuminuria have also been reported, respiratory arrest, pulmonary embolism, dyspnea, pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower

extremities, purpura, fever, chills, flushing, pruritus, urtigaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, photosensitivity. Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. Also experienced were decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, a bad taste, agranulocytosis, prolongation of prothrombin time, and possible exacerbation of myasthenia gravis, change in serum phenytoin, postural hypotension, vasculitis, agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis, constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis. (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), agranulocytosis, hemolytic anemia, methemaglobinemia, prolongation of prothrombin time, elevation of serum triglycerides, cholesterol, blood glucose, serum potassium, myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture, albuminuria, candiduria, renal calculi, vaginal candidiasis, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, anosmia, taste loss.

Post-Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug. Agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, monoliasis moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendonitis, tendon rupture, torsades de pointes, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis.

Are there many antibiotics with this list of proven, officially admitted serious toxic side effects? No, there are not. Are there many antibiotics that are forbidden for persons under age 18? No, there are not. Is there any antibiotic with the capacity to rupture tendons? No, there is not. Is there any class of antibiotics with so many of its derivatives withdrawn from the market? No, there is not. Except for quinolones. So it is difficult to understand the “history of harmlessness” of fluoroquinolones.

32. SOCIAL QUINO-EXPERIMENTATION

You have the opportunity to conduct your own social research about the impact of the fluoroquinolones. In a few months time you can complete an experiment that all top (useless) researchers have failed to do with all of their paraphernalia and supposedly scientific methodologies. We have done it.

First part of the experiment. For several months ask the people you know about the final events before the passing of their elderly loved ones. You will find interesting situations. Examples of real ones:

- An old woman that lives entirely on her own in good health. She gets a chest infection and is prescribed an antibiotic. In two days she lost her mind, she did not even recognize her own sons and daughters. Soon she is unable to stand up with a lot of pains and is put in bed. She dies 10 days later of "generalized stroke". Cipro was the antibiotic prescribed during the 10 days.

- An old neighbor in good health and very active. Not on any medications. He gets a urinary infection (burning during urination) and is prescribed cipro. In three days he dies pacefully. Official cause of death–a heart arrythmia with stroke.

- Middle-aged man, co-worker. His appendix is surgically removed. Profilactic cipro is administered. Kidney failure and death.

- Middle-aged woman. She has a first stage pancreatic cancer. During surgery levaquin is administered. Her pancreas and liver enzymes skyrocket and the doctors switch to another antibiotic. Too late. She dies of liver and kidney insufficiency.

- Middle-aged man. Carpenter. His wife says that he has to leave his job because he has developed a very debilitating tendinitis that already lasts for more than 9 months and is unrelenting. When questioned, the man confirmed he had taken levaquin for the first time in his life, 9 months before, for a sinus infection.

- Brother-in-law comes complaining of numbness in toes, and throbbing pain along the shins. Nothing has changed in his life, and nothing explains this recurrent symptoms. Asked about the drugs he has taken lately he reports none, "well, except an antibiotic that I take a few times per year for oral herpes". The antibiotic was cipro. After sifting to another antibiotic his long-term symptoms have disappeared in 8 months time.

- A veterinarian prescribed a quinolone to the dog of a floxed person (enrofloxacin). Instead of giving him the prescribed quinolone, the floxed person administered the pet levaquin for humans. The floxed person was crippled by a dose of 11 mg per day per kilogram of body weight. He gave the dog 15 mg per day per kilogram of body weight for two weeks. Now, as he puts it, both are floxed. The dog that used to be very active, alive, running the whole day and hyperactive now spends its days just lying in its favorite places and refuses to move. There are innumerable reports of injuries caused by enrofloxacin to all sort of pets and animals, like horses, cats, dogs, etc.

And then ask your co-workers and friends about the antibiotics that they took, and how they fared. You will learn a lot, for sure.

Our social quino-experimentation has lead us to the firm conclusion that to administer fluoroquinolones to old people equals putting them at a very high risk, an unacceptable risk, of not regaining their health ever again, and even of putting them on the verge of dying, depending on many particular factors. If quinolones are not to be used for people under 18, and many doctors start to warn about administering them to older persons, then how can we believe that they are safe medications in general?

We are not saying or insinuating that fluoroquinolones are behind each death or adverse or fatal outcome of a surgery or an illness. But it is interesting to note how many times fluoroquinolones are just there, and sometimes they are the only drugs there, when a person's health deteriorates so rapidly that compromises his/her life. The point we want to raise is that we have never heard of any suspicion or investigation about it. As you will see later in this report, in many medical cases that end in the death of the patient, the quinolone is never scrutinized for its toxicity, when in some cases it seems to be a crucial factor in the fatal outcome. This is specially true in America, where doctors are extremely reluctant to raise issues that are uncomfortable for the industry.

PART V: EVOLUTION OF RECOVERY

33. IF YOU SUFFER AN ALLERGIC REACTION

(It is a complete incompatibility between your body and the drug)

If you are allergic to quinolones, as soon as you take a few pills or even one single dose, your body reacts negatively according to the patterns of a so called anaphylactic shock and is not covered by this article, you will need emergency treatment and to stop the drug immediately.

34. EXPECTED EVOLUTION FOR A SEVERE REACTION

This report deals especially with SEVERE reactions, so it is of little use for less serious intoxications, and could increase your worries and anxiety because many people tend to harbor too negative of thoughts when they are suffering reactions so strange as those that quinolones cause. Let us say that if you are looking for some information, if you do not know the severity of your intoxication, and do not know what to expect in terms of evolution, this section of the report could lead you to wrongly believe that you are facing an extremely bleak future.

For everyone with a body weight around 160 lb or less there is an extremely high risk of experiencing a SEVERE reaction for doses of fluoroquinolones of 1,500 mg of ciprofloxacion (or its equivalent potency of other quinolones) per day for 7 or more days or 1,000 mg daily for 2 months.

Severe reactions are very distinctive because they are extremely long lasting and feature many permanent injuries, especially in the 5 following groups:

- neuropathies, including peripheral, central (insomnia, ...) and autonomic (heart, intestines, ..)
- dry syndrome damages (eye, sinus, ears, skin, mouth)
- cartilage destruction, joint and muscle pains
- vision injuries (floaters, blank points, retina degradation)
- organ damage (liver, kidney, pancreas, lymphatic system)

For a severe reaction, the most probable pattern of evolution consists of feeling early disorders of medium or high intensity, reduced to a group of a few symptoms, and from then on the whole state of the floxed person will worsen for many months until reaching a peak of damage. Some people feel very bad at the middle of the drug treatment, which prompts them to stop it, thus saving a lot of further trouble for them. Others feel bad after really long treatments of 4 or 6 weeks of 1,000 mg daily (always in reference to the potency of ciprofloxacin). Normally those persons took quinolones before for shorter periods and they all thought they had worked fine. Later, they discovered that they had experienced those mild inconveniences pointing to a reaction, but they had never linked both things, symptoms and antibiotic. This latter group of people tends to be hit very strongly because their higher tolerability to the drug allows them to take a lot of it before they get strongly hit.

The most noticeable symptoms have already been explained above.

If according to table 8 your profile after 6 or 9 months after drug cessation resembles a severe reaction and half or more of the symptoms are very intense, then you might be suffering a SEVERE reaction and this report is especially devoted to such cases. The evolution of the pathology is very characteristic of this syndrome. For severe reactions, new symptoms keep emerging for up to nearly two years after the last pill

has been ingested. The worst disorders become apparent between months 6 to 9, but others still appear up to month 20. It varies a lot with each individual, but very typically it evolves as follows:

Month 1-2: (acute phase) Maximum musculoskeletal symptoms; possibly crutches or wheelchairs needed, high level of pain, and crippling physical limitations. Still not very systemic symptoms that affect vital functions of the body. Some people cannot even walk for weeks, and stay in bed or have to remain seated on a chair. Most have to use crutches, casts and have curtailed all physical activity.

Month 6-9: (acute phase) Maximum damage, irrespective of symptoms. Maximum vascular-matrix degradation damage, that affects eyes (floaters, photofobia, flashes of light, dead vision areas, diplopia, eye pain), joints (noises, cartilage grinding, tendon popping, enthesitis, inflammation in some cases), heart (arrythmias, palpitations, irregularities), ears (tinnitus, abnormal hearing, wave pressures moving in stereo fashion), and so on. Erosion of cartilages can be felt and also diagnosed by physical examination and imaging (only by very capable radiologists).

Month 9-30: Increasing of symptoms, people are very much affected all over. The intoxication manifests in its full force. Pains all over, with soreness, stiffness and loss of range of movement. Musculoskeletal pains on a constant basis, limiting activities. A strong feeling that something is going very wrong. New symptoms of this toxic problem may arise, like dry eye, dry sinus, dry mucous membranes in general, and abnormal reactions to otherwise normal infections like flu or colds that lead to a trail of deeper symptoms. Severe insomnia and restlessness. Brain fog and inability to form new memories. Mental implications typical of long lasting illnesses, including depression, anxiety. If dry mucous membranes syndrome does not develop or if it is not long lasting, the chances of overall recovery seem to be far greater. Very intense neuropathies in legs and other areas of the body that can be detected in ordinary testing. Maximum muscle pains, especially after activity. Subtle but clear loss of strength in muscles and weight loss.

Month 31-54: (From 2.5 years to 4.5 years). Cycling of symptoms in good cases. In bad cases there is a prolongation of the anterior period of maximum damage and misery and cycling does not start yet. Some disorders may experience an improvement with insomnia and some central nervous system issues, normally at around the 3.5 year mark. Panic attacks tend to stop by 2.5 years and from then on they recur only very seldom. Still very sensitive to any food or supplement with vaso-constrictive properties. Somewhat better from myalgic pains and stiffness towards the end of year four. In really bad reactions, there is on average an improvement that starts around month 42 or 45, that somehow equals the situation at month 30 of people with plain severe (not complicated, not highest severe) reactions. Still present are exercise intolerance, dry mucous syndromes, and vision injuries. Neuropathies and limitations, with fasciculations, pains migrating along the body, cold fingers, numbness, ulnar neuritis, etc.

Month 55-66: (From 4.5 years to 5.5 years). Recovery predominant, slow progress but firm. You can feel strong and determined and your spirit might go up too. You start to see what permanent injuries the quinolones have caused. Less neurological pains but still twitching, fasciculations, trembling, itching and other similar symptoms. Less stiffness and soreness, less range of movement limitations as the muscles start regaining some strength. Little or no photophobia; floaters less prominent but still present. Heart arrhythmias gone or recurring only occasionally. Atrophy in muscles and motor nerve death still noticeable due to the lack of function of all muscles innervated by large nerves if they have been affected.

Month 66-72: (From 5.5 years to 6.0 years). In roughly 40% of the cases, noticeable recovery for sedentary people (recovery is not complete but normal inactivity prevents the endurance damage from showing up). Slow recovery for active people because strenuous exercises make symptoms reappear; endurance is still low, and the body is not still able to recover normally after physically demanding activity. In the remaining 60% of the severe cases, by month 72 (6 years out) people feel better than a year before but are still far away from recovery.

From the 6th year on: depending on the individual, near complete or partial recovery is reached in another one or two additional years. This means that a severe reaction takes from 6, 8 or more years to recover from, and in many cases a lot of permanent injuries remain. This matches quite precisely with the information given by a reputed doctor of an American university, based on his experience with floxed persons. Typically irreversible damages include dry eye, dry sinus, dry ears, dry skin, floaters, blank points in vision, some palpitations, liver and pancreas injuries, muscle destruction (high CPK and aldolase), neuropathic pains-bearable, soreness, stiffness, cartilage erosions, permanent muscle function loss due to nerve necrosis, intolerance to many products due to injuries on neurotransmission, exercise intolerance and occasional muscular pains.

IN SHORT:
Severe reactions present themselves with intense, long-lasting joint and neuromuscular symptoms as well as eye disorders and dry mucous parts.

Total recovery time: ranging from up to 3 to 8 years or never in some cases that end up with different permanent injuries.

35.EXPECTED EVOLUTION FOR AN INTERMEDIATE REACTION

Symptoms from a quinolone antibiotic intoxication of a lesser intensity start with mild pains during the treatment or soon afterwards, that are of small intensity and can even pass unnoticed. In any case, during the first months, most of the problems are musculoskeletal and tend to resolve without complications. All the rest of the symptoms can be present. But some six to fourteen months after cessation of quinolone antibiotic therapy, the active athlete can become suddenly prostrated and severely affected, normally in one single or a very few joints.

Month 1-12: Minor musculoskeletal symptoms; limited activity, incorrectly associated with overuse, or mechanical problems. Acute phase for other minor effects.

Month 12: (Acute phase, for active, athletic people only) due to accumulated damage, peak symptoms are reached. Collapse of a joint is typical. There are no or very mild accompanying symptoms (vision, neurological, etc...).

Month 12-22: Recovery predominant, relatively fast progress.

Active and athletic people will see their endurance drop a lot and they will develop osteoarthritis early, perhaps some ten years earlier than non-floxed people, and depending on dosage.

36.EXPECTED EVOLUTION FOR A MILD REACTION

In these cases, apparently there are no symptoms associated with the quinolone treatment and the individual can feel no adverse reactions after taking a quinolone prescription, especially a short one or one with low doses. But the quinolone takes its toll and after several treatments spaced weeks, months, or even years apart, subtle symptoms will begin to develop, and the sufferer will probably never link them to the antibiotic.

These symptoms will probably be: restlessness, especially at night, brain fog, some minor twitching, increased coolness of hands and feet, slower recovery after strenuous activity, increased stiffness after exercise. And the unavoidable erosion of cartilages will be inevitably added to the list.

In MILD reactions, recovery is reached between months 4 and 12 on average. In some cases they have an acute phase of up to 3 months.

37.TYPICAL PATTERNS OF EVOLUTION OF RECOVERY

As explained above, the typical progression of the intoxication and its recovery follow quite typical patterns that have been outlined in the diagram-figure 4.

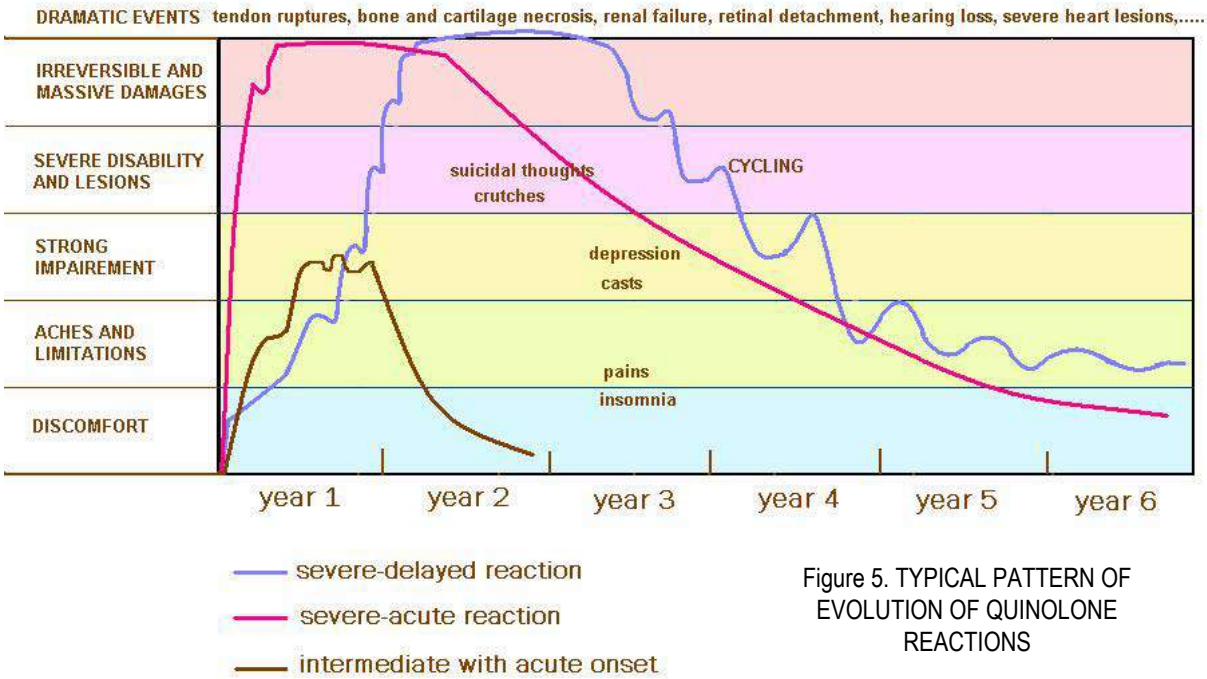


Figure 5. TYPICAL PATTERN OF EVOLUTION OF QUINOLONE REACTIONS

Figure 5. This figure shows the typical evolution of several sorts of reactions as classified in the present paper. Do not take it as a reference for your case. Each individual develops different patterns. The coloured lines in the graphs show the OVERALL status of the floxing and average tendencies. A floxed person may have an overall intermediate reaction and at the same time one or two symptoms of a very high level, corresponding more to a severe reaction.

- SEVERE-DELAYED REACTION. Is the most dreadful. There is an acute reaction soon after finishing the treatment, and then for more than a year all the symptoms develop until reaching very dangerous levels and surpassing well beyond the point of irreversibility of injuries. Then until about the 3-year mark, the floxed person experiences a desperate and miserable life. By then an improvement plagued with cycles starts. By year 6 permanent aches and irreversible damage is common.
- SEVERE ACUTE REACTION. Is similar to the severe-delayed one, but the symptoms develop in a shorter time and then resolve more rapidly. Cycles are not shown for simplicity purposes, but are typical. Usually it leaves less permanent injuries.
- INTERMEDIATE REACTION. Does not reach very high intensities of injuries, but the affected persons are equally anguished and tend to think that something very severe is happening to them. It can heal without sequela, although not in all cases, because at least some loss in endurance (only perceivable by push-to-the-limit athletes) is always present.

38.WHICH KIND OF ADVERSE REACTION TO QUINOLONE ANTIBIOTICS ARE YOU SUFFERING FROM?

Reactions to drugs vary among individuals. This report can provide little help in assessing any particular case, because all information stated here is based on average experiences. But there are some very common patterns of bodily responses to quinolone intoxication. First of all, you should discern among:

- ACUTENESS. Some reactions are sudden and very acute, causing a lot of distress to their

sufferers, but they resolve in a few months because the reaction has manifested abruptly but not deeply.

- SEVERITY. Other reactions have a medium intensity of symptoms at onset but they insidiously develop progressively to very severe reactions over time (usually 12 or 18 months).

In other words, a person suffering from QTS (QUINOLONE TOXICITY SYNDROME) **cannot infer from his/her initial symptoms** what kind of reaction he/she is experiencing.

Many people suffer acute reactions during the first days. Even though they get very scared the acuteness has no direct relation with the severity of the reaction as a whole. You will only be in a position of making a judgement on the severity of your QTS after a few months after the cessation of the drug, when you line up the whole list of symptoms, their intensity and their evolution.

From the study of many cases we have concluded that is useful to create a simple scale of severity of the reactions: MILD, INTERMEDIATE and SEVERE. We do not take into account the acuteness of the initial reaction, because it has been proved that it has no relationship with the evolution of the QTS. According to this scale you can end up having a mild, intermediate or severe reaction. Obviously there are no clear delineations between them and every reaction is unique and personal, but if from your experience, or from your exchange of information with other people or doctors, you can assess as to which kind you are experiencing, you will acquire a more precise diagnosis and will be able to address your problem accordingly.

See next table for the average categories for a floxing. Everyone is different and can have, for example, 20 symptoms belonging to the intermediate reaction level, and 1 or more with a greater intensity, typical of a severe reaction.

TABLE 8. INTENSITY OF SYMPTOMS AT THE END OF MONTH 6 POST-FLOXING FOR DIFFERENT LEVELS OF REACTION

SYMPTOM	if you are suffering from a		
	SEVERE REACTION	INTERMEDIATE REACTION	MILD REACTION
joint pains, arthritis, osteoarthritis	Severe	limiting	mild
generalized pains	intense, growing	no	no
tendinitis	Widespread	limited to a few places	mild, localized
soreness, stiffness	High	medium	mild or none
recovery of physical traumas	Impeded	normal	normal
skin injuries, rash	Common	some times	no
cool hands/feet, poor circulation	very intense	some degradation	no
brain issues	yes	no	no
depersonalization, panic attacks	very common	usual	not usual
twitching, numbness, tingling...	severe	noticeable	unnoticeable
insomnia, anxiety, brain fog	Universal, intense	very common	common, but mild
vision (floaters, lights, blank points)	very common	uncommon	unusual
photophobia	universal	common	uncommon
focusing problems	possible	uncommon	no
impotence	increasing	no	no
sensitization to foods, chemicals, odors	very common	uncommon	no
dry sinus, dry eye, dry ear, dry skin	yes	no	no
neurological spasms	yes	no	no
heart palpitations, arrythmias	worsening	occasional	possible
elevated serum enzymes and titers	yes	no	no
tinnitus, ringing in ears	frequent	sometimes	unnoticeable
peripheral neuropathies	universal, worsening	common, limited	unusual

The entire list of the adverse reactions to a typical quinolone is included in another section of this report.
For a more precise diagnostic, the comparative study of symptoms should be done at the end of month 6.

TABLE 8-cont'd. EVOLUTION OF THE SYMPTOMS (see later in the article)			
new disorders appearing or increasing	up to month 18	up to month 10	unnoticeable
peak point of disorders (downturn)	at month 20	at month 12	early months

If you suffer a MILD reaction you can expect a good recovery in 4 or 6 months. For an INTERMEDIATE reaction, typically there is a convalescence of 1 to 2.5 years with a diminished but acceptable life quality. SEVERE reactions mean a miserable living for at least 3 years plus another 2 or 3 years to get acceptable pain levels, ending up with permanent injuries and life limitations. Remember that this article focuses primarily on severe reactions.

Everyone behaves slightly different to the floxing because daily habits and personal conditions can somewhat modify the evolution of the recovery.

Severe reactions have a much worse prognosis (likely future outcome) than the rest. For a rapid evaluation, the main characteristics of a severe reaction are:

1) *caused by long or high dose treatments (6-8 weeks of 2x500mg daily or more than 1 week 2x750 mg daily of cipro)*
2) *existing symptoms increasing or new ones emerging after month 6*
3) *dryness syndromes (eye, sinus, ear, mouth) that do not clear up by month 14th or so*
4) *multiple joint (cartilage-tendon) and muscle pathologies*
5) *general stiffness and inability to gain muscle mass no matter how much exercise is done*
6) *extraordinary soreness a few hours after attempting vigorous exercise or activity*
7) *constant pains already present on waking up instead of increasing during the day*
8) *vision floaters and flashing lights that not subside after 2 years*
9) *reactions to foods and over the counter drugs that you did not have before*
10) *cold hands that persist in normal situations, with poor blood circulation*

If you have the first two plus another 5 or more of these afflictions and they are intense, then you might be suffering from a severe reaction.

In fact, it is the CRITICAL ISCHEMIC POINT that distinguishes between severe and non-severe floxings. This is, by definition, the level of toxicity that provokes an overall ischemia (narrowing, flood depriving of blood vessels and extracellular matrix) all over the body, in such a way that ANY small increase in vasoconstriction or matrix status (see later in the report) sharply worsens the condition of the floxed person. This vascular implication is explained later.

SUMMARIZING:
Many reactions are mild and intermediate and heal in a few months or years with no serious sequelae, but only after a lot of suffering.

In mild and intermediate floxings, the ischemia of the blood vessels-degradation of the collagenous matrix has not reached its critical point and still can endure more narrowing before more nerves and tissues start to massively die off. However, in severe floxings the critical point of ischemia has been surpassed and there is not any margin left for further vasoconstriction, and therefore small amounts of foods, substances, or actions that induce even more narrowing of the vessels cause immediate pains in nerves, exacerbation of vision issues, and many more relapsing symptoms.

Mild and intermediate reactions cause more concentrated injuries, especially neurological, and other smaller disorders. Severe reactions cause massive disturbances all over the body, as the entire network of nerves and organs are damaged, and some cannot heal properly, so the medical picture is overwhelming.

As said at the beginning of the report, you should avoid the temptations of over rating your reaction. Although the toxicity of quinolones affects many many people, severe reactions are not frequent. Seen from an exclusion perspective, you probably do not have what we call severe reaction if

do not have strong dry mocuous membranes symptoms
or
you do not have very intense and widespread neuropathies
or
you do not have debilitating musculoskeletal injuries
or
you do not have long lasting central nervous system damage (insomnia, brain fog, coffee intolerance...)

A severe reaction exhibits all those four groups of abnormalities at the same time. If you miss one or more, you probably do not belong to the group of severe reactions, although you can have some symptoms really scaring and profound injuries.

39.WHAT ARE YOUR CHANCES OF RECOVERY?

As explained before, most people recover from the quinolone intoxications. Many do not. Everyone with intermediate and severe reactions sustains permanent damage although it can be internal and it can remain more or less unnoticed if it does not affect their daily lives much (cartilages, central nervous system). Some people end up with permanent chronic pain, physical difficulties, heart or vision damage, and many other irreversible injuries.

Therefore, if the toxicity level is not high, that is to say, if there are little nervous and vascular system alterations, the average person will probably recover, albeit with the cartilages of the weight bearing joints slightly eroded. The athlete will enter an accelerated course of decay because his/her cartilage will not keep up. The endurance athlete will no longer be able to perform at a decent normal level.

REMEMBER:
For a severe reaction, the chances of complete recovery are lower than 40%.

For instance, in severe cases photophobia resolves in some two years on average, focusing impairments in 3.0 years, and flashies and floaters take many years to fade off. Another indicator of the severity of the floxing is a dry mucous condition. If you have long-lasting dry eyes, plus dry mouth, ear and sinus, that are present after more than one year, you are probably suffering a severe reaction and running the risk of ending up with permanent injuries.

If the toxicity level is high, the average person might eventually get a decent daily life similar to the one he or she enjoyed before taking a quinolone, but with some physical limitations for repetitive and strenuous activities. The athlete will no longer be able to return to competition in any impact sport, and in the best case he will be capable of enjoying biking, hiking, swimming or other sports that put little stress on the joints. Healing and recovery time until reaching this point is more than three years on average. There is a concerning number of cases for which recovery seems to be elusive after five or more years after the last quinolone pill ingested. Perhaps during the coming years we will see the confirmation of a vast number of cases of permanent disability, or lifelong pains and misery caused by quinolone antibiotics.

The successful recovery stories of people enduring intermediate and mild reactions are currently overrated because many people that end up feeling normal are still far behind a complete recovery but they cannot tell because they are sedentary. Those persons can report that they are cured some two years earlier than the real healing takes place. Nobody really gets out undamaged. Although it is difficult to trace enough people long enough to get a conclusion, it is widely admitted nowadays that many people remain symptomatic in a permanent, irreversible manner.

Chances of recovery are predominant for the age bracket of 20-40 years. After the age of 40 recovery can take much longer. Beyond the fifties more permanent damages are recorded. For people above 70 years old, recovery is completely unlikely in the case of severe reactions. We believe that administering

fluoroquinolones to people over 70 is putting them at serious health risk.
It is summarized as follows:

TABLE 9. LIFE AFTER RECOVERY			
	reaction that you suffered		
	SEVERE REACTION	INTERMEDIATE REACTION	MILD REACTION
average recovery time	5 years, or never	two years	months
permanent damage	frequent	uncommon	no
ISSUE	DISORDERS AFTER 5 YEARS	DISORDERS AFTER 2 YEARS	DISORDERS AFTER 1 YEAR
joint+muscle pains	occasional	no	no
cartilage erosions, early osteoarthritis	permanent	common	no
decreased endurance	permanent	permanent	no
stiffness of joints and limbs	common	uncommon	no
vision (floaters, ziggies, flashies, blank points)	common	no	no
photofobia	no	no	no
focusing problems	no	no	no
insomnia, anxiety, brain fog	no	no	no
depersonalization, panic attacks	no	no	no
heart palpitations	occasional	no	no
numbness, tingling, twitching	occasional	no	no
tinnitus, ringing in ears	occasional	no	no
peripheral neuropathies	Very common	no	no
sensitivity to foods, chemicals, substances	common	no	no
this table shows the expected sequelae of a floxing on a healthy young individual			
"occasional" means that you will notice it occasionally *"permanent" means that you will suffer it for life* *"common" means that the issue is still common after 5 years*			

Nearly all floxed persons can tell when they are recovering, because at a precise point in time they begin to experience less problems with foods (recovery of the toxicity and neuropathies that prevent intestines and organs from working properly), a lower level of pains, less stiffness and soreness, more flexibility, there is a weight gain, insomnia improves, and they feel stronger in every sense. Then some anxiety develops in all floxed persons because they all see a glimpse of normalcy on the horizon, and would like their ordeal to stop immediately after long years of suffering. But in severe floxings, on average, you feel some recovery when you are halfway through the reaction, that is to say, at the 2.5 year mark for a 5 year recovery period. The second part of the floxing is more compatible with a normal life (except for sports or strenuous activities) but you still cannot eat freely, you endure many periods of cycling, and many neuropathies and permanent injuries (vision; eye, ear, and skin dryness) are still present and the floxed person gets concerned about the quality of life already lost and the perspectives lying ahead.

40. SOME WAYS OF MEASURING THE EVOLUTION

The following study demonstrates that more than half of 55 patients with inmediate adverse reactions (that took place during the treatment), had inmunological IgE specific for quinolones, circulating in their blood, up to 4 years after the treatment. The report also concludes that if you have suffered a reaction to a quinolone, you have to avoid all quinolones, as we already know. In our opinion, this IgE test should be standard practice to detect many cases of reactions to quinolones, in order to provide ignorant doctors with a tool for diagnosis, and to check the evolution of the reaction, by measuring the concentration of those specific IgE markers. Nevertheless, most of floxed persons seem to have a response more based on IgG than on IgE. Very likely, more studies like this one could focus on the syndrome of toxicity of quinolones with a relatively small effort.

DETECTION OF SPECIFIC IGE TO QUINOLONES.
Manfredi M, et al.Allergy Clinic and Laboratory, Nuovo Ospedale San Giovanni di Dio, Florence.
BACKGROUND: In the last years, immediate reactions to quinolone antibiotics have been observed with increasing frequency, mainly urticaria, angioedema, and shock.
OBJECTIVE: We sought to assess whether these reactions are IgE mediated and whether an in vitro test for quinolone-specific IgE is useful in the diagnosis and understanding of cross-reactivity.
METHODS: We assayed specific serum IgE to quinolones using epoxy-activated sepharose 6B as the solid phase in 55 patients with immediate adverse reactions; specificity of IgE binding was demonstrated by inhibition tests.

RESULTS: The test yielded positive results in 30 (54.5%) patients who were tested 1 to 48 months after the reaction had occurred. The quinolone-specific IgE seems to disappear more slowly in atopic patients. The cross-reactivity between various quinolones allowed us to identify a common structural motif within quinolones that might be responsible for clinical and serologic cross-reactivity.
CONCLUSION: A substantial portion of immediate reactions to quinolones appear to be IgE mediated. Cross-reactivity of IgE among different quinolones is frequent and suggests that a common avoidance of quinolones should be attempted in all patients with respective symptoms.

41.THE MOST CLASSICAL PERMANENT INJURIES

Please, note that this paragraph makes reference to severe floxed persons only. Based on self reporting, after 5 or 7 years, the most typical permanent injuries, that many severe floxed persons exhibit, and some other floxed persons as well, are:

- Dry eye, dry ear, dry nose, dry mouth. At 3 years many feel a partial improvement, and then comes a sort of a plateau that seems to become chronic, permanent, for life.
- Other dryness symptoms (sweat, intestinal secretions, internal organs). Their evolution is difficult to follow up with, because symptoms are so subtle or impossible to feel, except for those floxed persons with special activities.
- Cartilage erosions, osteoarthritis, joint necrosis in some cases, grinding of the cartilages, pains and inflammation after exercise, many cases of meniscus injuries, spinal discs injuries.
- Tendinitis. Chronic tendinitis is extremely common after 5, 6 or 7 years in all severe cases and in less severe ones if the floxed person is very active physically.
- Neuropathies. Fasciculations are present periodically in people after the 5-year mark, although quite diminished. Ulnar neuritis is as frequent and intense at year 5 that at the onset for many severe floxed persons. Almost constant pains are still present in more than half of the severe floxed persons by the 5-year mark. Lack of proper nerve functioning in fingers and toes is still present in most severely floxed persons after the 7-year mark, with cold hands, cold feet, and fingers that tend to freeze in not so cold temperatures along with numbness and lack of sensitivity (apparently it is due to nerve-vein spasm).
- Insomnia does not usually become permanent. Almost all severely floxed persons become partially or totally healed of this neurotransmission deficit before the 5 year mark. Brain sharpness, and superior brain thinking and acuity is regained by the 4th or 5th year, so they do not become permanent injuries in general.
- Floaters are a permanent injury of the vitreous caused by the quinolones, and do not improve a bit ever, although they are less noticeable as the floxed person becomes accustomed to them.
- Big flashing and zigging lights in the vision tend to lessen a lot at around the 4th or 5th year.
- Erectile dysfunction of severe floxed persons is still present at year 5 but in much less intensity that at its height (normally 18 months out).
- Muscle atrophy and inability to build mass is present in many severely floxed persons after 6 or more years.
- Kidney injuries (proteinuria, hypercalciuria); liver injuries (hyperbilirrubemia, impaired P450 metabolism); pancreas damage (revealed by sustained abnormal levels of the main markers).
- Endocrinal permanent injury is very common in terms of thyroid and other hormones abnormalities for many years after the floxing. Sometimes, complete resolution is seen.
- Permanent nerve-muscle-fascia damage, with intolerance to exercise, pains, stiffness, high CPK and aldolase counts, fascia adhesions and destruction of the connective tissue with many trigger points.
- Sharp pains from time to time, are a sign of injured nerves acting up randomly along the body. Many long-term floxed persons occasionally have shooting pains in several parts of the body, that last a few seconds but that are extremely intense.

More details about most of these health issues are included later in the report.

PART VI: VASCULAR DAMAGE

42. THE TWO HEADS OF THE HYDRA

There are two toxic mechanisms of the fluoroquinolones that explain most of the injuries that they cause:

- VASCULAR DAMAGE (injury to the small vessels and extracellular matrix)
- FAULTY NEUROTRANSMISSION (alteration to the transmission of nerve signals)

In this chapter we address the first one, a complex issue that simplifying is called vasculitis.

43. THE VASCULAR-MATRIX CONNECTION

This area of the report is a hypothesis on the ultimate cause of some of the injuries of the floxing syndrome. We cannot aim to discover anything of medical importance. But we can argue about some ideas that correspond well with our experiences, the clinical symptoms that allow us to favor some habits and avoid others in our daily lives, with some basic understanding about the why and why not.

Although it is not generally accepted, we think that one of the main damaging paths used by fluoroquinolones is vascular. There are many scientific papers that relate vasculitic events induced by quinolones but they are presented as exceptional or rare happenings. However, the fluoroquinolones unfailingly provoke a specific sort of vascular injury(s).

While it is true that all living things are made of cells, that is only part of the story. Most of the cells in humans are surrounded by a complex mixture of nonliving material that makes up the extracellular matrix. In some cases, the extracellular matrix accounts for more of the organism's bulk than its cells.

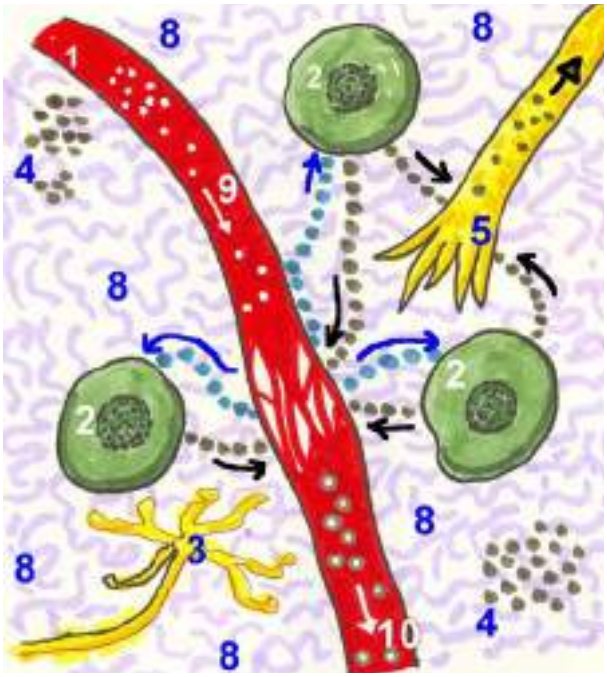


Figure 6. You have to pay attention to the attached figure. This figure has been prepared by a floxed person based in a diagram of Martin Keymer. The figure shows what you are made of. Arteries (1) supply nutrients and oxygen by means of the blood (9). The cells (2) of the organs need that supplies and also to get the toxins away (dark dots). All the exchanges are done through the capillaries (8) that spread like little worms in the extracellular matrix (the substance that bathes it all). Blue arrows show the in-path of oxygen and nutrients, exclusively from the arteries, via the microvessels and extracellular matrix, to the cells. Black arrows show the detoxification out-pathway, addressed to the veins (10) and to the lymph vessels (5), that begin blind in the tissue (let us say the matrix). The veins remove the wastes (10). When there are toxins, like quinolones, on top of damaging the cells, degrading the matrix, and injuring the microvessels, they create deposits of byproducts (4) in the matrix (not necesarily quinolones properly). All organs are stimulated by nervous cells (3), that are also served by

the microvessels (8) and those nerve cells can get damaged too by the toxicity.

As a general conclusion, take notice that the transfer of nutrients and oxygen from the arteries to the cell depends on the extracellular fluid. Nerve supply to the cell is also seen via terminal autonomic (do not depend on your will) axons with their blind endings in the extracellular matrix. Cellular waste is carried away from the cell via the extracellular fluid and transported to capillaries and lymph vessels. This sponge-like matrix also stores toxins and serves as a buffer to prevent damage to vital tissues. A heavy onslaught of toxins owerwhelm the body's capacity to clear and evacuate and can be stored in the matrix and then released at a slow rate later, if the clearance mechanisms have not been toxically destroyed beyond repair.

The matrix is composed of a mesh of high-polymer sugar-protein complexes, mostly proteoglycans and structural glycoproteins like collagen and elastin. You can consult many medical articles describing how quinolones are specially active at destroying proteoglycans for example.

The extracellular matrix and all its microvessels can be damaged by toxins from multiple origins and by fluoroquinolones that is the subject that we are treating. The primary mechanism of the damage is free radical oxidation and chronic inflammation. The tissues become impregnated with the quinolones and the products originated by the oxidating reactions they provoke and finnally the organs become damaged and cellular metabolic processes become altered.

Once the extracellular matrix is compromised, the transmission of intercellular information is impaired. The accumulation of toxins (quinolones, remains of quinolones half metabolized, and toxic byproducts of the intoxication) within the extracellular matrix creates multiple problems.

In other words, between the cells of the body and the capillaries that serve them there is a sort of broth that is called extracellular matrix, because is the substance that is outside the cells, and bathes it all, allowing the exchanging of debris and nutritionals between the vessels and the cells. This matrix has to be in perfect state to do its vital functions. Many many dysfunctions of the body take place when this extracellular matrix is degraded by agressive factors.

> JEREMY NORMINGTON, DPT, DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
> A recent histological exam was aimed at understanding the direct pathologic mechanism underlying fluoroquinolone-induced tendinopathies. Williams et al. suggests that fluoroquinolones alter fibroblast metabolism. The study examined the effects of one type of fluoroquinolone ciprofloxacin on the fibroblast metabolism of canine Achilles tendons, paratenons and shoulder capsules.
> Researchers looked at fibroblast metabolism from three standpoints: cell proliferation, matrix synthesis (collagen and proteoglycan) and matrix degrading activity. The study revealed the following: a 66 percent to 68 percent decrease in fibroblast proliferation; a 36 percent to 48 percent decrease in collagen synthesis; and a 14 percent to 60 percent decrease in proteoglycan synthesis, compared to control groups. Ciprofloxacin also induced a significant increase in matrix degrading activity over 72 hours.

Descending to the detail, we have to point out that along this report, when we say that probably fluoroquinolones act injurying the microvessels we are implying that fluoroquinolones damage the microvessels and also the extracellular matrix that is the interface between the cells and the vessels, disorganizing many critical functions.

The role of extracellular matrix is extremely important. For instance, wound healing involves close interaction between several different cell types, extracellular matrix components and growth factors. In hard-to-heal wounds, like all the injuries caused by quinolones, the healing processes are disrupted by cellular and biochemical imbalances that compromise the repair processes. All these afirmations have been extracted by us from medical papers.

The degradation of the extracellular matrix is caused by the toxicity of quinolones, directly and/or by means of stimulating a large family of enzymes that degrade the extracellular matrix, called matrix metalloproteinases.

Matrix metalloproteinases have been implicated in cancer metastasis, bone remodeling, embryogenesis, angiogenesis, arthritis, and periodontal disease. Matrix metalloproteinases are put to work by quinolones in the whole body. Doctors call this phenomenom *"expression of matrix metalloproteinases"* that means induction of production of metalloproteinases, that cause matrix degradation. The following paper manifests this effect of quinolones on the eyes, but could be extrapolated to any other area of the body:

> EFFECT OF TOPICAL FLUOROQUINOLONES ON THE EXPRESSION OF MATRIX METALLOPROTEINASES IN THE CORNEA
> Victor E Reviglio, The Wilmer Eye Institute, Johns Hopkins Baltimore, Maryland, USA
> Matrix metalloproteinases play an important role in extracellular matrix deposition and degradation. Based on previous clinical observations of **corneal perforations during topical fluoroquinolone** treatment, we decided to evaluate the comparative effects of various fluoroquinolone eye drops on the expression of matrix metalloproteinases in cornea. Methods: Eighty female Lewis rats were divided into two experimental groups: intact and wounded corneal epithelium. Uniform corneal epithelial defects were created in the right eye with application of 75% alcohol in the center of the tissue for 6 seconds. The treatment groups were tested as follows: 1) Tear drops: carboxymethylcellulose sodium 0.5 % (Refresh, Allergan); 2) Ciprofloxacin 0.3% (Ciloxan, Alcon); 3) Ofloxacin 0.3%(Ocuflox, Allergan); 4) Levofloxacin 0.5%(Quixin, Santen). Eye drops were administered 6 times a day for 48 hours. Results: matrix metalloproteinases MMP-1, MMP-2, MMP-8 and MMP-9 expression were detected at 48 hrs in undebrided corneal epithelium roups treated with the topical fluoroquinolones. No statistical difference was observed in quantitative expression of matrix metalloproteinases among ciprofloxacin .3%, ofloxacin 0.3%, levofloxacin 0.5%. When the artificial tear group and the fluoroquinolone groups with corneal epithelial defect were compared, increased expression of matrix metalloproteinases was observed as a result of the wound healing process. However, the fluoroquinolone treated group exhibited high statistically significantly levels of matrix metalloproteinases expression.
> Conclusions: Our study provides preliminary evidence that **topical application of fluoroquinolone drugs can induce the expression of matrix metalloproteinases** MMP-1, MMP- , MMP-8 and MMP-9 in the undebrided corneal epithelium compared to artificial tear eye drops.

The above article shows what we already knew due to our physical experiences. Fluoroquinolones induce the expression of matrix metalloproteinase, that means that the interface between cells and vessels is degraded (destroyed) causing unpredictable and potentially serious injuries all over the body, that in the case of eyes take the form of corneal perforations, impaired healing and overall degradation. So simple, so unknown, so ignored.

Another research abstract that treats the influence of the degradation of the extracellular matrix on the tendons of the human body:

> FLUOROQUINOLONES CAUSE CHANGES IN EXTRACELLULAR MATRIX, SIGNALLING PROTEINS, METALLOPROTEINASES AND CASPASE-3 IN CULTURED HUMAN TENDON CELLS.
> Sendzik J, et al. Institute of Clinical Pharmacology and Toxicology, Berlin, Germany.
> Antimicrobial therapy with fluoroquinolones can be associated with tendinitis and other tendon disorders as an adverse reaction associated with this class of antimicrobials. Here we investigated aspects of the mechanism of quinolone-induced tendotoxicity in human tenocytes focussing mainly on the question whether fluoroquinolones may induce apoptosis. Monolayers of human tenocytes were incubated with ciprofloxacin or levofloxacin at different concentrations (0, 3, 10, 30 and 100mg/L medium) for up to 4 days. Ultrastructural changes were studied by electron microscopy, and alterations in synthesis of specific proteins were determined using immunoblotting. At concentrations, which are achievable during quinolone therapy, 3mg ciprofloxacin/L medium significantly decreased type I collagen; similar changes were observed with 3mg ciprofloxacin or 10mg levofloxacin/L medium for the beta(1)- integrin receptors. Effects were intensified at higher concentrations and longer incubation periods. Cytoskeletal and signalling proteins, such as activated shc or erk 1/2, were significantly reduced by both fluoroquinolones already at 3mg/L. Furthermore, time- and concentration-dependent increases of matrix metalloproteinases as well as of the apoptosis marker activated caspase-3 were found. Apoptotic changes were confirmed by electron microscopy: both fluoroquinolones caused typical alterations like condensed material in the nucleus, swollen cell organelles, apoptotic bodies and bleb formation at the cell membrane. Our results provide evidence that besides changes in receptor and signalling proteins apoptosis has to be considered as a final event in the pathogenesis of fluoroquinolone-induced tendopathies.

The explanation of the above report is as follows. Fluoroquinolones cause reductions of key proteins that help maintaining healthy tendons. Additionally, quinolones increase matrix metalloproteinases (that degrade the substance that acts as medium for exchanging metabolites with cells), quinolones increase the marker that send signals to cells to commit self-destruction (apoptosis), plus many other damages like condensed material in the nucleus, swollen cell organelles, apoptotic bodies and bleb formation at the cell membrane. In summary, fluoroquinolones disorganize the very basic of cell metabolism. Are there many other antibiotics with this profile? Why then are quinolones considered benign antibiotics?

After knowing the basics of the two articles above, you can deduct correctly that the same effect of degradation of the extracellular matrix and microvessels can take place all over the body, what is coherent with the extremely vast array of injuries that a fluoroquinolone cause in persons.

Only recently we have found these summary of a medical report:

> JEREMY NORMINGTON, DPT, DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
> The exact mechanism of fluoroquinolone-induced tendinopathies is unknown. In 1994, Szarfman et al. provided an early hypothesis. The disruption of the extracellular matrix or cartilage and the depletion of collagen in animal models led Szarfman to hypothesize that similar degradation may occur in humans with tendon ruptures.
> In another study, Gillet et al. viewed three Achilles tendons of symptomatic fluoroquinolone therapy patients with magnetic resonance imaging. Clinical findings were typical of Achilles tendonitis in all cases. Two cases showed thickening of the tendon and one case exhibited prominent peritendinous edema.

44.THE "QUINO-VASCULITIS" IN MORE DETAIL

We can profundize a little more on the subject. The cellular matrix is the ground material for connective tissue in which nerve fibers and vasa vasorum (small vessels) are dispersed. The vasa vasorum exist within the extracellular substance of the end organs (see figure 5). These vasa vasorum include the capillaries, that are approximately the size of a red blood cell. The very small vessels that surround and supply the nerves are called vasa nervorum.

Blood has to travel all over the body in order to supply every cell of the body with nutrients and oxygen, and to remove the wastes from all the tissues. The blood has to be able to send its white blood cells into the surrounding tissue of cells to clean it up and respond to injury.

These functions of blood require that it can exchange its materials with its surrounding tissues. Arteries and veins are not designed for exchange but merely for transport. It is *in the tissue* where the exchange has to take place. Therefore, the capillaries (microvessels), which lie in the cellular matrix between arteries and veins, must be the regions for exchange.

The quinolone antibiotics alter the cellular matrix and also target the vasa vasorum and vasa nervorum, either changing the capillaries permeability (the microvessels are one cell thick and allow the exchange of substances through openings), or inducing the deposition of immunological complexes inside them, or causing a spasm-like narrowing of their ducts, or simply chemically damaging them. In any case, the result is the same: muscles, skin, nerves, heart, brain and other organs are deprived of adequate blood flow (ischemia), and owerwhelmed by toxic intermetiate compounds and they die or do not work properly. For the sake of simplicity, in this report we call quinolone-vasculitis the degradation of the extracellular matrix plus an alteration of the microvessel walls with vascular damage or attendant tissue injury.

What nobody knows and requires much more research are the factors that determine the duration of disease, the type of tissues involved and their damage, as well as how to target therapies at inflammation

without interfering with healing. Apparently, part of the process explained earlier is vehicled through an inmune response of the body.

Immune complexes with certain immuno-chemical characteristics activate a complementary cascade that induces neutrophil mediated damage to the vessel wall. The presence of granulocytes is usually associated with fibrinoid necrosis as would be expected on the basis of their release of toxic enzymes during inflammation. Necrosis in the vessel wall is a large contributor to scarring and the delayed sequelae present in some cases of vasculitis, such as the quinolone-induced vasculitis.

Accumulation of inflammatory cells in the vessel wall is the common feature of common vasculitis, although it is not well understood how tissue damage occurs. It is widely admitted that there is a three-stage process:

- initiation of the injury
- recruitment of inflammatory cells and tissue damage
- regulation of the immune response.

Quinolone vasculitis is a systemic vasculitide (so called because of its multi-organ nature). Inflammation and damage can be transient or more permanent. The alterations in coagulation and vasomotor tone result from local damage to the endothelium (inner part of the walls of the ducts of large calibre and is the only layer of the wall of microvessels) as well as intrinsic components of the cytokines that are released through the process. Drug toxicities are among the causes and processes strongly associated with vascular injury.

Normally, quinolone vasculitis appears some time after exposure, and is a link in the chain of adverse events that take place for months on end. All of the vasculitides are likely secondary to some form of inflammatory stimulus, usually infectious or toxic, as in our case. In quinolone vasculitis the real underlying cause either cannot be identified (no doctor is willing to admit that quinolones are the direct cause of vascular disorders) or has long since been cleared by the host, leaving only a chronic or recurrent inflammation focused on the vasculature.

Toxins as a cause of vasculitis are increasingly established. Overall, vasculitis secondary to a defined infection or toxin is clearly the most frequently encountered vasculitis and an important etiology in peripheral nerve vasculitis. Because quinolone vasculitis is so varied in its presentation and clinical pace, early identification may be difficult. In this vasculitis, neuropathies are frequent, occurring in 80%-100% of patients. Mono-neuropathy multiplex is the most distinctive pattern in intermediate reactions to quinolones, although nerve alterations of other kinds are very common as well (twitching, throbbing, pins and needles, numbness, sensory poly-neuropathies). See the paragraph devoted to neuropathies.

Then, there is the issue of diagnosis. The diagnosis of vasculitis is fundamentally an invasive process (biopsy). A critical feature is the identification of inflammatory cells that diminish the delivery of blood to tissue. Furthermore, the numerous causes that may result in vasculitis can often be distinguished only at the cellular level. Histological studies characterizing injuries on the basis of the infiltrating cells may provide information on both the mechanisms inducing inflammation and predict the sequelae of the injuries. There is an urgent need to determine the underlying mechanism for appropriate treatment.

For most floxed persons the blood studies may be entirely normal. There is no serological test that confirms or excludes a vasculitis. Quinolone-vasculitis is:

- Seronegative (non-ANCA, negative SSA, SSB, anti-Sm, normal anticardiolipine, antiphospholipid, soft muscle markers, halotypes....). This alone convinces all doctors that floxed persons do not have any alteration in their inmune system.
- Drug-induced, non-abating with drug withdrawal, delayed-onset, and typically reaches its acute phase many months after drug discontinuation, when the ischemic process has managed to kill enough nerves or cells. This is considered impossible by almost all doctors, although is a proven fact.

- Not responsive to any known treatment; very long lasting or permanent, because many nerves die and cannot be regenerated.

Being non-ANCA, the floxing vasculitis is normally classified by some advanced doctors as drug-induced immuno-complex vasculitis that shares similarities with other immuno-complex vasculitides like systemic lupus erithematosus, rheumatoid arthritis and Sjögren's disease.

In summary, blood ducts extend in smaller and smaller conducts, called arterioles and venioles. The real ends of them reach every part of the body and spread in the extracellular substance that serves as substrate for all cells in the organs of the body. The arterioles bring the oxygen and the nutrients and the venioles and limphatic system collect the by-products and CO2 (carbon dioxide) resulting from cell activity.

There are zones with very little arteriole and veniole supply: cartilages, tendons, nerves and connective tissue. Due to the vasculitis caused by quinolones, the small vessels and the substance that surrounds them is degraded, damaged, and its properties deeply altered. The result is that the microvessels (and larger vessels up to certain extent too) cannot correctly supply the tissues or take away the waste. The consequences are:

- Lack of blood supply (injury to vasa nervorum) in nerves that cause intense neuropathy-like numbness, tremors, twitching, tingling, neuritis and dying of nerves, escalating the pain response and perpetuating the injuries. Nerve dying causes muscle dysfunction (lack of strength) and muscle wasting.
- Lack of blood supply to cartilage, in addition to the toxic assault, causes necrotizing, and erosion with osteoarthritis in weight-bearing joints.
- Lack of blood supply in tendons and "overuse" with daily movements causes tendinitis.
- Heart arrhythmias, palpitations, poundings, that last for years and in some cases require the implantation of a pacemaker. Many deaths have been associated with quinolone-induced cardiopathies.
- Poly-myositis and muscle destruction are frequently seen in severe reactions.
- Lack of blood supply in the extremely narrow ocular vessels causes sparkling, zig-zagging, wandering small lights. Floaters are a result of dying cells due to lack of blood supply. Many floxed persons get ischemic areas in the outer margins of the retina. Optic neuritis is very common.
- Temporary and complete loss of vision, occurring in some cases from month 5 to month 13th: lack of irrigation of the eyes.
- Lack of blood supply near the skin in the more distant areas of the body and a tendency to have cool feet and hands.

This quinovasculitis seems to have an autoimmune component. According to many medical reports, mild reactions are responsive to most conventional treatments such as corticosteroid therapy, immunosuppressive drugs, and the like. In the case of a severe reaction, long-term treatments with corticoids are contraindicated (increase very much the likelihood of experiencing a tendon rupture) and also ineffective.

The search for a non-invasive marker for quinovasculitis remains disappointing. Some of the most effective treatments for quinolone-induced toxicity are substances with a strong vaso-dilation activity or active blood thinners. On the other hand, substances with vaso-constrictive properties are nearly always detrimental for floxed persons and induce relapses, an increase of symptoms and delayed recoveries.

Remember:
Your problems after the reaction are the tip of the iceberg. The quinolones have damaged all your body systems to different degrees.

There is a specific disorder caused by quinolones, especially ciprofloxacin, (and other antimicrobials as well) called haemolytic anemia. The drug (i.e. cipro) attaches to some proteins in the body (creating an immuno-complex) and targets the surface of the erythrocytes (red blood cells) causing the blood to clog in certain situations, especially in low temperatures. Then, much cold is felt in hands and feet and in some other areas of the skin because the clots block the blood flow through the very narrow small vessels of the affected areas. For average temperatures, the immuno complex detaches from the red cells and no clots are formed, because both the complex and the red cells circulate separately.

There are some tests to check the extent of the affliction by a potential haemolytic anemia, including the Coombs test and others that many doctors are aware of. Whereas cold hands and feet are extremely common for years in quite intense floxings, haemolytic anemia is rare among floxed persons.

Figure 7. Example of vertical ridges in a thumb's nail. A sharp increase or the appearance of new ridges is common in floxed persons with vascular conditions, as Raynaud's-like syndrome.

Note: There are many conditions that cause vertical ridges in nails, some of them even benign. So, the appearing or increasing of vertical ridges is not an indication of being intoxicated by quinolones, neither a factor useful for rating the severity of the reactions. It has simply been noticed that many floxed persons report this kind of incidence or rapid increase of it.

45.NERVES OR VESSELS, WHICH ONE IS INJURED FIRST?

The quinolone pathologies of the peripheral nervous and microvascular systems are inseparably intertwined by their physiological codependence. In the simplest terms, blood vessels depend on nerve regulation for normal function, and neurons depend on capillaries for nutrients.

So we do not know if the microvessel malfunction is primarily a consequence of toxic nerve spasms, or if the nerve abnormalities caused by fluoroquinolones are caused by deficient support by the microvessels.

Perhaps the first pathological change in the microvasculature is a physiological shift favoring vasoconstriction, evidenced by blunted vasodilation and elevated vasoconstrictor activity. It has not been investigated so far the potential role of vasodilator agents (e.g., angiotensin-converting-enzyme inhibitors) that could theoretically lead to substantial improvements in neuronal blood flow, with corresponding improvements.

In any case, both nerves and microvessels are damaged, with a multiplying effect.

46.VASCULITIC RASHES

Many severe cases of intoxication by quinolones have a skin rash present. There is a predilection for the distal ends of the limbs: hands and feet. The following picture is an example of a vasculitic rash induced by ciprofloxacin in a young athlete.

These rashes tend to resolve spontaneously, but signal serious reactions to quinolones.

In all, about 15% with severe or intermediate adverse reactions to quinolones actually develop a vasculitic rash.

-Figure 8- Rashes of a floxed person, coincidental with the areas of maximum physical impairement due to deep injuries in tendons and nerves. The points marked as "B" are red points, like pustules but with no secretion.
The point marked as "C" is a purple type of hematoma-like area.

47.MORE ON CONNECTIVE TISSUE QUINOTOXICITY

The problem for us the floxed persons is that the cells of connective tissue are embedded in a great amount of extracellular matrix. And the connective tissue is an essential element of many parts of our body. So the connective tissue is going to have a hard time after a quinolone intoxication. The connective tissues of our bodies are:

Supporting connective tissue

Gives strength, support, and protection to the soft parts of the body.

- CARTILAGE. Example: all the cartilages in the joints. The extracellular matrix of cartilage is secreted by specialized cells derived from fibroblasts called chondroblasts. You can see many medical papers describing the damage of quinolones to chondroblasts, so it is a well proven effect of quinolones.
- BONE. The matrix of bone contains collagen fibers and mineral deposits. The extracellular matrix of bone is secreted by specialized cells derived from fibroblasts called osteoblasts.

Binding connective tissue

It binds body parts together. Binding connective tissue is derived from cells called fibroblasts, which secrete the extracellular matrix. You can consult many medical papers describing the damage of quinolones to fibroblasts, so it is a weel proven effect of quinolones.

- TENDONS connect muscle to bone. The matrix in the tendons is principally collagen, and the fibers are all oriented parallel to each other. Tendons are strong but not elastic. After a quinolone intoxication the matrix is degraded, the fibers dye and rupture and the regrown ones do not keep alineated with the rest, creating bundles and disoriented arrays of fibers.
- LIGAMENTS attach one bone to another. They contain both collagen and also the protein elastin. Elastin permits ligaments to be stretched.

Fibrous connective tissue

It is distributed throughout the body. It serves as a packing and binding material for most of our organs. Collagen, elastin, and other proteins are found in the matrix. Fibrous connective tissue is derived from cells called fibroblasts, which secrete the extracellular matrix. You can see many medical papers describing the damage of quinolones to fibroblasts, so it is a weel proven effect of quinolones.

- FASCIA is fibrous connective tissue that binds muscle together and binds the skin to the underlying structures. Many muscular problems and pains associated to quinolones are due to the degradation of the properties of the fascia that covers all muscles and permit the relative movement between them. Remember also that after a quinolone intoxication, the fascia of fibrous connective tissue that binds the skin to the underlying structures (muscles and bones)

is so owerwhelmed by the reaction that in severe cases you can feel lumps, clots, behind the skin when rolling-squeezing it as in figure 12.

- **ADIPOSE TISSUE** is fibrous connective tissue in which the cells, called adipocytes, have become almost filled with oil. It is also altered by the intoxication, disturbing its role in body metabolism.

That quinolones target the connective tissue is very bad news, because it is distributed all over the body, in essential organs, muscles, joints and skin.

MEHDI SHAKIBAEI, ET AL. FREIE UNIVERSITÄT BERLIN, 14195 BERLIN, GERMANY
Quinolones exhibit a pronounced affinity for connective tissues. Concentrations in cartilage, bone, and other tissues shortly after dosing exceed those measured simultaneously in plasma. Although no specific data are available, it appears reasonable to assume that in tendons also these drugs reach high concentrations. This peculiar pharmacokinetic behavior is one important aspect explaining why connective tissue structures are rather sensitive to the action of these drugs.

Furthermore, severe injuries to connective tissue caused by quinolones are almost incurable as the experience of thousands upon thousands of cases in France, USA and other countries show.

JEREMY NORMINGTON, DPT, DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
Fluoroquinolones appear to produce injuries in tendons. These injuries are replaced by fibrotic tissue, which is normal with most tendon injuries. Fluoroquinolones decrease collagen and cause irregular alignment. It's also hypothesized that nitrous oxide and the seventh position substitute may play a part in these tendinopathies. This stems from the fact that two of its most potent inhibitors completely stopped all injuries by the drug.
In addition, most toxic drugs had the same substitute. And researchers believe that **fluoroquinolones inhibit fibroblast metabolism and stimulate matrix-degrading activity** to resemble the effects of tendon immobilization.
Tendons are biological tissues that respond to mechanical stresses placed on them by constant catabolic and anabolic activity. If the healing phase can't keep up with the injury phase, overuse injuries occur. If cell proliferation is decreased in tendons as a result of fluoroquinolones, tendons can't keep up with the repair of normal daily microtraumas. Rupture, inflammation and pain may result. With the decrease of collagen and proteoglycan synthesis, and the destruction and malalignment of collagen, tendons are in prime position for injury.

CIPROFLOXACIN CAUSES CYTOSKELETAL CHANGES AND DETACHMENT OF HUMAN AND RAT CHONDROCYTES IN VITRO.
Egerbacher M, et al. IV Medizinische Abteilung mit Infektions- und Tropenkrankheiten, Kaiser Franz Josef Spital, Kundratstrasse, 1100 Wien, Austria.
Quinolones cause damage of articular cartilage in different species by forming chelate complexes with divalent cations and inducing magnesium deficiency. Cations are important for regular function of integrins, a group of transmembrane proteins which connect extracellular matrix proteins with the intracellular cytoskeleton. We have shown that cultivation of rat chondrocytes in ciprofloxacin supplemented and Mg(2+)-free medium led to pronounced changes in the cytoskeleton and decreased adhesion of cells to the culture dish. In order to test whether or not these effects are species-specific, we extended our studies on human chondrocytes. Human chondrocytes cultivated in ciprofloxacin -supplemented medium (10, 40, 80 and 160 microg/ml) or Mg(2+)-free medium showed decreased ability to adhere to growth support, cell shape changes, and alterations in actin and vimentin cytoskeleton in a concentration dependent manner. Attachment of human chondrocytes to collagen type II coated cover slips was reduced to 90% in ciprofloxacin group and 75% in Mg(2+)-free group on day 1. This effect even increased after 4 days of culture in the respective medium (32% in ciprofloxacin and 58% in Mg(2+)-free group). We concluded that Mg(2+) deficiency is exerted via integrins, resulting in decreased ability to attach to extracellular matrix proteins and cytoskeletal changes. These effects are not species-specific. The attachment assay proves to be an easy to use experimental set-up to test ciprofloxacin and other quinolones for their chondrotoxic effects.

INHIBITORY EFFECTS OF THE QUINOLONE ANTIBIOTICS TROVAFLOXACIN, CIPROFLOXACIN, AND LEVOFLOXACIN ON OSTEOBLASTIC CELLS IN VITRO.
Holtom PD, et al, University of Southern California School of Medicine, Los Angeles 90033, USA.
We studied the inhibitory effects of the fluoroquinolones levofloxacin, ciprofloxacin, and trovafloxacin on growth and extracellular matrix mineralization in MC3T3-E1 osteoblast-like cell cultures. Levofloxacin had the least inhibitory effect on cell growth, with a 50% inhibitory concentration of approximately 80 microg/ml at 48 and 72 hours. Ciprofloxacin had an intermediate degree of inhibition, with a 50% inhibitory concentration of 40 microg/ml at 48 and 72 hours. Trovafloxacin exerted a

profound inhibitory effect on cell growth, with a 50% inhibitory concentration of 0.5 microg/ml, lower than clinically achievable serum levels. The decreased cell counts with up to 2.5 microg/ml of trovafloxacin and with up to 40 microg/ml of ciprofloxacin were not associated with decreased rates of 5-bromo-2'-deoxyuridine incorporation per cell. Alatrovafloxacin, the L-alanyl-l-alanine prodrug of trovafloxacin, exerted effects on proliferation and 5-bromo-2'-deoxyuridine incorporation similar to those of the parent compound. The quinolones evaluated also inhibited extracellular matrix mineralization by MC3T3-E1 cells. Treatment of confluent cultures with trovafloxacin, ciprofloxacin, or levofloxacin resulted in strong inhibition of calcium deposition, as determined on day 14 by alizarin red staining and biochemical analysis. The effect was apparent with 2.5-5 microg/ml of each of the three antibiotics tested and progressively increased to more than a 90% decline in the calcium/protein ratio with 20-40 microg/ml antibiotic concentration. Further in vivo studies are advocated to evaluate the relevance of the in vitro cytotoxicity reported here to bone healing in orthopaedic patients.

There are literally hundreds of medical reports on the damage caused by fluoroquinolones to the connective tissue, specially tendons and cartilages. You may consider visiting www.fqresearch.org for a comprehensive review of this and other topics.

THE EFFECT OF CIPROFLOXACIN ON TENDON, PARATENON, AND CAPSULAR FIBROBLAST METABOLISM

Riley et al. Hospital for Special Surgery, Cornell University Medical Center, New York

The pathologic mechanisms underlying fluoroquinolone-induced tendinopathy are poorly understood. The observed incidence of tendinitis and tendon rupture in patients treated with ciprofloxacin hydrochloride suggests that the fluoroquinolone antibiotics alter tendon fibroblast metabolism. The purpose of this study was to examine the effect of ciprofloxacin on fibroblast metabolism in vitro. Canine Achilles tendon, paratenon, and shoulder capsule specimens were maintained in culture with ciprofloxacin (5, 10, or 50 µg/ml). Fibroblast proliferation, collagen synthesis, proteoglycan synthesis, and matrix-degrading activity were analyzed. Incubation of Achilles tendon, Achilles paratenon, and shoulder capsule fibroblasts with ciprofloxacin resulted in a statistically significant 66% to 68% decrease in cell proliferation compared with control cells at day 3 in culture. Ciprofloxacin caused a statistically significant 36% to 48% decrease in collagen synthesis compared with controls in all fibroblast cultures. Ciprofloxacin caused a statistically significant 14% to 60% decrease in proteoglycan synthesis in all fibroblast cell lines. Compared with unstimulated control fibroblasts, culture media from Achilles tendon, paratenon, and shoulder capsule cells that were exposed to ciprofloxacin demonstrated statistically significant increases in matrix-degrading proteolytic activity after 72 hours in culture. This study demonstrates that ciprofloxacin stimulates matrix-degrading protease activity from fibroblasts and that it exerts an inhibitory effect on fibroblast metabolism. The increase in protease activity and the inhibition of both cell proliferation and the synthesis of matrix ground substance may contribute to the clinically described tendinopathies associated with ciprofloxacin therapy.

PART VII: NEUROLOGICAL DAMAGE

48. THE SECOND HEAD OF THE HYDRA

There are two toxic mechanisms of the fluoroquinolones that explain most of the injuries that they cause:

- VASCULAR DAMAGE (injury to the small vessels and extracellular matrix)
- FAULTY NEUROTRANSMISSION (alteration to the transmission of nerve signals)

In this chapter we address the second one, an issue that has been relatively well studied by doctors.

49.NEUROLOGICAL IMPLICATIONS

The longest lasting damage from quinolones is perhaps the neurological alterations. Neurotoxicity is a common feature of all quinolones since such adverse reactions have been described with all quinolone derivatives to date. Some research suggests that quinolones bind to some neuroreceptors (see later) both in the nervous system and in the muscular fascia (contact between nerve and muscle).

TABLE 10. SIMPLISTIC CLASSIFICATION OF NEURO-FLOX-PATHIES			
Focal	not associated with floxing		
Multifocal	Axonal	Fiber motor	**In SEVERE floxings only**
		Sensory motor	**INTERMEDIATE and SEVERE floxings**
		Sensory only	**Possible in all floxings**
		Small fiber / autonomic	**Possible in all floxings**
	Demyelinating		uncommon in floxing
NOTE: Multifocal axonal neuropathies are prevalent in floxings.			

In other sections of this flox-report, you can find included this simplified table, that classifies the neuro-flox-pathies acording to the areas of the body affected and the type of fibers injured. You will become familiar with the terms used later on. Focal means that only one nerve is affected. Multifocal nerve damage, is used when isolated nerves in different areas are damaged, also called mono-neuropathy multiplex or multi-focal mono-neuropathy (hamstring, ulnar-elbow, ankle, peroneal, sural nerve, cranial nerves...).

As for the cause of the damage, not very conclusive research has been done. Continuing with the vascular hypothesis, maybe the injuries to nerves are secondary (a consequence) to the vasculitic mechanism that would damage the astrocytes in the first instance (see later in this same section).

Neuropathies are a prominent feature of the toxic vasculitides. The reasons for this frequency are not immediately clear. The rich blood supply and the capacity of nerves to function reasonably well with anaerobic (no oxygen) metabolism normally render the nerve relatively resistant to ischemia (disruption of blood supply). That might be a justification for delayed symptoms.

As said, there is no proof that quinolones cause a vasculitic-like neuropathy. Immediate cause of the vasculitic neuropathies is inflammation or deposition of immuno-complexes that eventually harden, thicken, and develop scar tissue, thus decreasing the diameter and impeding blood flow with occlusion of the vasa nervorum, resulting in ischemia of the peripheral nerves that end up damaged or dead. There are other mechanisms, different from vasculitides, that could be the cause. There are several anecdotical reports of patient's recovering from floxings when administered corticoids, that suppress the inmune

reaction. However, nothing is mention in those reports about the increased risk of tendon rupture of the concomittant use of quinolones and corticoids.

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> Furthermore, the pefloxacin-induced tendon injuries were completely inhibited by the coadministration of dexamethasone. At first glance, this finding stands in contrast to the clinical experience that patients undergoing corticosteroid therapy are prone to quinolone-induced tendon disorders, but it could be explained by the fact that patients are usually on continuous therapy, whereas the animals had been treated for a short period only.

There is a group of neuropathies of nerves that do not govern big muscles or limbs, that can be damaged resulting in a vast array of symptoms called peripheral neuropathy. Nearly all the floxed persons have peripheral neuropathy. Peripheral neuropathy describes damage to the peripheral nervous system, the vast communications network that transmits information from the brain and spinal cord (the central nervous system) to every other part of the body and vice versa. Because every peripheral nerve has a highly specialized function in a specific part of the body, a wide array of symptoms can occur when nerves are damaged. Some people may experience temporary numbness, tingling, and pricking sensations (paresthesia), sensitivity to touch, or muscle weakness. Other floxed persons, particularly in severe reactions, may suffer more extreme symptoms, including burning pain (especially at night, very exacerbated by heat), muscle wasting, paralysis, or organ/gland dysfunction. People may become unable to digest food easily, maintain safe levels of blood pressure, sweat normally, or experience normal sexual function.

Some forms of neuropathy involve damage to only one nerve and are called mono-neuropathies that in many cases are difficult to recognize properly and are then diagnosed as normal musculoskeletal injuries. Sometimes two or more isolated nerves in separate areas of the body are affected, called mono-neuritis multiplex. Often though, multiple nerves affecting all limbs are affected, called poly-neuropathy. Toxic drug-induced neuropathy usually involves nerves on both sides of the body, although not always symmetrically (many floxed persons become far more rigid and/or stiff and have more pain on one side), and pain is a common symptom. The neuropathies floxed persons experience are predominantly asymmetrical and they seem to migrate around certain areas of the body, with a marked predilection for lower limbs (large myelinated axons) and distal areas (hands, feet).

In short, quinolones damage both the central and peripheral nervous systems. It is very typical to feel pins and needles sensations, as well as throbbing pains, numbness, trembling, fasciculations (crawling under the skin), tremors, twitching, and neurological pains migrating all over the body. In most severe floxings the associated pain typically does not respond to simple analgesics, and can become chronic and may interfere with sleep (more intense in hot areas of the body) and also be present at rest. Neuropathic pain is difficult to control and can seriously affect emotional wellbeing and overall quality of life. As has been shown earlier: insomnia, nervousness, anxiety, overreactions to stress, anger and anguish are also very common.

The damage is very extensive and symptoms fit well in many neurological sub-diseases, like all kinds of peripheral neuropathies: mono-neuritis multiplex, sensory-motor neuropathies, demyelinating neuropathies, axonal neuropathies, autonomic nerve damage, and many more specific disorders. Central nervous system neuropathies affect many organs like the heart, eyes, brain and intestines.

Floxed persons land powerful blows against their cardiac systems, mucous membranes, skin and peripheral nerves, nearly all are sustained through very severe insults to the nerve functions. The main problem with this toxic neuropathy is that recovery for severe reactions is often only a partial recovery.

50. THE BASIC MISSIONS OF A NERVE CELL

One can find basic texts about neurology that will help to become familar at least with some terms and features of the human nervous system. That will make a lot of easier for you to understand some of the

contents of the most interesting research papers that have been published. Here we include some brief explanations about neuron physiology and functions.

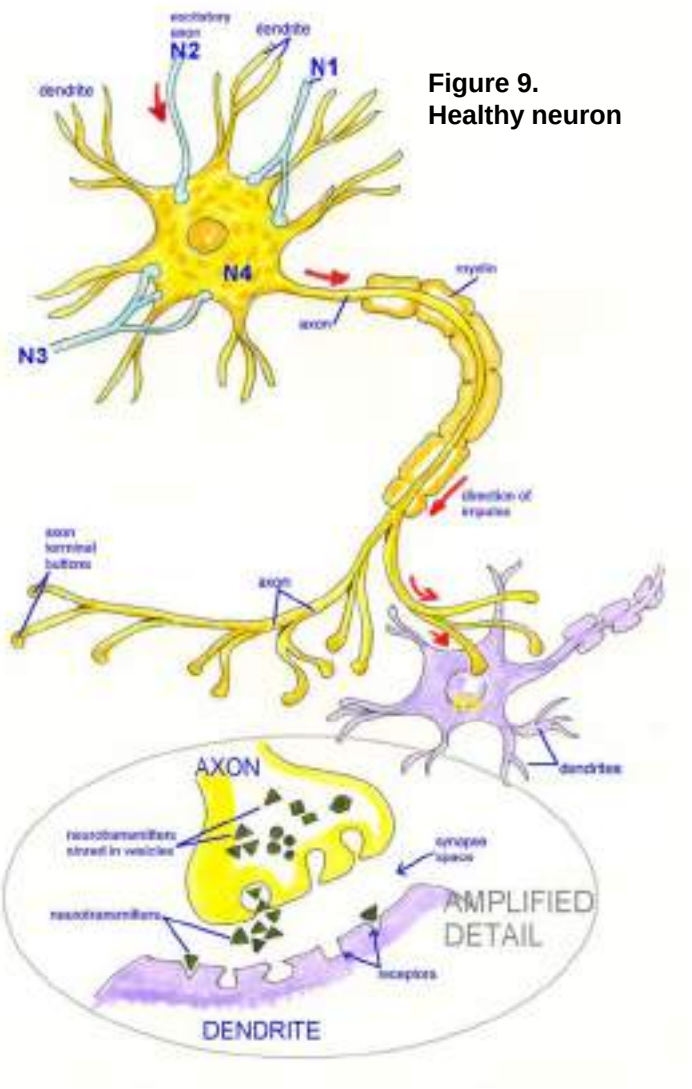

Figure 9. Healthy neuron

Figure 9. (drawing courtesy of a collaborator of the report). Let's suppose a healthy neuron named N4 and depicted in yellow. It receives multiple signals from other neurones' ends (neurons N1, N2 and N3 in blue) and it passes the signal on through its axon (red arrows).
The "head" of the neuron is called the nucleus. The branches of the nucleus are the dendrites. The "trunk" is the axon that is covered by myelin. The other side branches (roots) are the axon terminals.
The signal reaches de branched ends of the axon, where some terminals called "buttons" are placed. These buttons are close to the dendrites of other neurons (for example, neuron N5 in this sketch in purple). We want to know how the yellow nerve cell will transmit the signal received from the blue cells to the purple cell.
The axon has different kinds of neurotransmitters stored in "pouches" vesicles and it releases them according to the signal to be sent (see the amplified detail). The neurotransmitters are released in a free space called synapse. There they are modulated (destroyed, reabsorbed, or metabolized) or left to fit into very precise receptors of the dendrites of the neuron N5, that are specific for each type of transmitter. Once the neurotransmitters have docked in the receptor dendrite, the circuit has been completed and the operational signal has been succesfully transmitted.

This figure has illustrated a nerve-to-nerve connection but there are two basic types of junctions: NERVE-TO-NERVE and NERVE-TO-MUSCLE. For floxed persons is extremely important to know what happens at both kind of junctions, because both types are severely damaged by fluoroquinolones, some in a very long term, irreversible manner.

Explained in precise technical terms: Synaptic transmission refers to the propagation of nerve impulses from one nerve cell to another. This occurs at a specialized cellular structure known as the synapse, a junction at which the axon of the presynaptic neuron terminates at some location upon the postsynaptic neuron. The end of a presynaptic axon, where it is juxtaposed to the postsynaptic neuron, is enlarged and forms a structure known as the terminal button. An axon can make contact anywhere along the second neuron: on the dendrites (a dendritic synapse), the cell body (a somatic synapse) or the axons (an axonal synapse).

Nerve impulses are transmitted at synapses by the release of chemicals called neurotransmitters. As a nerve impulse, or action potential, reaches the end of a presynaptic axon, molecules of neurotransmitter are released into the synaptic space. The neurotransmitters are a diverse group of chemical compounds. The mechanisms by which they elicit responses in both presynaptic and postsynaptic neurons are diverse.

51.THE SPECIFICITY OF THE NERVE-MUSCLE JUNCTION

The above explained nerve-to-nerve junction is one of the two types of nerve signals. The other is the nerve-muscle (neuromuscular) junction. Logically, the nerves that transmit the signals to the muscles, are called motor neurons. The detailed interaction is a bit different from the one depicted in figure 9.

A different type of nerve transmission occurs when an axon terminates on a skeletal muscle fiber, at a specialized structure called the neuromuscular junction. An action potential occurring at this site is known as neuromuscular transmission. At a neuromuscular junction, the axon subdivides into numerous terminal buttons. The particular transmitter in use at the neuromuscular junction is acetylcholine.

In figure 10 (courtesy of a contributor of the flox report) you can see a sketch of a neuromuscular junction. The tip (terminal) of each axon comes into proximity with a muscle fibre, it forms a synapse (small gap) with that fibre. The arrival of a nerve impulse at the neuromuscular junction causes thousands of tiny vesicles (pouches) filled with a specialised neurotransmitter called acetylcholine to be released from the axon tip (terminal) into the synapse.

On the opposite side of the synapse (gap), this acetylcholine then binds to the surface of the muscle fibre at special sites where there are large numbers of acetylcholine receptors (also called nicotinic receptors).

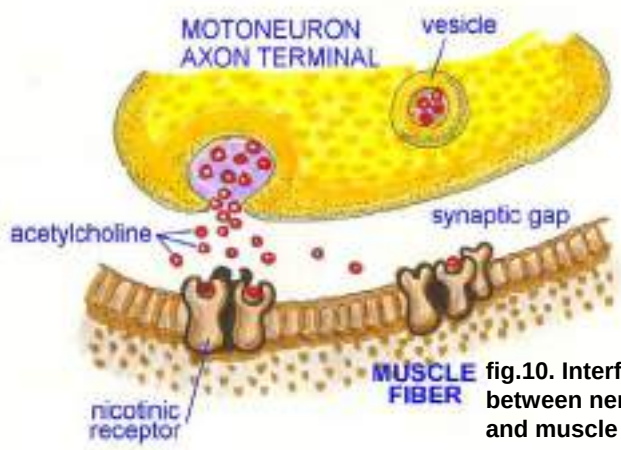

fig.10. Interface between nerve and muscle

Just like in a synapse between two neurons, when this neurotransmitter (acetylcholine) binds to a receptor, it triggers a new nerve impulse on the muscle fibre membrane. Because of the special way that muscle fibres are structured, this nerve impulse propagates rapidly throughout the fibre and makes it contract.

In short, acetylcholine is a small molecule that acts as a chemical messenger to propagate nerve impulses across the neuromuscular junction between a nerve and a muscle.

The reason that these receptors are called nicotinic is that nicotine can bind to them just as well as acetylcholine. Nicotinic receptors at neuromuscular junctions are not the only place in the nervous system where acetylcholine plays a role. It is also active at many other locations, where it can bind to another, very different type of receptor. As you will see later, we think that acetylcholine seems to play an important role in many of the symptoms that floxed persons exhibit, as we postulated some years ago.

In summary, basically the neuromuscular junction works when acetylcholine is released by the nerve terminal and docks and is recognized by the muscle fiber.

FLUOROQUINOLONE ANTIBIOTICS BLOCK NEUROMUSCULAR TRANSMISSION.
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Fluorinated 4-quinolones are widely used antibiotics. Several case reports describe the exacerbation of muscle weakness in myasthenia gravis patients treated with fluoroquinolones. We studied the effects of norfloxacin, ofloxacin, and pefloxacin on miniature endplate potentials (MEPPs) and currents. These antibiotics progressively decreased the amplitude of the MEPPs as drug concentrations were increased from 12.5 to 100 mg/L. Fluoroquinolones should be used only with great caution in disorders that compromise the safety margin of neuromuscular transmission.

Since acetylcholine is inactivated by cholinesterases, inhibition of cholinesterases leads to a rise in acetylcholine concentration. If this rise remains moderate, it can have beneficial effects for those persons with a problem related to nerve-to-muscle junctions but if the inhibition of cholinestareses is too high it causes toxic effects. In this latter case, the stimulation of acetylcholine receptors by

acetylcholine which accumulates induces glutamate release which makes sodium and calcium enter the cell inducing cellular damage. The use of antagonists of glutamate could thus be considered. However, no substantial neither conclusive data warrant an action in this sense.

52.THE NEUROTRANSMITTERS

We have already seen that once the molecules of a neurotransmitter are released from a cell as the result of the firing of an action potential, they bind to specific receptors on the surface of the postsynaptic cell. As well as being present on the surfaces of postsynaptic neurons, neurotransmitter receptors are found on presynaptic neurons. In general, presynaptic neuron receptors act to inhibit further release of neurotransmitter. In other words, there are also receptors in the same terminal that release the neurotransmitters, in order to detect when too much neurotransmitter has been released.

The vast majority of neurotransmitter receptors belong to a class of proteins known as the serpentine receptors. One additional characteristic of neurotransmitter receptors is that they can become unresponsive upon prolonged exposure to their neurotransmitter.

Unlike other neurotransmitters, nitric oxide is not stored in synaptic vesicles. Rather, nitric oxide is released soon after it is produced and diffuses out of the neuron. Nitric oxide then enters another cell where it activates enzymes for the production of "second messengers."

We believe that practically all neurotransmitters are negatively affected by fluoroquinolones, and their impact become clearly manifested on all floxed persons. Later we try to identify what neurotransmissions are more altered.
Look at the role of arginine as a mediator of nitric oxide neurotransmitter, and the vast influence of acetylcholine (found mainly in soy) in all the nervous subsystems.

TABLE 11. MAIN NEUROTRANSMITTERS

Group	Transmitter Molecule	Derived from	Site of Synthesis
Acetylcholine	Acetylcholine	Choline	CNS, PNS, ANS
Serotonin	Serotonin (5-HT)	Tryptophan	CNS, cells of the gut, enteric cells, PNS
Aminoacids	Glutamate		CNS
	GABA	Glutamate	CNS
	Aspartate		CNS
	Glycine		spinal cord
Histamine	Histamine	Histidine	hypothalamus
Catecholamines	Epinephrine (adrenalin)	Tyrosine	adrenal medulla, some CNS cells
	Norpinephrine	Tyrosine	CNS, sympathetic nerves
Neuropeptides	Endorphins		
Dopamine	Dopamine	Tyrosine	CNS
Nucleotides	Adenosine	ATP	CNS, PNS, ANS
	ATP		
Nitric oxide	Nitric oxide, NO	Arginine	CNS, gastrointestinal tract

CNS=Central Nervous System, PNS= Peripheral Nerv. Syst., ANS= Autonomic Nervous System

53.THE CHOLINERGIC NEURONS AND ACETYLCHOLINE NEUROTRANSMITTER

Acetylcholine is a simple molecule synthesized from choline and acetyl-CoA through the action of choline acetyltransferase. Neurons that synthesize and release acetylcholine are termed cholinergic neurons. Once released, acetylcholine must be removed rapidly so that the muscle receives the order of contracting and nothing else, so it stops; this step of removing, called hydrolysis, is carried out by the enzyme acetylcholinesterase.

Two main classes of acetylcholine receptors have been identified on the basis of their responsiveness to the toadstool alkaloid, muscarine, and to nicotine, respectively: the muscarinic receptors and the nicotinic receptors. Both receptor classes are abundant in the human brain. Nicotinic receptors are further divided into those found at neuromuscular junctions and those found at neuronal synapses. Later, some discussions with nicotinic and muscarinic receptors' implications will be argued.

Floxing causes a general drying up of glands and an excitation of the central nervous system. That seems compatible with a blocking or a destruction-injuring of the receptors of acetylcholine. All drugs that block or irreversibly destroy the receptors of acetylcholine cause decreased secretions (saliva, sweat, tears, ear wax, skin grease), dilate pupils, decrease intestine secretions, cause blurred vision, cause tachycardia and provoke disorders of the central nervous system. We theorize that quinolones could fit in this group. We do not know of medical research that backs up this theory so you may take it with reserve.

If we are right, an important implication is the potential adverse effect of acetylcholine on floxed persons. If a lot of acetylcholine precursors are ingested (e.g. soy), acetylcholine cannot dock on its receptors that are damaged ("occupied" by quinolones according to the medical theories) and would build up around the nerves and then it would cause insomnia, tense muscles of jaw, neck and shoulder, irritability, depression, headache and restlessness. Acethylcholine neurotransmitter is EXCITATORY. We will have to resort to this basic concepts several times later through the report.

Numerous compounds have been identified that act as either agonists (favor their action) or antagonists (oppose to their action) of cholinergic neurons (the neurons that release acetylcholine). The principal action of cholinergic agonists is the excitation or inhibition of autonomic effector cells that are innervated by postganglionic parasympathetic neurons and as such are refered to as parasympathomimetic agents. The cholinergic agonists include choline esters (such as acetylcholine itself) as well as protein- or alkaloid-based compounds. Several naturally occurring compounds have been shown to affect cholinergic neurons, either positively or negatively.

The responses of cholinergic neurons can also be enhanced by administration of cholinesterase inhibitors because cholinesterase destroys acetylcholine, so more acetylcholine becomes avalaible if there is a reduction of cholinesterase.

Acetylcholine is widely used at synapses in the peripheral nervous system and released at the terminals of:

- all motor neurons activating skeletal muscle voluntarily.
- all preganglionic neurons of the autonomic nervous system (involuntary functions)
- the postganglionic neurons of the parasympathetic branch of the autonomic nervous system.

Acetylcholine also mediates transmission at some synapses in the brain. These include synapses involved in the acquisition of short-term memory. Drugs that enhance acetylcholine levels -through acetylcholinesterase inhibition- are now used in elderly patients with failing memory if the receptors are in good shape.

Cholinesterase inhibitors, also called anticholinesterase agents, are schematically classified, according to their intensity and duration of action and consequently of their toxicity, into reversible and irreversible inhibitors.

In human beings, inhibition of cholinesterases induces, by accumulation of acetylcholine, muscarinic and nicotinic effects. These effects are predominately central or peripheral according to whether the inhibitor penetrates or not into the brain.

Inhibition of cholinesterases of insects is a way to obtain their destruction.

Reversible inhibitors

Cause transient elevation of acetylcholine plus some adverse effects because their multiplicity of effects is often a disadvantage in therapeutics where only an effect is generally sought.
The reversible inhibtors, which inhibit enzyme in a transitory way, as long as their concentration is sufficient, are used in therapeutics and, for the majority of them, are known for a long time. Some give primarily muscarinic effects and crosses the blood-brain barrier.

It increases the gastric and intestinal peristalsis and induces bronchoconstriction and contraction of ureters.

It increases bronchial and digestive secretions (gastric, intestinal, salivary), as well as lacrimal secretion.

Its cardiovascular action is complex but, in general, it has a muscarinic action: bradycardia and decrease of the force of cardiac contractions.

Eserine elicits miosis, spasm of accommodation, fall of intraocular pressure, hyperemia of conjunctiva and lacrymation.

Generally, it stimulates neuromuscular transmission, what results in muscle fasciculations. In addition to its indirect action by inhibition of cholinesterases, it could directly stimulate neuromuscular nicotinic receptors. It does not have an action on the uterus.

Irreversible inhibitors

Irreversible inhibitors of cholinesterases, while being fixed at enzymes by covalent bonds, inhibit them irreversibly. In fact they are mainly organophosphorus compounds which, because of their toxicity, are only exceptionally used in therapeutics.

Irreversible inhibitors of cholinesterases are largely used in agriculture as insecticides and some of them, because of their very great toxicity, were retained as chemical warfare agents, also called nerve gases.

54. CATECHOLAMINE NEUROTRANSMITTERS

The principal catecholamines are norepinephrine, epinephrine and dopamine. These compounds are formed from phenylalanine and tyrosine. Tyrosine is produced in the liver from phenylalanine through the action of phenylalanine hydroxylase. The tyrosine is then transported to catecholamine-secreting neurons where a series of reactions convert it to dopamine, to norepinephrine and finally to epinephrine.

Catecholamines exhibit peripheral nervous system excitatory and inhibitory effects as well as actions in the central nervous system such as respiratory stimulation and an increase in psychomotor activity. The excitatory effects are exerted upon smooth muscle cells of the vessels that supply blood to the skin and mucous membranes.

Cardiac function is also subject to excitatory effects, which lead to an increase in heart rate and in the force of contraction. Inhibitory effects, by contrast, are exerted upon smooth muscle cells in the wall of the gut, the bronchial tree of the lungs, and the vessels that supply blood to skeletal muscle.

In addition to their effects as neurotransmitters, norepinephrine and epinephrine can influence the rate of metabolism. This influence works both by modulating endocrine function such as insulin secretion and by increasing the rate of glycogenolysis and fatty acid mobilization.

The catecholamines are also known as adrenergic neurotransmitters; neurons that secrete them are adrenergic neurons. Norepinephrine-secreting neurons are noradrenergic.

55. SEROTONINE NEUROTRANSMITTERS

Serotonin (5HT) is formed from tryptophan. The greatest concentration of 5HT (90%) is found in the cells of the gastrointestinal tract. Most of the remainder of the body's 5HT is found in platelets and the central nervous system (CNS). The effects of 5HT are felt most prominently in the cardiovascular system, with additional effects in the respiratory system and the intestines. Vasoconstriction is a classic response to the administration of 5HT.

Neurons that secrete 5HT are termed serotonergic. Following the release of 5HT, a portion is taken back up by the presynaptic serotonergic neuron in a manner similar to that of the reuptake of norepinephrine.

Some serotonin receptors are presynaptic and others postsynaptic. Some serotonin subtype receptors mediate platelet aggregation and smooth muscle contraction. Other subtype receptors are present in the gastrointestinal tract and are related to vomiting. Also present in the gastrointestinal tract are some subtype receptors where they function in secretion and peristalsis (gut movements that make food to progress through the intestine). Other subtype receptors are distributed throughout the limbic system of the brain.

56. GABA NEUROTRANSMITTERS

Several amino acids have distinct excitatory or inhibitory effects upon the nervous system. The amino acid derivative GABA is a well-known inhibitor of presynaptic transmission in the central nervous system, **and also in the retina**. Doctors believe that quinolones bind to GABA receptors. So when GABA is released in the gap (synapse) it finds all the docking bays occupied by quinolones, and cannot calm down the excitation of the nervous system, resulting in very excited systems, for instance, radical insomnia. That is a true experience of all floxed persons. GABA also inhibits signals in the retina, so when the quinolones occupy (or damage according to us) the GABA sittings, the retina continues to send aberrant signals (probably this has something to do with the numerous vision abnormalities of floxed persons).

The formation of GABA is made from glutamate catalyzed (assisted, favoured, facilitated) by glutamate decarboxylase. Glutamate decarboxylase is present in many nerve endings of the brain as well as in the cells of the pancreas. Perhaps this has something to do with the long term abnormal panchreatic counts that most severe floxed persons have for several years post-exposure to quinolones.

GABA neurotransmitters are INHIBITORY (calming). We will have to resort many times to this basic concepts later through the report. In consequence, the quinolones impede the calming action of the GABA neurotransmissions, resulting in overwired brains.

We have not found any information explaining why the toxicity of quinolones induces panic attacks (it is a central nervous system injury) , but by comparison with other drugs that have that effect already acknowledged, the cause could be the alteration of different acetylcholine and GABA subtypes.

57. TURNING NEUROTRANSMITTERS OFF

Once its job is done, the neurotransmitter must be removed from the synaptic gap to prepare the synapse for the arrival of the next action potential. Four methods are used:

1. Reuptake.

   The whole neurotransmitter molecule is taken back into the axon terminal that released it. This is a common way the action of norepinephrine, dopamine and serotonin is stopped. In other words, the neurotransmitter is taken back into the synaptic knob ("button") of the presynaptic neuron by active transport. All the neurotransmitters except acetylcholine use this method.

2. Enzymatic degradation (deactivation).

A specific enzyme changes the structure of the neurotransmitter so it is not recognized by the receptor. Acetylcholine is removed from the synapse by enzymatic breakdown into inactive fragments. The enzyme used is acetylcholinesterase that breaks acetylcholine into choline and acetate.

3. Diffusion:

The neurotransmitter drifts away, out of the synaptic cleft where it can no longer act on a receptor.

4. Glial cells:

Astrocytes remove neurotransmitters from the synaptic space. Astrocytes are cells that perform a variety of functions in the CNS. Astrocytes provide physical support to neurons and clean up debris within the brain. They also provide neurons with some of the chemicals needed for proper functioning and help control the chemical composition of fluid surrounding neurons. Finally, astrocytes play a role in providing nourishment to neurons.

In order to provide physical support for neurons astrocytes form a matrix that keep neurons in place. In addition, this matrix serves to isolate synapses. This limits the dispersion of transmitter substances released by terminal buttons; thus aiding in the smooth transmission of neural messages.

Astrocytes also perform a process known as phagocytosis. Phagocytosis occurs when an astrocyte contacts a piece of neural debris with its processes (arm of the astrocyte) and then pushes itself against the debris eventually engulfing and digesting it.

Astrocytes provide nourishment to neurons by

a) receiving glucose from capillaries

b) breaking the glucose down into lactate (the chemical produced during the first step of glucose metabolism)

c) releasing the lactate into the extra cellular fluid surrounding the neurons. The neurons receive the lactate from the extra cellular fluid and transport it to their mitochondria to use it for energy. In this process astrocytes store a small amount of glycogen, which stays on reserve for times when the metabolic rate of neurons in the area is especially high.

We have not found so far references of toxicity of quinolones to the processes that make possible to neutralize the effects of neurotransmitters, or direct toxic influences in the work done by astrocytes.

58. ALTERATION OF NEUROTRANSMISSION BY DRUGS

When looking for the toxicity of quinolones to the neurotransmitting mechanisms, one finds little information but many examples of natural substances and other drugs that cause modifications in the way neurotransmitters work. In the following table you can see some examples.

TABLE 12. ALTERATIONS OF NEUROTRANSMISSION BY MEDICATIONS

drug	neurotransmitters targeted	effects on a healthy person
Sedatives like phenobarbital Beverage **alcohol** (ethanol) **benzodiazepines** (anti-anxiety drugs) like valium, librium, halcion	Bind to the $gaba_a$ receptor. They bind at sites different from the spot where gaba itself binds, but increase the strength of gaba's binding to its site.	Thus they enhance the inhibitory effect of gaba in the central nervous system
Tricyclic antidepressants like amitriptyline	Interfere with the reuptake of noradrenaline and serotonin from their synapses	And thus enhance their action at the synapse
Antidepressant **fluoxetine** ("Prozac")	Seems to block only the reuptake of serotonin.	So all the serotonin produced is filling up the synaptic gap until it acts on the receptor
Chlorpromazine and haloperidol	Dopamine receptor is bound by such drugs	Binding of these drugs leads to increased synthesis of dopamine at the synapse and eases some of the symptoms of schizophrenia
Heroin	Re released at synapses on neurons involved	Enkephalin synapses provide this intrinsic pain

Morphine Codeine Methadone	in transmitting pain signals By binding to enkephalin receptors, they enhance the pain-killing effects of the enkephalins.	suppressing system If use of the drug ceases, the now relatively insensitive synapses respond less well to the soothing effects of the enkephalins, and the painful symptoms of withdrawal are produced.
addition done by us		
fluoroquinolones	GABA receptors. Acetylcholine receptors (muscarinic); Adenosine receptors	Blocking or destruction of at least these three type of neuroreceptors, what causes a cascade of injuries, described along this flox report.

59.THE DAMAGE CAUSED BY QUINOLONES TO NERVE FUNCTIONS

The medical literature talks recurrently about neuropathies caused by quinolones, some of them irreversible (2004 additions to the package inserts), as you have learned from other references within this flox report. The most detailed studies about quinolones mention the binding of the fluoroquinolones to the GABA receptors. According to the official theory, the quinolones would have to be removed, chelated or flushed before feeling some recovery. That does not fit with the real life experience of most floxed persons.

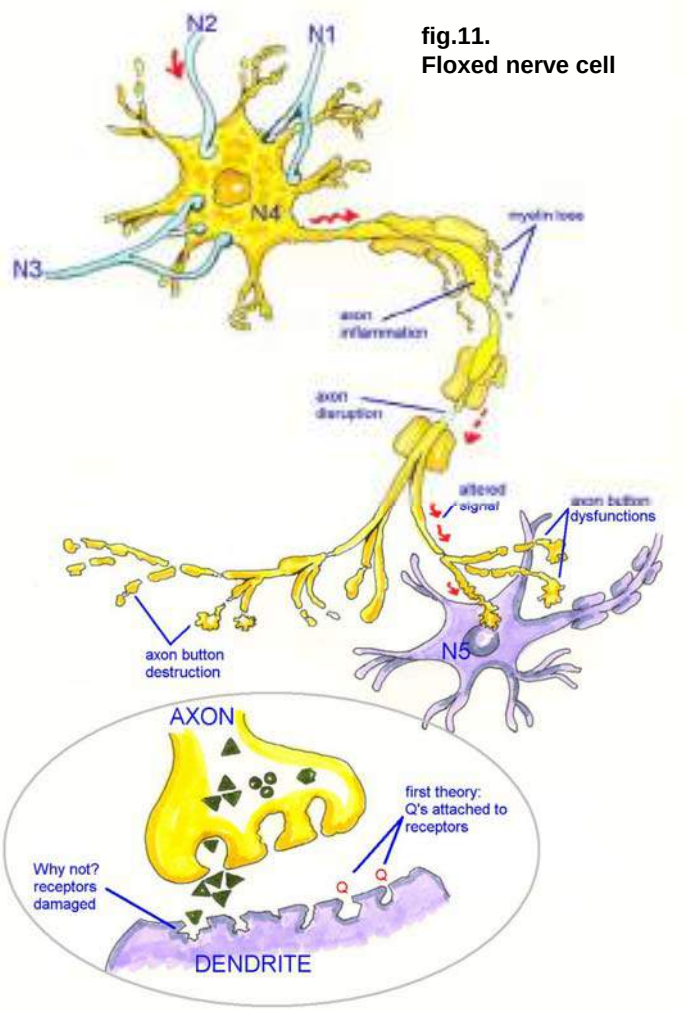


fig.11. Floxed nerve cell

Contrary to the acepted medical theory, we prefer to believe that not only GABA and adenosine receptors are affected by quinolones, but instead that nerve terminals of many kinds are simply injured and destroyed. That fits better with our symptoms. We do not have any proof of it but neither we have found any literature that rules out that possibility. Our hypothesis would be supported by the abnormalities found in nearly all kind of nerves and by the findings of biopsies of floxed persons, that show loss of density of nerve endings.

This drawing is just a very simplistic illustration of the problem. Figure 11 (drawing courtesy of a collaborator of the report). First, after a severe intoxication by quinolones there are nerves that DYE, neurons just cease to exist. The rest of the neurons are more or less damaged by the quinolones, and one, several or all their functions might be altered resulting in motor or sensitive neuropathies, some of them very long lasting and also permanent for severe cases. The injuries affect the receptive capacity of the dendrites and the ability of the axon to transmit signals.

Many biopsies of floxed persons show axon inflammation. In some cases (the least) some demyelination has been reported. If the axon has been disrupted, the signal is not transmitted. In many other biopsies of floxed persons, the density of nerves has dimished, that is to say, many nerves of small caliber have disappeared. The destruction of the top end nerves and nerve's terminals, has devastating effects on the patient, because all functions of the body are impaired.

Find here an example:

SAFETY OF THE FLUOROQUINOLONE ANTIBIOTICS, from *Infections in Urology* ®
Many of the side effects of fluoroquinolones as a class are associated with modifications of the quinolone pharmacore at positions 1, 7, and 8. The following discussion focuses on these specific class effects with respect to structural modifications at these positions.
Although much about the pathophysiology of fluoroquinolone-related CNS effects remains ill-defined, one hypothesis suggests that drug interactions with the g-aminobutyric acid receptor ($GABA_a$), an inhibitory neurotransmitter, may explain CNS-stimulating effects. ...Ciprofloxacin, enoxacin, and norfloxacin demonstrate high-affinity binding to $GABA_a$ and interfere with GABA binding to its receptor.
Studies have suggested that CNS penetration by these drugs does not appear to correlate with reported incidences of CNS effects. A possible reconciliation of these discrepancies is that fluoroquinolones can also induce excitatory effects through direct activation of *N*-methyl-D-aspartate (NMDA) and adenosine-receptor mechanisms. Thus, it may be that it is only under specific conditions of sufficient CNS penetration, coupled with threshold antagonism of inhibitory pathways (GABA) and stimulation of excitatory pathways (NMDA, adenosine), that observable CNS symptoms are manifested.
[CNS means central nervous system]

No matter how many proposals we may make, it is clear that for lack of medical research, we do not know whether the quinolones damage the synaptic processes, cause real axon degradation, kill neurons, all together, or act in different ways to cause our disorders. We have here described the basic mechanics of the nerve-to-nerve (brain) functioning, and the nerve-to-muscle junction (body), so that you can understand your doctors, and can attempt to make your own interpretations of what might be happening to you.

TABLE 13.
IMPACT OF FLUOROQUINOLONES ON NEUROTRANSMITTERS

Group	Transmitter Molecule	Impact by quinolones	Site of Synthesis
Acetylcholine	Acetylcholine	Suggested here	CNS, PNS, ANS
Serotonin	Serotonin (5-HT)	not proven	CNS, cells of the gut, enteric cells, PNS
Aminoacids	Glutamate	not proven	CNS
	GABA	Official research	CNS
	Aspartate	not proven	CNS
	Glycine	not proven	spinal cord
Histamine	Histamine	not proven	hypothalamus
Catecholamines	Arenalin	not proven	adrenal medulla, some CNS cells
	Norpinephrine	not proven	CNS, sympathetic nerves
Neuropeptides	Endorphins	not proven	
Dopamine	Dopamine	not proven	CNS
Nucleotides	Adenosine	Official research	CNS, PNS, ANS
	ATP	not proven	
Nitric oxide	Nitric oxide, NO	not proven	CNS, gastrointestinal tract

CNS=Central Nervous System, PNS= Peripheral Nerv. Syst., ANS= Autonomic Nervous System

In the following table we have tried to summarize the outcome of the toxicity of fluoroquinolones over your nervous system:

TABLE 14. REPERCUSSION OF THE NERVE TOXICITY OF QUINOLONES

receptor	subtype	negative effects on your body when these receptors are blocked or damaged (action done by fluoroquinolones)	Substances that increase those negative effects	Substances that should have positive effect but normally do not
Acetylcholine (not proposed yet by the medical research)	muscarinic	Decreased secretions of the intestine (impaired digestion). Decreased secretions. Dry eye, mouth, skin. Blocked sweat glands. Blurred vision. Tachycardia, arrythmias, increased heart rate.	Atropine. Amytryptyline. Many pharmacological substances and venoms.	Acetylcholine released in the gaps can not be rapidly cleared and causes insomnia, tense muscles (jaw, neck, shoulder), depression, irritability, restlessness, headache.
	nicotinic		Nicotine	
GABA (official theory)		Anxiety. Convulsions. Tense muscles. Increased pain threshold. Excitation	Many pharmacological substances and toxics.	Many pharmacological substances. Benzodiazepines
Adenosine (official theory)	A1	Increased heart rate, increased responsiveness to adrenaline. Increased electrical excitability of central nervous system. Does not inhibit the excitatory action of aminoacids, as it should. Increased diuresis (urination). Hypertension. Impaired wound healing. Impaired hair growth.	caffeine teophylline Many pharmacological substances	Many pharmacological substances
	A2a	Narrowing of blood vessels and decrease tone at the coronary arteries, ischeming the heart muscle and causing arrythmias and abnormalities. Pro-inflammatory effect of the central nervous system. Deprivation of blood flow to the brain. Impaired wound healing.		
	A2b	Impaired intestine relaxation. Pro-inflammatory.		
	A3	Suppressed inhibition of growth of melanoma cells.		

In a few occassions we will use the term neuro-flox-pathy to name the very specific sort of injuries that quinolones inflict to the human nervous systems.

PART VIII: NEUROLOGICAL SYMPTOMS

As a result of the neurological damage explained earlier, many neurological symptoms and signs are classical in a floxing. Symptoms is more or less what you feel whereas signs is what your doctor can see either by personal exploration or through medical tests.

The fluoroquinolones are toxic antibiotics that act directly on the nerves. When the intensity of the toxicity is sufficiently high, the floxed person starts to feel many symptoms. But do not forget that the damage reaches to the whole nervous system and each cell takes its share. The neurological symptoms of a severe floxed person, that can amount to more than 50, is only the tip of the iceberg.

You know that the nerves control all organs of the body. For instance, your intestines will malfunction but all the multiple chemical sensitivities that you will develop, the reactions to foods, the dry intestine, the feeling unwell are not as easily attributed to a neurological failure as tremors or numbness of your fingers. So in the following sections we only treat very obvious simptoms of quinolone toxicity, the most common ones, knowing in advance that they are normally only a small part of the health damage, and not the most critical one.

60.PERIPHERAL NEUROPATHY CAUSED BY QUINOLONES

Peripheral neuropathy caused by quinolones affects a variety of peripheral nerve cells and fibers, including sensory (temperature, touch, vibration…), motor (muscles, by altering the neuromuscular junction as we have explained before), and autonomic fibers (those that you do not control, like orthostatic pressure, erection). Most quinolone induced peripheral neuropathies affect all fiber types to some extent. However, a single fiber type may be predominantly or exclusively affected in some cases producing very particular neuropathies. In some floxed persons, peripheral neuropathies involve single peripheral nerves (single=mono neuropathies), or numerous individual peripheral nerves, the so-called mono-neuritis multiplex syndrome. In addition, peripheral nerve disorders may involve the brachial plexus, lumbosacral plexus, or a single root, that is to say, the low spine, resulting in signs and symptoms in one limb, with pains that can be excruciating (in the hamstrings, ankle, lower leg, knee, hip, etc). Most cases of floxing conform to a poly-neuropathy syndrome, which usually implies both sensory and motor fiber involvement in a relatively symmetric fashion and typically with a distal-to-proximal gradient of involvement (more intense the more distant from the trunk). These conditions are termed sensory-motor poly-neuropathies, and they represent the most common form of peripheral neuropathy. They also cause a diminished quality of life.

Although we do not know for sure, it is plausible that quinolones might induce pathologic reactions in the nerves: wallerian degeneration, axonal degeneration, and segmental demyelination. In wallerian degeneration, the axon degenerates distal to a focal injury that interrupts the continuity of the axon. This reaction often occurs in focal mono-neuropathies that result from nerve infarction as a result of an ischemic vasculitic process. The toxicity plus the ischemia interfere with nerve metabolism. They affect the longest neurons first, since long neurons have greater metabolic demands than short ones. Symptoms therefore may begin in the feet, then progress up the legs and then affect the hands. It is a typical pattern of severe reactions. In intermediate reactions the neuropathy does not usually progress up.

Axonal (rod) degeneration starts at the most distal (distant from the trunk) extent of the axon. Axonal degenerative poly-neuropathies are usually symmetric (although frequently with different pain intensities in both sides), and are the most common in floxings. Floxed persons also predominantly show signs of

segmental demyelination that refers to focal degeneration of the myelin sheath with sparing of the axon. This reaction can be seen in focal mono-neuropathies but also in generalized sensory-motor or predominantly motor neuropathies. Toxic segmental demyelinating poly-neuropathies might be the result of the immunological reaction.

In those peripheral nerve disorders that are characterized by either wallerian degeneration or axonal degeneration, prognosis (likely outcome) is less favourable due to the fact that the axon must regenerate and re-enervate muscle, the sensory organ, blood vessels, and other structures before clinical recovery is noted. That may be why the new warning (October 2004) in the package insert of quinolones mentions "irreversible condition" with respect to neuropathy. Recovery may be more rapid with segmental demyelination because remyelination is accomplished more quickly, in turn re-establishing normal conductivity of the axon and return of function.

Whereas it is difficult for us to get a proper disagnosis about our nerve injuries, it is easy for the floxed person to feel and describe the multiple symptoms of his/her peripheral neuropathy.

> Sensory symptoms: Sensory symptoms include sensory loss, a sense of numbness, tingling, prickling, and pins-and-needles sensations, pain, thermal sensation, vibratory sense and intolerance to light touch. Damage to large sensory fibers lessens the ability to feel vibrations and touch, resulting in a general sense of numbness, especially in the hands and feet. People may feel as if they are wearing gloves and stockings, or having the foot in a cast. In most generalized poly-neuropathies, these symptoms begin in the most distal (far from the trunk) extent of the longest sensory fibers, like the toes and feet and then crawl their way up to the knee point in which the disorder also starts at the fingertips spreading the process to the upper extremities. In addition to sensory loss, patients frequently complain of paresthesias and dysesthesias, often characterized by a sense of numbness. Pain is a serious symptom for many floxed persons. It may be described as a dull aching sensation, an intense burning sensation or, occasionally, as intermittent lancinating pulses of pain (called 'throbbing' in this report). Intractable and high level pain is very common during acute reactions and also in long term, chronic severe reactions to quinolones.
>
> Motor-muscle: Muscle weakness is the most common symptom of motor nerve damage. All severe reactions present with a loss of muscle mass that cannot be regained regardless of how much exercise or workouts are done. Oddly, many people take a long time to realize that they are lossing strength or wasting muscle because visually it is not so apparent. Other symptoms may include painful cramps and fasciculations (uncontrolled muscle twitching visible under the skin, or at least felt), muscle loss, bone degeneration, and changes in the skin, hair, and nails (these more general degenerative changes also can result from sensory or autonomic nerve fiber loss). Impairment of motor function typically begins with weakness in the toes, and as the poly-neuropathy progresses, ascends up the distal lower extremities to the level of the knees, at which time motor involvement in the hands may be observed.
>
> In the toxic segmental demyelinating poly-neuropathies, proximal muscle (quads) weakness resulting from root (polyradiculoneuropathy) involvement may be observed. Axonal degenerative poly-neuropathies tend to produce weakness along with muscle atrophy, but atrophy is much less conspicuous in segmental demyelinating poly-neuropathies because in these disorders the axon remains in continuity with the muscle, preventing denervation atrophy. Therefore, your doctor can measure the perimeter of your thighs and tell you that he/she finds both the same size, even though you feel your more painful one nearly useless, soft, idle and deprived of strength. A common symptom (but not universal) in severe floxing poly-neuropathy is weakness in dorsiflexion of the big toe. That disability is somehow a measure of the initial severity of the mono-neuropathy of the distal peroneal, tibial and flexor groups of the lower leg, and progresses up for severe reactions to weakness of quads or even gluteus in the worst cases.
>
> Motor toxicities have a much deeper influence on the health of floxed persons than is normally acknowledged. Motor nerve injuries caused by quinolones provoke a lack of function of the related

muscles, and they become atrophied. The atrophy causes the limb to work improperly and other muscles and nerves are overstressed, causing further pains, sometimes very intense and for many years. The bad news is that some of these motor nerves have a limited capacity of healing, and normally they also have deadlines for healing (around 2 years) after which time they cannot recover and the injuries and pain cannot be reversed, apparently.

Autonomic nerves: Some floxed persons report symptoms that indicate that autonomic fibers are also affected. Symptoms of autonomic nerve damage are diverse and depend upon which organs or glands are affected. Autonomic nerve dysfunction can become life threatening when the heart begins beating irregularly (extremely common in floxed persons) or there is difficulty with breathing. Other common symptoms of autonomic nerve damage include an inability to sweat normally (floxed persons notice reduced or absent sweating in the legs and hands, and at the same time excessive sweating confined to the head and neck region), a partial loss of bladder control and an inability to control muscles that expand or contract blood vessels to maintain safe blood pressure levels. A loss of control over blood pressure can cause dizziness, light-headedness, or even fainting when a person moves suddenly from a seated to a standing position (orthostatic hypotension).

In severe floxings other autonomic symptoms include dryness of the eyes and mouth (another marker of the severity of the floxing) and gastrointestinal dysfunction (nerves controlling intestinal muscle contractions frequently malfunction), often manifested by alternating constipation and diarrhea or by early satiety. Many people also have problems eating or swallowing if certain autonomic nerves are affected. In intermediate and severe floxings in men, partial erectile dysfunction or incontinence is one of the first autonomic symptoms.

More details on autonomic nerve dysfunction (neuropathy) are treated later on this paper.

Diagnosis. Such a vast array of presentations of peripheral neuropathy in floxed persons makes precise diagnosis a challenging task and is the reason that physicians reach different conclusions depending on the predominance of the axon/myelin, phocal/diffuse, symmetric/asymmetric, sensory/motor/autonomic involvement, and adding the difficulty posed by the fact that floxed persons develop all of them to different degrees.

Doctors may order a set of tests to evaluate your disorder: nerve conduction studies, needle electrode examination, brain and spine MRI, lumbar puncture for cerebrospinal fluid analysis. Blood and urine tests can include glucose tolerance test, vitamin B12, serum protein, anti-GM1 antibodies and anti-myelin antibodies, plus investigations of markers of various connective disorders associated with vasculitis. The ultimate analysis is a nerve biopsy, that when performed with the most advanced techniques by well-trained physicians can assist in the complete characterization of the injuries. It is an invasive procedure and few floxed persons have undertaken it because it is mainly ordered only in severe reactions and when a diagnosis of vasculitis or immune reaction of another type is being considered. Less common are precision sensory testings, and studies of sudomotor function, and autonomic responses to provocative physical maneuvers.

In many cases the electrical conductivity tests render normal results, as well as MRIs of the brain and spine, and spinal taps. But it is also very typical that well conducted studies discover alterations in the sensory and motor status of the nerves in many parts of the body. Muscles also show decreased responses in electromyographic (EMG) studies.

Other very common findings are decreased or altered signals in the nerves that control the hands, especially the ulnar nerve. You will know that your ulnar nerves are affected if your small and ring fingers become numb, normally if you exert pressure around your elbow or when bending your elbows sleeping at night. Some doctors will tend to diagnose you as having ulnar or carpal tunnel syndrome, but you are really suffering toxic ulnar neuritis.

Other nerves very commonly implicated are the nerves of the legs. Pains occur predominantly in the hamstrings, lateral or medial knees, outer gluteus, calves, quads, groin, and several areas of the ankle, plus the toes. Many times pains mimic strains, tendinitis, muscular fiber disruptions, and sprains, but they are toxic neuritis.

Remember:
In severe reactions neurological pains can last for years and impair your quality of life.

In general, we have multiple peripheral nerve injuries. They can occur sequentially and in a random fashion (now the upper left leg, then the right ankle, etc...). As stated before, the earliest findings are loss of vibratory sensation in the toes, atrophy of intrinsic foot muscles, and reduced or absent ankle jerks. In severe reactions there are signs of lower motor neuron injuries: weakness, more generalized atrophy and fasciculations. Sometimes fasciculations are referred to as "twitching" and they are a serious symptom of denervation that normally shows up as motor (axonal) nerve damage that is mainly irreversible and can only be recovered through new nerve fiber regeneration.

Double or triple mono-neuritis dominates in intermediate reactions. For instance, the right leg (hamstring and ankle-Achilles) plus heart arrhythmias and perhaps an elbow epicondylitis. Multiple neuritis is more typical of severe reactions. For instance, this includes the right leg, plus heart disorders, plus elbow, shoulder, hips, wrists, and above all- optic neuritis.

Optic neuritis reflects a injury of the optic nerve and is a secondary effect of the damage caused by the quinolones to the small blood vessel complexes of the eye (in fact is an ischemic optic neuropathy). The optic nerve dysfunction usually manifests with blank spots, difficulties in focusing, and in severe cases transient complete losses of vision with a solid white vision in one or both eyes. These blindness episodes have been reported with ciprofloxacin and last for some minutes, are very terrifying, appear suddenly, so they are also dangerous depending on the activity in which the floxed person is engaged. These events of blindness can happen periodically up to 18 months after the treatment with ciprofloxacin and at any time in the following years if the floxed person experiences a high re-exposure to quinolones through poultry ingestion, for instance.

If the intoxication of the quinolones has been intermediate, these neurological symptoms tend to dissapear in two years time on average. If the intoxication has been severe, the neurological disorders linger on for many years without abating, although in the 4th or 5th year mark the floxed person can experience an improvement. Some injuries of the eye become almost always permanent if they have not resolved after 2 or 3 years (see other parts of the report).

61. THE NEURO-FLOX-PATHY AND DOCTORS IGNORANCE ONCE MORE

Had you given a chance that the most reputed clinics and doctors in the field of neuropathy would be aware of the toxicity of quinolones?

> THE NEUROLOGY AND NEUROSURGERY FORUM. Escalating Burning Sensory PN
> QUESTION: I have been diagnosed with Sensory peripheral neuropahty (PN) following the use of a fluoroquinolone.
> My question is this. It is noted in the insert that: 1). That physicians use Medrol to counteract an adverse and or allergic reaction. 2). But, it also states that the use of steriods can predispose someone to Tendon Rupture/Tendonitis. If that's the case, what role could Medrol play in escalating Sensory PN? or escalating nerve damage/inflammation. It seems in many cases people with Burning Sensations after fluoroquinolones are given Medrol to counteract the reaction and their conditions escalate to more acute burning!. 3).I don't know what the clinical picture is for Steroid Myopathy but I didn't think it was Sensory PN? I am trying to determine if the antibiotic alone did this or the combination of both! 4). Could you explain what the term Arthralagia Means? I not only have the burning but it feels like my skin is stretched and there is alot of stiffness/joint pain. 5). Can a paresthesia cause acute burning pain that does not go away for months?
> ANSWER: Regarding the neuropathy - I realise that isolated reports have been popping up

(especially on this forum) about a toxic neuropathy from fluoroquinolones, **but I don't believe this is an established cause of neuropathy**. Plus **medication neuropathies are quite uncommon** and difficult to establish cause and effect. So the first thing I would make sure is that all the treatable/common causes of neuropathy have been evaluated for - diabetes, thyroid disease, paraproteinemic neuropathy (with an SPEP and immunofixation), inflammatory (with ESR / ANA). Sometimes a spinal tap and nerve biosy is necessary to fully evaluate neuropathies.

Well, although this text is a few years old, the fact that it belongs to a very reputed hospital specialised in neurological disorders and the firm and stuborn illiteracy of neurologists makes it appalling.

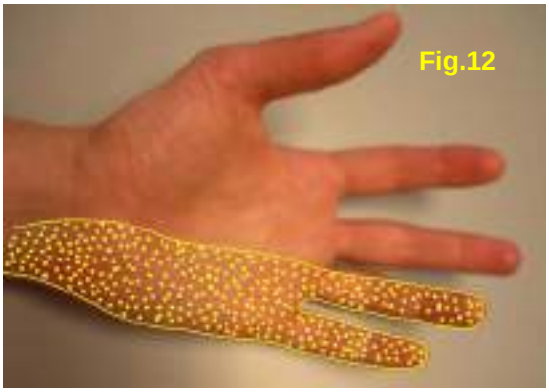
Many medical reports state that chemical and drug induced neuropathies account for about 30% of all neuropathies. The rest have mechanical-surgical-traumatic, inmunological and other causative factors. Another of our homemade experiments has been to survey on a daily basis for more than a year the final diganosis of the neuropathies of patients at two very popular forums moderated by medical hospitals. Between 1,5% (sure diagnosis) and 2,5% (probably diagnosis) of all neuropathies consulted there had been caused by quinolones. If we give some credibility to this rude experiments and extrapolate them, that would mean that roughly between 5 % and 8% of all neuropathies caused by medicines, would have their origin in ingestions of fluoroquinolones. All of them non-reported as side effects, of course. Not valid research again but undeniable little piece of scientific evidence.

Look to this thread on one of the many internet forums, where people look for answers to their long lingering health problems. It mentions two sites, one of them ours:

From	Post
patient A 1/13/2006	Help I am seriously worried about my worsening medical condition. I have had headaches every last day for the past 5 months and I'm developing sharp pains in my right wrist right where the palm meets the arm, also Ive had severe knee cramps while sleeping, wake up and can't move my legs because the pain is so bad, but after 5-10 agonizing minutes I work the pain out by moving my legs at the knees. I also notice a far milder but similar sensation at my ankles as in my wrist. Again, the knee pain works out with movement, but the wrist pain is made worse but certain movements. Also i have notice an occasional "buzzing" or tingling down my lower back, and in addition I have had random acid relfux attacks even on an empty stomach.... plus nausea and shortness of breath at rest. I have a MRI of my brain...it's negative completely.... but I'm still very worried i also had about 10 different blood tests which included ANA and Lyme titer. I am a 26 year old man who is 40 pounds overweight (gained weight like crazy after symptoms started) but otherwise healthy. would a spinal puncture be the next logical step or what
Doctor of the forum. 1/19/2006	Its not clear whether your symptoms are neurological or not - typical neurological symptoms result in weakness, clumsiness or loss of sensation on one side of the body, loss of ability to see or speak etc Tingling down the back that is precipitated by neck movement, associated with stiffness in the leg muscles could potentially be from a spinal cord problem - the neurological examiantion should reveal more, and somatosensory evoked potentials of the posterior tibial nerve might be used to investigate this. Otherwise, there may be a more rheumatological flavour to your symptoms. Have you seen your doctor? the best place to start is a thorough physical examination, then your doctor can decide which alleyway to follow in terms of further investigation. The headaches could be from a whole variety of causes - I cannot tell from what with just the above information but headaches can be from a more systemic medical condition (for instance rheumatoid arthritis or ankylosing spondylitis - possible rheum conditions in your age group) - in which case they need to be investigated promptly. I suggest seeing your doctor as soon as you can to follow this up. Good luck
patient B 1/15/2006	Hello! Have you taken any antibiotics within the past few months?
patient C 1/15/2006	as a matter of face, back in July I took a combonation **course of Tequin**, ketek, and amoxicillan for a suspected "sinus infection" which of course turned out to be a wrong diagnosis. Some of the antibiotics made me feel a little loopy. Why do you ask?
patient B 1/15/2006	Check out this page **http://antibiotics.org/** I have had the same problem. 3 MRI's, just had a spinal tap, they've suspected MS but the CSF showed negative. I've been through test after test. There is a adverse effect of neuropathy from the family of antibiotics that had taken. This has been happening to me since July 2004. Feel free to write for more info *********@yahoo.com
patient D 1/18/2006	I have had alomst the exact situation as you, starting in July with daily headaches and a change in my distance vision. I had a negative brian MRI and many sets of bloodwork done (Lyme, HIV, ANA, Thyroid etc.). My ENT gave

	me **Levaquin** because she thougt it may be a sinus infection (it wasn't). Since then I have had muscle aches, stiffness and random twitching. I'm scheduled to see the neurologist again in Feb. If you have any insight I would be interested to hear it.
patient E 1/21/2006	Does a negative MRI completely rule out MS?
patient F 1/26/2006	I have also been **on levaquin** for a sinus and ear infection. About 4 days after taking this medication, I started experiencing additional symptoms besides the ones I posted on a different message. I have been very weak and twitching mostly at night.
patient B 1/29/2006	Hello! July 2004 I started having electrical sensations in the middle of the night. For a year and a half anytime during the day I get a electrical shock type pain. I have edema, I've been through every test they can think of, 3 different neuro Dr's and still no diagnosis. I can't pull a wrapper off a straw, I have problems writing. **All started from the Ciprofloxacin**; This is a KNOWN adverse effect from Bayer. It is irreversible, and still to this day with all the people effected by these drugs, the Dr's still don't believe it. Check out this info. **http://www.fluoroquinolones.org/**

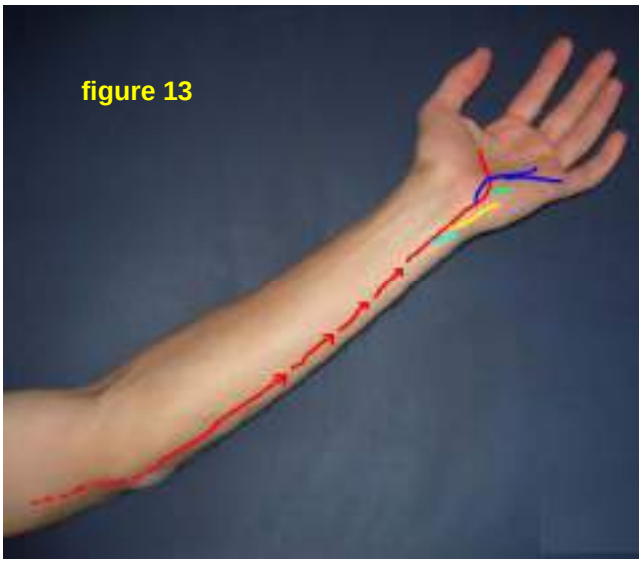
62. ULNAR NEURITIS. A PERIPHERAL NEUROPATHY



We have chosen an example of mononeuropathy that all severely intoxicated floxed persons have, and also some other floxed persons as well.

All severe reactions produce a very intense toxic ulnar neuropathy, that is a degradation of the ulnar nerve that provides some motor and sensitive functions to the hand, specially to the ring and pinky fingers. The main symptom is numbness in the area shown in picture 12. During the intense episodes, the numbness is felt at all times, but during the chronic phase the agent that elicites it is the bending of the elbows at night.
You can loss entirely all sensitiviness on your affected fingers and only vigorous massage and straightening of the arm will bring them to normalcy.

Ulnar neuritis tend to heal slowly, and is present in many severe floxed persons after five and more years, with the same intensity than at the onset. Some people sleep with their elbows in casts but this injury seems to be almost intractable.



Here you can see (figure 13) the ulnar nerve (red) and its main branches when it approaches the hand. Digital sensory (blue) responsible of the sensitivity at the ring and pinky fingers. Motor branch, that supplies the force signals to those same fingers (green). Cutaneous sensory of the palm, that innervates the skin of the palm (yellow). Dorsal cutaneous sensory that innervates the dorsum (opposite to the palm) surface of skin of those fingers (light blue).

This neuropathy is easy to diagnose by means of electricity conduction tests. And what do our doctors think about this ailment? Well, all of them believe that we have acquired it due to other causes, suggesting mechanic like origins like compressions at the elbow. The solution that they offer matches the futility of the missed diagnostic: surgical release of the ulnar nerve at the elbow. We are still waiting to find a doctor that gives a chance to the possibility that this intense neuropathy has been caused by the antibiotic (nearly half of the people of the cohort of table 1 plus some other 50 have reported us having

this symptom very intense).

The only way to speed the healing is to strengthen all the muscles of the arm, upper and lower arm, and hand included. Nevertheless, even with daily care, we have recorded many cases of unremitting ulnar flox-neuropathy after 5 years out and longer, what prompt us to believe that is another possible permanent injury because the intensity of the neuropathy seems to be the same after 5 and more years than at the onset.

63. AUTONOMIC NEUROPATHY

Classical presentations of autonomic neuropathy associated with quinolones are orthostatic hypotension, impotence or ejaculatory dysfunction, decreased sweating, and urinary incontinence. For example, when floxing mimics Sjögren syndrome, dry mouth and eyes along with anhidrosis (abnormal lack or diminished sweating) prevail as initial presentation. In general, common symptoms are:

- Facial - Facial pallor, anhidrosis
- Ocular - Blurring then graying of vision, blacking out, tunnel vision, sensitivity to light, difficulty with focusing, reduced lacrimation, loss of pupillary size over time (which is often correlated with loss of visual symptoms).
- Cardiovascular - Orthostatic onset of palpitations, nausea, tremulousness, presyncope with light-headedness, visual blurring, tinnitus, and even chest pain and shortness of breath
- Orthostatic hypotension. Supine hypertension and a loss of diurnal variation in blood pressure may occur later.
- Episodes of palpitations, angina, dyspnea, and syncope may relate to cardiac arrhythmias as well.
- Gastrointestinal - Constipation, episodic diarrhea, early satiety, increased gastric motility, dysphagia, bowel atony, bowel incontinence, hyposalivation, and altered sense of taste.
- Renal - Nocturia, bladder urgency, bladder frequency, enuresis, incomplete bladder voiding, urinary retention, and urinary incontinence
- Sexual - Impotence (mainly parasympathetic) and loss of ejaculation (mainly sympathetic), retrograde ejaculation, and possibly, female sexual dysfunction.The impotence rarely is complete, so some kind of soft erection can normally be achieved.
- Sweating - Anhidrosis or hypohidrosis, compensatory hyperhidrosis, gustatory sweating
- Temperature regulation - Hypothermia (from loss of shivering and inability to vasoconstrict to prevent heat loss) and hyperpyrexia (may be of concern to patients with anhidrosis who are exposed to high temperatures)
- Feet - Burning feet most commonly observed in small-fiber sensory neuropathy (itching of feet may precede burning),
- Pruritus, dysesthesia, allodynia, hyperalgesia, nocturnal exacerbation of symptoms, dry skin, loss of distal leg hair, brittle nails, and cold feet.

In floxings, the common occurrence of arthralgias and pseudo-arthritis, rash, renal disease in very high doses, can suggest to many well trained doctors a connective tissue disorder, such as rheumatoid arthritis, systemic lupus erythematosus, or Sjögren syndrome and therefore one could obtain such diagnosis after the quinolone intoxication.

64.WHAT ABOUT THOSE ANNOYING CRAMPS AND TWITCHING

It is well known and accepted that severe cases of quinolone toxicity are distinctive for the high level of toxic myopathy (muscle abnormality) developed by all floxed persons. But the quinolones have been conceptually sold to the prescribing doctors like the perfect antibiotic when in fact they cause devastating, long lasting (for years, and many times permanent) myopathies and motor neuron disorders. On the other hand, many other drugs have been clearly associated with muscular toxicity (AZT with mitochondrial myopathy; corticosteroids with myosin deficiency myopathy; statins and cyclosporine with rhabdomyolysis; etc...).

A very worrying symptom that many people experience as part of their strong reactions is muscle twitching. Twitching can be of very different types, but could be simply classified as:

- Fibrillations, imperceptible fasciculations, only detectable by electric devices. They are characteristic of inflammatory myopathies and denervation. They are spontaneous action potentials in a single muscle fiber, not visible on physical examination. Physically they last 1 to 5 miliseconds in duration and their firing rates is between 1 to 30 per second, being 13 on average, and are usually quite regular. Increase in conditions of muscle warming. The cause is a decreased resting membrane potential in the denervated muscle.
- Fasciculations: long wave movements, crawling under the skin, very visible palpitations of the muscles. They are a spontaneous discharge of an axon causing contraction of muscle fibers in rippling unit and produce visible rippling of muscle. May originate anywhere along the course of the axon. In floxed persons they are a consequence of the motor neuron injuries caused by the toxicity of the quinolones. Once again, they are exacerbated by caffeine (that floxed persons cannot metabolize) and some drugs like theophylline or lithium.
- Fasciculations: short wave movements, a sort of buzzing of the flesh, perceived by the victim, but not easily visible. They are identical to the long wave fasciculations, but with a lower amplitude.

Twitching is a muscle reaction to abnormal nerve firings. There is a type of benign fasciculations but in floxed persons it is a symptom of neurological damage. In many floxed persons it starts in the eyelids and hands, but it is very common to have them in arms and legs. It is accompanied by a certain degree of weakness with no true prominent atrophy, especially in arms and legs. Areas plagued with fasciculations have normal sensory feelings. Fasciculations move from one part of the body to another and some days have a long wave amplitude and other days a short wave one. Normally the fasciculations are asymmetric at any given time. Some electromiograms of floxed persons have shown discreet signs of demyelination-- without conduction blocks. The fasciculations become chronic for months or years. Not more than two of the 42 floxed persons studied in cohort of table 1 have had in common any serum antibody consistently elevated or abnormal. In fact, 97% overall of the serum analysis and antibodies in those subjects have not shown any abnormality, and those out of range readings have revealed a return to normalcy in further tests.

Many times, twitching is also accompanied by muscular cramps, especially in the gastrocnemius and other areas. Cramps are sometimes induced by exercise or touching the muscle and they can spread along the transverse direction across the muscle. Tendon reflexes are normal. Twitching does not usually develop in mild reactions. It is a typical symptom of intermediate and severe reactions. It starts any time from during the treatment up to several months later.

Fasciculations and/or cramps are early symptoms of myastenia gravis, or amiotrophic lateral sclerosis, for instance. That is why these symptoms are so distressing especially when they last for years on end and are always ever present in daily life. Many severely floxed persons that take magnesium feel their fasculations increase, as well as their muscular pains (interestingly enough, magnesium is a well known counterindication in myastenia gravis and other muscular autoimmune disorders). Again, in all these cases, serum CK may be mildly elevated. Six biopsies performed on five floxed persons have all shown loss of small caliber end-axons and less density of nerve endings. None of these floxed persons tested

positive for antibodies to skeletal muscle, nor did the biopsies show any inflammation or lymphocytic proliferation. Other biopsies of floxed persons revealed axonal inflammation (swelling).

Some reports received from floxed persons tend to suggest that fasciculations that show up late in the reaction (one to three years) might herald the onset of a recovery in myofascial and neuropatic pains. Not enough conclusiveness though about this point.

PART IX: EXTENSIVE DAMAGE

65.TOXICITY GUARANTEED

Apparently there are not many studies of clinical significance that provide a wide explanation regarding the high toxicity level of quinolones. One can find medical reports suggesting that everyone having a bad reaction to fluoroquinolones had a previously underlying muscular disorder. We do not favor that theory. Also, there is no validity to the claim that all people having a reaction to quinolones have a common flaw or genetic component that make them more prone to suffer adverse events. The medical community will start to understand something about fluoroquinolones when they acknowledge that these antibiotics are just plain toxic.

Many of us have apparently not had an adverse reaction to the first three, four, ten or even twenty courses of quinolones over several years, but later on symptoms indicative of an adverse reaction culminate to the point where the patient is completely intoxicated from the quinolone. Many, many young, healthy and athletic patients just change in a short period of time from being the idyllic human model for every drug manufacturer, to becoming pharmaceutically intoxicated for many years or life, and then are labelled as psychotic, a hypochondriac, or diagnosed with serious neuropathies and pains that *"were just lying dormant"* .

That is simply not true. The fluoroquinolones are toxic from the first milligram. Some people have livers that can metabolize more quantities of drug or body tissues that are more resistant than others, but everybody becomes intoxicated. Each person has different potential thresholds of resistance to the damage caused by quinolones:

LOWER THRESHOLD

Has been exposed above. It is delineated by strange bouts of tendinitis, abnormally long recoveries after exercise, less sleep and poorer quality sleep, some small throbbing pains in different parts of the body, occasional twitching, feeling some stiffness, decreased tolerance to coffee, loss of memory, especially short-term.

UPPER THRESHOLD

The symptoms that you have experienced are those corresponding to the severe reactions, intermediate reactions and mild reactions. It is too late to expect a rapid resolution, and according to the level of the intoxication, long, hard and miserable times may lay ahead.

The toxicity of quinolones acts in two preferential ways:

- direct chemical destruction (cartilage, cellular functions and organs).
- mild, long-lasting or irreversible matrix-vasculitis, with neuropathic after effects.

Obviously, you will not find many doctors willing to admit these two phenomena do actually occur. But the sooner more research is conducted in that direction, the further we will advance in terms of understanding the problem.

The following section of the report deals with some of the most important problems caused by quinolones.

66. IMPAIRED HEALING IN THE FLOXED BODIES

This is another very distinct characteristic of quinolone disorders, of which every doctor is unaware. Once you become asymptomatic because you have been taking care of yourself and restraining from exertional activities, you might well think that your ankle is nearly recovered from an intermediate reaction (say in grade G2 according to table 22 at the end of the report). But if not enough time has elapsed since the ingestion of the drug (less than 2 years) then only a number of repetitions of an exercise with your foot against strong resistance can bring you again to Grade 9 (see same table 22). So, returning to normal pre-floxing levels of activity is not indicated by a lack of symptoms but by a continuously probing (trial and error) method, not without relapses and danger.

While we all floxed persons know perfectly well that our bodies have lost most of their capacity to heal from bruises, cuts, blows, traumas, if you dare to comment it with your doctor, you will see how a lunatic is stared at. Nevertheless, some studies have evaluated this situation, but it is still universally ignored by doctors.

> CIPROFLOXACIN INHIBITION OF EXPERIMENTAL FRACTURE-HEALING.The Journal of Bone and Joint Surgery 82:161-73 © 2000. P. M. Huddleston, M.D., et al, Rochester, Minnesota. Investigation performed at Mayo Clinic and Mayo Foundation, Rochester
> Background: Fluoroquinolones, such as ciprofloxacin, have an adverse effect on growing cartilage and endochondral ossification in children. This study was carried out to determine whether ciprofloxacin also has an adverse effect on the healing of experimental fractures. Conclusions: These data suggest that experimental fractures exposed to therapeutic concentrations of ciprofloxacin in serum demonstrate diminished healing during the early stages of fracture repair. The administration of ciprofloxacin during early fracture repair may compromise the clinical course of fracture-healing.

The floxed body has been depleted of nearly all of its natural healing capacity. To function properly, the body must continuously produce new tissue, especially cellular matrix, collagen and fibrous cells. For everybody, the toxicity of the quinolones kills these mechanisms, in a dose dependent manner.

So whenever you accidentally bump a part of your body, especially the hand or foot (more distant areas and less irrigated tissues) it takes an abnormal amount of time to recover. Small blows that in a normal situation would take three days to heal, can take up to three months of healing during the acute phases. A cut in the skin around the Achilles will take the same time to close as in any other area of the body, but ten to twenty times longer for the scar to clear off.

When the athlete approaches grades 6, 7, 8 and 9 (table 22), there is a lot of deposition of waste in the joints and under the skin. That causes the waste to adhere to the joints and worsen the symptoms. Massage helps to remove those deposits in most cases.

During the months that follow the acute phase, both mechanisms (healing and rebuilding) are slowly returning to normal, especially the quality of the rebuilding, although the healing response still cannot keep up with the requirements of our previous (pre-floxing) level of activity. There are many scientific reports that show ciprofloxacin impairs the healing of broken bones and connective tissue. Being floxed is not the best time to undertake minor surgery that could be avoided or rescheduled for later.

So, during the acute phase it is not possible to cope with strenuous or very repetitive activities. It is normally advised to maintain some degree of physical activity, but always testing and probing the limits, without surpassing them.

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> Based on this research, Movin et al. performed a histological evaluation on a healthy 49-year-old male who was given ciprofloxacin as a prophylaxis after a routine appendectomy. After 2 weeks, the patient developed localized pain at the right Achilles tendon and experienced ambulation difficulties. The symptoms were minimal at rest and with normal living. Several months later, the patient still couldn't take long walks or run. A clinical exam didn't reveal a rupture, but the histological exam wasn't normal. A microscopic evaluation showed irregular collagen arrangement, hypercellularity, and increased interfibrillar glycosaminoglycans. These findings suggest deficient healing, and are similar to pathological features of tendon overuse injuries.

Quinolones make it more difficult for people to recover after exercise, and can cause them to develop a frank intolerance or dislike to exercise. Pains and stiffness after exercise are very characteristic of this toxicity. That is most likely due to a chemical damage of the fascia (connective tissue) that exists between muscles and allows them to run smoothly and independently. These injuries can last for many years after the floxing.

67.AVOID ANY PHYSICAL TRAUMA

It has been previously elucidated how a normal strain on a floxed person can have more serious consequences than on a normal person. In severe reactions, small blows or edemas can cause a flare up of minor neurological problems all over the body in less than two hours; for example, twitching, lack of jaw coordination, tremors, as well as local alterations much more intense than usual.

Severe impacts or traumas directed against a limb (a quad or a calf for instance) can be devastating for a floxed person. The inflammatory process in the area will affect the main nerves and trigger a neuritis that can take several years to resolve. So, an injury that in normal conditions would take up to 1 to 3 months to heal can be a long-term threat, or become a chronically impairing condition for a floxed person. This provides another clue for investigators because it is clear that there is a link between the processes of inflammation and the exacerbation of the floxing conditions. After the traumatic event, there is a release of mediators in the bloodstream that induce alterations of the vessels all over the body and also promote the arrival of immuno-complexes to the site of the injury. Some of these compounds and mechanisms could be of the same type as the ones that cause the damage induced by the chemical toxicity of quinolones.

For the examples cited, in the case of a blow or strike to a quad, the neuritis can affect the whole upper leg, from buttock to knee, providing strong, stabbing neurological pains to the sufferer. A traumatic event in the calf can initiate a neurological response in the outer (lateral) knee, and in the Achilles tendon.

If the trauma affects directly a medium size nerve, we can be before one of the most dreadful situations that a floxed person can face, and with more irreversible consequences. Probably the hit on the already intoxicated nerve, will make it dye or loose most of its capacity to heal, and a permanent dysfunction typically develops. Some cases have been recorded within our data that show dramatic neuropathic injuries after normal contusions, that by a chance impacted very close to a nerve.

68. ACUMMULATION OF BYPRODUCTS OF THE FLOXING

The skin is a very important organ of the body, well irrigated by all kind of vessels, intricated with the lymphatic system and nervous system and with plenty of connective tissue. There is also a predilect zone for deposing fat stores. The skin has three layers: epidermis (outer), dermis (intermediate), hypodermis (inner layer)

After a severe floxing, all layers suffer an insult and many dermatological symptoms may appear, that we will not treat in this part of the report.the epidermis (inner layer of skin).

The dermis is connective tissue (collagen, fibroblasts, macrophages and inflammatory mediators). It also has blood and lymph vessels, and finnally sensitive nerves and other nerves of the autonomic system. So all the conditions are set for a disaster if a quinolone intoxication occurs. The innermost layer (hypodermis) is also connective tissue with a lot of fat. But the most dreaded influence of fluoroquinolones on the skin is cancer. After taking a fluoroquinolone, great amounts of carcinogens (substances that promote cancer) are produced when the skin is exposed to sunlight (natural ultraviolet radiation).

figure 14

Figure 14. For whatever the real reason, that we can guess from the precedent sections of this report, after the floxing, the skin becomes less souple, it has also a different bightness in some areas, and a lot of engrossment and adherences are felt beneath it. An expert physiotherapist can point all these defects. A good exercise is to roll over sections of the skin, setting in motion the deposits, that are somehow released and that partially come back to where they were but some of them enter the blood and lymphatic circulation and resetle somewhere or are metabolized and hopefully excreted. Some floxed persons believe that this practice is detrimental for them because stored quinolones are released again. The fact is that this deposits tend to dissapear on their own in three or four years time, or one year earlier if assited with this technique. Many chiropractors and physicians can also feel these depositions as a sign that something is going wrong.

PART X: MUSCULAR PAINS

69.PAIN LEVELS

If one thing defines a severe floxing that is pain. Too many times it is a matter of all sorts of pains at all times and unremitting. The three main group of flox pains are:

- Neurological, due to the nerve toxicity, experienced statically and with every movement
- Muscular, associated with all the muscles of the body
- Joint pains, mainly tendinosis, bursitis, enthesitis, synovial problems

Pain plus insomnia makes life absolutely miserable. Pains of great intensity that interfer continously with the daily life and the patient's mood can be present for five and more years.

Unfortunately, there is no pain reliever that works for all floxed persons, and all the experiences to treat the neurological pain, muscular pain and joint pain of floxed persons have contradictory outcomes.

Pain levels experienced throughout the floxing can range from very low to the maximum on a 10-point scale. Pains of the maximum severity: stabbing, jabbing, tearing, and ripping, can be felt when a joint or limb collapses neurologically or just because of no apparent reason. These pains are described as higher than passing a kidney stone or rupturing a testicle, for instance, and can completely block the affected joint. By blocking a joint we mean that the patient intentionally avoids the least movement that affects it, because of the inmense pain. For instance, when moving or bearing weight on a foot is so maddening painful, that the floxed person avoids at all costs any movement, any maneouver and any weight bearing on that foot for a week or two, until de pain becomes more endurable.

Intermediate pains are common with mono-neuritis in legs, arms and neck, especially at night and with some minor movements. Low intensity pains (that correspond to myalgias) typically spread all over and correspond to the *"normal"* state of a floxed person: just feeling like a person that is 40 years older than his current age. See later for more information on neurological pains, how they can affect daily life and how little can be done to palliate them.

70.CONSTANT PAIN ALL OVER. MYALGIAS

Besides the neurological pains, in severe reactions, constant, intense and body-wide pains are very common. Basically they are drug-induced myopathies, again probably secondary to the vasculitic reaction. The major symptoms in drug-induced myopathies are proximal muscle weakness (quads, hamstrings, shoulder, biceps, triceps), slightly increased muscle enzyme levels (for instance CPK, although sometimes can be normal), electromyographic changes and histological injuries. Quinolones induce painful myopathies associated with neuropathies that could be called painful neuro-myopathies. According to the established medical research, typical of these neuro-myopaties is a free period between the beginning of the treatment and the appearance of symptoms, and incomplete resolution after withdrawal of the treatment.

In fact, myopathy is defined as any abonormal condition or disease of the muscle tissues, commonly involving skeletal tissue. Many drugs have been implicated as causes of myopathy, although quinolones are frequently left out by medical manuals, normally because each manual copies from other previous fact sheets and there is little new research behind new editions. The widespread myopathies caused by the quinolones are another *"postmarketing anecdotical finding"* according to laboratories, and are not still

regarded as a common source of muscular pain.

Quinolone myopathy, like other drug-induced myopathies, usually develops insidiously. The onset of clinical manifestations can occur days to months after exposure to the causative agent, according to Zuckner and Mastaglia (see references). Commonly, patients present with non-specific complaints of progressive, generalized muscle weakness, muscle pain (myalgia) or fatigue. Severe reactions to quinolone antibiotics (prolonged courses or high doses) present with severe myalgias and debilitating weakness, especially in proximal muscles (quads, hamstrings, upper arms) that leave many floxed people completely crippled, bedridden or in a wheelchair for months.

Drugs may cause muscle injury by direct, indirect, or immunologically mediate mechanisms. Again, we do not know the exact mechanism of injury behind the quinolones but it might be off all types, including a drug-induced immunological action directed at the muscle, already mentioned as immune complex-mediated myositis. It is a type of inflammatory myositis and that might be the reason why floxings resemble other inflammatory illnesses so much.

Nevertheless, we do not have the means to discover the mechanism of the injuries, and the medical class is not devoting enough research to find an answer. As a consequence only a guess can be attempted. Quinolone myopathies could also have a direct myotoxicity, as the toxicity exhibited by the statins (used to treat high cholesterol, associated with vacuolar myopathy), or other common drugs that cause mitochondrial myopathy, which symptoms also resemble very much a floxing reaction.

The muscular pain caused by quinolones is defined by some doctors that have treated difficult cases of quinolone toxicity as a manifestation of a sort of *"low grade"* myoglobinuria-rhabdomyolisis. These illnesses, when fully developed, are very dangerous, and have a fatal potential. There are many reports of fulminated deaths caused by quinolones due to both of these mechanisms. But in general, for floxed persons, they tend to show a more manageable profile, although very damaging.

Severe reactions typically show a slight elevation of the serum myoglobin levels that can also stay at the upper normal range for some 4 years or more. For the same length of time the CPK enzyme (creatinephosphokinase) may be elevated–normally on the hundreds, or low thousands figures.

The cause of both alterations probably is muscular necrosis caused by the quinolone induced vasculitis. Symptoms are very well known for long term floxed persons: generalized pain, decreased range of motion, stiffness, soreness; and all of the symptoms increase with activity.

71. WHAT IS HAPPENING IN OUR MUSCLES?

The pathology exhibited by the floxed persons is necrosis of muscle fibers with a releasing of muscle components into circulation. The doctors consulted theorize that muscles are injured due to both:

- a rise in free intracellular calcium due to damage to muscle sarcolemma and a failure of energy supply within muscle cell.
- an activation of calcium-dependent neutral proteases & phospholipases that destroys myofibrillar, cytoskeletal, and membrane proteins and the ensuing lysosomal digestion of muscle fiber contents.

Typically, the severely affected floxed person exhibits clinical features of muscle involvement (weakness, stronger proximal, rather than distal; discomfort in terms of pain and tenderness; swelling). There are also many case reports of renal injuries like acute interstitial nephritis, renal impairment, proteinuria (i.e foamy urine), and extremely severe rhabdomyolysis that can be fatal, acompanied by a dark urine (that is tea colored). A good deal of floxed persons also have a fever for some months when the crisis is more acute.

As explained before, many sedentary floxed persons believe that they are healed two years earlier on average than when they are actually cured, because the symptoms of small neuromuscular damage do

not become evident unless the patient performs some type of physically demanding activity.

The main determining factors for neuromuscular pains in affected floxed persons seem to be: increased age, exercise, fasting, hypokalemia (low potassium levels).

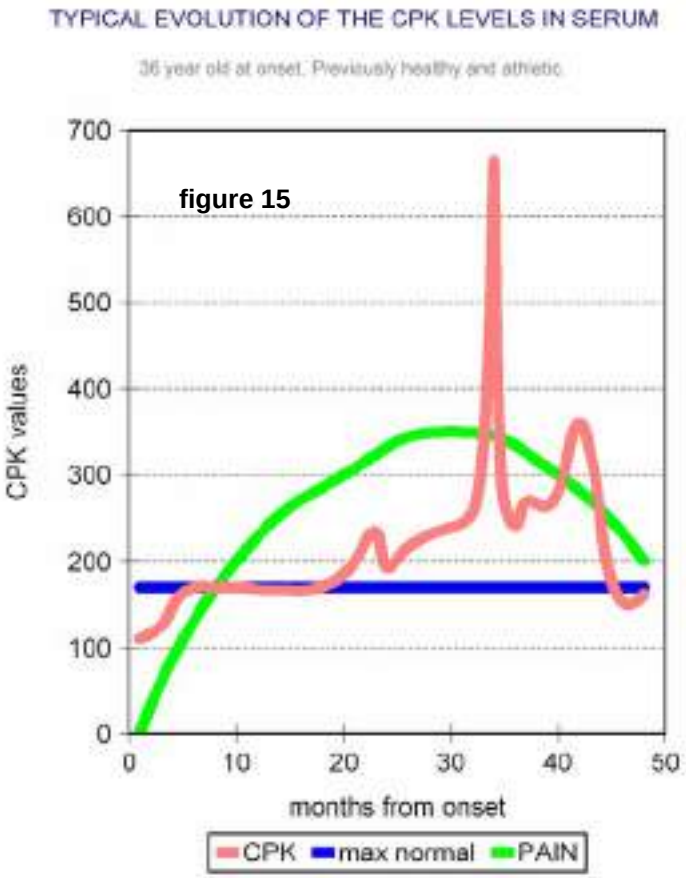
The main tests to be performed in order to assess the renal involvement of the muscular destruction are:

- Hyperkalemia (high potassium levels). High levels are caused by muscle breakdown and also by renal failure.
- Hypokalemia (low potassium levels): Causes myoglobinuria. Also painless proximal weakness.
- Hypercalcemia (high calcium levels): Due to release from muscle and possible reduced renal excretion.
- Hypocalcemia (low calcium levels): Due to binding by damaged muscle & hyperphosphatemia (high phosphorus levels)
- Hyperphosphatemia & Tissue calcification: Due to release of organic & inorganic phosphates from muscle.
- Test also for serum (blood) levels of myoglobin (high levels in muscular destruction and renal compromise, may be caused by quinolonic ischmemic vascular occlusion), hemoglobin, CPK (muscular, heart and brain destruction), lactate (see below), carnitine (if low the quinolones have affected the β-oxidation process)
- Test also for urine levels of myoglobin, albumin and hematuria
- Special meaning of the test for serum lactate: There is no increase with exercise in glycogenoses (disorders of the glycogen storage); but there is a rise with minimal exercise when the quinolones have induced a mitochondrial disorder.
- The ultimate test is a muscle biopsy usually showing destruction of small nerves, plus scattered muscle fiber necrosis and degeneration.

The quinolone family of drugs specifically may cause:

- glycogen metabolic disorders, especially those altering the aldolase, lactate dehydrogenase, phosphoglycerate kinase and phosphorylase kinase.
- fatty acid oxidation disorders
- mitochondrial disorders, the most common through a deficiency in coenzyme Q10.

This chart shows (figure 15) the evolution of the CPK levels of a 36 year old floxed person that was perfectly healthy prior to suffer a reaction that has been classified by himself as SEVERE. *(Reproduced with permission)*. His base level of CPK before the floxing was around 100 U/l. The maximum level of CPK considered normal is 170 U/l (blue stright line), and figures above that are considered a sign of excessive muscle destruction. These levels of the diagram are total CPK. The floxed person was tested for the specific



CPKs for heart, brain and musculoskeletal muscle, and the first two were within normal levels, althouh high, and the latter was abnormal for nearly four years. The floxed person had 3 measures of CPK prior to the floxing (all normal), and 26 afterwards in a period of 4 years. This chart corresponds to one floxed person, but we have recorded the data of another 5 individuals, and show patterns that are somehow similar.

The evolution shows a first phase of one and a half year where the level is close to the maximum (170 U/l), and then starts to rise up to month 45, with some peaks in the middle probably due to a fatiguing exercise or similar before the test of that day. Only at month 46 values descended below the maximum, although still being borderline.

Pain is a subjective measure, but the floxed person did not feel much pains during the first 6 months (but extremely strong tendinitis) and then the pains increased steadly to peak at month 32, with pains rated as 8/10. The overall aches and pains all over the body descended while approaching the fourth year and at month 48 (4 years out) the pain level is rated as 5/10.

So, perhaps the high CPK levels are a measure of the muscular pains, stiffness and intolerance to exercise. Please, notice that we use the term "intolerance to exercise" to designate a flox syndrome characterized by high pains, stiffness and soreness experienced after vigorous activity. Normally, doctors define intolerance to exercise to the inability to exercise because of extreme fatigue, high or low heart beats, and other abnormal responses of the body to exercise.

The coenzyme Q10 (also called ubiquinone) deficiency deserves a special consideration. Clinically it manifests as exertional fatigue, high myoglobinuria (precipitated by fever, and mild to moderate exercise), proximal weakness (quads, hamstrings, biceps, triceps) and afflictions to the central nervous system (mainly cognitive impairment). On a biopsy, muscles can show ragged red fibers with prominent lipid accumulation. Some floxed persons have been repeteadly tested for coenzyme levels in blood, resulting in extremely low readings. It seems that in those cases supplementation should help. Coenzyme Q10 also intervenes in the metabolism of cholesterol. Other drugs that deplete the body of Q10 are statins (drugs for lowering cholesterol).

From the perspective of other doctors, some floxed persons also have all the symptoms of a neuroleptic muscular disorder. The symptoms are muscle rigidity, dysarthria, dysphagia, hyperthermia (fever), tachycardia, incontinence, tachypnea, hyperhidrosis (excessive sweating), all of which usually resolve during the first stages of the recovery process.

In any case, the floxing myopathies have a toxic nature. There is very little information on the muscular destruction caused by quinolones, although it is a known side effect and listed in the package inserts. As in other sections of this report we have taken a look to the mechanism of toxicity that exhibit similar drugs to quinolones, that have been much better studied, just to get an idea as to what kind of injury we are facing. Obviously, fluoroquinolones could have a much different injury pathway but for now, to learn some basics about the toxicity caused by quite similar drugs is enlightening.

Doctors commonly classify drug induced myopathies in six groups. We do not know even if fluoroquinolones would fit in any of those groups.

DRUG-INDUCED AND TOXIC MYOPATHIES

Coquet M, Bannwarth B, Henin D. Service d'anatomie pathologique et de neuropathologie, groupe hospitalier Pellegrin 33076 Bordeaux.

"A large number of drugs and toxins may induce myopathic changes in several ways, they are probably more common than realized. The clinical and pathological features depend on the causative agent and on individual susceptibility to a given compound. Based on their pathologic mechanisms, there are 6 main categories of toxic myopathies: **necrotizing** myopathy mainly due to lipid-lowering drugs (fibrates and statines); **vacuolar** myopathy, usually associated with antimalarial agents; **inflammatory** myopathy induced by thiol derivatives; **mitochondrial** myopathy; **steroid** myopathy, and **hypokaliemic** myopathy. Toxic myopathies are usually reversible after discontinuation of the offending agent. Their prompt recognition may reduce their damaging effects or prevent a fatal outcome. Muscle

biopsy can be very useful for the diagnosis of toxic myopathies".

IATROGENIC AND TOXIC MYOPATHIES

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Abstract: There has been increasing awareness of the adverse effects of therapeutic agents and exogenous toxins on the structure and function of muscle. The resulting clinical syndrome varies from one characterized by muscle pain to profound myalgia, paralysis, and myoglobinuria. Because toxic myopathies are potentially reversible, their prompt recognition may reduce their damaging effects or prevent a fatal outcome. Interest in the toxic myopathies, however, derives not only from their clinical importance but also from the fact that they serve as useful experimental models in muscle research. Morphological and biochemical studies have increased our understanding of the basic cellular mechanisms of myotoxicity. Toxins may produce, for instance, necrotizing, lysosomal-related, inflammatory, anti-microtubular, mitochondrial, hypokalemia-related, or protein synthesis-related muscle damage.

Of all the explanations about muscular dysfunctions that diverse doctors have given to us, two fit better with the experiences of real life floxed persons. First the desregulation of the coenzyme Q10 mentioned in other parts of this report. Coenzyme Q10 is used by muscle cell mitochondria. Decreased levels of Q10 (ubiquinone) might lead to muscle injury. The other possibility is that quinolones may exacerbate exercise induced muscle injury. Or perhaps both.

Acute worsening of myasthenia gravis (serious illness with muscular implication) has been officially reported following administration of ciprofloxacin, a fluroroquinolone. Exacerbation of myasthenia gravis has been officially reported with use of perfloxacin and also norfloxacin. Worsening of myasthenia gravis would be reported with ALL fluoroquinolones if the treatments were adequately surveilled. Regarding myasthenia gravis, the British Columbia College of Pharmacists warns that the “adverse effect can be a very serious reaction and a frightening experience”, and advises patients to seek medical help should symptoms of weakness, facial paralysis, diplopia, ptosis or shortness of breath occur following use of these antibiotics.

The following report says that in three cases investigated, the muscular pathologies of the floxed persons were pre-existent before the treatment with quinolones.

INVESTIGATION OF FLUOROQUINOLONE-INDUCED MYALGIA USING 31P MAGNETIC RESONANCE SPECTROSCOPY AND IN VITRO CONTRACTURE TESTS

S. Guis 1, et al. Hôpital de la Timone, Marseilles, France

To investigate muscle function in patients with severe myalgia resulting from fluoroquinolone treatment. We used histology, in vitro contracture tests (IVCTs), and 31P magnetic resonance spectroscopy (31P MRS) to explore muscle contraction and metabolism.
We studied 3 patients with myalgia, hyperalgia tendinopathy, and arthralgia following fluoroquinolone treatment and 3 normal subjects after taking FQs. Results were compared with those of a control group of 9 subjects free of any muscle disease and not taking fluoroquinolone s. Muscle biopsies were performed on the left biceps, and IVCTs were performed in accordance with the protocol recommended by the European Malignant Hyperthermia Group. 31P MR spectra of forearm flexor muscles were recorded at 4.7T throughout a rest-exercise-recovery protocol.
Results: 31P MRS showed a significant reduction of pH changes measured at the end of exercise and a faster rate of proton efflux measured during recovery in all patients. IVCTs diagnosed 1 patient as being susceptible to malignant hyperthermia. No specific histologic anomalies were observed in muscle biopsy samples, which showed normal mitochondria.
Conclusion: The adverse effects recorded in the 3 patients are related to a preexisting muscular anomaly revealed by fluoroquinolone treatment.

This conclusion does not match with the thousands of experiences monitored by us, a few hundred of them quite closely (people that participated actively for the forming of this report plus people belonging to support groups).

72. INDIRECT APPROACH TO UNVEIL THE QUINOLONE TOXICITY TO MUSCLES

Many medical treaties include quinolones and quinolines in the same family of drugs. Most medical references stablish that quinolones are compounds derived from quinolines. Obviously, the derivatives (fluoroquinolones in this case) can exhibit completely different patterns of toxicity, but it has been repeatedly observed that toxicity to the main quinolines (antimalarials) and quinolones share a lot of the symptoms, perhaps 80%. That is the reason -out of lack of proper research on quinolones- that we have had a quick look at the toxic profile of chloroquine and hydroxychloroquine, antimalarials that belong to the quinoline group and that cause injuries partially similar to those of the fluoroquinolones.

More times along the report we resort to the antimalarials case, because it has openly studied, and is better understood.

TABLE 15 . TOXICITY OF QUINOLONES IN COMPARAISON WITH TOXICITY OF ANTIMALARIALS

Chloroquine (quinoline derivative)			**Fluoro-quinolones** (quinoline derivatives)
List of main features of chloroquine myopathy according to manuals			Observed in floxed persons
Clinical features		Proximal myopathy and atrophy, worse in the legs than the arms	☑
		Slowly progressive myopathy	☑
		Painless myopathy	☑
		Cardiomyopathy	☑
		Neuropathy with sensory loss	☑
		Decreased reflexes	occassional only
		Reversible when the drug is stopped	sometimes
Laboratory features	Blood tests	Elevated CK level	☑
	Electromyo-graphy	Mild slowing of motor and sensory NCV	☑
		Mild to moderate reduction in CMAP amplitude	☑
		EMG: Increased insertional activity. Positive sharp waves and fibrillation potentials. Myotonic discharges without clinical myotonia.	☑
		Voluntary MUAPs: BSAPs with early recruitment	☑
	Muscle biopsy	Vacuoles in up to 50% of skeletal and cardiac muscle fibers. Type 1 fibers most affected by direct toxic reaction. Type 2 fibers neurodamaged. Vacuoles stain for acid phosphatase and contain concentric lamellar myeloid debris, curvilinear structures, and other cellular debris (autophagic vacuoles)	?
	Nerve biopsy	Autophagic vacuoles	?
	Pathogenesis	Drug interaction with lipid membranes. Formation of complexes resistant to digestion by lysosomal enzymes. This results in autophagic vacuoles	?

NOTE: Hydroxychloroquine, a variant of chloroquine has similar but less severe neuromyopathy. Vacuoles are usually absent. EM: Abnormal accumulation of myeloid and curvilinear bodie.
☑: This symbol means that is observed in fluoroquinolones identically as in antimalarials.

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PART XI: SPECIFIC INJURIES

The quinolones cause many injuries in the whole body. More evident are those inflicted on the intestines, kidneys, liver, pancreas, heart and brain.

In this section, there are some references to them. For a quite exhaustive relation of medical reports of quinolone damages on all organs, visit www.fqresearch.org.

73.CENTRAL NERVOUS SYSTEM EFFECTS

Although much about the pathophysiology of fluoroquinolone-related CENTRAL NERVOUS SYSTEM effects remains ill defined, one hypothesis suggests that drug interactions with the g-aminobutyric acid receptor (GABA), an inhibitory neurotransmitter, may explain CENTRAL NERVOUS SYSTEM-stimulating effects. Ciprofloxacin, enoxacin, and norfloxacin demonstrate high-affinity binding to GABA and interfere with GABA binding to its receptor. (See previous chapters for an understanding of the role of GABA nerve receptors)

Furthermore, some NSAIDs (non steriod anti-inflammatory drugs) have been shown to enhance binding of fluoroquinolones to GABA receptors. Co administration of fenbufen and a fluoroquinolone can induce convulsive seizures.

Fluoroquinolones can also induce excitatory effects through direct activation of N-methyl-D-aspartate (NMDA) and adenosine-receptor mechanisms. Thus, it may be that it is only under specific conditions of sufficient CENTRAL NERVOUS SYSTEM penetration, coupled with threshold antagonism of inhibitory pathways (GABA) and stimulation of excitatory pathways (NMDA, adenosine), that observable CENTRAL NERVOUS SYSTEM symptoms are manifested.

74. EYE AND VISION ISSUES

It has already stated that vision damage is so disturbing and debilitating that just on the grounds of vision injuries, quinolones should be restricted only for special high-risk therapies.

This picture number 16 (courtesy of a collaborator) shows some of the main injuries and lesions that quinolones cause to the eye. Chemically insulted, the optic nerve no longer sends proper signals to the brain. Within the vitreous gelly substance, many floaters may develop, and normally remain forever. The retina and its attachment to the bottom of the eye ball gets damaged and originates flashes of light that seem to move across the vitreous when in fact they are confined to the retina itself. The lens may become opaque in certain areas. The muscles that elongate and compress the lens become injured and painful,

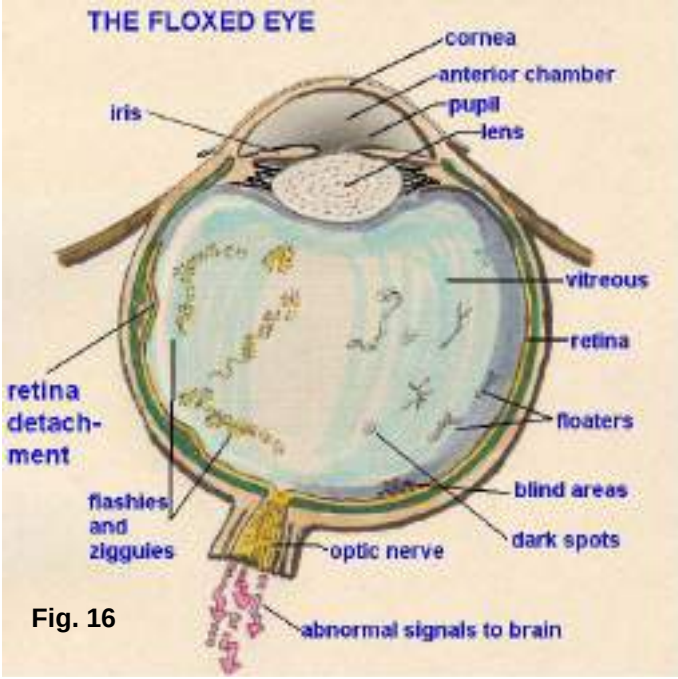


Fig. 16

so focusing becomes difficult. Sometimes the neurologic deficit of these muscles that deform the lens is a sort of inestability (twitching) that takes form as an overscanning that impedes focusing a single spot for long. Other times the coordination between the nerves of both eyes is impaired, and therefore, double vision and lack of precission focusing occurs.

On top of all these debilitating symptoms, do not forget that your eye cannot recover from illness or surgery as a normal eye, and that pain and photofobia-phototoxicity are common and long lasting. The residues of quinolones that are present in the eye for a long time after taking the drug, react with the ultraviolet radiation and cause very serious damage, and also skin cancer.

Many of the injuries caused by fluoroquinolones affect the optic nerves and the retina. Fluoroquinolone induced retinopathies are suspected to be caused by disruption to the blood flow to the retina, either by blockage or breakdown of the various vessels, being a common cause a drug toxicity (and diabetes or hypertension, for instance). This can lead to bleeding (hemorrhage) and fluids, cells, and proteins leaking into the area (exudates). There can be a lack of oxygen to surrounding tissues (hypoxia) or decreased blood flow (ischemia). This damage caused by quinolones is reversible in some cases.

Some of the pathologies caused by fluoroquinolones are the following:

Floaters: The mechanism of damage may be a toxic-vascular injury that in turn may cause a small amount of bleeding inside the eye (vitreous gel), which may appear as a group of floaters. They could also be caused by crystal-like deposits that form in the vitreous, and we have not still gathered a conclusive causative factor. In severe reactions floaters show up some months after exposure to the quinolone (the reverse does not apply, that is to say, if you develop floaters some months after exposure it does not mean neccesarily that you have a severe reaction). Floaters may sometimes interfere with clear vision, often when one is reading. If a floater appears directly in your line of vision, moving your eye around will cause the vitreous to swirl around and will move the floater out of the way. Looking up and down rather than back and forth will cause different currents inside the eye and may be more effective in getting the floater out of the way.
Floaters tend to be a permanent injury in severe reactions. They lose intensity with time but it is really improbable that they disappear spontaneously. Typically, a floxing that affects the eyes causes hundreds of floaters, some of which may be big.
Floaters have many causes but when they are caused by quinolones seems to be the consequence of vitreous hemorrahge and inflammation, as well as of the presence of red blood cells, pigment cells and pigment granules detached from the retinal pigment epithelium.

Flashies: Flashing lights is the sensation of one or a few lights that start crossing a part of the field of vision, and then fade off, lasting between less than one second and 3 seconds. As flashies are also referred thousands of little swirling little lights that swarm in the whole field of vision and that are difficult to detect unless you stare at a bright sky and unfocus your sight. Individual flashies tend to occur in only one eye at a time and persist even when the eye is closed. Some doctors hold the opinion that the flashes are caused when the vitreous, a clear gel-like substance that fills the inside of the eye, sometimes pulls or tugs on the retina. This pulling causes the appearance of flashing lights or lightning streaks, though there is no flashing light actually present. Given the toxic mechanism of all the disorders of the floxed persons, other doctors believe that the flashes are generated in the brain, caused by a spasm of blood vessels, what they call ophthalmic migraines, normally with a little or no headache but possible eye pain. These lights last many years in severe reactions and are very sensitive to foods and supplements, for instance soy and sugar provoke a massive proliferation of them in severe floxed persons. Unlike floaters, flashies tend to heal with time. They are rare after the 4 year mark in severe floxed persons and very rare 5 years after the intoxication.
Flashes of light (photopsias) last seconds, never more than 10 seconds, and are probably caused by posterior vitreous detachment induced by the fluoroquinolones.

Macular degeneration: At the back of the eye there is a thin layer of light-sensitive nerve cells and fibres called the retina. We see things because light entering the eye strikes the retina and is turned into an electric impulse that the brain understands as an image.
Near the centre of the retina is a small spot about the size of a pea called the macula. The macula processes the details in the central part of the image that the brain receives. The macula needs good light to work efficiently and works best in daylight. The rest of the retina is responsible for side, or peripheral, vision. It is especially sensitive to dim light, which makes night vision possible. If the macula deteriorates for some reason, the retina becomes like a camera with a spot on the film. The centre of the field of vision blurs and all detail is lost. This condition is called macular degeneration. Quinolones tend to damage the retinal blood vessels that supply the macula. In severe reactions, cut off from its source of nourishment, the macula is permanently damaged and some blurry central spots appear in one or both eyes. Ophthalmologists can diagnose these injuries, that are not accompanied by de-pigmentation. But do not expect that any of them accepts that the fluoroquinolone is behind your problem, because they prescribe fluoroquinolone drops continously.

Dry eye: Explained in other sections of the article. Can be very limiting also. Commonly appears some months after exposure (6 months on average) and symptoms start to alleviate after year 3 in severe reactions, but then progress stalks becoming a permanent injury. Very often floxed persons that are not aware of their reaction are diagnosed as having Sjögren's syndrome. Dry eye is a condition that looks as if it is about to be considered permanent because the follow up done on floxed persons after 7 years of suffering, says that dry eye reaches its down point around year 2, then improves a little at year three and it remains basically with that intensity of damage until year 7 postfloxing (and counting). See figure 17 on the right. It depicts the typical evolution of the dry eye syndrome of a severe floxed person along 5 years. Curiously, the eye that had the best moisturing ratio before the floxing, usually gets worse but also recovers earlier.

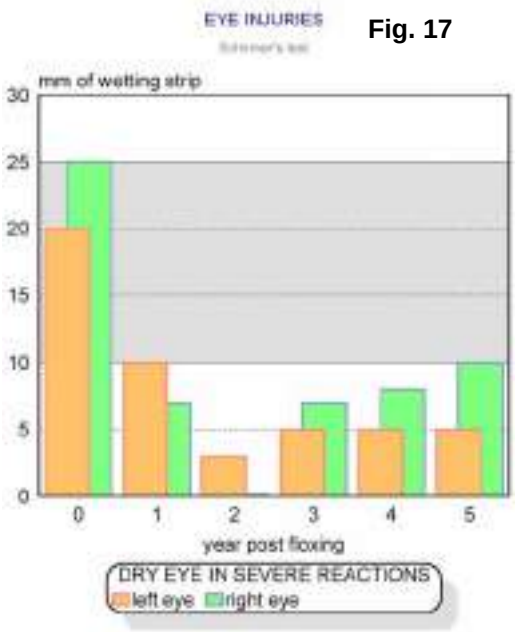


Fig. 17

Curtains: These are very long-lasting injuries of the visual field usually called curtains. They can be seen in the upper part of the vision field and move horizontally around bright fluorescent lights and brilliant backgrounds. They are like a string of water drops moving like a curtain from side to side of the upper part of the vision field.

Eye pain: Eye pressure and pain is typical. Sometimes eye pressure comes in wave-like bursts. It resolves earlier than the rest of vision issues. There is also a marked loss of strength on the muscles that move the eye and especially those that bend the cornea, making it very difficult for the eyes to focus. By year 2 cornea control starts to resolve and by year 3 the rest of the muscles of the eye begin to recover, so the floxed person feels clearly that he regains strength in the muscles of the eyes.

Complete transient loss of vision: Some floxed persons, very severely affected, have lost their vision completely up to 4 times. The loss of vision comes suddenly, and in a matter of seconds the floxed person can see only a solid blank field. It can last from 30 seconds to 6 minutes. This phenomenon is described in the medical literature for ciprofloxacin.

Phototoxicity: Two types of photosensitivity reactions have been associated with fluoroquinolone therapy: photoallergic reactions and phototoxic responses. Photoallergic reactions normally

> require previous exposure to a drug in the class. In contrast, phototoxic responses are more common and can develop without previous exposure to a fluoroquinolone if the dose of the photo-labile drug and exposure to UVA light (around 350 to 360 nm) are sufficiently high. Photosensitivity reactions are postulated to occur as a result of fluoroquinolone photodegradation, as well as the molecule's ability to generate free monovalent oxygen radicals. In turn, these oxidative radicals may attack cellular lipid membranes, initiating inflammatory processes, and eventually producing DNA damage. Evidence for photo-induced oxidative DNA damage is demonstrated by the development of murine tumors in mice treated with lomefloxacin.

Be aware that there are many ophthalmic preparations based on quinolones, especially cipro. If you have suffered a small reaction to any quinolone before, these medications can cause permanent damage to your vision. Some new formulations have been released for the pediatric population (older than 6 months) with a mixture of cipro and a cortico-steroid. It is also very well known and cited in medical researchs that cipro impedes seriously the healing of any eye wound, like the ones caused during eye surgery (in fact, quinolones jeopardize all healing processes in the body).

Some floxed persons have lost their vision completely for some minutes several times after taking the antibiotic. It is a frightening experience that can have a dramatic end:

> DEAF AND BLIND DUE TO THE INGESTION OF A FLUOROQUINOLONE. 2002.
> Canadian Adverse Reaction Newsletter. October 2002. Case Presentation - moxifloxacin (Avelox):
> Optic neuritis developed in a 22-year-old woman with sinusitis while she was receiving moxifloxacin (Avelox) therapy. After 1 dose she experienced fainting and somnolence, which resolved 2 days after initiation of therapy. After 4 days of treatment she lost vision in her left eye. She consulted an ophthalmologist and continued therapy for 6 days. An MRI scan ruled out multiple sclerosis. The patient was taking birth control pills concomitantly. It was reported that her vision would not likely return.
> Ciprofloxacin: suspected association with deafness and reduced hearing Health Canada has received 4 serious case reports of deafness or decreased hearing suspected to be associated with ciprofloxacin. They involved men aged 35, 47, 65 and 67 years old. Three were receiving 1000 mg/d orally and one was receiving 800 mg intravenously. In all cases, the reactions began within 1 week after initiation of therapy. Three patients recovered, and the fourth experienced partial permanent deafness.

We have only seen complete visual loss in severely affected persons, all of which had taken fluoroquinolones in the past without strong adverse effects, save the last one, that invariably was of a higher dose. What happened to all these persons is that their cumulative dose of quinolone was too high, what is the same as saying that the liver had very impaired its P450 pathway, and then new and stronger doses of quinolones caused extraordinary high concentrations of the toxic, acting over tissues and cells that were already abused. Doses of cipro that caused this on the floxed persons studied by us were 1,500 mg/day up from 1,000 mg/day of previous treatments.

The following report is not estrictly speaking about quinolones, but about another drug with a similar structure (that the text includes in the same family as quinolones [?]), but gives a very important clue towards understanding why quinolones are so harmful for the eyes, and why they cause so long term damage. The article supports the fact that the drug remains in the body for 5 and more years after ending the treatment. That could be the same in the case of fluoroquinolones, but no medical group wants to investigate it. Why not is what is hard to understand. In our opinion it is not a coincidence that the researchers do not belong to the western mainstream herd of doctors shepherded by the manufacturers.

> emedicine
> AUTHOR: MANOLETTE R ROQUE, MD, GENERAL MANAGER, OPHTHALMIC CONSULTANTS PHILIPPINES CO, EYE REPUBLIC OPHTHALMOLOGY CLINIC
> **Background:** Chloroquine and hydroxychloroquine **belong to the quinolone family**. They are related drugs with different therapeutic and toxic doses with similar clinical indications for use and manifestations of **retinal toxicity**.
> Initially, chloroquine was given for malaria prophylaxis and treatment, and, later, it was used by rheumatologists for treating rheumatoid arthritis, systemic/discoid lupus erythematosus, and other

connective tissue disorders. Dermatologists use these drugs for cutaneous lupus. Since it is far less toxic to the retina, hydroxychloroquine has replaced chloroquine, except for individuals who travel in areas endemic with malaria.
Expanded use of these drugs for nonmalarial disease entities has resulted in prolonged duration of therapy and higher daily dosages leading to cumulative doses greater than those used in antimalarial therapy. The first reports of retinal toxicity attributed to chloroquine appeared during the late 1950s. In 1958, Cambiaggi first described the classic retinal pigment changes in a patient receiving chloroquine for systemic lupus erythematous (SLE) treatment. In 1959, Hobbs established a definite link between long-term use of chloroquine and subsequent development of retinal pathology. In 1962, J Lawton Smith coined the term bull's eye maculopathy, regarded as the classic finding of macular toxicity. Many reports on chloroquine retinopathy exist. In contrast, only a few cases of hydroxychloroquine toxicity have been reported.
Pathophysiology: Chloroquine has an affinity for pigmented (melanin-containing) structures, which may explain its toxic properties in the eye [please, note that quinolone antibiotics also have a big affinity for melaning structures]. Melanin serves as a free-radical stabilizer and as an agent that can bind toxins. Although it binds potentially retinotoxic drugs, it is unclear whether the effect is beneficial or harmful. Chloroquine and its principal metabolite have been found in the pigmented ocular structures at concentrations much greater than in any other tissue in the body. With more prolonged exposure, the drug accumulates in the retina. The drug is retained in the pigmented structures long after its use is stopped. The kinetics of chloroquine metabolism are complicated, with the half-life increasing as the dosage is increased. **In patients with retinopathy, 5 years or more after discontinuation, traces of chloroquine have been found in plasma, erythrocytes, and urine**.

The antimalarials chloroquine and hydroxychloroquine exhibit practically identical toxic profile as fluoroquinolones in many aspects. As those antimalarials have been more extensively and honestly studied than quinolones, the causes of some symptoms caused by those antimalarials are known, but that is not the case for the fluoroquinolones. Knowing some facts about the antimalarials could provide us with some clues in order to orientate our search for answers to the toxicity of fluoroquinolones. According to the well stablished medical research, chloroquine can cause degeneration of the optic nerve. It can also cause a retinal degeneration which can lead to blind spots in the vision, reduced color vision, and blurred central vision. The risk of retinal problems may be related to the total cumulative amount of chloroquine taken over time. Its effects are cumulative. Taking more than 300 g of chloroquine in 3 years, it causes bull eye maculopathy, and corneal deposits, exactly the same than fluoroquinolones, that also provoke central maculopathy and corneal deposits. According to us, the cumulative dose of cipro that causes these very severe eye lesions might be around:

- 100 g (up to 100 days of 1g/daily in 3 years) plus one week of 1.5 g/daily, or
- 200 g (up to 200 days of 1g/daily in 3 years)

Nevertheless for the fluoroquinolones, the laboratories have been keen to hide the ocular toxicity, with a complete success up to now. For chloroquine and hydroxychloroquine, the retinal toxicity was discovered when the laboratories pushed for the expanded use of these drugs for nonmalarial disease entities resulting in prolonged duration of therapy and higher daily dosages leading to cumulative doses greater than those used in antimalarial therapy. Until more honest research is done, we theorize that the eye toxicity of the fluoroquinolones may be similar to the eye toxicity of chloroquine and hydroxychloroquine.

As the antimalarial chloroquine, fluoroquinolones have an affinity for pigmented (melanin-containing) structures, which may explain its toxic properties in the eye. Melanin serves as a free-radical stabilizer and as an agent that can bind toxins. Although it binds potentially retinotoxic drugs, it is unclear whether the effect is beneficial or harmful. Fluoroquinolones have been found in the pigmented ocular structures at big concentrations. With more prolonged exposure, the drug accumulates in the retina. The drug is retained in the pigmented structures long after its use is stopped (in other parts of the report it is explained how quinolones can be detected in dark hairs months after ingestion). For the antimalarial chloroquine patients with retinopathy, 5 years or more after discontinuation, traces of chloroquine have been found in plasma, erythrocytes, and urine. Probably the same happens with fluoroquinolones, but as far as we know the essays have not been conducted yet.

Quinolones cause diplopia (double vision) very frequently. It is unclear, for lack of research, whether the

diplopia is a direct effect or secondary to a quinolone-induced intracranial hypertension.

This big toxicity to the eye has not gone unnoticed to some researchers, and for instance, the Department of Optometry, at City University London, started a project in october 2002 that *"concerns the ocular adverse reactions of certain systemic medications. In particular, several drugs, e.g. cardiac glycosides, phenothiazines, quinolones, NSAIDs and chemotherapeutic agents, are associated with significant and selective retinal toxicity"*. We have not been able to get a copy of the outcome of this project.

Retinopathies caused by fluoroquinolones are basically considered as nonproliferative retinopathies.

Exogenous substances associated with idiopathic (theoretically unknown) intracranial hypertension include the antibiotic nalidixic acid (father of all quinolones), according to the research conducted by Mark Gans, MD, Director of Neuro-ophthalmology, Associate Professor, Department of Ophthalmology, McGill University. Nalidixic Acid can be associated with the development of increased pressure of the fluid around the brain, or "pseudotumor cerebri". This can lead to headache, visual changes, and a visibly swollen optic nerve. This has been experienced by many floxed persons with all fluoroquinolones (nalidixic acid is the chemical compound from which all fluoroquinolones have derived).

CIPROFLOXACIN MICROPRECIPITATES AND MACROPRECIPITATES IN THE HUMAN CORNEAL EPITHELIUM.
Eiferman RA, et al. Veterans Administration Medical Center, Louisville, USA.
In 4 corneal transplantation patients treated preoperatively with ciprofloxacin ophthalmic drops, microprecipitates associated with damaged corneal epithelium were noted in 2 patients. Another patient developed a large macroprecipitate in a corneal ulcer. All specimens were examined by electron microscopy and high-pressure liquid chromatography. The crystalline precipitates were pure ciprofloxacin. The macroprecipitate demonstrated a large zone of inhibition on agar plates seeded with a susceptible organism at 24 and 48 hours. It was bioactive and bioavailable in vitro.

Is there any need to mention that among 21 ophtalmologists asked by the floxed persons that have contributed to the flox-report, none new anything about any visual abnormality caused by fluoroquinolones, and that some of them contemptously despised the patient? Look at this rare paper on fluoroquinolones' toxicity. It is rare because it comes from the USA, where there is a sort of veto covers the issue.

REVERSIBLE VISUAL LOSS IN A PATIENT RECEIVING HIGH-DOSE CIPROFLOXACIN HYDROCHLORIDE (CIPRO). Vrabec TR, et al. Neuro-Ophthalmology Service, Wills Eye Hospital, Philadelphia, PA.
Bilateral acute visual loss characterized by cecocentral scotomas and acquired dyschromatopsia developed in a patient receiving large oral doses of ciprofloxacin hydrochloride (Cipro). The visual defects improved after cessation of this antibiotic. To our knowledge, this association has not been described previously. The use of this medication in high doses must be accompanied by careful monitoring of optic nerve function.

Fluoroquinolones are not a first choice for eye profilaxis (preventive treatment of infections):

TENOTOXIC POTENTIAL OF FLUOROQUINOLONES IN THE CHOICE OF SURGICAL ANTIBIOTIC PROPHYLAXIS IN OPHTHALMOLOGY
F Pouzaud,et al. J Orthop Res. 2003 Mar
PURPOSE: Fluoroquinolones are mainly used in ophthalmic antibiotic prophylaxis because of their broad spectrum activity and good ocular diffusion. But a single oral dose of fluoroquinolones can result in a serious source of tendinopathy and tendon rupture, especially in patients 60 years and older. It seems very important to investigate tendon toxicity of fluoroquinolones to improve the risk-benefit ratio in ophthalmologic antibiotic prophylaxis. MATERIAL and methods: The intrinsic tenotoxic potential of four fluoroquinolones (pefloxacin, ofloxacin, ciprofloxacin, levofloxacin) was directly evaluated on living adherent tendon cells in microplates. Cell viability and reactive oxygen species production was evaluated using neutral red, alamar blue, and dichlorofluorescin diacetate tests. RESULTS: Results showed a loss of viability associated with free radical production depending on fluoroquinolone molecules. Pefloxacin appeared more tenotoxic but no study

has confirmed its efficacy in surgical antibiotic prophylaxis and its use in the patient who is 60 years and older could be disputed. **Ciprofloxacin is highly toxic with a low ocular diffusion and seems to be inappropriate for antibiotic prophylaxis**. Ofloxacin and levofloxacin are less cytotoxic, associated with good ocular diffusion and a broad antibacterial spectrum. CONCLUSION: Ofloxacin and levofloxacin seem to be good alternatives for improving the risk-benefit ratio in surgical antibiotic prophylaxis in patients 60 years and older.

You will not find many stright-forward reports of this kind among american doctors. Almost all come from Europe, Japan, India and Australia, where the strongest medical systems are public. The rotten stink that floats over this issue confirms that doctors in America as a professional class are well controlled by the industry.

That quinolones are extremely toxic to all the structures and tissues ofn the eyes is no surprise to floxed persons. Some few research articles, mainly animal models, have been published. How many ophtalmologists have a knowledge about this? We haven't found any so far.

IN VIVO EFFECTS OF FLUOROQUINOLONES ON RABBIT CORNEAS
Pollock GA, et al. Centre for Eye Research Australia, East Melbourne, Australia.
PURPOSE: The use of topical fluoroquinolones to treat microbial keratitis is associated with an increased incidence of corneal perforation compared to other standard treatments. This study examined the effects of topical fluoro-quinolones on corneal collagen and keratocytes in intact rabbit corneas and corneas with an epithelial defect. METHODS: Studies consisted of one group of intact corneas and one group of corneas where a 6-mm epithelial defect was created with a surgical scrape. Within each group, eyes were randomly assigned to one of four topical medications (0.3% ciprofloxacin, 0.3% ofloxacin, fortified antibiotics (1.36% tobramycin, 5% cefrazolin) or Tears Naturale (Alcon Laboratories, Frenchs Forest, NSW, Australia). Two drops were instilled hourly for 48 h and then 2-hourly for an additional 48 h. At 96 h the corneas were removed and processed for light microscopy, immunohistology for collagen IV, V and VI, and apoptosis staining. RESULTS: In intact rabbit corneas there was no demonstrable difference between treatment groups. In corneas with an epithelial defect, **both fluoroquinolones delayed epithelial healing** when compared to fortified antibiotics or tears. Keratocyte loss was seen in all groups and was greatest in the ofloxacin group. Median stromal thickness with keratocyte loss were: ofloxacin 30%; ciprofloxacin 10%; fortified antibiotics 7.5%; and tears 15% (ofloxacin vs tears, Mann-Whitney = 16.0, P = 0.09). Keratocyte loss did not correlate with the amount of demonstrable apoptosis. Collagens IV, V and VI showed no differences between treatments. CONCLUSIONS: These results suggest that **ofloxacin is potentially cytotoxic to corneal keratocytes**. Such an effect could lead to the observed increased incidence of corneal perforation in microbial keratitis.

75.QUINOLONES AND DAMAGE TO THE HEART

[in preparation]

This is probably the quinolone disorder that kills more people. Many people develop heart beat irregularities that can be very life threatening.

Re-exposure to quinolones causes the heart irregularities to return with an increased severity, according to the experience of all the floxed persons that suffered repeat intoxications. Strong abnormalities with the heart last typically for some 2.5 years after a severe intoxication, and 1.5 years for intermediate intoxications with quinolones.

Heart pathologies caused by quinolones are one of the most under-reported adverse effects. People visit their doctors complaining about their hearts and none of them ask them about the medications they have taken in recent months, and we don't know of any case in which the cardiologist has asked about antibiotics taken in the past.

There have been many reports of cardiovascular effects, particularly prolongation of the QT interval corrected for heart rate (QTc interval), with quinolone therapy. This finding may relate to the incidence of severe cardiac events that resulted in the withdrawal of grepafloxacin. Furthermore, the manufacturer of

sparfloxacin recommends that the drug not be administered to patients with known QTc interval prolongation or to patients receiving concomitant pharmacotherapy that might increase the interval, induce bradycardia, or promote torsades de pointes (e.g. class I and III antiarrhythmic agents, bepridil, cisapride, erythromycin, or tricyclic antidepressants).

It appears that this effect may be more predictable with medications co administered with quinolones that inhibit cytochrome P-450-mediated metabolism because of increased drug accumulation. Different quinolones vary in the structural modification of the precursor- nalidixic acid. It seems that no specific structural modification has been associated with cardiovascular effects, including those that might influence cytochrome P-450-mediated metabolism, so it is a class effect. No structural modification has been associated with the increased incidence of serious cardiovascular events associated with grepafloxacin therapy, although clinical studies did show associated QTc prolongation. Grepafloxacin, which was introduced in August 1997, was voluntarily withdrawn from use in October 1999 because of reports of severe cardiovascular events among patients taking the drug.

Although is a class effect of fluoroquinolones, and all fluoroquinolones cause them if the dose is high enough, there is little information about the final cause of the heart arrythmias and prolongation of the QT interval. We also know that quinolones are very similar in many aspects to many antimalarial medicines. The antimalarials chloroquine is known to interact with the muscarinic pathway, so perhaps the quinolones have a similar effect.

Some floxed persons have required the implantation of pacemakers to have their heartbeats normalized.

76.QUINOLONES AND GENETIC TOXICITY

Quinolones have been shown to inhibit mammalian cellular topoisomerase II, which correlates with in vitro cytotoxicity in those cells. Some quinolones have an increased potential for cytotoxicity, with the effect being additive. However, disruption of the chromosome, or clastogenicity, usually occurs only at very high drug concentrations, and surveillance studies following clinical introduction of the drugs have not found any carcinogenic potential linked to fluoroquinolone use.

77.QUINOLONES AND DAMAGE TO THE DIGESTIVE SYSTEM

[in preparation]

78.QUINOLONES AND DAMAGE TO THE KIDNEYS AND URINARY SYSTEM

[in preparation]

Quinolones, and especially ciprofloxacin, are linked clearly with acute renal failure. They should be prescribed carefully to patients with impaired renal function. Quinolones can destroy some of the microtubules of the kidney that filter the blood. Once again it seems that it is due to a vasculitic ischemia (narrowing of the micro-vessels of the kidney) that induces a necrosis of critically important glomeruli and tubuli in the kidney. This condition leads to progressive kidney failure, an end-stage condition that requires either hemodyalisis or a transplant. The only visible symptom that causes a first stage kidney damage can be foamy urine.

We have also noted that many floxed persons have a tendency to bleed through the kidneys when taking small quantities of thinning or vasodilatory supplements, like gingko, blackberry, or others. This bleeding is not massive enough to taint the urine, but can be easily detected by means of dipsticks. This entitles us to propose that there is a substantial damage to the kidneys in all strong reactions.

Cases in which renal bleeding occurred due to Ofloxacine (confirmed by re-exposure) have been reported. Prof. Schoenhoefer and Dr. Moebius, editors of the drug alert newsletter "Arzneitelegramm",

Berlin (http://www.arznei-telegramm.de) wrote repeatedly about this. Nevertheless many doctors use ofloxacin for treating bleedings of the urinary tract system. This is seen many times over. Fluoroquinolones cause extremely similar symptoms to multiple sclerosis, lyme, and injuries to kidneys, heart, etc, and are used to treat those very same pathologies, out of plain ignorance..

As almost every floxed person knows, fluoroquinolones cause a serious increase in urination, constant thirst and abnormal fluid inputs-outputs, disorder that fits well under the classification of diabetes insipidus.

All fluoroquinolones cause diabetes insipidus, and almost all severe reactions exhibit diabetes insipidus, that lasts indefinitely, or at least longer than the 7 years of surveillance that on average this flox report covers. We suspect that diabetes insipidus might engross the list of permanent injuries experienced as part of severe reactions.

DIABETES INSPIDUS INDUCED BY OFLOXACIN

Anil Bharani, et al. Department of Medicine, MGM Medical College and MY Hospital, Indore, India

Nephrogenic diabetes insipidus occurs with agents such as lithium, methoxyfluorane, vitamin D, and demeclocycline. We report a case of diabetes insipidus induced by ofloxacin.

A 25 year old man was admitted with fever, a dry cough, and dyspnoea of three days' duration. He had had an influenza-like illness in the preceding week, and his doctor had prescribed ampicillin 2 g daily for three days. On examination he was febrile, toxic, dyspnoeic, and had poor oral hygiene. His pulse was 130 beats/min, blood pressure 110/70 mm Hg, and respiration 35 breaths/min. A chest examination showed signs of bilateral lobar consolidation of the mid zones. His total white blood cell count was 20×109/l with 90% polymorphs, the results of blood biochemistry were normal, and he had negative results for hepatitis B surface antigen, HIV-1, and HIV-2. A chest x ray film showed bilateral lobar infiltrates, no pleural reaction, and a normal cardiac silhouette. We diagnosed "typical" bilateral lobar pneumonia acquired in the community after influenza. He was treated with multiple antibiotics as sputum and relevant bacteriology results could not be obtained: penicillin G 2 million units four times daily, gentamicin 60 mg every eight hours, clarithromycin 500 mg twice daily, and metronidazole 400 mg every eight hours. He was also given a mucolytic, intravenous fluids, vitamins, and intranasal oxygen.

On the third day after admission his response was poor and he was given ofloxacin 200 mg twice daily. He seemed to improve, but on the fifth day he developed polyuria (>20 l/day) with excessive thirst (urine 264 mOsmol/kg with urinary sodium excretion 286 mmol/day). Ofloxacin induced diabetes insipidus was suspected, and the drug was stopped. His urine volume gradually decreased and his thirst normalised within 36 hours while the other drugs were continued. As he continued to improve we rechallenged him with ofloxacin 400 mg daily. Again his urine production increased in association with polydipsia. Ofloxacin was stopped. A chest x ray film showed resolution of the pneumonic consolidation. Multiple cavity formation bilaterally suggested infection with Staphylococcus aureus. He was given ceftriazone 2 g daily and cloxacillin 500 mg four times daily. His symptoms resolved after two weeks.

That the diabetes insipidus recurred when he was rechallenged with ofloxacin and resolved after the drug was stopped while other treatment was continued suggests a causal relation. We could find no report on ofloxacin induced diabetes insipidus in the published literature or from the product monograph. We reported this side effect to the manufacturer and the Central Drug Standard Control Organisation (west zone), both of which were unaware of any such report. Similarly, the other drugs the patient took were unlikely to interact to cause a diabetes insipidus-like syndrome. The mechanism of this interaction is not clear; it could be similar to that of lithium or demeclocycline, which interferes with the action of antidiuretic hormone on the collecting ducts.

You will not find any doctor willing to acknowledge this fact. There is no wonder that the majority of reports about the toxicity of quinolones come from abroad the USA, suggesting that in that country, where the medical arts are more advanced, doctors are usually hostages of the industry, whereas in Europe, Japan, India, Australia, there are more independent researchers, that work in their public health systems, much more powerful than its counterpart in North America.

Remember that diabetes insipidus is not what people normally know as diabetes. Diabetes insipidus is caused by the inability of the kidneys to conserve water, which leads to frequent urination and

pronounced thirst. Diabetes insipidus occurs when the kidneys are unable to conserve water as they perform their function of filtering blood. The amount of water conserved is controlled by antidiuretic hormone (ADH), also called vasopressin. We have asked to a selected group of floxed persons to report their ADH levels, to see if there is a correlation with the symptoms of their floxing, and the results are pending.

If you want to learn more about the assault that the fluoroquinolone antibiotics do on the human kidneys, have a look to the database of reference: www.fqresearch.org

Fluroquinolones also damage the nerves that control the urinary functions, so there is difficulty to hold urine in many cases, and the nervous system also send wrong signals of full bladder, with an insuperable urgency to evacuate.

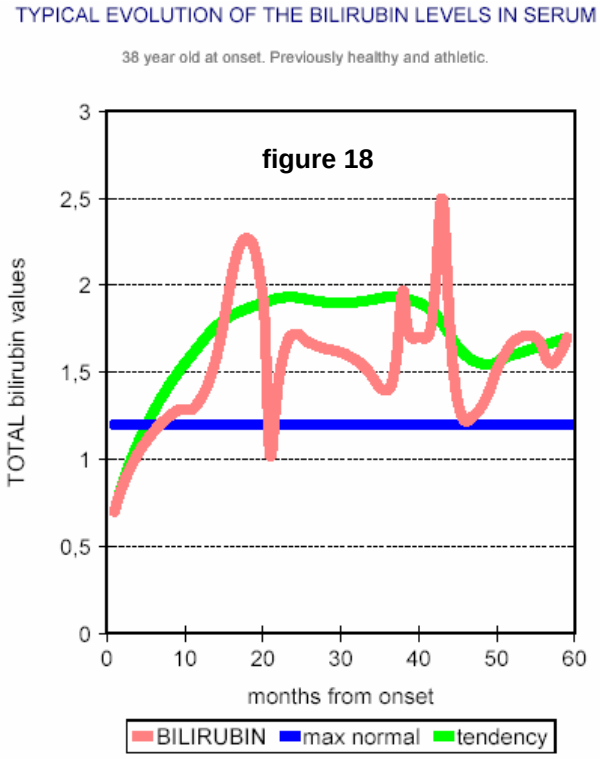
79.QUINOLONES AND DAMAGE TO THE PANCREAS

[in preparation]

Quinolones are very toxic drugs for the liver, pancreas and kidneys. It is typical to have elevated liver and pancreas enzymes counts for months or years after the treatment.

80.QUINOLONES AND DAMAGE TO THE LIVER

The official information of quinolones says: "*Other, uncommon* [??] *reactions include rash, hemolytic anemia, and elevated liver enzyme or bilirubin levels. High-dose or prolonged therapy may increase the likelihood of adverse drug reactions*".



The pathophysiology of adverse hepatic events and hypoglycemia caused by quinolones remains unknown. All quinolones are toxic for the liver, especially for long-term treatment and/or large dosage, as explained earlier. The most serious toxic effects have developed with the use of three agents: temafloxacin, trovafloxacin, and grepafloxacin. The "*temafloxacin syndrome*" was characterized by hemolytic anemia, renal impairment, hepatotoxicity, disseminated intravascular coagulation, and hypoglycemia. Acute renal failure developed in nearly two thirds of the patients with temafloxacin syndrome. In addition, mild hepatobiliary changes were observed in half of the patients and coagulopathy in one third. The development of these adverse drug reactions resulted in the withdrawal of temafloxacin from the market in 1992.

Quinolones, especially when taken in large doses or for extended periods of time, are toxic to the liver. It seems that the most common injuring action is cholestatic damage. Cholestatic means a reduction of the bile flow, due to reduction of the secretions or obstruction of the biliary tree. The damage manifests as hepato-cellular damage.

Quinolones cause elevations of liver enzymes that return to normal in most of the cases after several months, but that can be persistent in severe reactions. Bilirubin is usually elevated, indicating some sort of necrosis.

This figure 18 shows one of the typical injuries of the liver caused by quinolones, measured in terms of serum total bilirubin. *(Reproduced with permission).* The floxed person, already in his forties, was wrongly diagnosed by several doctors as suffering from Gilbert's syndrome (hereditary, benign elevated bilirubin, that he denied firmly as he had not had it before the intoxication by ciprofloxacin). The values are expressed in mg/dl. The chart was prepared with 23 measures post floxing, and 4 prefloxing. The maximum level considered normal is 1.20 md/dl (blue stright line). In green you can see the average value of the bilirubin levels measured. The tendency of his bilirubin levels seen in the chart show that they stayed above normal for 5 years, save on two readings at months 22 and 46. This floxed person has been rated as having a SEVERE reaction. At year four, this floxed person was experiencing some improvement. The floxed person correlates the high bilirubin levels with the vision abnormalities and the vision pathologies associated to the consumption of soy (acetylcholine). That means that when the floxed person takes soy, his vision abnormalities increase a lot, as well as a setback in his overall feelings. This sensitiviness to soy started to decline by the 4.5 year mark, when the floxed person could tolerate small amounts of it. We have the complete records of the data of liver analysis of 4 floxed persons along more than five years, and this figure shows only the ones of one of them.

The worst common effect on the liver is the impairement of the P450 pathway, what causes:

- inability to properly metabolize many other drugs that you may need to take in the future
- inability to properly metabolize coffee and some other common substances
- inability to properly metabolize more quinolones, so new treatments can rapidly reach toxic doses

81.QUINOLONES AND THE LIVER P450 ENZYME PATHWAY

The liver produces a compound of enzymes that metabolize (through a two phase degradation) most of the toxic substances and drugs that enter the body. The most important group of those enzymes is called the P450 set. The hepatic and intestinal cytochrome, or CY, P450 enzyme system is responsible for the biotransformation of a multitude of drugs.

Quinolones are powerful inhibitors of some of the P450 enzymes, primarily the P450-1A2 and the P450-3A4. But these two enzymes are needed to metabolize other substances that may enter your body. The substances that need those enzymes to be broken down and metabolized correctly are called substrates. Therefore, quinolones inhibit the metabolism of CYP1A2 and CYP3A4 substrates, with the consequence that these substrates reach toxic or inadequately high concentrations with unwanted effects. The toxicity typically encountered is identical to what would be seen from an overdose of the substrate drug. Some of these unwanted effects are actually considered interaction between drugs because one drug (the fluoroquinolone) impedes the normal acting of another drug (the substrate with which the quinolone interacts). In summary, enzyme inhibitors reduce the activity of a specific cytochrome P450 isoform, resulting in an accumulation of the substrate drug.

As new drugs reach the marketplace and patients take an increasing number and variety of pharmaceutical agents for a host of medical conditions, the potential for serious drug interactions continues to grow. Ensuring that the medical histories of the floxed persons are up to date and acquiring knowledge of the various substrates, inducers and inhibitors of the CYP450 system will help practitioners avoid potentially serious adverse drug interactions, in other words, will help practitioners avoid causing new toxicities to floxed persons.

And for the floxed person, it is vital to know that his/her liver does not transform drugs as it should do, so he/she must adopt the measures towards limiting or carefully studying the use of all substrates of the enzymes forced to malfunction by the fluoroquinolones.

The human CYP3A4 isoform is the most abundant cytochrome family expressed in the human liver and intestine, and thus is involved in the metabolism of a greater number of drugs and a greater proportion of

adverse drug-drug interactions than are other CYP isoforms.

On the other hand, inducers of a specific CYP450 isoform increase the amount and subsequent activity of that particular enzyme in hepatic and small intestinal tissue. From the therapeutical point of view that means that inducers cause a higher release of enzymes, and the drugs and substances that are their substrates are rapidly metabolized so they some times do not reach the adequate plasma levels needed for a particular effect.

If some of your liver enzymes (P450-1A2, P450-3A4 and others) are still inhibited (not active in enough quantities) by the action of the quinolones some time after your floxing, the concentration of some of the new substances that enter your body can reach toxic levels. For instance, as your P450-1A2 enzyme is largely inhibited after you have ingested cipro or levaquin, if you drink a cup of espresso coffee, the caffeine concentration in your body can be 6 to 10- fold higher than in normal situations, bringing you to the edge in terms of nervousness and agitation.

(NOTE: in this report, following the medical terminology, when we state "inhibition" we mean a partial drecrease in efectivity. Obviously, we do not mean that the liver is completely unable to metabolize certain substances, because in a matter of minutes that would result in direct death of the liver and its host body).

FLUOROQUINOLINES: PAST, PRESENT AND FUTURE OF A NOVEL GROUP OF ANTIBACTERIAL AGENTS.
AMERICAN JOURNAL OF PHARMACEUTICAL EDUCATION, 2002 . ERIC M.
The quinolones interact with a number of drugs which have the potential for altering their clinical effects. Some of these interactions can reduce the intestinal absorption of the quinolones after oral administration and some can result in potentially serious problems via inhibition of various metabolic pathways. Alterations of the cytochrome P450 system in the liver is especially likely to occur upon interaction with other drugs.
A second major type of quinolone interaction results from **inhibition of various metabolic pathways, especially the cytochrome P450 enzymes and GABA neuroinhibitory** pathways. For example, one of the most clinically significant interactions between the fluoroquinolones and other drugs occurs with xanthine derivatives such as theophylline and caffeine. Inhibition of the cytochrome P450 system by the quinolones and resulting reduction in plasma clearance may cause nausea, vomiting and convulsions during coadministration of theophylline. By a similar mechanism fluoroquinolones interfere with caffeine metabolism and both sleep disturbances and upper gastrointestinal symptoms become apparent. Patients taking quinolones should be advised against excessive caffeine intake
Hematologic changes associated with quinolone therapy include decreased and elevated platelet counts, leukopenia, leukocytosis, neutropenia, eosinophilia, elevated sedimentation rate, anemia and hemolysis. The most serious problem experienced with a fluoroquinolone has been the temafloxacin-associated syndrome of hemolysis with in some cases, uremia, coagulopathy and hyperbilirubinemia. This has resulted in the withdrawal of temafloxacin from the market.

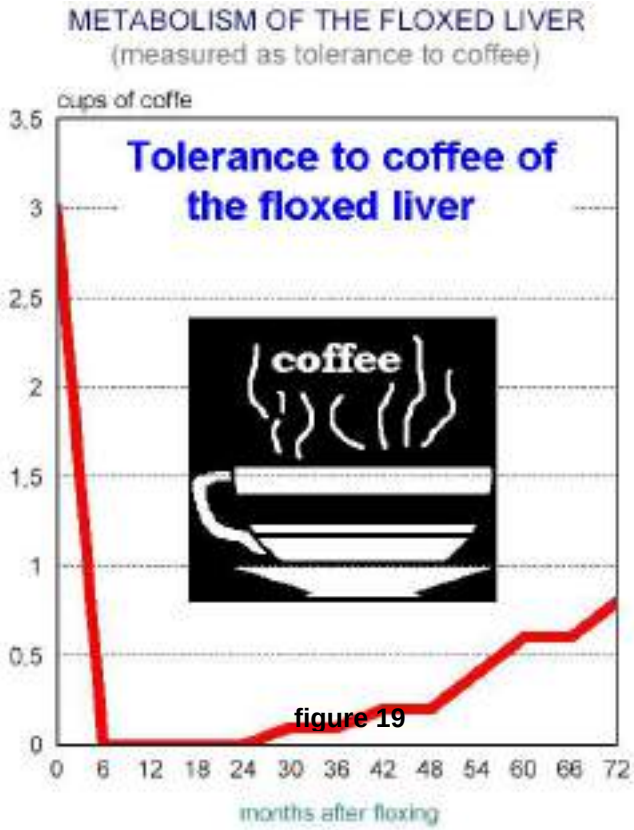


figure 19

All drugs that are substrates of the isoforms 1A2 and 3A4 can reach very toxic levels within the body of the floxed person for months or years after the treatment with the quinolone.

The inhibition of the P450 enzymes by the quinolones helps explain many facts that floxed persons experience, for instance:

- Some foods, chemicals and medications for pain or

inflammation control have different consequences in floxed persons, depending largely on the level of normalcy of the P450 enzymes that tend to be inhibited by quinolones.

- Recovery takes much longer for people with strong inhibition of enzymes caused by the quinolones. The inhibition of the P450 enzymes caused by quinolones is usually regarded as reversible, but some evidences point to long term, or semi-irreversible inhibitions.

- Perhaps, the different type of metabolization capacities of people is the most idyosincratic or the only individualized aspect of a quinolone reaction. We mean to say that the only factor that up to now has been revealed as a predisposing factor for getting floxed is to have a poor liver degradation of quinolones.

There are some commercial tests available that can assess the status of the main P450 enzymes. A simplistic way of checking how your liver is returning to normal availability of P450-1A2 enzymes is to take some caffeine from time to time and check whether the effect is far from or the same as before the floxing. In severe floxings, returning to aceptable levels of P450-1A2 enough to metabolize coffee properly, can take 5 years or more. The figure shows the typical response of a liver to a severe intoxication. The floxed person could take up to three expresso coffees during the day without trouble. After 6 years he is starting to tolerate a little less than one expresso. By the fith year he could manage half an expresso. Roughly speaking that would mean that caffeine reached six-fold concentrations in the blood of the floxed person, in reference with his normal levels prior to the floxing. It is forseable that the same can happen with all substrate medicines. In fact this floxed person has had some bad reactions to some drugs listed as 1A2 or 3A4 substrates, and to which he was not intolerant before. In mild floxings, the sufferer can resume drinking coffee after a few months.

Curiously enough, smokers could have a slight protection against inhibition of the P450 enzymes caused by quinolones, because smoking promotes (activates) the P450-1A2 production.

In the case of quinolones, once again, the evidence of dose-dependent inhibition of P450 is consistent with a number of recent studies suggesting the determination of in vivo inhibition constants based on plasma concentration of inhibitor, the higher the doses, the greater the inhibition.

All the quinolones more or less suppress the same enzymes, but for ciprofloxacin, probably the most extensively studied quinolone in regard to this aspect, it significantly suppresses gene expression of P450-1A2, P450-3A4, and to less extent P450-2C11 and P450-3A1.

Ciprofloxacin is a quinolone antibiotic and a potent competitive inhibitor of CYP1A2. Ciprofloxacin is metabolised up to 75% and partially excreted, unchanged in the urine. In many trials the inhibitory potency of ciprofloxacin caused a 70% reduction in the CYP 1A2-mediated demethylation rate of caffeine in vitro. Furthermore, the activity of CYP3A4 was decreased by 65% in human hepatic microsomes by ciprofloxacin.

As said before, enzymes in the liver often metabolize medications so that the medication can be more effectively removed from the body. The biggest mistake that the medical class is making again is considering that the inhibition of the enzymes caused by quinolones takes place as long as the drug is ingested. Doctors and researchers believe (because they have not investigated counter wise) that activation of P450 enzymes return to normal once the quinolone is discontinued.

That is a big mistake with serious consequences. After a floxing, the P450 inhibition can last for months or years, depending on the severity of the fluoroquinolone toxicty. Thus, there can be a *"virtual interaction"* between the quinolone and a new drug that a floxed person takes one year after being floxed. This can be difficult for your doctors to understand because they think that the quinolone is no longer in your body, and perhaps they are right, but crudely true, as the effect on the P450 pathway is still present.

So, floxed persons can exhibit signs of drug *"interactions"* with his/her formerly taken quinolone when the

liver damage interferes with the removal of another medication. For instance, ciprofloxacin taken in the past after a strong reaction can inhibit (prevent the activity of) one of the pathways that is used to eliminate medications from the body some years later. Some of the medications that use CYP1A2 for an elimination pathway are listed below. If CYP1A2 (another way of naming P450-1A2) is inhibited, and the dose of these medications is not reduced, the medicine could accumulate in the body to levels that could cause serious adverse drug reactions.

In addition to inhibiting drug metabolism, ciprofloxacin could be involved in other types of drug interactions. Since ciprofloxacin can have adverse effects in the brain, including seizures, it should be used cautiously with other drugs that can have similar effects.

For instance, drugs that can reach toxic levels after a former reaction to ciprofloxacin are:

> 1A2: acetaminophen (paracetamol), amitriptyline (elavil), diazepam, caffeine, chlordiazepoxide, clomipramine, clopidogrel, clozapine, cyclobenzaprine, desipramine, estradiol, flutamide, fluvoxamine, haloperidol, imipramine, mexiletine, mirtazapine, naproxen, nortriptyline, olanzapine, ondansetron, phenacetin, propafenone, propranolol, riluzole, ropivacaine, tacrine, theophylline, verapamil, warfarin, zileuton, zolmitriptan.
>
> 3A4, 3A5, 3A7:Macrolide antibiotics: clarithromycin, erythromycin (not 3A5, NOT azithromycin), telithromycin; Anti-arrhythmics:quinidine (not 3A5) ; Benzodiazepines:alprazolam, diazepam, midazolam, triazolam; Immune Modulators: cyclosporine; HIV Antivirals: indinavir, nelfinavir, ritonavir, saquinavir ; Prokinetic: cisapride; Antihistamines: astemizole, chlorpheniramine, terfenidine; Calcium Channel Blockers: amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil; HMG CoA Reductase Inhibitors: atorvastatin, cerivastatin, lovastatin, NOT pravastatin, simvastatin; Steroid 6beta-OH: estradiol, hydrocortisone, progesterone, testosterone; Miscellaneous: alfentanyl, aprepitant, aripiprazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, odanestron, pimozide, propranolol, quetiapine, quinine, risperidone, NOT rosuvastatin, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, ziprasidone, zolpidem.

The floxed person only has reason to worry if his/her reaction has been severe. For mild and intermediate reactions, the inhibition of the P540 pathways returns to normal in some month's time. Do not make any decision on your own, always consult your doctor and do as you agree with him. If you have to take any of the above listed drugs for an extended time, suggest to him to test you prior to and during the treatment, to detect possible overdosing effects.

Differences in individual availability of P450 enzymes might very well be behind many susceptibilities to quinolone treatments because these enzymes play an important role in chemical sensitivity. Thus, those with a mutation of CYP1A2 could detoxify cipro at only 0.5%-20% of the normal capacity, resulting in acute hypersensitivities (not allergies) after a single pill.

It is well known that in the Korean War, soldiers with G6PD deficiency were hypersensitive to an anti-malarial drug. Among healthy people there is a 40-fold variation in P450 1A2, the most important of the P450 enzymes necessary to detoxify quinolones and chemical substances. Many subjects suffering from multiple chemical sensitivity are now known to be P450-compromised. It seems possible that different reactions to quinolones can also be modulated by P450 availability. It also looks plausible that repetitive treatments with quinolones can impair the P450 pathway even for people that initially had a large metabolic capacity, so the patients tend to become more and more sensitive to quinolones with successive treatments.

82.QUINOLONES AND SKIN CANCER

All persons that take fluoroquinolones, are subjected to the risk of developing skin cancer and severe eye

injuries, if exposed to direct sunlight. Obviously, the probability of acquiring quinolone-induced cancer is higher for high doses and long treatments and depends on the level of ultraviolet radiation. In severe reactions, the recommendations are:

- Big risks of getting serious damage from sun exposure last not less than three years, During that time eye pain is also experienced when standing on bright sunlight.
- High ultraviolet radiation has to be avoided during some years. Dangerous situations are high altitude sunlight, and summer, midday exposure.
- Wear protective clothes and quality eyeglasses.

DIFFERENT MECHANISMS FOR THE PHOTOINDUCED PRODUCTION OF OXIDATIVE DNA DAMAGE BY FLUOROQUINOLONES DIFFERING IN PHOTOSTABILITY
Thomas E. Spratt, et al. American Health Foundation, Division of Pathology and Toxicology, New York , and Bayer AG, Wuppertal, Germany. American Chemical Society 1999
Several fluoroquinolone antibacterial agents exhibit an adverse phototoxic effect in humans and are photo-cocarcinogenic in mice. The UV-induced production of reactive oxygen species plays a role in the toxicity and may be involved in carcinogenicity. Four fluoroquinolones were examined for the ability to photochemically produce oxidative damage in naked DNA. .../..... Thus, the evidence suggests that fluoroquinolones can photochemically produce DNA damage by both type I and type II mechanisms.

Not many drugs have the speciality of damaging DNA and as a consequence promote skin cancer when people are just living outdoors, but fluoroquinolones do.

MOLECULAR RESPONSES TO PHOTOGENOTOXIC STRESS INDUCED BY THE ANTIBIOTIC LOMEFLOXACIN IN HUMAN SKIN CELLS: FROM DNA DAMAGE TO APOPTOSIS
Laurent Marrot, et al, L'Oreal Research, Aulnay-sous-bois, France and Laboratory of Genetic Instability and Cancer, Villejuif, France, 2003.
Photo-unstable chemicals sometimes behave as phototoxins in skin, inducing untoward clinical side-effects when exposed to sunlight. Some drugs, such as psoralens or **fluoroquinolones, can damage genomic DNA, thus increasing the risk of photocarcinogenesis**. Here, lomefloxacin, an antibiotic from the fluoroquinolone family known to be involved in skin tumor development in photoexposed mice, was studied using normal human skin cells in culture: fibroblasts, keratinocytes, and Caucasian melanocytes. When treated cells were exposed to simulated solar ultraviolet A (320–400 nm), lomefloxacin induced damage such as strand breaks and pyrimidine dimers in genomic DNA. Lomefloxacin also triggered various stress responses: heme-oxygenase-1 expression in fibroblasts, changes in p53 status as shown by the accumulation of p53 and p21 proteins or the induction of MDM2 and GADD45 genes, and stimulation of melanogenesis by increasing the tyrosinase activity in melanocytes. Lomefloxacin could also lead to apoptosis in keratinocytes exposed to ultraviolet A: caspase-3 was activated and FAS-L gene was induced. Moreover, keratinocytes were shown to be the most sensitive cell type to lomefloxacin phototoxic effects, in spite of the well-established effectiveness of their antioxidant equipment. These data show that the phototoxicity of a given drug can be driven by different mechanisms and that its biologic impact varies according to cell type.

Lomefloxacin, as all fluoroquinolones is phototoxic (its toxicity is greatly increased by light exposure) and phototumorigenic (causes cancer when exposed to sunlight).

THE PHOTOCARCINOGENESIS OF ANTIBIOTIC LOMEFLOXACIN AND UVA RADIATION IS ENHANCED IN XERODERMA PIGMENTOSUM GROUP A GENE-DEFICIENT MICE
Taketo Itoh et al. Department of Dermatology, Kansai Medical University, Osaka, and Human Cell Biology, Osaka University, Japan; 2005
Lomefloxacin (LFLX) is phototoxic and phototumorigenic, but the mechanisms of phototumorigenesis of quinolone drugs have not been fully elucidated. Formation of cyclobutane pyrimidine dimers (CPD) by UVB radiation is primarily involved in the carcinogenesis of ultraviolet (UV) radiation. On the other hand, UVA region is responsible to photobiologic reactions of quinolone drugs. To know if CPD can be formed by UVA radiation in the presence of LFLX and is involved in the phototumorigenesis, we used xeroderma pigmentosum (XP) group A gene-deficient (XPA(-/-)) mouse, which is defective in nucleotide excision repair. XPA(-/-) and XPA(+/+) mice were irradiated to 5 J per cm2-UVA with or without the administration of LFLX. In XPA(-/-) mice treated with LFLX, the first skin tumor appeared after exposures to 75 J per cm2 in 5 wk. In XPA(+/+) mice treated with LFLX, the first tumor appeared after exposures to 345 J per cm2 in 23 wk. Immunohistochemically, CPD formation was observed after UVA-exposure in the skin of

XPA(+/+) as well as XPA(-/-) mice which had been given LFLX. The CPD disappeared, however, earlier from XPA(+/+) mice than from XPA(-/-) mice. The acute inflammatory reaction after LFLX administration and exposure to UVA were greatly enhanced in XPA(-/-) mice. **These results indicate that UVA exposure induces DNA damage in the form of CPD in the presence of lomefloxacin, which exerts phototoxicity and phototumorigenesis**.

83. IMPAIRED GLYCEMIA CONTROL. HYPERGLYCEMIA. HYPOGLYCEMIA

Hyperglycemia and hypoglycemia, is a terrible consequence of quinolone treatments that has not been properly acknowledged until very recently. It is a disturbing and recurrent finding of our research the potential induction of diabetes by fluoroquinolones. In effect, fluoroquinolones cause profound desregulations of the sugar metabolism, as all strongly floxed persons know by personal experience. All severe floxed persons suffer from hypoglycemia or hyperglycemia, and do not tolerate any sweet food at all because it causes relapses in multiple aspects.

Many of the symptoms caused by fluoroquinolone toxicity resemble a diabetic pathology. There is some concern that all or many severe floxed persons develop diabetes after some years. We are doing a follow up on this subject.

It has been widely recognized since years ago that diabetics run an increased risk of having a long lasting hypo or hyperglycemia disorder if put on fluoroquinolones. Recently (2006) there has been a raising concern about very bad cases of hyper and hypoglycemia among non diabetic fluoroquinolone patients. The case has been particularly severe among tequin users, so much as to include a new warning.

QUINOLONES AND BLOOD GLUCOSE ABNORMALITIES (HYPOGLYCEMIA, HYPERGLYCEMIA)
Dysregulation of blood glucose has been noted with all the available fluoroquinolones (ie, ciprofloxacin [Cipro], gatifloxacin [Tequin], gemifloxacin [Factive], levofloxacin [Levaquin], lomefloxacin [Maxaquin], moxifloxacin [Avelox], norfloxacin [Noroxin], ofloxacin [Floxin]), including some fatalities. Hyperglycemia has been reported with all the available fluoroquinolones. Hypoglycemia has also been reported with every agent but gemifloxacin (Factive), the newest agent. The quinolones increase insulin release from pancreatic islet cells as a class, therefore caution may be warranted with all quinolone antibiotics.
Based on postmarketing data, disturbances in blood glucose may be more common with gatifloxacin than with other fluoroquinolones. The FDA and Bristol-Myers Squibb are revising the gatifloxacin product labeling to reflect this increased risk. Gatifloxacin will be contraindicated in diabetic patients when the changes are finalized. Other changes to the product labeling include additional information about risk factors for blood glucose abnormalities and additional monitoring recommendations. Risk may be increased in patients receiving concomitant therapy with hypoglycemic agents, elderly patients, or patients with renal dysfunction.

But although they want us to believe that it is a problem confined to tequin and the elderly and kidney sufferers, the real fact is that all fluoroquinolones pose the risk over everyone that takes them.

LEVOFLOXACIN-INDUCED HYPOGLYCEMIA IN A NONDIABETIC PATIENT.
Susan Wang; Ali A Rizvi. The American journal of the medical sciences.
The fluoroquinolones can cause severe hypoglycemia in older individuals with diabetes who are taking oral hypoglycemic agents. We describe a patient without diabetes who had new-onset hypoglycemia when given oral levaquin for pneumonia that developed after cardiac bypass surgery. The condition manifested with profound neurologic disturbances and required intravenous dextrose and parenteral glucagon for treatment. No other cause could be identified, and the problem remitted a few days after administration of the antibiotic was stopped. Laboratory evaluation showed relatively inappropriate insulin elevation at the time of the hypoglycemic episodes, consistent with pancreatic beta-cell stimulation. The report highlights glucose-lowering as an adverse effect of the fluoroquinolone class of antibiotics in persons without diabetes or taking hypoglycemic medication. Although levaquin is useful as broad-spectrum therapy in a variety of situations, clinicians should be cognizant of the occurrence of potentially serious or even fatal hypoglycemia with its use.

QUINOLONES AND BLOOD GLUCOSE ABNORMALITIES (HYPOGLYCEMIA, HYPERGLYCEMIA)
February 17, 2006. University HealthCare.
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The following are reasonable actions to help prevent and manage quinolone-induced hypoglycemia.
Check the patient's age, diabetic status, and renal function. If patient is elderly, has renal dysfunction, or is diabetic, consider other antibiotic therapy. Avoid gatifloxacin use in diabetic patients.
Consider that the hypoglycemia may be drug-induced in any patient who develops hypoglycemic symptoms while on quinolone therapy. The reaction often occurs after the first dose and may persist until fluoroquinolone discontinuation.
Please report any adverse events involving quinolones that you find. At University HealthCare, this may be done by using the web-based Patient Safety Net tool .

This excerpt contains a big mistake, but it is quite revealing. The mistake is that the reaction normally persists months or years after fluoroquinolone discontinuation, and not UNTIL fluoroquinolone discontinuation.

For Tequin, the Dear Health Provider letter issued by the manufacturer is:

FEBRUARY 15, 2006, DEAR HEALTHCARE PROVIDER:
Bristol-Myers Squibb Company has notified the Food and Drug Administration and would like to inform you of important safety information regarding TEQUIN (gatifloxacin) Tablets and Injection. The TEQUIN Prescribing Information has been revised to include a CONTRAINDICATION in diabetic patients due to serious reports of hypoglycemia and hyperglycemia (dysglycemia). Additionally, the WARNINGS and PRECAUTIONS sections have been updated to identify other risk factors for dysglycemia (older age, renal insufficiency, concomitant glucose-altering medications) while taking TEQUIN, and include a recommendation for close medical monitoring.
In postmarketing experience worldwide, serious cases of both hypoglycemia and hyperglycemia have been reported in patients receiving TEQUIN. Although most of these cases were reversible, very rare events of dysglycemia were life-threatening, and a few resulted in fatal outcomes. In light of this data, Bristol-Myers Squibb Company has revised the product labeling for TEQUIN. The following language has been added:
• CONTRAINDICATIONS
TEQUIN is contraindicated in patients with diabetes mellitus.
The following sections have been revised:
• WARNINGS: Disturbances in Blood Glucose
Disturbances of blood glucose, including symptomatic hypoglycemia and hyperglycemia, have been reported with tequin, usually in diabetic patients. However, hypoglycemia and particularly hyperglycemia have occurred in patients without a history of diabetes. In addition to diabetes, other risk factors associated with dysglycemia while taking tequin include older age, renal insufficiency and concomitant glucose-altering medications (particularly hypoglycemic medications). Patients with these risk factors should be closely monitored for glucose disturbances. If signs and symptoms of either hypoglycemia or hyperglycemia occur in any patient being treated with tequin, appropriate therapy must be initiated immediately and tequin should be discontinued.
Transient disturbances in glucose homeostasis including an increase in serum insulin and decrease in serum glucose usually within 3 days of initiating therapy, sometimes associated with severe hypoglycemia, have been reported. Hyperglycemia, in some cases severe, also

> have been observed, usually after the third day of TEQUIN administration. During the postmarketing period, there have been very rare reports of serious disturbances of glucose homeostasis in patients treated with TEQUIN. These include hyperosmolar non-ketotic hyperglycemic coma, diabetic ketoacidosis, hypoglycemic coma, convulsions and mental status changes (including loss of consciousness). Most of these events were reversible when appropriately managed, although a few resulted in fatal outcome.

The Dear Health Provider letter of Bristol-Myers contains several big mistakes. The mistakes are that the injury is not usually reversible, or at least we have seen dozens of cases that are lasting more than 5 years, and this pathology is not rare, but frequent.

This toxicity causes lesions in the pancreas, affecting the whole process of regulating blood sugar. When a severely floxed person takes small amounts of sugar, in a matter of minutes his general state worsens, and the main symptoms are overstimulation of the central nervous system, visual flashes of light and abnormalities, and increase in other neurological symptoms.

Our doctors do not believed our complaints about the quick appearance of glycemia symptoms after ingesting sugar. They suggest it is psycologic, a creation of our minds. They should be better informed and read more, for instance the following report:

> POSSIBLE GATIFLOXACIN-INDUCED HYPERGLYCEMIA
> Amy R Donaldson, PharmD et al Auburn University, Auburn, Huntsville Hospital, Methodist University Hospital, Memphis
> OBJECTIVE: To report a case of possible gatifloxacin-induced hyperglycemia in a nondiabetic middle-aged woman.
> CASE SUMMARY: A 64-year-old Indian woman with an extensive cardiovascular history was admitted for urosepsis. On admission, her blood glucose was 117 mg/dL. She was empirically started on gatifloxacin 400 mg/day; after 3 days of gatifloxacin therapy, her blood glucose was 607 mg/dL. On day 4, therapy was changed to cefazolin for sensitive Escherichia coli and her blood glucose levels began to return to normal.
> DISCUSSION: Although gatifloxacin has been previously reported as a potential cause of both hyper- and hypoglycemia, the exact mechanism is unknown. Several factors that may have been involved in our patient's hyperglycemia are discussed. **She experienced hyperglycemic changes more rapidly than did the typical patients of previous reports**. The Naranjo probability scale suggests a possible drug-related event.
> CONCLUSIONS: The temporal relationship between gatifloxacin administration and the patient's hyperglycemia suggests an iatrogenic cause. Based on our experience and the product labeling, clinicians should be more aware of the blood glucose–altering effects of gatifloxacin.

There are many official reports, but until people have died of it, and a few honest and independent doctors have reported it, this critical aspect of fluoroquinolone therapy was not admitted even by the FDA, agency that has sistematically refused to listen to the complaints of victims, eventhough affected patients keep on denouncing the sugar imbalances caused by quinolones since more than 8 years ago.

The Mayo Clinic say patients taking Tequin need to be aware of the signs and symptoms of blood sugar fluctuations which include:

- Confusion
- Visual disturbances
- Heart palpitations
- Tremors
- Frequent urination
- Increased thirst
- Dry mouth

84. PSEUDOTUMOR CEREBRI CAUSED BY FLUOROQUINOLONES

This is a sort of central nervous system -brain injury also known as intracraneal pressure. Common signs and symptoms of pseudotumor cerebri in the floxed include headache, vomiting, blurred vision, and diplopia.

Headaches are intermittent, diffuse, worse at night, and often aggravated by sudden movement. Visual disturbances include visual obscurations, blurred vision, double vision, and photophobia. Diplopia is almost always horizontal horizontal lines like as on an out of order TV set and it is believed to be secondary to toxicity of the sixth cranial nerve.

Other signs of increased intracranial pressure include lethargy, irritability, neck stiffness, tinnitus, dizziness, clumsiness, and paresthesias. Physical findings of adrenal or thyroid dysfunction may also be present as a consequence, or as a direct toxicity over the adrenal glands, the pancreas, the pituitary and other hormone-producing glands.

It is also accompanied of optic disk nerve swelling (papilledema). Visual acuity is usually preserved helping to distinguish acute papilledema from optic neuritis, that is also caused by direct toxicity.

85. ENDOCRINE MALFUNCTIONS

One of the consequences of a floxing is the alteration of the endocrine (hormonal) system. Hundreds of pages could be written about it, but we just leave here some notions. You can profundize on your own because there is a lot of good information avalaible out there.

The damage caused by fluoroquinolones to the endocrine system is also long lasting. In severe reactions, abnormal ranges of hormones can be detected for many years. Cortisol, growth hormone and thyroid hormones are the best studied among floxed persons. We use here some basic information about the endocrine system, extracted from the Adam database and others.

The endocrine system helps regulate and maintain various body functions by synthesizing (making) and releasing hormones, chemical messengers. The major areas of control and integration include responses to stress and injury, growth and development, absorption of nutrients, energy metabolism, water and electrolyte balance, reproduction, birth, and lactation. The endocrine system is composed of glands that release their hormones directly into the bloodstream for chemical signaling of target cells. These glands include:

- the pituitary gland
- the pineal gland
- the hypothalamus
- the thyroid gland
- the parathyroid glands
- the thymus
- the adrenal glands
- the ovaries (in females) or testes (in males)
- the pancreas

Typically, the body synthesizes hormones in one part and transports it to another through the bloodstream or lymph. Endocrine glands have a rich blood supply through which hormones travel to reach their target organs. Hormones alter the metabolism of target organs by increasing or decreasing their activity. These changes in activity are strictly balanced to maintain homeostasis (a stable internal environment).

Glands are of two types. Endocrine glands do not have a duct system and are called ductless glands. These glands release hormones directly into the blood or lymph. Exocrine glands such as the sudoriferous (sweat) glands contain ducts. Ducts are tubes leading from a gland to its target organ.

The endocrine system and the nervous system are so closely associated that they are collectively called the neuroendocrine system. Neural control centers in the brain control endocrine glands. The main neural control center is the hypothalamus, also known as the "master switchboard." Suspended from the hypothalamus by a thin stalk is the pituitary gland. The hypothalamus sends messages to the pituitary gland; the pituitary gland, in turn, releases hormones that regulate body functions.

Many endocrine glands are linked to neural control centers by homeostatic feedback mechanisms. The two types of feedback mechanisms are negative feedback and positive feedback. Negative feedback decreases the deviation from an ideal normal value, and is important in maintaining homeostasis. Most endocrine glands are under the control of negative feedback mechanisms.

Negative feedback mechanisms act like a thermostat in the home. As the temperature rises (deviation from the ideal normal value), the thermostat detects the change and triggers the air-conditioning to turn on and cool the house. Once the temperature reaches its thermostat setting (ideal normal value), the air conditioning turns off.

An example of negative feedback is the regulation of the blood calcium level. The parathyroid glands secrete parathyroid hormone, which regulates the blood calcium amount. If calcium decreases, the parathyroid glands sense the decrease and secrete more parathyroid hormone. The parathyroid hormone stimulates calcium release from the bones and increases the calcium uptake into the bloodstream from the collecting tubules in the kidneys. Conversely, if blood calcium increases too much, the parathyroid glands reduce parathyroid hormone production. Both responses are examples of negative feedback because in both cases the effects are negative (opposite) to the stimulus.

Positive feedback mechanisms control self-perpetuating events that can be out of control and do not require continuous adjustment. In positive feedback mechanisms, the original stimulus is promoted rather than negated. Positive feedback increases the deviation from an ideal normal value. Unlike negative feedback that maintains hormone levels within narrow ranges, positive feedback is rarely used to maintain homeostatic functions.

PITUITARY GLAND

The pea-size pituitary gland is called the "master gland" because it regulates many key functions. The pituitary gland produces and secretes seven hormones in response to commands from the hypothalamus:

- Thyroid Stimulating hormone (TSH) , usually altered by fluoroquinolones.
- Adrenocorticotropic hormone (ACTH) , sometimes altered by fluoroquinolones.
- Follicle Stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin (PRL)
- Growth hormone (GH) , usually altered by fluoroquinolones.
- Melanocyte-stimulating hormone (MSH)

The TSH, ACTH, FSH, and LH hormones are tropic hormones that simulate other endocrine glands. In response, the other endocrine glands produce hormones that affect metabolism. For example, TSH from the pituitary gland stimulates the thyroid gland to produce thyroid hormones. In turn, thyroid hormones inhibit the release of calcium in the blood.

Other hormones have unique effects upon metabolism. ACTH acts upon the cortex (outer area) of the adrenal gland to produce steroid hormones. FSH and LH act upon women and men in regulating various sexual characteristics.

Prolactin and growth hormone act upon certain body tissues; they do not affect specific organs. Prolactin travels to the breast tissue glands of nursing mothers, causing milk production. Growth hormone stimulates protein synthesis and cell division in cartilage and bone tissue. Gigantism results when excessive amounts of growth hormone are produced during childhood. Pituitary dwarfism occurs

when too little growth hormone is produced. Acromegaly occurs when too much GH is produced during adulthood.

Neuron cell bodies of the hypothalamus produce two hormones: antidiuretic hormone (ADH) and oxytocin. These hormones are transported along the axons to the axon terminals in the pituitary posterior lobe. Both hormones are stored in the terminals until they are released into the blood vascular network surrounding the posterior pituitary gland.

ADH acts upon the kidney tubules to help maintain a constant level of body water. This level is accomplished by increasing the water reabsorption amount when body water levels are low. Oxytocin triggers milk release from breast tissue when infants nurse and causes muscle contractions in the uterus during labor.

THYROID GLAND

The thyroid gland has two lobes connected by an isthmus (small connecting stalk) and is in the lower part of the neck just below the larynx. The thyroid gland produces three hormones:

- Thyroxine (T4), usually altered by fluoroquinolones.
- Triiodothyronine (T3) , usually altered by fluoroquinolones.
- Calcitonin, usually altered by fluoroquinolones.

T3 and T4 are collectively called thyroid hormone and are produced in the follicles (hollow spherical structures) of the thyroid gland. Thyroid hormone affects body growth, metabolic rates, and the development of bones and skeletal muscle. Thyroid hormone also increases the sensitivity of the cardiovascular system to sympathetic nervous activity. This effect helps maintain a normal heart rate.

Parafollicular cells (C cells) between the thyroid gland follicles produce calcitonin. Calcitonin lowers blood calcium levels.

The parathyroid glands are embedded in back of the thyroid gland and secrete PTH (parathyroid hormone). PTH increases blood calcium by stimulating bone calcium release into the bloodstream and by increasing the calcium absorption rate in the gastrointestinal tract and kidneys.

Fluoroquinolones may cause both hypothyroidism, and hyperthyroidism, with some prevalence of the latter. The following list illustrates the spectrum of possible signs and symptoms associated with the various causes of hyperthyroidism:

- Nervousness and irritability
- Palpitations and tachycardia
- Heat intolerance or increased sweating

- Tremor
- Weight loss or gain
- Alterations in appetite
- Frequent bowel movements or diarrhea
- Dependent lower-extremity edema
- Sudden paralysis
- Exertional intolerance and dyspnea
- Menstrual disturbance (decreased flow)
- Impaired fertility
- Mental disturbances
- Sleep disturbances (including insomnia)
- Changes in vision, photophobia, eye irritation, diplopia,or exophthalmos
- Fatigue and muscle weakness
- Thyroid enlargement (depending on cause)
- Pretibial myxedema (in patients with Graves' disease)

TABLE 16
MAIN SYMPTOMS OF HYPOTHYROID

Low stamina, low energy	Major anxiety/worry
Long recovery period after any activity	Irritable, intolerant of others
Inability to stand on feet for long periods	Handwriting nearly illegible
Chronic Low Grade Depression	Internal itching of ears
Suicidal Thoughts	Ringing in ears
Often feeling cold	Lactose Intolerance
Cold hands and feet	Aching bones/muscles , joint pain
High cholesterol	Carpal tunnel symptoms
Bizarre and Debilitating reaction to exercise	Plantar fascitis (painful soles of feet)
Hard stools , constipation	No sex drive
No eyebrows or thinning outer eyebrows	Swelling/edema/puffiness
Dry Hair , hair loss	No Appetite
Dry skin	Fluid retention
Dry cracking skin , broken/peeling fingernails	Swollen legs that prevent walking
Nodding off easily , naps in the afternoon	Blood Pressure problems
Inability to concentrate or read long periods of time	Varicose Veins
Forgetfulness	Tightness in throat; sore throat
Foggy thinking	Swollen lymph glands
Inability to lose weight , always gaining weight	Nausea

► box in green means that this symptom coincides very much with a floxing
► box in orange means that this symtom is contradictory with a floxing

The signs and symptoms of hypothyroidism can include one or more of the included in table 16.

ADRENAL GLANDS

The adrenal glands are on top of each kidney. Each gland has a cortex (outer region) and a medulla (inner region). The cortex secretes glucocorticoids such as cortisol, mineralocorticoids, and small amounts of androgens and estrogens responsible for some secondary sex characteristics. Glucocorticoids raise blood sugar levels by increasing gluconeogenesis (synthesis of glucose from amino acid). This action ensures glucose supplies for the body when it is under stress. Mineralocorticoids such as aldosterone promote sodium (salt) reabsorption by stimulating the kidneys to absorb more sodium from the blood. Cortisol is normally raised a lot by fluoroquinolones. Aldosterone too.

The medulla "emergency gland" develops from nervous tissue; the autonomic nervous system controls its secretions. The medulla secretes epinephrine (adrenaline) and norepinephrine (noradrenaline), chemicals that raise the blood levels of sugar and fatty acids. These hormones also increase the heart rate and force of contraction. These effects prepare the body for the "Fight or Flight" response (instant physical activity), enabling the individual to think quicker, fight harder, and run faster. These hormones also constrict the blood vessels supplying the skin, kidneys, gastrointestinal tract, and other areas of the body not needed for the response.

OVARIES AND TESTES

The ovary is the site of estrogen and progesterone synthesis. Estrogen is required to form the ovum (egg) during oogenesis and prepares the uterus for implanting a fertilized egg. Progesterone prepares the breasts for lactation during pregnancy and works with estrogen to regulate the menstrual cycle.

The testes produce the hormone testosterone. Testosterone is required for sperm formation during spermatogenesis, the development of male external genitalia, and secondary sexual traits such as beard growth, chest hair, and enlarged thyroid cartilage. Testosterone is decreased below normal levels by fluoroquinolones.

This section is under more detailed preparation, for the next edition of the present report.

86. SURVIVING FLOXING INSOMNIA

Quinolones cause insomnia that can be very radical. It is a direct injury of the central nervous system. There are persons that cannot sleep more than 2 or 3 hours a day for 2 years or more and never feel the need to fall asleep, no matter how collapsed their minds can get. They are wired and alert all the time. Insomnia puts a lot of people on the verge of collapsing both physically and mentally. For many, it is the heaviest burden imposed by the quinolones.

Some floxed persons, particularly those that do not have a severe reaction, respond well to conventional man-made sleeping pills. Most severely floxed persons get no relief with sleeping medications, and their side effects can be very harmful, given the weakened state of the neurons that they target.

For the first months (acute phase) nothing seems to help, neither with the insomnia, nor with the panic attacks that overwhelm people when getting momentarily asleep or eyes-wide-open distracted. Later, people can try less aggressive tactics, among which success has been reported with the following:

- Herbs like hawthorn and valerian root. All vasodilators like hawthorn help with insomnia.
- Amino acids like arginine (with vitamin E and C), that is also a potent vasodilator, and the vitamins act as antioxidants.
- A combination of bilberry, vitamin E and probiotics.
- Deep breathing plus relaxation, brings blood to the brain.
- Lowering the temperature of the limbs with the worst neurological nocturnal pains
- Favoring foods with vaso-dilating or soothing effect: red peppers, lettuce,....
- And, of course, avoiding all coffee, chocolate, caffeine and sugar

Example of useful preparations for tackling insomnia, as reported by a floxed person that has experienced it with some success for him and others:

- Do not drink caffeine, cokes or eat chocolate during the whole day.
- Avoid stressful situations during the day, if possible.
- Do not take sugar (including soft drinks) during the whole day.
- Do not take garlic or thinners during the day.
- Two hours before bed, have a dinner with the following dishes (if you like them), all selected on purpose:
    - Plenty of green leafed lettuce with olive oil, natural salt and organic apple vinegar.
    - Some oceanic king prawns or shrimps, just grilled (no sauces) with a large roasted red pepper, all with some virgin olive oil. Or an organic egg.
    - Some red grapes and/or bilberries.
- Half an hour before bed take some chlorella and probiotics with half a glass of organic milk and a teaspoon of organic bee honey.
- At bed, prepare the room so its temperature is adequate, and then do breath slowly and very deeply some fifteen times, to the fullest capacity of your lungs.
- If you want to add an extra strong aid, take some top quality hawthorn, that acts vasodilating and therefore, the brain can be properly irrigated and sleep is ensued.

87. FLOXING AND CANDIDA

All chronically floxed persons have thought at one time that an answer to their problems could be in a yeast overgrowth.

Although candida overgrowth do happen in many cases, its erradication and treatment has not made a difference on the course of a floxing.

If you follow a diet specifically intended for a floxing, you will not take sugars and that helps to keep

yeast under control. A radical elimination of all carbohydrates from your diet is not adivsable, specially if you are a carbohydrate type, unless candida has become your main health issue, confirmed with tests.

88. FLOXING AND HELICOBACTER PYLORI

There is a pathogen bacteria, called helicobacter pylori that colonizes the stomach mainly, from where it is very difficult to erradicate. The treatment consists of the combined administration of two antibiotics and a stomach acid modulator at the same time. The rate of recurrence is very high. This bacteria is strongly linked with stomach ulcers, and eventually with stomach cancer. It strives in low acidic stomach fluids.

Infection may be symptomatic or asymptomatic (without visible ill effects). It is estimated that up to 70% of infection is asymptomatic. The bacteria have been isolated from feces, saliva and dental plaque of infected patients, which suggests gastro-oral or fecal-oral as possible transmission routes.
It is estimated that about 2/3 of the world population are infected by the bacterium. Actual infection rates vary from nation to nation - the West (Western Europe, North America, Australasia) having rates around 25% to 50% and much higher in the Third World. In the latter, it is common, probably due to poor sanitary conditions, to find infections in children. In the United States, infection is primarily in the older generations (about 50% for those over the age of 60 compared with 20% under 40 years) and the poorest.

Helicobacter pylori. Up to one third of the population of the western countries, and 50% of certain ethnic groups are or have been infected by this bacteria that resides in the stomach and is linked to ulcers and perhaps cancer. Some of the symptoms of an helicobacter infection are similar to those of a floxing. Some floxed persons have resolved all their remaining symptoms after a therapy of erradication of helicobacter. The standard treatment requires a combination of two or three antibiotics (not quinolones, fortunately).

On the other hand we know of a woman that developed a floxing after being treated with cipro and another antibiotic for helicobacter. These cases are rare.

One can test for H. pylori infection with blood antibody or stool antigen tests, or with the carbon urea breath test (in which the patient drinks 14C- or 13C-labelled urea, which the bacterium metabolizes producing labelled carbon dioxide that can be detected in the breath), or endoscopy to provide a biopsy sample for testing for the presence of urease "rapid urease test", histology or microbial culture.
None of these test methods are completely failsafe. Blood antibody tests, for example, range from 76% to 84% sensitivity. Medication can affect H. pylori urease activity and give "false negatives" with the urea-based tests.

Today the standard triple therapy is amoxicillin, clarithromycin and a proton pump inhibitor such as omeprazole. Proton pump inhibitors are a group of drugs whose main action is pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today.

Many floxed persons have positive antibodies for helicobacter (the same ratio than the general population), what means that they have been infected by helicobacter in the past, or are currently infected. We do not know what links exist between the bacteria helicobacter pylori and the intensity of the symptoms of a floxing, despite having investigated it a lot. Apparently, the abrupt temporary decrease in the level of symptoms when a severely floxed person vomits makes some people think that it is due to the diminished helicobacter concentration, until their numbers reach the maximum again. So there is a tendency to believe that symptoms are worse and stronger on infected subjects.

We do not handle any report about erradication therapies on floxed persons infected with helicobacter.

89.OTHER DISORDERS YOU MIGHT EXPERIENCE

As we have seen before, half of the quinolones marketed since their creation have been withdrawn from the market because of their potentially fatal toxic profile. Some had a marked inclination to destroy the liver (trovafloxacin), others the heart, and all are very toxic to vital organs as a class effect. It is not uncommon to get abnormal results in serum tests for many months after discontinuation of the drug.

On top of the general problems that you may have due to the toxicity of the quinolones, many people have additional problems, due to alterations of functions or systems that were working well but in delicate equilibrium before taking the quinolones. For instance, if without knowing it you suffered a little osteoarthritis because of overuse during your endurance sports, or a short leg, asymmetrical muscle mass, lack of flexibility or the like, all of them will become very noticeable when your floxed body cannot compensate for any minor flaw.

When you suffer strong quinolone-induced neuropathies of the extremities, you will experience a great loss of function and some atrophy (wasting) of the main muscles. Sometimes it is very difficult to detect unless tested by a professional. But you can notice that your legs can hardly raise you up, or are nor longer able to climb stairs by the many. Muscles most frequently subject to wasting are the tibialis anterior (outer part of the shin), soleus (deep to the calf), gastrocnemius (calf), vastus medialis (inner quad close to the knee), the other quadriceps muscles, and the shoulder and forearm muscles.

Atrophy of the muscles that control a joint make this joint more prone to injury, normally from repetitive loads. So the vicious cycle starts: the neurological injuries waste the muscles, so joints are overloaded, or eccentrically or abnormally loaded, and they degrade, creating another layer of pains and disability that combines with the previous one and that contribute to a never ending “snowball effect” injury.

So, it is important that as soon as you feel well enough that you begin a stretching (mild to avoid neurological irritation and cartilage injuries) and strengthening (mild to avoid cartilage degradation) training program for your most affected joints.

The neuropathies caused by fluoroquinolones also affect the nerves that control the chest muscles, so the floxed person tends to breath abnormally, and with very shallow chest movements. As a result, not enough oxygen is introduced in the system, and some metabolic processes become even more impaired. Insomnia is greatly worsened by shallow breathing.

90.MIXED CONDITIONS

This report does not deal with a floxing in context with other previously existing health conditions. Floxing is a very debilitating illness in and of itself, but its complications can multiply if before the drug intoxication there were other pre-existing disorders such as lupus, lyme disease, rheumatoid arthritis, multiple sclerosis or even osteoarthritis.

PART XII:
CAN THIS REALLY BE HAPPENING TO ME?

91.THE PSYCHOLOGICAL ASPECT IN SEVERE REACTIONS

You were a young active person, lead a healthy life, and ate healthy. You had a good job and were a brilliant professional. Your family is lovely. You merely had a minor health problem like a sinus infection, a sore throat, a urinary tract infection or a suspected or actual prostatitis. You trusted your medical system and you were prescribed a quinolone antibiotic. Finally, you have had a severe reaction.

Now you cannot play any sport, not even playful wrestling with your children. You have cognition problems that disrupt or stress your career. You can hardly sleep. Your vision is constantly bothering you, reminding you all day long that you are ill. You feel constant, intense and strange pains, you cannot sit in any comfortable position, you have problems getting in and out of the car, and you resemble an 80- year old man. You have to watch what you eat carefully, so you are barely able to attend social events anymore. For months on end your symptoms get worse by the day.

Some nights you cry in solitude. You have little understanding and/or compassion from your loved ones because you still look normal on the outside. It is 3 years since you got hit and your youngest child does not know what you were like before the floxing because he was too young; he only knows you as a permanently ill father that cannot even eat normally. Perhaps your co-workers think that you are exaggerating or pretending that you are ill. Your doctors are not willing to listen to you correlating your problems and symptoms to a fluoroquinolone antibiotic. After a year or so, your symptoms have gotten worse, but surprisingly all of your acquaintances, friends and relatives give up sympathizing with your situation because it is lasting so long, so you start to feel more alone. Many suggest, or tell you boldly, that your problems are all in your mind.

Most tests are negative so you remain undiagnosed. All severe cases reveal abnormalities in neurological studies but they are attributed to physical compressions for instance and they offer you a surgical release that you know won't fix anything. Nothing seems to help with your recovery. Nobody seems to have any knowledge about your disorders. You spend enormous sums of money and time on doctors and palliative therapies. Your daily life is a constant struggle against your illness, and you cannot release yourself from your daily obligations because nobody acknowledges your chemically altered state, and so you become stretched to the limit.

After the first stage, in which you just fight for mere physiological and psychological survival, one day you find yourself staring at people just getting out of the car, sitting in awkward positions, walking up stairs, walking normally, eating normal food in a good restaurant, planning to trek, bike, travel or play, and dream of a day in which you will also do it as effortless and so unaware of doing so as you did before the floxing.

Note:
Try to seek help from loved ones and caring doctors. You will need it.

You are going to need some help, either from a professional, your family, from friends or from support groups. But it is very difficult for a non-floxed person, even a loving and caring one, to truly grasp the magnitude of your chronic suffering from a quinolone antibiotic. This is not a matter of weeks or months, but of many years. After 2 or 3 years you cannot remember any longer how it was like to feel physically normal. You become increasingly weary and long for a normal life. You are scared about the permanent injuries you seem to be facing, and above all you do not know what lies ahead in terms of limitations and deterioration. Your mental drive

sometimes falters and you are overwhelmed by the floxing in every way. Depression will linger. Suicidal thoughts are not uncommon, but in most cases, they are short lived or insufficiently based, although repetitive. Some floxed persons have taken their lives.

Be prepared for very distressing and disheartening states of mind and body and be determined to keep moving forward. Stay positive as much as possible. Time is your only real friend in this unequal and unfair fight. Mild and intermediate floxings usually have a happy end. After a severe floxing it is unlikely that you will recover your former self entirely. And after realizing it you will have to admit it and then restructure your life because of it.

92.IT IS ALL IN YOUR HEAD

As a result of the intoxication, you may have actually suffered mental damage. These cases are not treated in this paper. We are assuming that you have been lucky enough that your brain has withstood the treatment with the quinolones, so most likely, your mental status will have suffered but your mental integrity will be untouched except for those initial alterations very common in the acute phase: depersonalization, crying episodes, brain fog, memory loss, confused thinking, inability to focus and concentrate and having cluttered, racing or abstract thoughts, panic attacks and the like.

On the other hand, if you have suffered a strong reaction and if you were healthy before, you know perfectly well what are your symptoms and you do not need help to identify them or to asses the limitations that they impose on your life. You might also be frightened by the unknown evolution of your injuries, and be a little depressed by your overall current situation.

Many people that surround you will perceive this sadness, that is humanly natural, and perhaps one of your doctors suggest that you should pay a visit to a psychiatrist. In principle, a good psychiatrist can be very helpful. But an arrogant and ignorant psychiatrist can cause you a lot of harm.

From a floxing point of view, many psychiatrists are incompetent: because they do not have any notion or knowledge about toxicity of quinolones and are not inclined to study these new situations posed by patients. It is totally unacceptable that psychiatrists are uneducated in regards to and know virtually nothing about the high potential of brain damage that all quinolones can cause. With extreme frequency, the fluoroquinolones cause mental alterations that can last from a few weeks up to permanent damage.

Anyhow, regardless of the ignorance of your physician, you have to be honest with your psychiatrist. So, while answering his questions, you will probably at some point tell him that:

- You are having a reaction to an antibiotic and you are ill since long ago, that symptoms do not seem to abate but sometimes they even increase; that you have cycling of symptoms. [INCOMPETENT INTERPRETATION: long illness, strange illness, weird theory about antibiotics, worsening after stopping the treatment while everybody knows that all reactions start to clear after the drug is discontinued, cycling linked to mood changes].
- Some or all of the tests they have done on you are clean: your blood tests, the MRIs, and so on. [INCOMPETENT INTERPRETATION: this patient has clearly invented and is imagining his ailments; had he any real problem, it would clearly show up on his tests].
- Some people around you no longer sympathize with your situation because you look fine on the outside, so you do not talk much about it any longer. [INCOMPETENT INTERPRETATION: normal persons that live with him have got fed up of his rarities]
- Some other doctors think you have fibromyalgia or nothing at all. [INCOMPETENT INTERPRETATION: I am right and this patient has become obsessive about an imaginary severe illness].
- You follow a carefully selected diet, avoiding aggravating foods and foods that may contain quinolones [INCOMPETENT INTERPRETATION: clearly you see quinolones in every corner that are

lying in wait for you]

So, your psychiatrist may conclude that you:

- Are suffering a paranoid delusion of the somatic type, that is to say, that you harbor false beliefs about your body - for example that a physical illness exists (your intoxication) when it does not-.
- That your delusion lasts for more than one month (you have been believing for months or years, in fact since you discovered it, that cipro or levaquin is the cause and the sole cause of your miseries).
- You exhibit negative symptoms, for instance:
  - the inability to enjoy activities as much as before
  - low energy -lack of drive-
  - lack of interest in life, low motivation
  - lack of interest to socialize with other (healthy) people as before
  - social isolation- spend most of the day only with close co-workers or family

Does it all sound familiar to you? Do those symptoms fit with your situation? Well, bad luck, the above symptoms are the literal transcription of the full USA criteria for definitively diagnosing schizophrenia (paranoid delusion somatic type). Obviously you are going to leave the psychiatrist's office with the diagnosis tag of schizophrenic-paranoid-guy only if your psychiatrist does not give any credence to the possibility that your reaction to quinolones is real, no matter how little knowledge about it may he have, and if he does not take into account the whole picture in detail.

Some floxed persons have patiently and humbly confronted the first diagnosis of paranoid delusion handed to them by their psychiatrists. They argued that if they are cured, all would be forgotten, and their doctors responded almost invariably that in that case, they (the patients) would inadvertently look for another obsessive delusion because it is all in their heads.

If you insist over the issue, stressing that you believe that you are suffering the bad effects of a fluoroquinolone antibiotic, it is possible that you give the position to your psychiatrist to ratify his initial diagnosis. Some of the things that you can, and must say freely if you believe are that way, but that might reinforce his conviction that you are suffering a delusion state (paranoid) are:

- Certainty (you hold your position with determination)
- Incorrigibility because you do not change your idea when confronted with proof to the contrary (his educated knowledge about medicines that he is supposed to have)
- You maintain an impossibility (it is patently untrue that quinolones are benign antibiotics)
- Your speech abilities are now impaired, you forget things or words, and sometimes you are mentally low.
- Your wife is a little weary with your situation because it affects your daily habits and diet
- You do not sleep as well as before

In summary, not few floxed persons have ended up with a diagnosis of paranoid delirium (a sort of schizophrenia) of the somatic type (the one related to exaggerated thoughts of an illness) and their doctors have prescribed them some anti-schizophrenic drugs like aripiprazole (Abilify), clozapine (Clozaril), ziprasidone (Geodon), resperidone (Risperdal), quetiapine (Seroquel), olanzapine (Zyprexa).

Your psychiatrist may explain you that there are several types of brain receptors like noradrenaline, GABA, dopamine, glutamate, acetylcholine or serotonin, whose alterations can cause severe psychotic behavior. Your problems were latent ("dormant") up to now, but now your dopamine receptors have degenerated because you were born prone to it and there are no other alternatives, your doctor says, and the medication is the only way out towards your cure.

Those anti-psychotic medications have many side effects that look very uncompatible with a floxing. They can be necessary for a true paranoid or delusion disorder but surely not for you. Think twice before you decide to take them. Looking to the experience of others, they might make you much worse because they block the dopamine receptors, or enhance the acetyl cholinergic effects on your brain, be it through inhibition of acetylcholine metabolism, or by acetylcholine substitution. If you are sure you have a severe reaction, do not take them because the first pills consumed of the above mentioned drugs would greatly damage you, according to absolutely all-previous experiences of other people. You should only risk taking them if you are sustaining a moderate floxing

And do not be afraid of reassuring yourself that you are not living in a delusion state, but that you are a true participant of a real nightmare. In some cases the delusion may be assumed to be false by the doctor or psychiatrist assessing the belief of the patient, because it seems to be unlikely or held with excessive conviction. Psychiatrists rarely have the time or resources to check the validity of a person's claims leading to some true beliefs to be erroneously classified as delusional. In other words, that when psychiatrists meet strange cases like yours they can make a mistaken diagnosis.

Note that the diagnoses of delusions are based on the subjective understanding of a particular psychiatrist, who may not know enough about the issue that might make a belief otherwise interpretable. So, if you are diagnosed as suffering a paranoid delusion, probably it is your doctor's fault because he/she knows nothing about the floxing syndrome.

93.THE TRUE BIOLOGICAL DAMAGE TO YOUR BRAIN

The neurotransmitters more affected by your intoxication are not the dopamine receptors as many psychiatrists tell their floxed patients, but the GABA (Gamma-aminobutyric acid) and cholinergic ones. You have learned in previous sections that in humans, GABA acts at inhibitory synapses in the brain and spinal cord. This means that whereas normal GABA function consists of landing at points (called GABA receptors) that act as brake-slowing down buttons of the nerves of the brain and spinal cord preventing the nervous system of becoming wildly wired, quinolones "attach" (or rather destroy, according to our theory) themselves to the GABA receptors so they impede the GABA molecules from doing their job. Delirium and hallucinations associated with the fluoroquinolones have been extensively reported, particularly with levofloxacin and ciprofloxacin (because they are the most prescribed but in fact is a class effect). The proposed mechanism involved in the development of such side effects seems to be related to the quinolones' ability to inhibit the binding of GABA to the GABA receptors, leading to CENTRAL NERVOUS SYSTEM excitation.

The structural component of the fluoroquinolone molecule believed to be responsible for improved gram-positive activity is also believed to be implicated in the production of CENTRAL NERVOUS SYSTEM adverse effects. Direct pro-convulsant mechanisms of quinolones may relate to gamma-aminobutyric acid (GABA)–like substitutes, which act as GABA-receptor antagonists. The damage can be enhanced by the co administration of NSAIDs and quinolones. This is one of the main reasons for avoiding NSAIDs during the recovery from a floxing. The NSAIDs pose high risks over the central nervous system; and in fact, all nerve-throbbing pain on joints is highly increased by all NSAIDs in severe floxings.

It would be nice if a highly toxic chemotherapeutic agent like the quinolones was very selective and only affected the GABA neuro-receptors. Although not so widely published and known, there are other negative effects the quinolones exert on the neurotransmitters as you can learn in previous sections of this report. There it is explained how quinolones seem to have an anti-cholinergic effect (because they appear to block acetyl-choline, so that there is less availability of acetyl-choline) both at brain and peripheral levels. Central side effects of blocking acetyl-choline include confusion, disorientation, memory loss, hallucinations and paranoia. Blocking acetyl-choline in the periphery can result in a fast heart rate, dilated pupils, dry mouth, constipation, difficulty urinating, and dry skin for instance, symptoms all present in a severe reaction to a quinolone.

The side effects result from blocking acetyl-choline centrally, in the brain, in a region called the Nucleus Basalis. The Nucleus Basalis is related to the amygada which orchestrates the brain's response to anxiety and fear, and the hippocampus which stores the brain's memories. So your anxiety, panic attacks and memory issues in your acute phases do not seem so unexplainable.

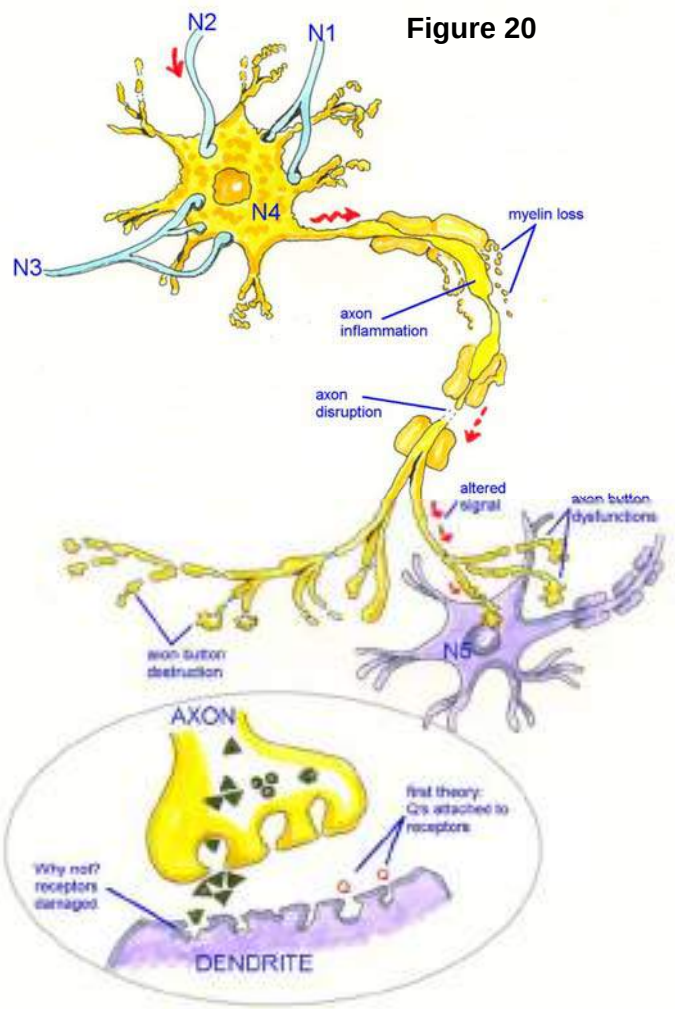
Well known drugs that are very hard on the acetyl-choline functioning, causing multiple health problems, include antibiotics such as gentamycin, cipro, erythromycin and ampicillin; beta-blockers such as propranolol (Inderal) and timolol, calcium channel blockers such as verapamil, lithium and magnesium (many floxed persons cannot tolerate it) and in general anti-cholinergic drugs.

Figure 20 (repeated here for details concerning interpretation). When the neurons have been damaged by the quinolones, one, several or all of their functions might be altered resulting in motor or sensitive neuropathies, some very long lasting and also permanent for severe cases.

After a severe intoxication by quinolones there are nerves and nerve endings that simply DIE. Some other nerves are more or less injured. The injuries affect the receptive capacity of the dendrites and the ability of the axon to transmit signals.

Biopsies of floxed persons show axon inflammation. In some cases (the least) some demyelination has been reported.

If the axon has been disrupted, the signal is not transmitted. In many other biopsies, the density of nerves has diminished.



In most cases, the alterations are known to happen at the transmission-reception level. The official theory that we have read in so many medical reports is that quinolones "bind" to receptors (above all GABA receptors), blocking the entrance of the GABA neurotransmitters.

We prefer to believe that the receptors are **damaged**, and not only the GABA ones but all of them, altering the whole neurological process.

According to the first (official theory), the quinolones would have to be removed, chelated or flushed from the sites of GABA receptors before feeling some recovery. That does not fit with the real life experience of most floxed persons. We believe that in order to feel better again and recover it is necessary that nerves regenerate either by recovering or by growing new terminals, and that takes time.

All the fluoroquinolones are distinctive for having proven adverse effects, very sudden and with severe intensity in some cases, over the central nervous system. How can they be considered benign antibiotics by most doctors is a question that remains to be answered.

FLUOROQUINOLONES AND THEIR ADVERSE EFFECTS ON THE CENTRAL NERVOUS SYSTEM
Fluoroquinolones differ from other antimicrobials, not only structurally, but also by their mechanism of action and quite unique profile of adverse drug reactions. The adverse reactions include the more unusual characteristic of tendinitis. Other characteristics, almost as rare, are the adverse drug reactions on the central nervous system, attributable to all drugs in this group. Adverse drug reactions related to the central nervous system are observed in ½ - 2% of patients treated with fluoroquinolones, depending on the substance and the dosage. Fluoroquinolones can cause convulsions in susceptible patients especially when taken with antiinflammatory analgesics. The increased tendency to convulsions due to interaction is reason enough to **avoid the consumption of fluoroquinolones with antiinflammatory analgesics**, also bearing in mind the patient's potential consumption of over the counter analgesics. Furthermore, the interaction of fluoroquinolones with malaria drugs, especially mefloquine, is worth remembering when looking for causes for sudden unusual psychiatric symptoms.

We do not agree entirely with the contents of the above report, obviously. The information is biased as always, because it does not differentiate among dosages. Perhaps those rare events and low percentages correspond to doses of 250 mg of cipro for a week, however, the real toxicity for the highest therapeutic doses is indicated in table 3 of this floxing report. The World Health Organization report states that taking anti-inflammatory medications together with quinolones causes a well-known worsening of symptoms. When taken with quinolones, anti-inflammatories can cause susceptible people to develop convulsions and seizures, and experience increased neurologic pains. It is also interesting to consider the "interaction" between quinolones and malaria drugs. It is not a true interaction, but a doubling of effects because both drugs compete for the same metabolism and share 80% of the same adverse effects.

DETERMINATION OF THE EXCITATORY POTENCIES OF FLUOROQUINOLONES IN THE CENTRAL NERVOUS SYSTEM BY AN IN VITRO MODEL. Antimicrob agents chemother. 1998 july. Copyright © 1998, american society for microbiology
Gabriele Schmuck, Anja Schürmann, and Gerhard Schlüter
Quinolones have been reported to induce central nervous system (CNS) reactions in humans including seizures and psychiatric events with an incidence of 0.9 to 2.1%. However, severe psychiatric or neurological reactions like hallucinations, periods of depression, nightmares, or convulsions are relatively rare. Convulsive seizures are reported after quinolone treatment mostly in the elderly or in patients with a history of epilepsy, cerebral trauma, or alcohol abuse. The proconvulsant activity of fluoroquinolones depends on the chemical structure and might be a critical endpoint of some new representatives of this valuable class of antimicrobials.
In this model, enoxacin, nalidixic acid, and ofloxacin were the most potent convulsants, whereas ciprofloxacin, norfloxacin, and pefloxacin were less active.
Different drugs, such as methylxanthine derivatives or nonsteroidal **anti-inflammatory drugs, potentiate the convulsant activity** of fluoroquinolones. The adenosine or γ-aminobutyric acid (GABAA) receptor has therefore been proposed as a possible target for quinolones. In addition, interactions of quinolones with the dopamine and opiate receptors were also postulated
Interestingly, Tanaka et al.showed that fluoroquinolones decreased the blocking effects of Mg2+ and MK 801 binding to the receptor channel. They therefore characterized the fluoroquinolones as "open channel blockers." This is supported by our findings on the effect of Mg2+ on the population spike amplitude, again underlining the involvement of the NMDA receptor in the fluoroquinolones' convulsive action. Considering the Mg2+ chelating properties of fluoroquinolones, which have been also postulated as a mechanism for fluoroquinolone action in juvenile cartilage, it is tempting to speculate that the excitatory potency of fluoroquinolones might be based on activation of the NMDA receptor by abolishing the Mg2+ block in the ion channel. This would prolong the opening time of the channel, thus increasing intracellular Ca2+ concentrations and the excitability of the neuron.

94. SOMETIMES THE DELUSION IS NOT MISDIAGNOSED

Not always the brain of floxed people withstand the chemical onslaught of the fluoroquinolones. There are hundred of reports like this one

PSYCHOPHARMACOLOGY REVIEWS: February 2007. David L. Ginsberg, MD
Tisch Hospital's Department of Psychiatry at New York University Medical Center. CIPROFLOXACIN-INDUCED MANIA
The fluoroquinolone ciprofloxacin is among the most frequently prescribed antibiotics. As a class, the fluoroquinolones are an underrecognized cause of drug-induced neuropsychiatric effects, with cases reported of psychotic reactions to ciprofloxacin both orally and topically in the form of eye drops. A newer fluoroquinolone, gatifloxacin, has also been associated with delirium and psychosis..../...
The temporal sequence of events in the case described is consistent with oral ciprofloxacin-induced mania. As in the patient reported here, adjunctive treatment with anti-manic drugs may also be required, at least temporarily. The prognostic implications psychiatrically for patients who develop these reactions is unclear; while many likely will never experience a recurrence of mania, it is possible but unproven that those with a latent bipolar disorder are more susceptible to developing these reactions to begin with.

95. SPONTANEOUS REPORT ONE YEAR POST FLOXING

Reproduced with permission of the person who posted it in an open online forum:

Obviously, if I was doing much better, I probably wouldn't be writing this. The fact is that my joints, tendons, and nerves are at their worst point yet, but I haven't given up hope that they'll get better. All these symptoms kicked in one year ago, soon after I took 14 days of Cipro 500mg.
I never thought I'd miss those early months of Cipro poisoning -- "floxing," as other victims call it -- but unfortunately I do, because my symptoms/ADRs have only intensified over the months since then. In fact, I miss just TWO months ago. I was better then. Here's some of the adverse reactions I've suffered from this antibiotic:

TENDON/MUSCLE RUPTURE: Like a lightning bolt out of the clear blue sky, a muscle in my calf tore away from its tendon and right down the middle about like five or six inches, two months after Cipro. I was just walking to my car when it ruptured spontaneously and I was instantly crippled. Could only hobble. Unbelievable pain, especially if I tried to use that leg in normal ways. No surgery required, though, just physical therapy and a leg splint/boot, and it has healed decently, god bless, though it cramps up for days if I try to run (apparently from all that scar tissue in there). I take it easy now. No jumping, running.

ULNAR NEURITIS: This is at its worst. Pinky and ring fingers go completely numb more than ever, particularly when sleeping, but now somewhat in the day, too. Muscle weakness in forearm muscles that control those fingers is horrifying and somewhat disabling. (Muscle weakness is a much more unpleasant and horrifying symptom than you'd imagine if you've never experienced it). Also have muscle weakness in many other areas, including legs. Any hardcore muscle use for even a small amount of time causes days of soreness/rubbery-ness.

JOINT PAIN/MUSCLE/TEDONITIS PAIN: this has really amplified to great degree in last few months, especially in shoulders/neck/collarbone area. Sitting still is the worst: a one- hour plane flight is just murder. Also has worsened in elbows, hips, ankles, forearms, thighs.

JOINT NOISES/"POPS"/PAIN: All over my body, but especially in shoulders and collarbone and rotator cuff area, this has only intensified. Started with just big joints. Now occurs even in tiny joints (fingers, toes). Shoulders, when 'rotated' produce gross gristly noise, and much discomfort. My jaw joint is possibly the worst of all. It has developed clicks/pops on both sides and the tension around it is unbelievable...sometimes it goes beyond popping and it sounds like something is cracking violently in there when I yawn; sometimes it feels like it's gonna dislocate... seriously. Could be stress-related TMJ syndrome; could be joint has changed like so many others in my body seem to have changed.

DRY EYES: This persists, sometimes waking me up as my eyelids feel like sandpaper. The worst, though, is dry mouth. (this wakes me up too, and is very uncomfortable. When it's bad, nothing makes it go away.). Also have developed dry nose/sinuses, which just sucks. Used to have really, really waxy ears too. Now Q-tips come up empty, as wax is drying up. This general dehydration seems tied in to more frequent headaches.

MUSCLE SPASMS/FASCICULATIONS: Actually decreased in first year but have come back with increased intensity. Calves are the worst for these symptoms, but I get muscle fasciculations

anywhere in my body, even in tiny muscles in my face. Buzzing has come back too, though not so much in feet and calves where it first started.

NUMB MOLARS: Dentist is suprised that suddenly I have no sensitivity molars starting earlier last year. He says it could be nerve damage near the teeth or 'further upstairs'.... Hmmmmm.

INSOMNIA: This side effect has been an up and down battle. There have been periods where it has not been so bad. but, it still strikes about 50 percent of the time, like right now. Contributes to...
MEMORY PROBLEMS: This is so REAL. I forget stuff like never before. For example, I'l open a cold bottle of water from the fridge, take a few sips. A minute later, open fridge, get another bottle, open it, forgetting I already have freshly opened one on the counter.... that kind of stuff. Remembering names is perhaps the most difficult. Forgetting where I'm going when driving (i.e. spacing out and missing turns, etc., lapsing into default driving routes), is very common now too..It's directly tied into ...

BRAIN FOG/DEPERSONALIZATION: This has been an up and down battle and was pretty scary at times. It's with me constantly since Cipro, often accompanied by gag-y feeling in my throat and difficulty speaking long sentences, but I have noticed that two things help minimize it: Sleep (if possible) and not focussing on it. Also seems tied into minor balance/ coordination problem. I have taken no meds of any kind since Cipro, other than tylenol and a little aspirin/ ibuprofen. And I took no medicine before Cipro either for about ten years.

There are more symptoms that I don't post here. Cipro has changed my life, but my doctors don't believe it. I can understand somewhat because they're not trained to understand or believe in things they cannot directly observe: Their whole approach is based on measuring things, and few of my symptoms are tangible to them.... They can't SEE my major problems, and they dismiss the smaller problems (dry mouth, dry eyes, eye floaters, ringing in ears, dizziness, memory problems, insomnia, etc) as unrelated to Cipro...."You took Cipro MONTHS ago. It's not in your system anymore." I think they agree the tendon/muscle rupture was Cipro caused, but they seem to think that since that healed, I should be fine now. They don't realize that that rupture was just the tip of the iceberg; that IT was a symptom of something much bigger that has happened to my entire system. Plus, they (at least some of them) just don't READ! They don't read the latest prescribing info (my doctor didn't know Cipro can cause tendon ruptures until I informed him!), and they certainly don't read studies that have documented these adverse reactions. All they know is that they prescribe Cipro all the time to patients and rarely do any of those patients report bad side effects (because the side effects often manifest much later). Honestly, if I only had a mild reaction -- say dry eyes, some muscle pain, and dry mouth -- as nasty and long lasting those symptoms are, I might never have realized they were from Cipro. And never reported them. I believe many people diagnosed with fibromyagia, chronic fatigue, arthritis, Sjogren's syndrome, and even mutiple sclerosis may in fact actually be suffering the long-term side effects of an adverse reaction to Cipro, Levaquin, Floxin, or other fluoroquinolone ("flox") antibiotics.

96. SOME REFLECTIONS TWO YEARS POST FLOXING

Reproduced with permission of a person that was floxed, describing his state at the two year mark:

I was prescribed 3 weeks worth of cipro (fluoroquinolone antibiotic) twice per day for a suspected prostate infection. The doctor never performed a culture to detect for presence of bacteria or actual infection.

I did not think anything of taking this drug Cipro; and had no inkling as to what was about to happen to my life and my body. Around the time of finishing the prescription, I developed eye issues: depth perception issues, blurring of vision, double vision, floaters, and photophobia. And my nervous system went into overdrive. I began to feel heaviness in my legs and some pains in my knees. It was as if a shotgun went off in my body and all of these strange symptoms occurred all at once.

Being a healthy young athletic male in my late 20s, I didn't think too much of all these symptoms...they were strange, indeed. At the time I never made the correlation with my symptoms and the prescription of Cipro.

Later that year I was prescribed more Cipro and took it for one week. At this time I developed even more disturbing and alarming symptoms throughout my body: joint pain in my knees, hips, ankles, wrists, and shoulders. I developed Achilles tendinitis in both Achilles, and my Achilles would stiffen up and claudicate so much that I could barely walk or move my ankle in a normal motion. My legs began to pulsate, vibrate and throb with pain, as if someone had wired electricity into them. My skin burned

all over. Eyes became very sensitive to light. Ears began to ring (tinnitus) loudly and became very sensitive to normal sounds, let alone loud sounds like traffic or a loud ambulance siren. My mind began to experience extreme anxiety, depersonalization, and depression.

Something was not right. How could I be a normal healthy young male in peak athletic shape with a love for running and all of the sudden be in so much pain all over my body and barely able to walk down the street? I researched the side effects (or adverse reactions, ADR) of fluoroquinolone antibiotics (cipro, levaquin, floxin, tequin, noroxin) and realized that of the over 40 side effects I was experiencing, all were listed in the pharmaceutical drug insert for cipro. Why did the doctor never warn me?

I stopped taking the drug immediately. It was too late. By that time I had consumed approximately 60 pills between the two prescriptions. I read and researched all that I could --to survive and understand all of the life-altering adverse effects that were besetting me.

Went to the doctor to have everything else ruled out. All blood work tested fine.
According to the doctors, I was the picture of health. They could not explain these toxic side effects from cipro. They said I would have to deal with it. My eyes tested normal when thoroughly examined by a neuro-ophthamologist four times in the first year of my floxing. Floxing is the term used to describe the condition in which a person suffers a severe disabling reaction of many toxic side effects after taking a fluoroquinolone antibiotic (cipro, levaquin, floxin, tequin, noroxin, etc), This reaction may occur during drug therapy or many months after last ingestion of the drug.

After being looked at by so many doctors, combined with the fact that they could find nothing wrong with me, I knew I was on my own to deal with the intense pains and side effects increasing by the day!

The first month after I stopped taking cipro was the worst physical experience of my entire life. I could barely walk, needed to use a cane, could not stand for more than 10 minutes at a time. I began to limp as my Achille would claudicate from the intense cutting and tearing pain in my ankles and legs. My legs were constantly vibrating and pulsating in pain. My skin burned off and on. I had intense drug-induced physiological anxiety all throughout the day, and especially when trying to fall asleep at night. My legs hurt and throbbed as I tried to walk. I had to stop my exercise regimen of running and jogging due to the crippling and debilitating leg pains caused by cipro.

I had to sit a lot. Standing was a luxury at this point, due to the prostrating and crippling joint and tendon pains.

The next few months were a continuation of the first month post-floxing. I could not walk for more than a block without having to limp and endure intense neuropathy in my legs. I was becoming depressed at the lack of physical activity in my life...but I had to go on to earn a living and take care of my life.

The pain in my in my legs would become so bad after various small amounts of walking (5 - 10 minutes) that I would have to find a seat anywhere, even if that meant on the ground. The pain was that bad.

At about 9 months after the last cipro pill ingested I was trying very light bike rides.
But I would come home and be in such pain afterward and have a difficult time standing for the rest of the day or night.

I tried a very light jog about one year out and was in pain the entire time. I could only last for about a mile. Then I had to stay sitting the rest of the night due to the severe leg and joint pains in my knees and hips.

I could only try a jog once or twice per month. Before I had the reaction to cipro, I could run 5 miles several times per week. That was out of the question now. I began to battle this toxic syndrome but I was becoming lost, lonely and tired.

At about a year and a half later, I was able to run once or twice per month. There was always knee, hip, ankle and Achille pain during the jog. And afterward I could not stand for the rest of the day or night.

Many other adverse effects from cipro continued: all the eye damage--blurring, floaters, photophobia, drug induced over-stimulation of the nervous system; peripheral neuropathy--nerve pain in and around my hip and knee joints, burning and tingling in my legs to my toes, pulsating and throbbing in my lower legs constantly.

At 2 years after the initial floxing, I am about the same. Some pains are less but still present. The eye damage continues. The nervous system damage is somewhat better. I am no longer able to run competitively. I can only last for a few light jogs once per month or so. The damage is deep and long-lasting. It has permanently changed my life in a debilitating way. When pains become too severe, I have to sit while cooking dinner at the stove. I cannot walk for more than 20-30 minutes without being in disabling pain and having to sit down. I can only ride my bike 2-3 times per week. And pay for it afterward with having to sit often to endure the debilitating knee and hip pains. I used to be the epitome of athletic health, but all that changed after my encounter with the toxic antibiotic cipro.

97. A LETTER AT THREE YEARS OUT

This is the letter of a floxed person three years out from his second floxing. Reproduced with permission.

I thought that cipro was a good antibiotic because it is very expensive and my doctor had said it was part of the last generation of antibiotics and she hadn't mentioned any side effects. She prescribed cipro several times in the last few years for my sore throats. They were always short prescriptions of 1 week of cipro. In retrospect, I don't think that it worked so well because even though cipro systematically cleared up my throat symptoms, during those times I also complained of alterations and disturbances of sleep and had two sleeping tests performed during separate years. I also began to experience sore muscles after vigorous exercise that I thought were due to my natural aging process at 35 years of age.

I had never had any health problem at all in my life, and I hadn't taken any drug for any reason because I didn't need to.

Then I was put on 6 weeks of cipro for a bladder infection; two pills of 500 mg per day. I have always been a top-notch athlete and the urologists ordered me to refrain from exercise. After the first week, the tests showed the complete clearance of the infection, but the urologist (the most renowned and most expensive in the state) said that we had to wipe out the roots of the infection and he told me to visit him every 10 days. During the middle of the treatment I felt a pain in the ankle and I told him about it because as a very active athlete I knew this pain was not normal. He said that the ankle pain could not be related to the cipro. At home I decided to have a look at the package insert and read that "if you feel pain at the Achilles tendon, refrain from exercise and inform your doctor".

During my next visit I voiced my concern with the urologist and he dismissed my comments saying, "if we paid attention to all the information on the drug inserts, we wouldn't take any medicine at all. Take the drug and finish the treatment". So I did.

After that, the urologist allowed me to resume my athletic regimen. In a few days the pains in my Achilles tendon area were so intense that I couldn't run or play any sports. As soon as I felt the pain subside I tried to engage in my sports competitions again, only to experience a complete relapse. My urologist denied any relationship with the cipro, and said that sooner or later athletes become old and start having problems. So I went to several podiatrists, doctors and therapists, and told all of them that my problems had started with the ingestion of cipro. They all thought this notion was very strange--almost unbelievable, and of course none of them had heard about similar cases. All of them said that we had to look at other causes. As instructed by them, I followed a very strict routine of physical therapy three days per week during two years: strengthening, stretching, ultrasound, etc., until I eventually could play hard again; not as intensely as before, but at a decent level.

Less than one year later, I had a sinus infection that was not cured after a short prescription of amoxicillin, so my doctor prescribed cipro again. I mentioned that I believed that the last time it had caused me problems, but he said that all my doctors questioned that link, that now it was not going to be 6 weeks but one, and that I had to remember that I had taken cipro successfully in the past. The last day of my one-week course of cipro I experienced such an intense pain in my ankle that I had to use crutches for 2 weeks. This kind of pain is unbearable for me; excruciating, unbearable at the slightest movement of the ankle, of a higher intensity than anything else I had experienced in the past. Soon my pains spread to my entire body, and I had to curtail my activities a lot, because I could hardly walk or drive for months. I had to use my crutches again several times during this period. In several more weeks time, a whole cascade of symptoms, injuries and disorders swept over my body ruthlessly and relentlessly: floaters, areas of blank vision, complete temporary blindness, brutal palpitations and arrhythmias, absolute unending insomnia, sensitivity to sunlight, rashes on several areas of the skin,

panic attacks, mental fogginess, cracking and popping of all the main joints (shoulders, wrists, elbows, fingers, knees, ankles, hips, back, neck), ringing in the ears, very dry eye, dry sinus, dry mouth, impotence, cold hands and feet, lack of normal sweating, neuropathies of all kinds, fasciculations, sudden sensitivity to foods and chemicals, and many more. All the damage and injuries increased relentlessly for more than 20 months. For more than two years I only got 2 or 3 hours of non-restful sleep. The first weeks I had clean and normal MRIs and radiographs, but months later, the new MRIs and ultrasounds revealed erosions and destruction of cartilages in hips, one knee and one ankle plus tendonitis and cystic changes in ankle and hip. I tested negative several times to all the autoimmune markers. I have had more than 30 blood tests during this time, plus urine, saliva and other tests.

During the first months I also had normal neurological tests, but now the needle and electrode tests began to show intense neuropathies- both "motor and sensory" in many of my muscles. I have refused to undertake a biopsy up until now.

My family and friends were sympathetic at the beginning of my adverse reaction but cold and distant later on. My children are a big concern for me as I cannot play and wrestle with them or take them outdoors for normal activities like baseball, cycling, etc. I work as a research technician at high national level and my professional career was stressed to the limit and I lost many opportunities. And many times I couldn't cope with my job but I still had to pretend that nothing was happening to me in order not to risk losing my job. My family relations suffered a lot too. To play any sport is a long forgotten dream for me now that I still have to endure so much damage and disability.

Today, 38 months (more than three years after I took the last pill of cipro), I am better than when I was at my lowest point -the 28 month mark-. I have improved in terms of my heart condition and rarely feel those worrisome abnormalities of the heartbeat. My photofobia is better and I don't feel as much pain in the eyes. I am less confused mentally and no longer have panic attacks (an unpleasant experience for those of us that didn't know what they were like). My brain seems to work better. I talk with more normalcy and do not get stuck in the middle of a sentence or lose my memory as much as during the first years. I no longer have any rashes.

But I am still a shadow of my former self. I have intense pains all day long. I walk with a limp. Some days I have problems getting in and out of small cars. I cannot play any sport at all because of the tremendous pains, soreness and stiffness. My neuropathies are widespread and of every kind (extreme sensitivity to cold, numbness, twitching, stabbing pulsating pains, some itching, etc…). My vision is a complete mess because my floaters interfere with my sight at all times; I also see brilliant lights and have areas of blurred-dead vision. My eyes are still very dry, as well as the rest of the mucous membranes. I cannot sleep more than 3 or 4 hours a day. I can never take a nap--this is something impossible for me now. I am still sensitive to many foods.

I have not taking any drug to treat the symptoms of my intoxication from cipro. I believe that supplements can't do much to help with recovery. I have suffered devastating reactions to poultry raised with enrofloxacin (I visited the local farm to check on it later). If I take a sip of an espresso I can become physically over stimulated for two days. I don't drink any alcohol and I eat healthy--very much as I have done my entire life.

My life has been destroyed by cipro and by the ignorance and the pharmacological illiteracy of the top ranked doctors. I would give everything I have to get my life back. I would offer Bayer the rest of my life working for them 50 hours a week for free as ransom for my lost health, that they have stolen from me with their policy of hiding the destructive and permanent damages and injuries that cipro causes, and keeping doctors perpetually ignorant of them.

I only pray that Dr. Flockhart was right when he told me that in 6 years I could feel more normal. It also depresses me that he also mentioned that in many cases recovery is far from complete.

I don't understand why this has happened to me because I only had some occasional minor infections that could have been treated easily with far less toxic antibiotics. My life on earth has turned in an unending nightmare.

And the most ironic aspect of all: as I live in Europe and thanks to the pressure of the manufacturers, the state doesn't allow me to personally report my adverse reaction to cipro, and the two doctors that prescribed them refuse to due it because of fear of legal claims. The consequence is that the two treatments that have almost killed me appear in the statistics as perfect successes of cipro. That is the way the pharmaceutical post-marketing evaluation is done, and this is the objective data on which medical research is based and decisions are made. I am sorry for myself and for the thousands that will follow.

98. FOUR YEARS IN HELL

We have compiled the status of 8 long-term floxed persons that meet certain common criteria of age and health history, and summarized it in table 17.

For every symptom, the highest and lowest values stated by the 8 floxed persons, have been discarded, and the number on the table reflects the mean of the other 6 values rounded to the nearest tenth percentage.

TABLE 17. SYMPTOMS AT 4 YEARS OUT
(average values for 8 floxed persons with SEVERE reactions)

SYMPTOM	Healing (100% = fully healed)
dry eye	30%
dry nose (dry mucous membranes of sinus and upper throat)	20%
dry ear, producing small amounts of wax dust, not viscous	20%
dry skin all over, specially face, upper torso and shoulders	30%
dry mouth and rough-dry palate	60%
complete transient blindness	100%
floaters in vision	50%
blurry areas in field of vision	60%
watery curtains or strings of watery drops in field of vision	60%
flashes, sparks, lights in vision	70%
giant lights zig-zagging in vision	80%
photophobia	70%
eye pain, eye pressure	90%
headache, head pressures	100%
joint pains	40%
use of crutches, wheelchairs, casts or walking aids	80%
abnormalities in joints (ankle, knee, hip, wrist, elbow, shoulder, neck)	60%
tendinitis, stenosing tenosynovitis	30%
cartilage deterioration, osteoarthritis	40%
muscular atrophy (hamstring, gluteus, quads, peroneus, tibialis)	30%
nerve pain (femoral, sciatic-like)	60%
overall aches preventing from daily activities	60%
myopathies, pain in muscles	70%
noisy joints and tendons, popping and cracking	70%
extreme stiffness, in legs, arms, central body, specially after exercise	60%
limited range of motion in several areas of the body	60%
heart arrythmias, palpitations, irregularities, abnormal pounding	90%
skin rashes	100%
Insomnia	80%
Interrupted, unrefreshing sleep	60%
panic attacks, frightening and vivid dreams with fear of dying	90%
memory loss of recent events	80%
mental foginess	70%
dificult speaking and finding words	80%
jaw discoordinations biting oneself at the same point always	90%
eyelid twitching	60%
rectal spasms with neurological pain	100%
nerve pain at night	70%
fasciculations all over the body	60%
buzzing in muscles and under the skin	60%

trembling after sustained exercise	70%
sexual numbness, impotence, loss of libido	70%
hand numbness due to ulnar neuritis or carpal-like syndrome	30%
cold hands and feet	40%
toe numbness, loss of sensitivity	50%
difficulty to keep the body properly warm	80%
loss of sweat production	50%
increased pains in stressful situations (throbbing, stabbing pains)	80%
pains prickling and grasping the skin	80%
itching all over the body, scrotus, back, torso, legs, arms, scalp, face	90%
pre-frozen fingers with low temperatures (numb, pale, cool, blue)	60%
weight loss	80%
blue eyelids	80%
haematomas caused easily after light contusions	70%
caffeine intolerance, overreactions	40%
food intolerances, not present before	50%
foods cause undesired effects (insomnia, lights in vision, dry eye..)	70%
malabsortion syndrome, leaky gut	60%
hypersentivity to chemicals, odors, fumes, solvents...	70%
abnormal liver tests	80%
abnormal muscular tests (CPK, aldolase,)	60%
abnormal Q10 or cholesterol	70%
abnormal hormones (cortisol, thyroid)	70%
positive findings in EMG	40%
positive or abnormal findings in MRIs	30%
Average age of the 8 floxed persons (at onset)	39 years
Sex	7 male, 2 female
The 8 floxed persons were healthy and athletic prior to the floxing	
Ocupational and leisure risks non existent	

99. ANXIETY AND DEPRESSION

As we have related above, just imagine that you had a healthy and happy life, and that one day you felt some burning when urinating, and your doctor, without any culture of your urine, put you on a course of three weeks of levaquin and you ended up having many injuries, very debilitating, and very long lasting,. Now it is uncertain when and whether you are ever going to regain your health again. Nothing helps with your intoxication, and new symptoms keep on showing up for months on end. Your brain fog, and anxiety are intractable.

The physical, chemically induced anxiety caused by fluoroquinolones via damaging the neurotransmitters of the brain is so strong and long lasting that many persons suffer greatly. In severe reactions anxiety is a main issue for the first five years on average. This anxiety may cause inability to work, and to live normally. Fluoroquinolone anxiety can be so extreme that in some cases it causes proteinuira, loss of protein with the urine, that if it is not reversed, may cause permanent kidney damage. There are no natural, side effects-free treatments to this kind of anxiety. Persons with severe reactions have to endure it on their own, without the aid of drugs, if they want to increase their chances of a decent recovery. For people with no severe reactions, drugs can be tried. As usual, we have not recorded any experiences with prescription drugs, although many have been used by floxed persons with mixed results. If you need to take a drug for your anxiety, do some research on your own, and then exchange your ideas with your doctor.

We have seen strong minded people, emotionally stable and optimistic, with high education, without a hint of what anxiety was like, fall down prey of a strong fluoroquinolone anxietyand being unable to

tackle it for up to 6 years and destroying their lives. Many times, on top of the chemical anxiety, the floxed person adds a psycological anxiety caused by the long and incapacitating floxing, that seems to last forever at times, at that seems to have no cure. Easier said than done, one has to stay positive to have some chances to manage the anxiety. Always remember, that unless you have taken a lot of psycotic drugs to help your floxing, you will feel better, the lattest by the 5 year mark if you have a true severe reaction and much earlier for the rest of the cases. We have not recorded a single case of a person that has not improved over time, save the cases of those that had very severe reactions and opted the way of helping the symptoms with drugs for sleeping, for anxiety and for the pain. And even taking those medicines, you can recover from a severe reaction, but it is less likely.

In other words, the majority of people that have used anti-anxiety medications during their severe reactions, have evolved much worse than the ones that have endured it without drugs acting on the brain. In severe reactions, there is a clear link, a very strong relationship between the psycotic drugs taken and the outcome after 5 or 6 years. The more drugs taken for depression, anxiety, insomnia, nerve pain and seizures, the worse the prognosis (likely outcome). Most of severe cases that have not improved some way after 5 or more years fall within the group that approached the brain damage with the help of one or several drugs taken regularly. Many severely affected floxed persons that did not take drugs for the central nervous system also exhibit permanent injuries after 5 or more years, but are in much better condition than the ones that consumed the psycotics.

This does not mean that one severely intoxicated person cannot take a pill of an anti-anxiety medication. Probably, small doses intended to lessen the severity of the symptoms, not to suppress them alltogether, and taken for short periods of acute anxiety, may be tolerated without jeopardizing recovery.

Whatever the decision about drugs that you take, life around you still goes on but you cannot enjoy it. You were an athlete but sports and physical activities are out of the question, and your brain does not work properly. You are prone to a severe depression and depending on your mental strength, depression can hit you hard.

The state of mind of a chronically floxed person goes through different phases that have been well studied by many researchers for critical or severe illnesses, in general, and of which a floxing is not an exception, although a floxing is not an inmediate life threatening condition. In general, it is accepted that the victim enters a mourning state. The mourning process is composed of five stages:

- STAGE 1. Denial and isolation.
- STAGE 2. Anger.
- STAGE 3. Bargaining.
- STAGE 4. Depression.
- STAGE 5. Acceptance/closure, resignation with/without hope

Severely floxed persons that are disabled and chronically ill and were young, active and healthy at the onset, progress along the five stages. The evolution of the process is fed by the permanent injuries, not allowing to return to prefloxing stage zero. Some times the floxed person starts cycling around stage 3 and 4, because he/she does not accept other horizon than healing. Very active people suffering a severe floxing inevitably confront stressors like deterioration and difficulties throughout their lives. Their grief does not diminish or resolve, so the mourning process never ends and the patients cycle without finding a settling state.

STAGE 1. Denial and isolation. Shock and desbelief.
How can one person understand that his doctor has prescribed him/her an antibiotic for a sinus infection that is approved by the FDA, that has crippled him/her for life?. Is it easy to comprehend that a package of levaquin pills can destroy forever a healthy, promissing life full of joy and positiviness? It is impacting that nobody offers a solution or a cure, and that almost all medical professionals do not

want to hear about the intoxication because of ignorance and because they also want to protect their conciences by denying to themselves that they are maiming patients.

“Denial” is a temporally and strong psychological defense mechanism that deals with acute emotional crisis at illness onset. It buffers initially the shock by denying or refusing the illness. “Denial” is seen as a negative stage because it may delay or stagnate the mourning process, and can become pathological if a person does not move beyond it.

Floxed persons, as chronically ill people, must deal with everyday affairs, such as domestic duties, family matters, school, work, etc. This means that their illnesses cannot always be the centre of attention. In such cases, “denial” is effective because it temporarily pushes aside the illness and enables the sufferer to deal with other priorities. Others just deny it because it is easier to get attention if they are diagnosed with fibromyalgia, lyme, or any rheumatic disease. Your doctors are plainly ignorant or dismissing, and when your friends and family start to get wary of your long lasting reaction, you start to feel isolated.

STAGE 2. Anger.
The grieving person may then be furious at the person who inflicted the hurt (the doctor), or at the system (the FDA, the hospital, the medical community, the goverment), for letting it happen. He may be angry with himself for letting the event take place (had he/she researched before, he/she could have avoided it,or if he/she had interpreted correctly the first signs of intoxication, they think sometimes), even if, realistically, nothing could have stopped it because things are like this .

STAGE 3. Bargaining.
Normally the victim tries to interpret too optimistically all medical results and symptoms, and prefers doctors that tell him/her that all will be short-lived and that recovery will be complete. He looks eagerly for small pieces of information that donot show the real damages he/she may be facing according to the symptoms.
The victim tries to start attitudes to counter the losses, and sometimes offers a deal to God.

STAGE 4. Depression
The person feels numb, although anger and sadness may remain underneath. This situation has been discused above.

STAGE 5. Acceptance.
This is when the anger, sadness and mourning have tapered off. The person simply accepts, some times ignoring it, the reality of the loss.

PART XIII: YOUR DOCTORS

100. THE MAIN QUESTIONS REMAIN UNANSWERED

Apparently, there are no answers for the main questions that afflict people suffering from the floxing syndrome. The scientific questions in desperate need of answers are:

- What are the exact mechanisms of the damage?
- Does the drug remain in the body (tissue bound) after cessation of treatment?
- Why do the most severe symptoms develop months after the treatment has ended?
- Is there a condition that makes some people more prone to being damaged?
- How deep or permanent is the neurological damage?
- Why some foods and substances trigger another amplified reaction?
- What are the irreversible internal injuries we are facing?
- What type of recovery period is to be expected?
- What can be done to limit the extent of the damage caused by these toxic chemical antibiotics?
- What can be done to help or expedite the recovery?
- What other health problems can we expect in the very long run (cancer, early morbidity, etc...)?

We have tried to find answers for almost all of the questions, however, no matter how logical the conclusions in this paper appear, the fact is that we know very little. Obviously, there is insufficient scientific research on the subject of quinolone toxicity. And to date there is no known cure. It is difficult to understand why with so much clinical data available from us as victims and the availability of willing volunteers for studies, no scientific research is being done on a great scale. The negative influence and pressure of the drug manufacturers is the only explanation as to the reason for eluding and avoiding such desperately needed research.

From the social point of view, the critical questions about the subject are:

- Why nobody undertakes a follow up (OVER A MINIMUM PERIOD OF THREE YEARS) study of large populations of people that have taken fluoroquinolones, (especially high doses or long-term treatments) like the U.S. postal workers?
- Why the public health administrations do not begin a true, real, and accurate study, and not merely a manipulated or washed over study, about the safety of the quinolone class of antibiotics, taking into account that half of the quinolone family of antibiotics have been withdrawn from the market over the years due to severe toxicity?
- Why quinolone antibiotics are not strictly forbidden in the raising and production of cattle, poultry and fish for human consumption; because substantial amounts of the antibiotic remain in the food, irrespective of the time elapsed from administration to slaughter, and pass on to unsuspecting people?

Many thousands of people are diagnosed every year as having fibromyalgia, lyme, osteoarthritis, immune disorders and neurological problems, when in fact they are just poisoned from a quinolone, either by direct ingestion through a drug prescription or through the food supply (poultry, beef, fish, dairy).

101. WHY DOES THE MEDICAL CLASS IGNORE THE TOXICITY OF QUINOLONES

Being floxed is a very hard, life-altering experience, and sometimes a life experience of misery and accelerated physical and mental decay. You have to be prepared to add your doctor's ignorance to your despair. The average doctor, irrespective of his/her specialization, is fed technically on propaganda from the drug manufacturers. Manufacturers generously sponsor medical magazines, many medical reports, symposiums, conferences, and travel. Their advertising and information highlights the alleged benefits of quinolone antibiotics, hiding the true toxic profile.

Prescribing doctors know virtually nothing about quinolones and their use, apart from the biased information provided to them by the laboratories and drug companies, or perhaps by medical associates or other fellow physicians, that know nothing either. The main and nearly only technical information available the doctors have about these drugs comes from the advertisements in the medical magazines and visits from the drug representatives of the manufacturers. So they all think that quinolones are very safe drugs. No other antibiotic enjoys a 'safety profle' that matches the profile of the quinolones, except for maybe amoxicillin; but bacteria can be resistant to amoxicillin, so quinolones are the preferred alternative for all purposes, according to the clinical ignorance of many doctors.

This table is a summary of the notes taken by 42 volunteers after visiting their doctors. The results are based on the outcomes of the first visit to each doctor.

TABLE 18
HOW DOCTORS SEE THE PATIENT INTOXICATED BY A QUINOLONE

DOCTOR'S RESPONSE	NUMBER OF DOCTORS	PERCENTAGE
Number of doctors visited by 42 floxed persons with proven reactions to quinolones seeking for medical advice and treatment	327	100%
Number of doctors that knew that quinolones caused tendon problems in "rare" cases or arthropathy "only in animals"	31	9%
Number of doctors that said that they had never heard of toxic reactions to quinolones	285	87%
Number of doctors that had heard of other serious adverse reactions of quinolones that are different from the tendon problems (neurological, vasculitic, inflammatory)	8	2%
Doctors that dismissed any possibility of quinolones being the cause of the reaction of the patient	257	79%
Doctors that dismissed any possibility of quinolones being the cause of the reaction of the patient even after the floxed person mentioned that those adverse effects were included in the drug package inserts	219	67%
Doctors that believed that the adverse reactions were going to be short lived (less than 15 days) once the drug was stopped	198	61%
Doctors that mentioned that the reaction would subside in about one month	16	5%
Average number of doctors floxed persons had to talk to before finding one doctor willing to consider the quinolone connection as one possible cause of their health problems	13	
Number of floxed persons that have participated in this poll	42	
Number of floxed persons that have participated in this poll that have suffered rechallenge reactions	7	
Countries from where the floxed persons gathered information	USA (35); France (2); UK (1); Sweden (1); Spain (1); Germany (1); India (1) *Two floxed persons reported from 2 countries each but have been asigned to a single country.*	

The "industry" is one of the most dishonest that exists in the legal market. The manufacturers manipulate all the trials until they render the results (mostly forged) that they want to show. From the investigative work of Stephen Fried in his book "Bitter Pills": ...

> A fifty seven year old woman had enrolled in an Omniflox [a quinolone] trial in October 1990 after being diagnosed with a bacterial infection on top of her chronic bronchitis. It was a double-blind trial (two unmarked drugs) and the patient initially got better. But after ten days on her study drug, she was hospitalized with kidney failure and disseminated intravascular coagulation, a life-threatening blood coagulation disorder. This was a serious dysfunction in two separate body systems. Four days later, the study *"blind"* was broken to reveal that she was taking Omniflox.
>
> The patient's physician believed that the antibiotic had caused both of her conditions, and indeed, she recovered from both ailments, after she stopped taking the drug. However, when, as is customary, Abbott [the manufacturer] sent a letter about her case to all the other Omniflox clinical investigators who were testing the drug, the company reported her doctor's findings in a more equivocating manner, saying that the *"precise relationship of the study drug.....is difficult to ascertain"* because the patient had not been *"rechallenged"*. .....Who in their right mind would do it, except by accident? -but drug companies invariably note that is wasn't done.

As you have already learned, many people involved with the present paper have been re-challenged by a quinolone treatment, and their symptoms have always reproduced, increased in intensity dramatically, and become chronic or permanent.

More than 90% of all the prescriptions of quinolones could be avoided, using other safer, less toxic antibiotics. It is very normal and standard for urologists to prescribe a long-term course of fluoroquinolones for a suspected case of prostatitis without obtaining a culture test or a more definite diagnosis. They argue that they have a good *"penetration"* through the prostate and blood/brain barrier; so good a penetration that they wreak havoc on all bodily systems.

Let us have a look again at another passage from the book of Stephen Fried "BITTER PILLS":

> While discussing antibiotic use, Blum [FDA medical officer who had approved some quinolone antibiotics] said something that stopped me in my tracks. He said authoritatively that he didn't *"perceive quinolones as first-line therapy for anything"..."There are definite niches where quinolones are important to have like limiting hospitalizations of patients"*, he said, but for anything else, they are *"second- or third-line therapy"*. I asked if he was aware that many doctors were using quinolones first. He said he was. I asked what he and other medical officers had done to let prescribing doctors know that this could be a problem. He conceded that the FDA *"had not really tried to get out"* the word on this issue.
>
> This is the kind of information that all medical officers know, but aren't supposed to share with the public because, technically, they aren't allowed to recommend therapies. This is one of the cruelest scientific ironies of drug regulation: the only people in the world who are in a position to actually see and compare all the proprietary information on competing drugs are not permitted to tell doctors and patients what they have learned.

The arrogant ignorance of the medical class puts them in a situation prone to block any input and knowledge from their patients. The vast majority of the doctors will not listen to their patients complaining of the first signs or pains associated to the drug reaction. If your doctor tells you "it cannot be the drug" you are dealing with one of these doctors. They are firmly convinced that they behave professionally but in fact they are just frivolously superficial.

Your doctor is likely to dismiss any of your complaints if you suggest a link to the antibiotic. He will probably tell you that it is impossible, that you should never read about medical issues on the Internet, and that this is the first time he heard of something like this. He will tell you that the drug left your system long ago (perhaps it is true although quinolones can be detected in hair myelin 2 years after ingestion), and that you are somatizing your pains. If he despises your arguments, saying that you are the first person that he has met with these complaints, then he is unable to learn and cannot get beyond his limited understanding and awareness. You definitely need another doctor at this point.

A typical doctor is not willing to accept information from his/her patients. Neither he is going to rush to study or investigate your suggestions linking your alterations and the antibiotic. He does not care for them and he will not make a follow up of the evolution of his patients. There is not a single urologist or doctor that asks his patients for adverse effects one or two years after having administered them 6 weeks of ciprofloxacin (2x500mg/day), when all of them would relate the entire array of symptoms described previously in this report. In other words, he cannot discover delayed symptoms. There are reputed doctors that treat their fibromyalgia patients with quinolones; that is the same aberration as using the acid from

your car's battery as eye drops for a pollen allergy. We have a strong suspicion that many fibromyalgias are caused by the ingestion of quinolones and other toxins through prescription or the diet. If you are in one of these situations you have to choose whether to follow your doctor's advice, or think twice and look for a second, or even third opinion. In the end, the only thing at stake is your life and well-being.

Many doctors do not report adverse effects to the post-marketing surveillance system. According to the most optimistic studies, it is estimated that only one in 20 adverse reactions is reported either on insistence of the patient or by the doctor's initiative. They are too busy, they are too unsure, and they do not want to be listed as too proactive in drug awareness. A floxed person needs on average 13 doctors before he/she meets one that is willing to listen that he/she was an athlete in perfect health, with rock solid joints just until the very same moment that he/she took the quinolones.

But not all doctors are equally ignorant. In the primary care system we have found quite some of them that never, under any condition prescribe a flouroquinolone because they have concluded from study and observation that they are useful but extremely toxic antibiotics that should be reserved for life or death cases.

In the scientific field there are many researchers that share the same opinion. Some medical investigations have already pointed out the shocking toxic profile of the quinolones. According to some articles that you can consult in the reference list at the end of the article, there has been an important time lag between the first reports of fluoroquinolone-related tendinopathies and the official recognition of this toxic phenomenon. Those doctors argue that this delay, along with the widespread use of fluoroquinolones, makes it difficult to return to more reasonable prescribing guidelines for these very useful and effective antibiotics. The reasons why potentially serious adverse effects of fluoroquinolones were not anticipated before their commercialization would be related to the lack of adequate in vitro and in vivo models, and the unexpectedness of the events. Increasingly -their argument follows- fluoroquinolones are being prescribed for benign infections of the urinary or bronchial-pulmonary tracts. Sometimes, they are even used for antimicrobial prophylaxis before surgical or endoscopic procedures.

Those investigators believe that for any prescription, the risk/benefit ratio of the fluoroquinolones should be carefully considered, since better-tolerated, less expensive and less toxic drugs can usually be prescribed. Clear information dedicated both to physicians and patients regarding the cautions for use and possible adverse effects of fluoroquinolones would help reduce the risk and severity of adverse reactions. They state that this is especially important for phototoxicity, tendinopathy and cardiovascular adverse effects. We would also add the rest of extremely serious reactions described throughout this article.

Note: Talk with your doctor about your concerns. Ask him to become informed because he is the person that can help you best.

And they finally identify the key error that many victims have been complaining about since the nineties: given the absence of an adequate model and the poor predictability of animal manifestations in injuries in humans, careful monitoring of patients during phase II and III trials and, more importantly, long term pharmaceutical vigilance during the post-marketing period, are an absolute need. But despite patient's and researcher's claims, it is not being done. The manufacturers of these drugs would not allow it and the FDA acquiesce.

If you want your doctor to cooperate you have to first convince him about the real toxic nature of the quinolone antibiotics. You will have to bring him some good papers like the ones published by Doctors Cohen and Casparian. You may get some help if he takes interest in your story.

102.SHOULD I REPORT MY REACTION

Americans are allowed to report their individual adverse events caused by drugs to the FDA through the Medwatch program. You should absolutely submit a report to Medwatch in order to create progress in

promoting awareness as to the true toxicity and long-term physical disabilities caused by fluoroquinolone antibiotics. You should also insist that your doctor report it professionally as well.

Many European countries, with heavy state rules that leave very little room for individual expression and following the century's old tradition of considering citizens as poor little ignorant people prone to panicking, have suppressed any right to directly report adverse effects to the medication agencies, so it has to be done by doctors exclusively. The drug manufacturers have imposed this in order to get the reporting level even lower.

Once more from Stephen Fried's book "Bitter Pills":

> And how bad was the ADR reporting problem? Kessler [FDA chairman] said that 90 percent of all adverse events involving drugs and devices, and perhaps as high as 99 percent of the most serious adverse events, were never reported to the FDA. The reason, he speculated, was that when doctors were confronted with an unexpected outcome of treatment, they were more likely to blame the event on *"the course of the disease"* than on the drug they had prescribed. He blamed this on the *"limited training"* that medical students receive in clinical pharmacology and drug therapy, citing a study that found only 14 percent of American medical schools required courses in the core skills needed to understand how drugs functioned in the body and properly prescribe them. Most schools *"taught only a few hours of clinical pharmacology*", he said, and only in the early years of training. So it was hardly surprising that prescription errors are the second most common cause of malpractice claims.

Generally speaking, doctors do not like reporting adverse reactions because of arrogance, dismissal of intellectual capability and interpretation of symptoms by their patients, self-complacency with their medical practices in the cases that they themselves prescribed the drug, fear of involvement in litigation, guilt, dislike of being involved in more future administrative work, avoidance of being characterized as too meticulous by their colleagues and the manufacturers, ignorance of the requirements for reporting, indifference about reporting mere suspicions, and lethargy.

103. THE SYSTEM IS AGAINST THE PATIENTS

The following examples, a minute sample of the real world today, illustrate that if you are affected by an adverse reaction to a quinolone antibiotic, you are going to discover a medical world full of:

CYNICISM:

When asked about the extremely severe adverse effects reported by thousands of patients treated with cipro, Mr. MacCarthy, vice president of U.S. Medical Science at Bayer's West Haven facility states, *"If you are telling me that someone had these effects and they were persisting, long term, months to years after treatment I would be surprised."*

FRAUD:

(We reference yet another excerpt from Stephen Fried's BITTER PILLS):

> A rush of articles about Omniflox [a toxic quinolone] were set to appear in major journals. The company [manufacturer- Abbott in this case] apparently hadn't taken any chances that the articles wouldn't toe the party line. One revealing internal memo about some of those articles described an industry practice I had heard about but never seen so clearly documented: scientific papers being written by the marketing department instead of by the scientists. Dr. Reid Patterson, Abbott's director of drug safety evaluation, was complaining in the memo about publications on Omniflox in an upcoming supplement of the American Journal of Medicine. *"Certain manuscripts"*, he wrote, *"...were being labeled as being authored by more impressive, outside, expert consultants, who had nothing to do with the design or generation of the data"*. In the memo Patterson, a company drug safety expert, seemed less concerned about the academic fraud than with the *"loss of recognition"* for the people who had actually done the work, as well as the possible *"impact on their advancement within Abbott.*". But he was also concerned that *"marketing has decided that our data will be assembled by ghost-writers.....reviewed by us, the published as though they were authored by us or by some better known consultant*".

INDOLENCE, LACK OF CARE:

In the forums you can find thousands of testimonies of persons that were dismissed by their doctors when they explained to them that they were having a bad reaction to the quinolone. It is sad to read though them. Some doctors get angry with the patients; and become aggressive, indolent, uncaring. Others just send registered letters stating that they are no longer their doctors. All become suspicious, uneasy, or hasty to get you out of their office if you mention the Internet. Many, ignorant of the devastation that is surrounding the patient, prescribe medications that will extraordinarily worsen their injuries (corticoids, NSAIDs, some neuroleptics).

IGNORANCE:

From the neurology forum of the Cleveland Clinic, that is a very helping and high quality board, whose questions are answered by doctors from the Clinic, consistently ranked one of the best hospitals in America:

> QUESTION: I'm a 28 year old male, and recently took Cipro (4 weeks) and then Levaquin (4 weeks) for a prostate infection. I was fine on the Cipro, but started to experience muscle twicting a couple of days after switching to Levaquin. Since I've stopped taking the Levaquin (7 weeks ago), I've continued to have muscle twitching and burning muscle pain. The muscle twitching involves just a small part of the muscle and is sporadic. The twitching usually occurs in the calves, but I also notice it in the arms, back, butt, and feet. Sometimes it is just a single twitch, and other times it is a couple in a row. The burning/achy pain is somewhat all over (like after the flu), but usually in upper arms, shoulders and thighs. One of my calves also seems a little stiff, but I don't know if it's related. I can move my leg fine; just the upper part of the calf (below/around the knee) seems tight.
> So far I've gone to my primary care physician, and he did some strength tests and tested my reflexes... he said all were perfectly normal, and there was no need for me to see a Neurologist. He seemed to think everything could be benign, and possibly caused by stress/anxiety. He didn't mention the Levaquin though.
> My questions: Do you think the Levaquin could cause my symptoms? If not, what would cause them? How does stiffness start in motor neuron disease, and would it start before weakness? If I went to a Neuro, would they even do an EMG if strength and reflexes were fine?
>
> ANSWER: I am aware of no relationship between your symptoms and Levaquin. I cannot find any references to suggest that the Levaquin caused this. It is possible that these symptoms are a reaction to a viral illness, or possible from stress (as your primary doctor suggested). If your examination is entirely normal then there may be no use for an EMG. I think it is unlikely that this represents motor neuron disease. Good luck.

As you can see, unfortunately, not even the most capable teams of doctors are informed about this real tragedy. In this case, several lay members of the forum adequately informed the person that had suffered the reaction to levaquin.

SHEER INCOMPETENCE

Look for instance to the story of the quinolone trovafloxacin:

> THE EMERGING ROLE OF FLUOROQUINOLONES IN COMMUNITY-ACQUIRED PNEUMONIA.9th European Congress of Clinical Microbiology and Infectious Diseases. Berlin, Germany / March 1999
> *"Ten years ago I would have been howled down for including fluoroquinolones in a list of agents for the management of community-acquired pneumonia,"* remarked Dr. Peter Ball, Senior Lecturer at the Department of Bio-Medical Sciences, University of St. Andrews, St. Andrews, Scotland. "Why should we use these new fluoroquinolones?" Dr. Ball asked. The advantages, he answered, include excellent activity against both typical and atypical respiratory pathogens, very high penetration into tissues and fluids where the infections are centered, activity with once-daily intravenous or oral administration and excellent tolerability. Dr. Ball believes, too, that the incidence of dizziness and lightheadedness sometimes attributed to trovafloxacin is not entirely justified. "The more than 400,000 patients from post- marketing surveillance studies I have reviewed reveal this to be a very, very small problem," he said. And, he said that while sparfloxacin frequently produces skin problems attributable to phototoxicity, trovafloxacin and moxifloxacin are associated with extremely low levels of such phototoxicity.
> Recognizing that dizziness/lightheadedness is the most common adverse event with trovafloxacin, particularly in young women, Dr. John Vincent, Groton, Connecticut, reported that those effects can be significantly reduced by taking the drug with food or at bedtime.

Unfortunately, it didn't occur to all those "top level" investigators to check for incapacitating neuropathies, rupturing of tendons, destruction of cartilage, or liver function during the trials; and shortly after these extraordinary claims were made, trovafloxacin was withdrawn from all European and many first world countries, because of the severity of the injuries that the drug caused and the numbers of deaths due to sudden, severe liver failure.

FRIVOLITY - IRRESPONSIBILITY

The following excerpt does not need further comments:

> PEDIATRICS Vol. 113 No. 1 January 2004, pp. e40-e46. Objective. To determine the efficacy and safety of topical ciprofloxacin/dexamethasone otic suspension compared with ofloxacin otic solution in the treatment of acute otitis media with otorrhea through tympanostomy tubes (AOMT) in pediatric patients. Group study was conducted at 39 sites in 599 children aged 6 months to 12 years with an AOMT episode of 3 weeks' duration. The mean age of patients was 2.5 years
>
> Adverse Events: ..... Ciprofloxacin/dexamethasone or ofloxacin administered twice daily in the affected ears is safe and well tolerated in pediatric patients with AOMT. No serious treatment-related adverse events were reported during the study. Fewer patient discontinuations as a result of adverse events were noted in the ciprofloxacin/dexamethasone group (32 patients; 5,3%) compared with ofloxacin (46 patients; 7,7%).
>
> The safety evaluation was conducted on all patients who were randomized into the trial and received at least 1 dose of study drug. The safety analysis was based on the extent of exposure to the study drug, adverse events, and audiometry examination. The occurrence of adverse effects was assessed at each study visit and via questioning of parents or guardians during daily telephone calls relating to completion of the patient [mean age 2,5 years!] diaries. All adverse events were recorded in the patients' case report forms. Patients who experienced adverse events that, in the opinion of the investigator, presented a significant risk to their safety or well-being were withdrawn from the study. ..... Both topical otic preparations are safe and well tolerated in pediatric patients

GREED:

Of the many tens of thousands of people with deep neurological injuries, osteoarthritis, fibromyalgias, and all the rest of damage caused by quinolones, more than 95% could have been spared if the prescription of quinolones was done properly. The rest are persons for whom the quinolones were a lifesaver, with complicated or life threatening infections. Real things are very different because of the greed of the manufacturers.

COLLUSION:

There is a public outcry about the ever-increasing evidence of the collusion between the FDA and the manufacturers. In the next section of this paper you can get a glimpse.

SICKENING INDECENCY

Take a look at a survey of the Atlanta's Center for Disease Control that shows clearly how deep a knowledge the persons in charge of studying the adverse effects of ciprofloxacin have :

> ADHERENCE TO ANTIMICROBIAL INHALATIONAL ANTHRAX PROPHYLAXIS AMONG POSTAL WORKERS, WASHINGTON, D.C., 2001. Jefferds MD, et al. Emerg Infect Dis Available from: URL: http://www.cdc.gov/ncidod/EID/vol8no10/02-0331.htm
>
> *"Many workers mistook signs of stress (e.g., complaints of fatigue, lack of sexual drive, and increased crying) for adverse effects of the antimicrobial therapy. Further, the stress associated with the bioterrorist event magnified the adverse effects associated with prophylaxis. For some symptoms, distinguishing between adverse effects of stress and those of the antimicrobial therapy, such as gastrointestinal upset, was impossible".*

Laboratories and doctor's sects can only attempt to create their own reality for so long. All these real adverse effects that have long been denounced by victims are now coming to become evident by the sheer humbers of people injured, and while there are still the nay-sayers, many of them on the payroll, or getting grants from laboratories, still trying to deny and confuse the issue, it has become a short of moral issue, because it has to do with the right of people to not to be maimed for life just for nothing.

The positive thing is that a small part of the medical system is there to help you, ... if you ever find it.

104. SOMETHING ELSE IS ALWAYS THE CULPRIT

The literature is wrought with reports of events in which quinolones are implicated in very serious or fatal complications but 'systematically' some other factor is the culprit. It seems that for doctors taking quinolones has the same influence on the health of a patient as drinking spring water or breathing pure air.

> JARISCH-HERXHEIMER REACTION ASSOCIATED WITH CIPROFLOXACIN ADMINISTRATION FOR TICK-BORNE RELAPSING FEVER.
> Webster G, et al.Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA.
> A 14-year-old girl was seen at a community clinic with a chief complaint of abdominal pain and fevers and was treated with oral ciprofloxacin for presumed pyelonephritis [afection of the kidneys]. She became tachycardic and hypotensive after her first dose of antibiotic, and she developed disseminated intravascular coagulation. She was admitted to our hospital for presumed sepsis. Her outpatient peripheral blood smear was reviewed, revealing spirochetes consistent with Borrelia sp. To our knowledge this is the first reported case of the Jarisch-Herxheimer reaction to ciprofloxacin.

A herxheimer reaction means that ciprofloxacin killed or damaged so much bacteria, that the toxins released by them while dying provoked a severe reaction in the girl. You can see that the research team has ruled out the possibility of ciprofloxacin being the cause of her symptoms, some of which are extremely common after ciprofloxacin ingestion. The girl took the cipro and some dying bacteria get the blame. There are many reports linking quinolones and disseminated intravascular coagulation (two of those reports have been cited previously in this flox report). We know of many people with extremely acute non-allergic reactions to cipro after one pill. Perhaps the doctors may have attempted to rule out that ciprofloxacin had caused disseminated intravascular coagulation, before excluding by principle that cipro had anything to do with the issue.

> FATAL RHABDOMYOLYSIS CAUSED BY LIPID-LOWERING THERAPY
> from Southern Medical Journal
> "A 68-year-old man was admitted to the hospital after complaining of progressive weakness. He had a medical history of type 2 diabetes mellitus with diabetic nephropathy, hypertension, peripheral vascular disease, and dyslipidemia. Four weeks before admission, gemfibrozil was added to his medical regime....". "Two weeks after starting gemfibrozil therapy, he noticed progressive weakness of his upper and lower extremities that progressed to the point that he had difficulty getting out of chairs, raising his arms over his head, and walking."
> ../..."After being admitted he was initially given intravenous levofloxacin and clindamycin, as well as fluids containing dextrose, and sodium bicarbonate. On the third hospital day hypercapneic and hypoxemic respiratory failure developed due to collapse of the left lung, and mechanical respiration was begun. The left lung reexpanded. Over the next several days renal function deteriorated and the CK level rose to >30.000 U/L. The patient became hypotensive and died on hospital day 7."
> "...rare but seriuos adverse effects of statin therapy include hepatotoxicity and myopathy, which may lead to rhabdomyolysis, either with or without renal failure. These side effects are dose-dependent and more likely to occur with escalating doses of statin therapy and / or when used in combination with medications such as fibrates, niacin, or medications that inhibit the cytochrome P-450 system. "../..."this is the first reported case of fatal rhabdomyolysis caused by the combination of simvastatin and gemfibrozil. Muscle toxicity led to rhabdomyolysis and diaphragmatic weakness, causing atelectasis and intermittent pulmonary collapse. It is possible that our patient might have been at increased risk for rhabdomylosis because of his underlying renal insufficiency, the high dose of simvastatin, the concomitant use of a statin and fibrate, and perhaps a superimposed infection. We recommend avoiding high doses of statins in combination with fibrates in patients whose renal function is compromised. Clinicians should be aware of the potentially serious consequences of this combination and be vigilant in the early detection of toxicity should it arise".

Look to the reasoning of the authors. The patient died chiefly from statin-induced rhabdomyolysis (acute massive muscle destruction that also destroys kidneys), because the concentrations of the statin could have risen a lot by administering fibrates and niacin that inhibit the P-450 system. The drama is that the authors did not even consider the possibility of an accompanying action of the quinolone that they administered him. Levofloxacin causes rhabdomyolysis on its own; enough to cause fatal outcomes in some cases, and also strongly inhibits the P-450 cytochrome. Therefore, the intravenous levofloxacin could have worsened the patient's state very much.

No need to mention that giving shots of quinolones to a patient with pre-rhabdomyolysis, myalgias, myositis, nephropathy and peripheral vascular disease (the condition of the patient on admission according to the report) is to put him in real danger of a fatal outcome, because levaquin induces all of the above mentioned in healthy people, and worsens them greatly in a person that already has those conditions.

They should have concluded: this is the first reported case of fatal rhabdomyolysis caused by the combination of levofloxacin, simvastatin and gembromizil. But no matter how intensely you research and study the literature, you will find it plagued with appalling errors, omissions, and fabrications. Where is the true scientific method?

In the following study, the researchers were baffled because people that took antibiotics (mainly fluoroquinolones) to fight an infection developed a higher risk of having symptoms of reactive arthritis (joint pain attributed to an inmune attack). All sort of theories are postulated, but the one that could possibly be the answer is: fluoroquinolones cause joint pain, which can be mistaken as a symptom of reactive arthritis. Many floxed persons are wrongly diagnosed as having reactive arthritis, or Reiter's syndrome (arthritis triggered by an infection). We have excerpted the following report and have inserted our comments in brackets and capital letters for ease of understanding:

> REACTIVE ARTHRITIS AND REITER'S SYNDROME FOLLOWING AN OUTBREAK OF GASTROENTERITIS CAUSED BY SALMONELLA ENTERITIDIS
> Mark S. Dworkin, et al.Centers for Disease Control and Prevention, Atlanta; Washington State Department of Health
> Definitions. We defined reactive arthritis as the onset of joint pain, swelling, or redness within 1 month of onset of Salmonella gastroenteritis [PLEASE, NOTE THAT THESE SIMPLE SYMPTOMS ARE CLASSIC PRESENTATIONS OF QUINO-ARTHRALGIA]. Reiter's syndrome was defined as arthritis, conjunctivitis, and urethritis or cervicitis within 1 month of onset of Salmonella gastroenteritis.
> A total of 217 cases of S. enteritidis gastroenteritis were identified (31 confirmed and 186 clinical cases; attack rate, 45%) [of 481 people studied]. Twenty-nine percent of case patients (63 persons) had symptoms of reactive arthritis, 3% (6 persons) had symptoms of Reiter's syndrome, and 10% (22 persons) had reactive arthritis with oral ulcers but lacked other findings of Reiter's syndrome. In contrast, 8% of persons without preexisting rheumatologic illness who were not ill had any joint complaints during the same period of time.
> 53 people were treated with an antibiotic. Among 27 case patients who recalled the name of the antibiotic with which they were treated, the antibiotics used were ciprofloxacin (18), ofloxacin (4), ampicillin (2), trimethoprim-sulfamethoxazole with cephalexin (1), cefuroxime axetil (1), and metronidazole (1) [THIS MEANS THAT 81% OF PATIENTS THAT TOOK AN ANTIBIOTIC WERE PRESCRIBED A FLUOROQUINOLONE].
> Prolonged diarrhea, illness severe enough to require an emergency room visit or hospitalization, and **treatment with antibiotics were associated with increased risk for reactive arthritis** [PEOPLE WERE TREATED WITH ANTIBIOTICS SUPPOSEDLY TO FIGHT A BACTERIA, BUT INSTEAD THEY HAD AN INCREASED RISK FOR REACTIVE ARTHRITIS, DEFINED AS JOINT PAIN; WHAT POSSIBLY HAPPENED IS THAT THOSE PEOPLE HAD A REACTION TO THE FLUOROQUINOLONES], or Reiter's syndrome among case patients with S. enteritidis gastroenteritis
> We found that treatment [WITH ANTIBIOTICS, 81% OF THEM FLUOROQUINOLONES] of Salmonella infection was associated with a small increased risk for reactive arthritis. If this finding is upheld with further studies, it will be important to determine the mechanism. One possibility is that the bacterial fragments that result in the inflammation of arthritis are altered in a key way when killed by antibiotics rather than solely by the body's immune system. This alteration perhaps makes their presence in joint fluid more likely, because of size, shape, or some other undefined characteristic. Another possibility is that antibiotic treatment prolongs carriage of Salmonella, which leads to increased immune system stimulation. [AND WHAT ABOUT BEING A SIDE EFFECT OF THE ANTIBIOTIC?]
> If antibiotic treatment does increase the risk for Salmonella enteritis-related reactive arthritis, then increasing physician knowledge [WHAT INCREASING KNOWLEDGE?] about the indications for empirical treatment of diarrheal disease might prevent some cases of reactive arthritis.

The problem is that the medical literature is flooded with thousands of studies with little or no scientific value at all. This present flox report that you are reading is a compendium of hypotheses, conjectures, unfounded theories and insufficiently worked out deductions but looks like a Nobel prize winner in comparison with some actual published medical papers. See this last one, with our comments in

brackets, as usual:

> SEVERE BILATERAL OPTIC NEURITIS ASSOCIATED WITH PROLONGED LINEZOLID THERAPY
> Frédéric Frippiat et al. Centre Hospitalier Jolimont-Lobbes, Haine Saint Paul, Belgium
> A 72-year-old woman with a history of rheumatoid arthritis and type 2 diabetes mellitus underwent total arthroplasty of both knees in 1995. In June 1997, she presented with a left prosthetic joint infection and bacteraemia due to methicillin resistant sterichia coli. A two-stage surgical procedure was performed, with re-implantation performed after a 14 week course of rifampicin plus ofloxacin [BEING A DIABETIC, IN ALL PROBABILITY THIS CAUSED THE FIRST UNRECOGNIZED FLOXING]. ../..
> [In november 2000] Therapy with linezolid plus rifampicin (for methicillin resistant sterichia coli) and ciprofloxacin (for *E. coli)* was initiated [SECOND POSSIBLE FLOXING]. Linezolid was obtained through Pharmacia & Upjohn's compassionate-use protocol and was well tolerated based on the weekly laboratory testings. The patient was progressively able to walk with two canes. It was planned to remove the material after consolidation and to continue antibiotics for 3 months after this, with a maximum of 12 months of antibiotherapy. Forty-one weeks later the patient presented to her ophthalmologist with sudden blurred vision [CLASSICAL CIPRO OPTIC TOXICITY THAT WE HAVE RECORDED IN ALREADY SOME HUNDRED CASES]. The situation worsened rapidly and 3 weeks later antibiotics were stopped and the patient was hospitalized.
> At that time, concomitant medications were insulin, citalopram and lormetazepam. ../... Visually evoked potential testing confirmed severe bilateral optic neuritis. Therapy with methylprednisolone (1 g/day, 5 days) was started [THE WORST CHOICE FOR A FLOXING]. The visual acuity recovered but not completely, whereas ocular hypertension normalized rapidly. Eight months later, evoked potential testing showed mild abnormalities predominantly in the left eye.
> Optic neuritis has been associated with the use of antimycobacterial agents such as isoniazid and ethambutol, but not with rifampicin or with fluoroquinolones [SHEER IGNORANCE; IT IS A GUARANTEED RESULT OF ALL INTENSE OR LONG TERM TREATMENTS WITH FLUOROQUINOLONES]. Only neurotoxicity—essentially central nervous system toxicity—has been reported with the use of fluoroquinolones, including ciprofloxacin, in 0.9%–7.4% of patients. In our patient, we believe that linezolid was the most probable offending agent since all other causes were reasonably excluded, e.g. glaucoma, multiple sclerosis and toxic optic neuropathies [ENTIRELY UNFUNDED CONCLUSION BASED ON FALSE KNOWLEDGE]. In these three cases, it is possible that several underlying diseases and drugs contributed partially to this side effect. In our case, linezolid is the most likely cause, but it is possible that the combination with rifampicin, and/or ciprofloxacin has enhanced the toxicity.
> In conclusion, we suggest that peripheral or optic neuropathy could be a rare but potentially severe complication linked to prolonged linezolid therapy.

Pretty scientific again, is it not? The conclusion should never have excluded the ciprofloxacin as a main suspected agent, because it alone causes all the optic pathologies described. Therefore, instead of concluding that linezolid, cipro and the other underlying circumstances caused this severe optic toxicity, cipro emerges unscathed and immaculate once more.

The manufacturers of quinolones have done much of the same during the years. First they had to conceive trials that rendered positive results, hiding those that were negative. Then, they limited the doses and the length of the treatments of the trials so that the true toxic profile would not show up clearly. And finally, they never conducted an honest or prolonged post marketing surveillance. They devoted the money that it would have cost for surveillance to spread propaganda and gifts among doctors (1.2 billion dollars per year in gifts and incentives in the U.S. alone).

Many of us suffer from long debilitating pains in muscles and joints caused by quinolones, with clinical symptoms and laboratory tests that show mild forms of muscle destruction, probably caused by a similar mechanism such as the one used by other drugs like the statins.

However nobody in the medical class would ever even consider it as a possibility.

105. KILLING IGNORANCE

One of the most striking and horrifying practices we have seen in all these years of research is how some chronic illnesses, whose symptoms mimic a floxing, are treated with quinolones. The chances of patients

emerging with a favorable outcome are bleak if not non-existent.

Look at the content of this article. There is no known human being that can withstand a therapy of 1,500 mg of cipro for 6 months without developing severe reactions and permanent, irreversible damage.

> CONSIDERATIONS WHEN UNDERGOING TREATMENT FOR GULF WAR ILLNESS /CFS (chronic fatigue syndrome) /FMS (fibromyalgia syndrome) /RHEUMATOID ARTHRITIS
> by Prof. Garth L. Nicolson. The Institute for Molecular Medicine, Huntington Beach, California
> **For GWI/CFS/FMS use, the recommended dose is 1,500 mg/day (oral, 3x 500 mg capsules, 2 in morning) for 6 months, then 6 wk cycles of therapy**. Ciprofloxacin may or may not be taken with meals. Initially, ciprofloxacin may exacerbate some signs/symptoms (Herxheimer reactions or adverse antibiotic responses) but these are usually gone within a few wks or so. Patients report that doses of 1000 mg/day or lower are not effective in alleviating symptoms. Patients usually start feeling better with alleviation of major signs/symptoms within 4-6 wks, but in some patients signs/symptoms are not reduced until after 6 wks. Ciprofloxacin has been used for patients in which doxycycline cannot be tolerated or in some patients that no longer respond to doxycycline. In a few cases ciprofloxacin has been used simultaneously with doxycycline. Herxheimer reactions, if present, usually pass within days to a few wks; prior damage to the gastrointestinal system may require i.v. 400-500 mg x2/day (over one hr per each infusion, rapid i.v. administration is to be avoided) for 2-4 wks, then the remainder on oral antibiotic (oral doses). Virtually all patients relapse (with major signs/symptoms) if drug is stopped at in 6-12 wk course of therapy. Additional antibiotic courses result in milder relapses after drug is discontinued. Subsequent cycles of antibiotics may require the use of doxycycline or other antibiotics.

By now you already could be familiar with all the brilliant conclusions of top-level doctors. If the symptoms of gulf war illness (nearly identical to a floxing) of a patient increase a great deal after taking massive doses of cipro, it is not due to the antibiotic but to a Herxheimer reaction. If 100% of patients "relapse" with "major" symptoms if ciprofloxacin is stopped at 6-12 weeks, it is not because of a mounting (delayed) reaction to the brutal dose of cipro, but they relapse because of their illness. You also must be wondering why -according to that doctors- people seem to feel better after some weeks of cipro. Many floxed persons that are not hypersensitive to cipro or levaquin have also noticed this. They can take large quantities of fluoroquinolones and most of their illnesses seem to dissapear (prostate inflammation, chronic sinusitis) because of the very potent anti-inflammatory, vasoconstrictive action of the quinolones. But months after the treatment is stopped, the accumulated damage takes its definitive toll.

Fortunately, the The Institute for Molecular Medicine prescribes other antibiotics to people that do not tolerate quinolones, (*"subsequent cycles of antibiotics may require the use of doxycycline or other antibiotics"*).

106. WHAT ALL UROGOLISTS UNKNOW

Fluoroquinolones is the most frequently class of antibiotics prescribed by urologists. Nevertheless we have not yet met a single urologist (surveillance of more than 50 professionals, some of them reputed as top-notch nationally) that knowed even the basics of fluoroquinolone toxicity.

This french report stresses the necessity of knowing the serious tendinitis caused by fluoroquinolones and asks for a judicious use of those antibiotics. Although it contains real facts, backed by the experience, and was published in 2001, you will not probably find today (2007) a professional doctor that knows its conclusions, let alone care about them.

> FLUOROQUINOLONE-INDUCED TENDINOPATHY: SUBJECTS AT RISK, PATHOPHYSIOLOGICAL MECHANISMS INCRIMINATED, THERAPEUTIC MANAGEMENT.
> The use of fluoroquinolones in urology has grown considerably over recent years. Unfortunately, although these molecules are not associated with severe life-threatening complications, they have nevertheless been associated with tendon injuries responsible for functional disability. The frequency of these complications is probably underestimated. There is a variable lag-time (3 to 5 days) between introduction of the antibacterial and onset of pain. The symptom most frequently reported is pain over the tendon affected and the tendons most frequently affected are those submitted to high constraints. Bilateral injuries are present in 66% of cases. Although Pefloxacin® is associated with the highest

frequency of tendon complications (2.7% versus 0.2- 0.3% for other fluoroquinolones), the duration of treatment appears to be important in every case, with a peak frequency after a fortnight of treatment. Although these complications were considered for a long time to be associated with patients presenting certain risk factors (age, steroid therapy, renal failure), they can also occur suddenly, in young adult sportsmen or nonsportsmen, with no known tendon disease. Several hypotheses have been proposed to explain the development of these cases of tendinopathy: immuno-allergic mechanisms, direct toxicity of the molecule on collagen fibres, cell-mediated oxidative aggression, or tendon necrosis due to vascular mechanisms. The outcome remains favourable in 75% of cases of tendinitis and in 49% of cases for tendon rupture. Contraindications must therefore be identified and the duration of treatment must be adapted, as the functional handicap can be long and particularly severe. CONCLUSION [translation by us] In spite of a great effectiveness, a good tissue diffusion and a anti-bacterial spectrum of quality, the side effects, in particular the tendon ruptures, must force prescribing the fluoroquinolones with many precautions. It is necessary to measure the counter-indications and to adapt the duration of the treatment. Indeed, the disabilities can be long and particularly harmful. If any antecedent of tendinopathy with fluoroquinolones constitutes a definitve counterindication for the use of fluoroquinolones, it is necessary to be vigilant with the young sportsmen not presenting tendon pathology. The patients must thus be informed of the risks and the clinical signs which can constitute an alarm. The treatment with fluoroquinolones must be supervised, and this vigilance must be extended over the time. It remains essential to evaluate the benefit versus risks before any treatment.

107. WE ARE NOT ALONE

Now look at yet another one of our "blind" homemade statistical experiments. We took the list of potential symptoms from the protocol for surveying chronic bacterial and viral infections in chronic illnesses, applied it to gulf war veterans–that sums up about 120 symptoms, added some 20 more invented symptoms, that did not correspond to the questionnaire for gulf war symptoms, and sent the list to 10 volunteer floxed persons, (only 4 of them belonging to the cohort of table 1; one of them could not answer back) asking them to mark the symptoms that they had experienced during their floxings. Once they returned the list with their symptoms checked, we noticed that the 20 fake symptoms had been rarely selected, so we omitted them and here is the result:

TABLE 19. EXPERIMENTAL COMPARAISON BETWEEN SYMPTOMS OF GULF WAR SYNDROME AND FLOXING

☑ = means that this symptom is frequent in floxing; ✓ = means that is sometimes present in floxing
(some or all symptoms listed may be present in gulf war syndrome)

Racing pulse	✓	Chest pain	☑	Diarrhea	☑
Chest pressure	☑	Gas, flatulence	☑	Stomach cramps	☑
Nasal congestion or stuffiness		Bloating	☑	Stomach pain	☑
Nasal mucus discharge		Lack bladder control (small volume)	☑	Change in, or lack of taste	☑
Sinus pain	✓	More frequent episodes of urination	☑	Less capacity for alcohol	☑
Sore throat	✓	Episodes of blood in stools		Swollen glands (neck, armpits, groin)	☑
Unable to breath deeply	☑	Episodes of blood in urine	✓	Toenail or foot fungus	
Wheezing		Nausea	✓	Weak voice or hoarseness	
Shortness of breath	☑	Vomiting	✓	Excessive thirst	☑
Coughing frequently		Regurgitate (throwing up) food	✓	Loss of sexual libido (sex drive)	☑
Coughing up thick saliva or phlegm		Bleeding gums	☑	Swollen abdomen	☑
Frequent clearing of throat		Dental abscesses	✓	Reduced joint mobility	☑
Excessive sneezing		Increased salivation		Joint pain or discomfort	☑
Loss of interest or enthusiasm	☑	Blurred vision	☑	Muscle spasms or cramps	☑
Suicidal thoughts	☑	Double or wavy vision	☑	Aching or burning muscles	☑
Depression	☑	Problems eyeglasses prescription	☑	Numb hands	☑
Nightmares	☑	Deteriorated night vision	☑	Tingling hands	☑
Unrefreshed Sleep	☑	Increased visual sensitivity to light	☑	Other loss of strength/endurance	☑
Irritable	☑	Black spots (floaters) in eyes	☑	Other numbness or tingling	☑
Mood swings	☑	Bothersome eye twitching	☑	Trembling, shaking, or twitching	☑
Chronic fatigue, excessive tiredness	☑	Dry eyes	☑	Swelling of ankles	☑
Night sweats	☑	Itchy eyes	✓	Swelling of body	

Intermittent fever at night	✓	Watery eyes		Black & blue bruising more easily	☑
Hair loss	☑	Headaches	☑	Aching joints	☑
Abnormal change of hair color		Short-term memory loss	☑	Pain in lower back	☑
Skin rashes	☑	Problems thinking and concentrating	☑	Pain in neck	☑
Reddening or flushing of skin	☑	Lightheadedness	☑	Excessive hunger	
Skin itching	☑	Poor balance or unsteadiness	☑	Loss of interest in food	☑
Cracking, peeling of skin	✓	Dizziness/vertigo	☑	Difficulty sleeping (insomnia)	☑
Cuts & wounds slow to heal	☑	Ringing in ears/tinnitus	☑	Difficulty waking up	
White "itchy-scaly" between toes		Hearing loss	☑	Sensitivity to cold (easily chilled)	☑
Unusual skin rashes	☑	Stuttering or stammering		Teeth easily chilled by cold foods	☑
Yellowing color of skin		Difficulty finding words	☑	Teeth loose	✓
Skin sunburn-like sensation	☑	Numbness of lips	☑	Frequent infections	✓
Wart-like growths on skin		Drooling		Frequent colds or flu	✓
Genital itch	☑	Frequent yeast infections	☑	White coated tongue	✓
Itchy scalp	☑	Irregular heart beats	☑	Mouth sores	☑
Difficulty swallowing	☑	Bothered by exhaust or fumes	☑	Lip sores	✓
Reduced sense of smell	☑	Bothered by cigarettes, smoke	☑	Dry "cotton" mouth	✓
Increase in allergic sensitivities	☑	Aching or swollen testicles	☑	Sexual impotence	☑

What does this mean? For us, our unscientific experiment demonstrates three things:

1. That many chronic illnesses with a toxic root share most symptoms, among them gulf war and floxing syndromes. (Did veterans take cipro?)

2. That treating gulf war victims that exhibit these symptoms with ciprofloxacin is an audacity that looks like a Gulf-War-II re-exposure for the veterans.

3. That all severe floxed persons could well be diagnosed as suffering gulf war syndrome for instance.

By now you know that not one but several groups of doctos have already discovered the best way of destroying forever any chance of recovery for patients of chronic fatigue syndrome, fibromyalgia and gulf war illness: administering them multiple courses of 6 weeks worth of cipro at the highest dose imaginable (1,500mg/day):

> NEW TREATMENTS FOR CHRONIC INFECTIONS FOUND IN CHRONIC FATIGUE SYNDROME (CFS), FIBROMYALGIA SYNDROME AND GULF WAR ILLNESSES
> by Garth L. Nicolson, Ph.D. ImmuneSupport.com. 1997. The Institute Molecular Medicine, California.
> Chronic Fatigue Syndrome (CFS), Fibromyalgia Syndrome (FMS) and Gulf War Illnesses (GWI) are characterized by their complex, multi-organ chronic signs and symptoms, including neurological, muscular-skeletal, rheumatic, mucocutaneous, gastrointestinal, sinopulmonary, and constitutional, among others. Also included in this complex clinical picture are increased sensitivities to various environmental agents and enhanced allergic responses. Often such patients have cognitive problems and are seen by psychologists or psychiatrists who usually decide in the absence of contrary laboratory findings that the condition is a somatoform disorder. However, there is another, quite different possibility--these patients may suffer from chronic infections that can penetrate the CNS and PNS as well as other tissues and organs and cause the complex signs and symptoms seen in CSF, FMS and GWI, including immune dysfunction that may underlie some of the environmental responses as well as increased titers to various endogenous viruses that are commonly found to be expressed in these patients.
> Few infectious agents can produce the complex chronic signs and symptoms found in CFS, FMS and GWI patients, but one type of airborne infection that has received renewed interest of late as an important element in these disorders is represented by the class mollicutes. These organisms, principally mycoplasmas and other rather primitive bacteria, although not well known agents, are now considered important emerging pathogens in causing chronic diseases and may be important cofactors in some illnesses, including AIDS .
> Interestingly, as these illnesses progresses, there are a number of accompanying problems, including in some patients MS-like, ALS-like, Lupus-like and arthritis-like signs and symptoms, and the presence of usually rare autoimmune responses is consistent with mycoplasmal infections that penetrate into

nerve cells, synovial cells, etc. [REMEMBER THAT CIPRO CAUSES MS-LIKE, ALS-LIKE, LUPUS-LIKE AND ARTHRITIS-LIKE SIGNS AND SYMPTOMS AND BE PREPARED FOR THE SHOCK AT THE PROPOSED TREATMENT LATER ON THE ARTICLE]. As mycoplasmas escape from cellular compartments, they can leave with pieces of cell membranes containing important antigens that can trigger immune responses. ...../.....

The identification of mycoplasmal infections in the leukocyte blood fractions of a rather large subset of CFS, FMS and arthritis patients suggests that mycoplasmas, and probably other chronic infections as well, may be an important source of morbidity in these patients. If such infections are important in these disorders, then appropriate treatment with antibiotics should result in improvement and even recovery. This is exactly what has been found. The recommended treatments for mycoplasmal blood infections require long-term antibiotic therapy, usually **multiple 6-week cycles** of doxycycline (200-300 mg/d), **ciprofloxacin or Cipro (1,500 mg/d**), azithromycin or Zithromax (500 mg/d) and clarithromycin or Biaxin (500 mg/d).

Multiple cycles are required, because few patients recover after only a few cycles, possibly because of the intracellular locations of mycoplasmas like M. fermentans and M. penetrans, and the slow-growing nature of these microorganisms. Treatment recommendations for mycoplasmal infections are similar to those used to treat Lyme Disease, caused by other slow-growing intracellular bacteria that are difficult to identify and treat. Interestingly, CFS, FMS, and GWI patients that recover after several cycles of antibiotics are generally less environmentally sensitive, suggesting that their immune systems may be returning to pre-illness states. If such patients had only chemical exposures as the reason for their illness, they should not respond to the recommended antibiotics and recover. .../.....

Are chronic, systemic mycoplasmal infections the answer to CFS, FMS, GWI and other disorders? Of course not! This is likely to be an appropriate explanation for a rather large subset of CFS, FMS, GWI and some arthritis patients, but certainly not every patient will have the same chronic infections. Some patients may have chemical exposures or other environmental problems as the underlying reason for their chronic signs and symptoms. In these patients antibiotics should have no effect whatsoever. ...../.....

It is quite clear that many treatments for gulf war syndrome, fibromyalgia, and multiple chemical sensititives are engrossing the ranks of floxed people that are unaware of it. And paradoxically, some of those patients treated with extremely high doses of quinolones may be not gulf war veterans or fibromyalgia patients after all but floxed persons.

108. DO I HAVE FIBROMYALGIA OR CIPROMYALGIA?

If you have been floxed, you might be diagnosed with fibromyalgia. You can also worry about it. Fluoroquinolones can cause fibromyalgia, but what actually happens is that you are floxed and floxing has similar symptoms to fibromyalgia. In some individuals, the symptoms are very similar indeed.

Many floxed persons are far more worried about having fibromyalgia than a floxing. That fear is only justified if the floxed person does not sustain a severe reaction, because a severe intoxication caused by a fluoroquinolone is much more damaging that a common course fibromyalgia.

A LETTER FROM A SUPPORT GROUP

I was floxed after just 7 days of Levaquin. Now 3 years 3 months after Levaquin therapy some conditions have subsided. I was a healthy 49-year-old female. I had never had surgery or any serious health condition, although I was overweight. I was an avid advanced downhill skier, active and healthy. I was given ten 500 mg samples of Levoflaxacin for treatment of sinusitis by my Family Practice Physician. Within 4 days I had severe adverse drug reactions:

- *Severe tendon/muscle pain and tightness*
- *Tendonitis*
- *Tingling, numbness, prickling, pins and needles sensations in my extremities.*
- *"Electrical" sensations*
- *Shooting pain*
- *Feeling of worms crawling under my skin*
- *Severe arm and leg weakness*
- *Erroneous muscle twitching, spasms and contractions*

Thanks to this Group [a victim's forum], *I realized what was happening to me and stopped taking the drug after 7 days. However, it was long enough to do damage. My doctors have disregarded my concerns about Levaquin and have labeled my* ***diagnosis as Fibromyalgia****.*

That's the frustrating part. I still can't walk long distances or use a keyboard and mouse for any length of time. I still suffer 24/7 tendon/muscle pain, tightness, and weakness, as well as tendonitis. Some days I'm in more pain than others. But the good news is that many of the tingling, twitching, crawling sensations have almost completely subsided. It is so sad that so few believe what this drug is capable of.

The following is a simplified comparison between both ailments.

TABLE 20. COMPARAISON BETWEEN SYMPTOMS OF FIBROMYALGIA AND CIPROMYALGIA

LIST OF SYMPTOMS OF FIBROMYALGIA	IN FLOXING?	COMMENTS
Widespread Pain	yes	The whole body in floxing, and focused in 18 specific points in fibromyalgia
Nausea	yes	The same in both ailments
Dizziness	yes	The same in both = Vertigo, Unsteadiness, Lightheadedness, Near Fainting, Headache, Sweating or chills, Blurred vision, Hearing problems, including tinnitus
Temperomandibular Joint Dysfunction Syndrome	yes	The same in both ailments
Skin Complaints	yes	Dry Skin, Itchy Skin, Mottled Skin, Tender Skin, Rashes
Depression	yes	The same in both ailments
Myofascial Pain Syndrome	yes	The same in both ailments
Weather Changes	**NO**	Floxing does not cause special sensitivity to weather changes
Morning Stiffness	yes	The same in both ailments
Sleep Disorders	yes	The same in both ailments
Chronic Headaches	yes	The same in both ailments
Multiple Chemical Sensitivity	yes	The same in both ailments
Chest Symptoms	yes	The same in both ailments, that is to say: sharp, stabbing pain in the front of the chest, ribs that are sore to the touch, pain in areas of chest and ribs, pain that radiates up the back of the neck and shoulders, rapid or irregular heart rate, shortness of breath or difficulty breathing.
Dysmenorrhea	yes	Don't know what happens in floxing
Muscle Twitches and Weakness	yes	The same in both ailments
Fatigue	yes	The same in both ailments
Urinary and Pelvic Problems	yes	The same in both ailments, that is to say Feeling a constant or persistent urge to urinate, difficulty "holding" urine, going to the bathroom to urinate more than once during the night, pelvic pain or pain on urination, urinary frequency, sudden need to urinate, pelvic pain or discomfort , episodes of incontinence, urge to urinate that occurs only seconds before urination.
Rhinitis	**NO**	Floxing does not cause rhinitis, but dry nose and more frequent infections.
"Fibrofog": Cognitive or Memory Impairment	yes	The same in both ailments, Ciprofog.
Anxiety	yes	The same in both ailments
Aggravating Factors (stress)	yes	The same in both ailments: Stress plays a big role in triggering fibro-cipro-myalgia symptoms. Episodes of emotional stress and anxiety can bring on muscle pain and headaches, or even cause anxiety attacks.
Memory Loss	yes	The same in both ailments

As you can see, almost all symptoms of fibromyalgia are present in cipromyalgia (floxing). The opposite is not true. Many symptoms of cipromyalgia (severe type) are not present in fibromyalgia. Severe cipromyalgias cause permanent irreversible damages (for instance, in the joints), which is not the case with fibromyalgia.

Look at this report by well known doctors in the field of chronic fatigue symptom and fibromyalgia. After years of prescribing cipro, something does not fit well in the picture for these doctors and they warn about cipro toxiticy with very acurate predictions:

ANTIBIOTIC-SENSITIVE INFECTIONS IN CFS/FIBROMYALGIA
Townsend Letter for Doctors and Patients, May, 2005 by Jacob Teitelbaum
Fortunately, both mycoplasma and chlamydia infections are usually sensitive to the right

antibiotics. The antibiotics most likely to affect these organisms are the following:
* Doxycycline or minocycline, usually at dosages of 100 milligrams 2 times a day. These two antibiotics are in the tetracycline family. They are very effective against a number of unusual organisms (including, at times, Lyme disease). They should not be given to children under eight years old because they can cause permanent staining of the teeth.
* Ciprofloxacin (Cipro), usually 500 milligrams twice a day has a very wide range of effectiveness against a large number of organisms. When treating males, Cipro has the additional benefit of treating any hidden prostate infections, as does doxycycline. Do not give oral magnesium or any supplement containing magnesium within six hours of the Cipro or it can decrease absorption of the Cipro. **I think that in time we will realize that Cipro can be fairly toxic in a subset of patients, actually causing fibromyalgia, tendonitis, and other musculoskeletal problems.** [UNFORTUNATELY, THE "SUBSET" OF PATIENTS IS THE WHOLE POPULATION]
Although all of these antibiotics can be effective, it is not uncommon for infections that are sensitive to the erythromycin antibiotics (Zithromax or Biaxin) to be resistant to tetracycline antibiotics (doxycycline, minocycline) and Cipro, and vice-versa. Therefore, it is best to try either doxycycline or Cipro first. If they are not effective, then try the Zithromax or Biaxin. The antibiotic should be taken for at least six months. If there is no improvement in ~2-4 months, switch to or add the other antibiotic or simply stop the treatment. It is helpful to check for low-grade fevers. As mentioned earlier, I am more likely to use antibiotics for CFIDS patients who have temperatures over 98.6[degrees]F, even if it is only 98.8[degrees]F (I consider 98.8[degrees]F a fever because CFIDS/FMS patients usually have low body temperatures). If the fever decreases with the antibiotic, it suggests that the patient does have one of these nonviral infections and that the antibiotic is helping. This would encourage me to continue the antibiotic trial--even if it takes up to 18 months to see an improvement in their symptoms.
It is very common to get what is called a Herxheimer (die-off) reaction that includes chills, fever, night sweats, and general worsening of CFS/FMS symptoms when the antibiotic first kills off the infection. These symptoms can be severe and last for weeks [WE FIRMLY BELIEVE THAT IN MOST CASES THESE SEVERE REACTIONS ARE REALLY SIDE EFFECTS OF THE ANTIBIOTIC]. If this occurs, lower the antibiotic dose to the level tolerated (e.g.-doxycycline 25 mg every other day) and increase as able. Dr. Nicolson encourages patients not to abandon therapy prematurely. He notes that if they have been sick for years, it is unlikely they will recover in less than one year of treatment, so they should not be alarmed by symptoms that return or worsen temporarily.

109.DO I HAVE MULTIPLE SCLEROSIS?

If one well-known illness resembles a floxing, it is multiple sclerosis. There are so many common symptoms that we are not going to include them here.

Fluoroquinolones do cause multiple sclerosis but only when a full autoimmune, uncontrolled and persistent reaction to the antibiotic is released. This is a rare event; a truly rare event, in the sense that manufacturers put it, and only very few people acquire it through the antibiotic.

Hopefully your doctor will order the routine MRIs, spinal taps, and other tests that will allow multiple sclerosis to be ruled out as the cause of your sickness.

INCREASED CD80+ B CELLS IN ACTIVE MULTIPLE SCLEROSIS AND REVERSAL BY INTERFERON beta-1B THERAPY
Anthony T. Reder. The Department of Neurology, and the Brain Research Institute, University of Chicago, Chicago, Illinois
...In addition, viral infections induce MS attacks (26, 27), superantigens released during bacterial infections reactivate EAE (28), and quinolone antibiotics (a relationship between worsening of the symptoms of MS and ciprofloxacin treatment [Reder, A.T., unpublished data]) sometimes worsen MS symptoms..../....

The most important support groups of multiple sclerosis sufferers, advice that: *"Since it may be difficult to distinguish between certain common symptoms of multiple sclerosis and some side effects of ciprofloxacin, be sure to consult your health care professional if an abrupt change of this type occurs* [WHEN TAKING CIPRO]*"*.

The present version of the report does not treat this differential diagnosis in detail, because it is not so important or relevant.

110.DO I HAVE AMYOTROPHIC LATERAL SCLEROSIS (ALS)?

So many fasciculations, twitchings and cramps lead people to worry a lot about having ALS. If you are strongly floxed, fasciculations, weakness, muscle wasting, cramps, and twitching are all quite common. See the corresponding section of this paper if you would like to obtain more information.

Many visitors to neurology forums are worried about the possibility of having ALS, but they just have a neuropathy of another kind, some of them toxic reactions to medicines, in particular to fluoroquinolones, as it has been demonstrated in many occasions.

The present version of the report does not treat this differential diagnosis in detail, because it is not so important or relevant.

111. DO I HAVE LYME?

If you live in some lyme-prone areas, especially some states in the United States, there is a possibility that you are checked for lyme. As lyme diagnosis is a clinical one (symptoms, signs, but not definitive tests), and due to the fact that many symptoms of lyme are so similar to those of a floxing, you can be studied by your doctors under the point of view of trying to rule out lyme.

The real problem is that some lyme sufferers, and some that do not have the infection but are wrongly diagnosed as having lyme, are treated with fluoroquinolones, so they run a very high risk of getting floxed, even without proof that they even have lyme. Long courses of antibiotics are popular among lyme sufferers. Some report big improvements after taking quinolones. May be they are good metabolizers of quinolones and did not reached their cummulative threshold, as it happened to many floxed persons that withstood well their first treatments along several years. But far many more report very debilitating adverse effects after taking cipro and levaquin. After reading hundreds of personal experiences with cipro and levaquin by lyme sufferers and contacting a big lot of them, it seems that adverse reactions are almost the rule for long treatments save exceptions.

Using figures, our research of more than a year, indicates that more than 75% of lyme sufferers that take long term fluoroquinolones end up floxed, some severely, and half of them without knowing it or at least not realizing the tragic future that lays ahead for them if they add to an active lyme a severe floxing. They always refer to the assistance of a LLMD (lyme-literate-medical-doctor), and almost all those doctors are in reality LLFIMD (lyme-literate-floxing-iliterate-medical-doctor). So there is a steadily increasing amount of the number of floxed persons as a result of lyme treatments.

Look how dramatic can be the situations caused by illiterate lyme doctors, reading the following post of a forum for lyme patients:

> ORIGINAL POST BY THE MOTHER OF A CHILD WITH SUSPECTED LYME
> Hello out there,
> My 3.5 yo has been on Cipro for Bart/Ehrlichia for about 6 weeks now. He is starting to have some irritability that is uncharacteristic. I am also noticing that his joints are showing some stiffness that we hadn't seen before. I think these are due to the Cipro and are similar to what I experienced on Levaquin. My question is, does anyone one know what to give a child for support of these sx? What doses did you use?
> My LLMD/Psych told me to take free form Glycine (among other things) for the irritability since it is a precursor to GABA and Levaquin reduces GABA in the brain. I also just remembered today that taking Magnesium, as I do, is advised to prevent tendon damage on this class of abx.
> With the Glycine my question is mainly about dose. I can mix it in his juice. With the Magesium the

> only appropriate form I could find was MagCitrate that is mixed with hot water but then I'm concerned about dose and making his stools too loose. I guess I could feed him more binding foods. Any help would be much appreciated. We have an apptmt with Dr. J in late March and hopefully with Dr. M the ped Naturopath in mid March. [one month after this message was posted, so the child was due to be 10 or 11 weeks on cipro].

Fortunately for lyme patients, fluoroquinolones are not the antibiotic of choice for the longer treatments.

The present version of the report does not treat this differential diagnosis in detail, because it is not so important or relevant for the main subject.

112. DO I HAVE LUPUS?

Fluoroquinolones do cause lupus, or drug-induced lupus. It is a rare event. In any case, floxing shares a lot of symptoms with lupus, but normally it is a different illness.

The present version of the report does not treat this differential diagnosis in detail, because it is not so important or relevant.

113. DO I HAVE REITER'S, SJOGREN'S, RAYNAUD'S?

If you have suffered an intermediate reaction, then you have secondary Sjögren's and Raynaud's, at least partially. And you also have symptoms that prompt many doctors to diagnose reactive arthritis (Reiter's). But you do not have it. Your body has been floxed and the problem is not that your body is reacting uncontrollably against tissues that resemble the bacteria that overgrew during your last infection.

The best ways of treating your Sjogren's and your Raynaud's caused by cipro or levaquin, is to follow the guide for recovery from a floxing, forgetting all the drugs recommended for Sjogren's and Raynaud's.

The present version of the report does not treat this differential diagnosis in detail, because it is not so important or relevant for the main subject.

114. PLEASE, DON'T PRESCRIBE ME A QUINOLONE AND DON'T TELL ME WHY

Citizens are little stupid, hypochondriac and feable minded persons and we do not deserve to participate of the decisions about our health. This inmoral way of behaving by doctors, plays havoc on their patients and makes it impossible to avoid drug reactions and impossible too to approach them when they have already taken place.

> JEREMY NORMINGTON, DPT, IS DIRECTOR OF PHYSICAL MEDICINE AND REHABILITATION AT SIOUX VALLEY MEMORIAL HOSPITAL IN CHEROKEE, IOWA
> Fluoroquinolones have been called one of the success stories of modern antimicrobial chemotherapy. However, many physicians are still unaware of tendinopathies induced by fluoroquinolones, despite the fact that side effects are listed in the Physicians' Desk Reference and more than 200 cases have been reported to the FDA.
> If you see that a patient is using a fluoroquinolone, such as Cipro or Levaquin, be aware of potential side effects and take appropriate action to avoid further damage to structures. But avoid telling the patient outright that a fluoroquinolone-induced tendinopathy may occur. Instead, contact the primary care physician to discuss the situation.
> A simple call can alert the physician to a potential problem so he can stop the medication or find an alternative. And it may help you gain new respect from referring physicians.

115. A DEAR DOCTOR LETTER

Not all doctors are the same. Some will be willing to listen to you and try to help honestly. You only have to find them. Doctor T. Plumb has prepared this "dear doctor" letter and authotised its reproduction here, just in case you might want it printed out and taken with you.

Dear Doctor,

As you are probably aware, the fluoroquinolone class of antibiotics is useful for certain serious infections. Unfortunately, fluoroquinolones also have a long history of serious adverse drug reactions, many of them long term . (1) As a consequence of these reactions, several of these drugs have been removed from clinical practice or their use severely restricted. Besides the severe life threatening immediate reactions, those of a more chronic nature may occur.

The spectrum of these adverse reactions is extremely broad. Patients suffering from these reactions are often misdiagnosed, referred for a psychiatric consult or even unfairly labeled as "difficult patients."

Many physicians have not been properly educated about the severe nature of these chronic adverse reactions, some of which result in life-long disabilities. Post-marketing studies of several flouroquinolones have shown an incidence of adverse reactions much higher than were originally reported in pre-clinical studies. (1,2,3)

You are probably aware that the fluoroquinolones are eukaryotic DNA gyrase and topoisomerase inhibitors very similar to many antineoplastic agents. Because of their similar mechanisms of action, it's no surprise that fluoroquinolones and many antineoplastic agents share similar toxicity profiles. Studies have even been conducted using fluoroquinolones to inhibit neoplastic chondrocyte growth in chondrosarcoma. (4)

There are many patients who have a syndrome of associated symptoms that include, but are not limited to: CNS agitation, depression, insomnia, new-onset anxiety and panic attacks, and even elevated intracranial pressure and visual abnormalities. They may also present with peripheral neuropathy usually of the small fiber type with temperature and pain sensory aberrations, but also often involving larger sensory and motor nerves. Spontaneous muscle activity with fasciculations, myokymia and myoclonic jerks may also occur. Many have musculoskeletal damage with degeneration of cartilage and tendons often leading to tendon rupture and severe ongoing musculoskeletal pain long after therapy has been discontinued. (1,2,3,4,5,6,7,8)

This complex symptomatology does not usually resolve after discontinuation of the inducing fluoroquinolone and may in fact worsen. Many patients go on to have disability that may persist for years. (1) Unfortunately, such patients are often seen by many physicians from multiple specialties who, given the complex symptomatology, fail to recognize a unifying diagnosis.

The mechanism of injury is not fully apparent, but several studies have been conducted and researchers have implicated the following possible mechanisms:

1. Inhibition or disruption of the CNS GABA receptor. (9)
2. Depletion of magnesium and disruption of cellular enzymatic function. (10)
3. Disruption of mitochondrial function and energy production. (11,12)
4. Oxidative injury and cellular death. (14)

This seems to be a functional disorder and structural abnormalities are not usually seen on radiological studies. (13) Patients may have abnormal EMG/NCV studies, abnormal skin punch neurologic density and morphology, abnormal vasomotor and sudomotor function on autonomic testing, and abnormal degeneration of tendons and cartilage on MRI. (13)

There may be a large number of these patients with coexisting endocrine abnormalities including: antithyroid antibodies and abnormal thyroid function, abnormal adrenal function with either hyper or hypocortisolism, hypogonadism, hypo or hyperglycemia and possibly impaired pituitary function. (13)

Most patients suffering from these side effects have a very clear onset of symptoms temporally related to a course of fluoroquinolone antibiotic. (13) They were often given the fluoroquinolone in conjunction with a corticosteroid or NSAID. Both of these classes of medications are associated with an increased incidence

of adverse drug reaction from fluoroquinolones. (10,13)

As of yet no scientifically proven effective treatment is known, however patients will definitely benefit from your caring support and appropriate informed care. Of course, other diseases with similar symptoms need to be carefully ruled out.

There exists a large community of these patients who share information on the World Wide Web. Their numbers grow as the prescription of fluoroquinolones increases. Many of these patients are professionals like myself who have been affected by these drugs. Thank you for your time and consideration.

Todd R. Plumb MD

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Note to readers: The purpose of this E-Letter is solely informational and educational. The information herein should not be considered to be a substitute for the direct medical advice of your doctor, nor is it meant to encourage the diagnosis or treatment of any illness, disease, or other medical problem by laypersons. If you are under a physician's care for any condition, he or she can advise you whether the information in this E-Letter is suitable for you. Readers should not make any changes in drugs, doses, or any other aspects of their medical treatment unless specifically directed to do so by their own doctors.

116. STATINS ARE WELL AHEAD

Statins have been better studied than fluoroquinolones and their side effects widely recognized. But there is a reluctancy to admit permanent injuries, as much as with fluoroquinolones, despite thousands of cases. In this sense, fluoroquinolones and statins share the same policy of denial. Both drugs alter also the Q10 metabolism and mevalonate pathway, and some of their neurological and muscular damages could have something in common.

PERMANENT SIDE EFFECTS FROM STATINS. Duane Graveline MD MPH

I was still in practice, twenty years ago, when lovastatin, the first statin drug, became available for use by we primary care physicians. We learned to expect liver inflammation and occasional muscle aches and pains. With the dosages used at that time and with a relatively small number of patients on the early statins, the side effect issue impressed me as being acceptable. This is no longer true. Today, with more potent drugs, millions of people taking them and doses triple and quadruple those of the past, our side effect profile has radically changed. Now, cognitive damage, emotional and behavioral change, neuropathies and even neuro-degenerative damage are increasingly recognized as associated with statin drug use. But there is something even more perverse – the element of permanence of some of these consequences.

The pharmaceutical industry has been quick to add such conditions as neuropathy and amnesia to their long list of “disclaimers” in their drug reference information. Yes, within the past six years, after

my own cognitive reactions to statins in the prevailing climate of complete physician denial, drug companies have belatedly added cognitive damage but not one word about permanent cognitive damage. And the same for neuromuscular – yes, most of the drug companies now admit that peripheral neuropathy may be a consequence of statin use but have never mentioned it might be disabling, crippling or permanent. The deliberate pattern of gross misrepresentation and disinformation of statin drug side effects to physicians who prescribe these drugs has created a climate where many physicians will summarily dismiss patient claims of damage as impossible, thereby placing them in harm's way. The first evidence of permanence came from reports of cognitive problems associated with statin use.

Michael Hope was one of the first to receive widespread media attention – a former CEO reduced to unemployable status due to persistent loss of short-term memory. Today, four years after the onset, Michael is still grossly impaired. He is one of many hundreds who have persistent cognitive deficits long after stopping their statin. Next came reports of muscle aches and pains brought on by statin drugs that persisted and even worsened despite promptly stopping the statin. Two astronaut friends of mine, having no history of muscle problems, experienced muscle pains shortly after their statin was started for mild hypercholesterolemia. Much to their dismay these pains have persisted years after they stopped the offending drug. They are but two of thousands of patients in this growing subgroup of people with persistent and apparently permanent muscle symptoms seemingly triggered by statin drug use.

Current research indicates that many of these have an unsuspected genetic predisposition. Some of these cases respond to CoQ10, many do not. Another growing reality is that of peripheral neuropathy, particularly unresponsive to treatment, coming on soon after statin therapy is initiated. Once this occurs, not only does it seems to be permanent but tends to worsen in many patients. Hundreds of victims are incapacitated, even crippled by this unfortunate side effect, seemingly related to alterations in CoQ10 availability brought on by statin drug interference with the mevalonate pathway. Mevalonate pathway disruption also seems to be the mechanism of action for another type of neurological disaster associated with statin use, that of neurodegenerative disease onset shortly after the start of treatment. Only in the past few years have we learned of the unfortunate tendency of statins to promote the tau protein formation while inhibiting the usual sequence of biochemical reactions in the mevalonate pathway.

Tau protein is now known to promote the formation of neuro-fibrillatory tangles with secondary neuronal damage, offering a possible explanation for the unusual number of cases we are seeing of amyotrophic lateral sclerosis, Parkinsonism, frontal lobe dementia and Alzheimers' disease and other neurodegenerative conditions shortly after statins are started. This suggests that these diseases are somehow being triggered by statins. Need I add that these diseases are both permanent and progressive.

Not only have statin drug companies failed to adequately warn prescribing physicians of permanent cognitive loss associated with statin use, they have failed to warn about permanent neuromuscular and neurodegenerative consequences. Thousands of unsuspecting patients have become victims and in most of these cases their doctors, having had no advance warning from the pharmaceutical industry, have tended to disregard patient complaints, offering almost any explanation other than the correct one. Unfortunately, as these damage claims come to the attention of the courts many MDs will be forced to share liability with the drug companies.

On hearing hundreds of patient complaints about doctor rebuff on this subject of statin side effects, I well recall the words of Doctor Ellsworth Amidon, my professor of medicine at Vermont College of Medicine, way too many years ago: "Listen well to the words of the patient, my young doctors, for they are telling you the diagnosis."

Perhaps this is too much wisdom for most high-tech and industry-prone doctors of today. We have reproduced this letter here because if you substitute "statins" by "fluoroquinolones", we could have written the letter ourselves.

PART XIV: THE ROLE OF THE FOOD AND DRUG ADMINISTRATION

117.THE IMMORALITY AND INSANITY OF THE DRUG MANUFACTURERS AND THE FDA

It is beyond the scope of this article to argue in depth about the role of the FDA (Food and Drug Administration of the USA) and the behavior of the pharmaceutical laboratories (the *"industry"*).

But it is crystal clear that none of the people that have been surveyed for the writing of this report would have seen their lives destroyed, had their doctors known the real toxic profile of these antibiotics. Almost all the other hundreds of people that we know that have suffered proven toxic reactions to quinolones could have been treated with less toxic antibiotic for their sinusitis, sore throats or prostatitis. Probably millions of people are suffering from "fibromyalgias", all sorts of pains, insomnia and neuropathies thanks to the low constant dose of quinolones (enrofloxacin, mainly) ingested through food. So much of this antibiotic is currently ingested that now many people would not get any medical benefit of a treatment with ciprofloxacin.

We do not propose to wipe out the quinolones from the pharmaceutical arsenal, but rather disclose their true properties, so that:

- they are only used when other less toxic alternatives are not available
- they are used with the minimum dosage that works and for the minimum length of time
- they are used the least number of times throughout a person's lifetime
- they are completely forbidden for treatment of animals that enter the human food chain

That should be the role of the Food and Drug Administration, but they fail appallingly. Instead, like the general that sends some thousand soldiers to be slaughtered on remote hills just to erode the fighting capacity of the enemy– for the Food and Drug Administration it doesn't matter how many people are killed or disabled as far as some lives are saved in critical medical situations and how much disproportionate profit is earned.

The point is that both issues are compatible. Hospitals can have the quinolones for critical cases and doctors should also know their real toxicity, a thing that will only happen if the FDA discloses it.

In consequence, the FDA bears the highest responsibility in all the suffering and destroyed lives of so many tens of thousands of people. There is enough evidence that the FDA knows so much about the quinolone toxicity epidemic that is happening, but their *"client"* is the *industry*, and the top officers work very much towards protecting the interests of the manufacturers.

Look to a passage of the interview of Food and Drug Administration (FDA) employee and Vioxx whistleblower Dr. David Graham (the whistleblower of Vioxx), conducted by Manette Loudon:

> ***Dr. Graham:*** *The FDA has a very peculiar culture. It runs like the army so it's very hierarchal. You have to go through the chain of command and if somebody up above you says that they want things done in a particular way well, they want it done in a particular way. The culture also views industry as the client.*
> *They're serving industry rather than the public. In fact, when a former office director for the Office of Drug Safety criticized me and tried to get me to change a report I'd written on another drug -- Arava -- he said to me and to a colleague who was a co-author on this report that "industry is our client."*
> *I begged to differ with him. I said, "No, industry is not the client, it's the American people, the people who pay our taxes. That's who we're here to serve." He said, "No! Industry is our client." I ended the conversation by saying,*

"Well, industry may be your client, but it will never be my client."

Dr. Graham: *..... But I've been a target of retaliation in the past. You take 10 drugs off the market well, no good deed goes unpunished at the FDA. I've experienced retaliation with many of those other episodes but not as severe as what I've experienced with Vioxx.*
This is the first time that my job was actually in jeopardy and where the FDA actually intended to fire me. That was stopped only because Sen. Grassley intervened. He put the heat on the FDA and told them, "Lay off. This guy has told the truth. He's helped America. Whose side are you on?"

There are also some books and investigative reports on the subject. We recommend "BITTER PILLS, INSIDE THE HAZARDOUS WORLD OF LEGAL DRUGS", (Bantam Publications, and author's webpage www.stephenfried.com) by Stephen Fried, whose wife suffered a mild, but debilitating, long-lasting and life altering reaction to a quinolone antibiotic (Floxin).

The book will help you to learn how the "industry" is the only provider of information on medications to the FDA, how they have hidden toxic drug profiles for years, how they fail in keeping a safe program of post marketing reporting, how the laboratories spend much more on advertising and gifts than in research and safety development and how the FDA is unarmed and understaffed before all the challenges related to consumer safety.

In summary, after knowing some of the facts going on in behind the scenes and observing the experience of many friends and relatives, and our own ordeal, it is not difficult to conclude that we are subjected to corporate terrorism of low intensity and vast range, that every year ends up with many thousands of avoidable deaths and an enormous social and economic cost.

The root of the problem is in the national policies that uniformly have been opted by the ostrich model. The main guidelines of this model are:

- Deliberately trying to keep the adverse events of drugs largely unknown and unrecognized to avoid uneasiness and distress among the population, and to make the system easier to manage with low conflict.
- Fictional creation of a common notion that the system cares for us and has a drug arsenal of perfect medications.

This model causes 250.000 deaths every year due to medical errors--mostly drug related--in the United States alone. Instead of this model, one that has not been tested so far and that could save many thousands of lives would be one of clearness, truth, and simplicity. There is no reason to hide the toxic profiles of medications from citizens and doctors. It should be widely known that all drugs have undesirable adverse effects-that there are no wonder drugs; and that any given drug is intended to cure a disease but at the cost of some adverse effects on the body. It should be very clearly stated in all the drugs inserts and/or prescription notes the dosage adjustments for weight, age, body type, renal and liver function and the real figures of toxicity, classified by dosing and length of treatment, that in many cases are on average 20 to 50 times higher than currently stated. People would think twice before self-medicating and doctors would be much more responsible in their practice, carefully choosing the best alternatives and making a complete follow up of patients, with a dramatic increase in testing.

And to refresh a little for the depraved drug marketing representatives and their respective companies---all advertising should be banned as well as any visit of any doctor or rep. to another doctor with the intention of selling a medication or buying the doctor's will by any means. All non- over the counter drugs (prescription drugs) would be exhaustively listed in, and only in, the apothecary books and their electronic compilations for consultation.

Some of the profits of the laboratories would go down but surely they would still be the most profitable activities in the world. And there would be much more money available for research. The market for testing would also soar up.

Unfortunately the legal drug policies seem to be forever ruled by the industry because of the corruption of the western political systems–with powerful lobbies influencing governments to act against general public interest to maximize private earnings of a few companies.

118.THEY CONTINUE TO LET THE DAMAGE OCCUR

According to the Journal of the American Medical Association (JAMA), *"Adverse drug reactions are the fourth leading cause of death in America. Reactions to prescription and over-the-counter medications kill far more people annually than all illegal drug use combined."*

Annually, drug companies spend billions on TV commercials and print media. They spend over $12 billion a year handing out drug samples and employing sales forces to influence doctors to promote specifically branded drugs. The drug industry employs over 1,200 lobbyists, including 40 former members of Congress. Drug companies have spent close to a billion dollars since 1998 on lobbying. In 2004, drug companies and their officials contributed at least $17 million to federal election campaigns.

Find reproduced another passage of the interview of Food and Drug Administration (FDA) employee and Vioxx whistleblower Dr. David Graham (the whistleblower of Vioxx), conducted by Manette Loudon (leading investigator of the team of health guru Gary Null):

> ***Loudon:*** *On November 23, 2004 (during the) PBS Online News Hour Program, you were quoted as making the following statement: "I would argue that the FDA as currently configured is incapable of protecting America against another Vioxx. Simply put, FDA and the Center for Drug Evaluation Research (CDER) are broken." Since you've made that statement, has anything changed within the FDA to fix what's broken and, if not, how serious is the problem that we're dealing with here?*
> ***Dr. Graham****: Since November, when I appeared before the Senate Finance Committee and announced to the world that the FDA was incapable of protecting America from unsafe drugs or from another Vioxx, very little has changed on the surface and substantively nothing has changed.*
> *The structural problems that exist within the FDA, where the people who approve the drugs are also the ones who oversee the post marketing regulation of the drug, remain unchanged. The people who approve a drug when they see that there is a safety problem with it are very reluctant to do anything about it because it will reflect badly on them. They continue to let the damage occur. America is just as at risk now as it was in November, as it was two years ago, and as it was five years ago.*
>
> ***Loudon****: In that same PBS program, you were also quoted saying, "The organizational structure within the CDER is currently geared towards the review and approval of new drugs. When a serious safety issue arises at post marketing, the immediate reaction is almost always one of denial, rejection and heat. They approved the drugs, so there can't possibly be anything wrong with it. This is an inherent conflict of interest."*
> *Based on what you're saying it appears that the FDA is responsible for protecting the interests of pharmaceutical companies and not the American people. Do you believe the FDA can protect the public from dangerous drugs?*
> ***Dr. Graham****: As currently configured, the FDA is not able to adequately protect the American public. It's more interested in protecting the interests of industry. It views industry as its client, and the client is someone whose interest you represent. Unfortunately, that is the way the FDA is currently structured.*
> *Within the Center for Drug Evaluation and Research, about 80 percent of the resources are geared towards the approval of new drugs and 20 percent is for everything else. Drug safety is about 5 percent. The "gorilla in the living room" is new drugs and approval. Congress has not only created that structure, they have also worsened that structure through the PDUFA, the Prescription Drug User Fee Act, by which drug companies pay money to the FDA so they will review and approve its drug. So you have that conflict as well.*
>
> ***Loudon:*** *Are you at liberty to discuss some of the problems your colleagues are finding with other drugs and if so, how widespread is the problem?*
> ***Dr. Graham:*** *I'm really not at liberty to talk about things that pertain to my official duties at the FDA. I can talk in my private capacity, but I can't talk about material that would be confidential.*
> *What I can say is that there are a number of other scientists within the FDA who have also worked with drugs that they know are not safe, even though the FDA has approved or allowed them to remain on the market. They face some of the same difficulties that I do. The difference is that either the problem isn't as serious in terms of the numbers of people that were injured or that it's a fatal reaction -- they're not willing to expose themselves to retaliation by the FDA -- and retaliation would surely follow.*
>
> *extracted from www. healthliesexposed.com*

119. THE CORRUPT POST MARKETING SURVEILLANCE OF DRUGS

In an annual report by the US Food and Drug Administration (FDA), the agency admitted that about two-thirds of the post-marketing drug studies it had mandated have never been finished.

US Representative Maurice D. Hinchey said *"while the agency insisted that it demanded that drug makers prove their medication safe, those demands 'continue to be blatantly ignored by the pharmaceutical industry.'"*

In reply, Dr John Jenkins, director of the FDA Office of New Drugs, emphasized that *"only 5 percent of promised drug trials were officially considered 'delayed.' In many cases, trials have been pending for more than a decade but are not considered delayed because the agency never insisted on a specific timeline for them."*

Harvard Professor Jerry Avorn reminded, *"This new information is an embarrassing continuation of similar reports issued by FDA each year on the appalling state of the medication safety studies it has 'mandated' drug manufacturers to perform. It is scandalous that of the supposedly active studies, about two-thirds haven't even been started yet"*

Demanding post-marketing studies to assess drug safety appears to be a compromise that the agency offered in the face of demands from patient advocacy groups and political conservatives that the agency approve potentially beneficial drugs more quickly, based on relatively limited data from small randomized controlled trials.

It is not clear why the FDA has been mandating these studies, but not mandating any deadlines for their completion. Patients and physicians are harmed by these delays in accomplishing honest post marketing studies.

The existing systems of post-marketing drug surveillance are inadequate as well. In approving a new drug, the FDA may demand that a company conduct additional safety trials after release to the public, but the agency can't enforce these post-approval studies, and more than half of those agreed to by the manufacturers never occur, according to a Department of Health and Human Services report.

From the most visited health site (www.mercola.com) run by Dr. Mercola, you can read:

> ...Once the drugs are on the market, the FDA virtually stops paying any attention whatsoever to whether or not they might cause harm.
> There are a number of good reasons for this, one of the primary ones being that they have never been funded to do this, as the powerful drug lobby cleverly helped to ensure that over 80 percent of their resources are directed to approving drugs, with a measly 5 percent directed to drug safety.
> The FDA's real purpose now is to give a seal of approval to drugs produced by their industry "partners," even if the drugs are dangerous or useless.
> Of course, the FDA's commissioner, Andrew von Eschenbach, denies any wrongdoing, no matter how damning the evidence. More proof than ever that you can't count on the FDA, as it's currently configured, to protect your health.
> This is in part because, when the Prescription Drug User Fee Act took effect in 1992, the drug companies actually started to fund the FDA. I assure you that this is true. It's the classic case of the fox guarding the henhouse. How can you possibly trust a system in which the people who approve the drugs are being paid by the people who make the drugs?
> The system has inevitably led to rampant conflicts of interest. The most egregious recent example of this was when 10 of the 32 FDA drug advisers whose total votes favored the controversial painkillers Celebrex, Bextra and Vioxx had financial ties to the drug industry.
> So wake up if you haven't already done so and realize that the FDA's primary purpose is to help multi-national drug companies increase their profits.

120. PUBLISHED RESEARCH ON FLUOROQUINOLONES

Many people wonder how fluoroquinolones can boast a safety profile when they are very toxic compounds. A common person tends to rely on the medical system. He or she thinks that drugs are on the market because they have passed strict controls and their safety has been fully tested, so that adverse effects are exceptional events that take place in special cases only.

We all have been naïve about medicine, felt protected and safe within the system. But the reality is quite different. Adverse effects have a difficult time ever becoming published or widely known. All independent trials showing negative effects of fluoroquinolones are either censored by the manufacturers or heavily sugarcoated. The trials that do get published are followed by a torrent of counter articles prepared for the occasion.

THE NEW ENGLAND JOURNAL OF MEDICINE -- MAY 18, 2000 -- VOL. 342, NO. 20 [extracted]. Thomas Bodenheimer

The Food and Drug Administration (FDA) requires manufacturers to show that their products pass tests of efficacy and safety. For such drugs as antibiotics for acute infections, large populations and long time lines are seldom needed to establish efficacy and safety. Seventy percent of the money for clinical drug trials in the United States comes from industry rather than from the National Institutes of Health (NIH). For each day's delay in gaining FDA approval of a drug, the manufacturer loses, on average, $1.3 million. Speed is paramount for pharmaceutical firms.

Many academic medical centers review contracts between industry and investigators, insisting on the investigator's right to publish the trial's results and allowing the company prepublication review, with a time limit of 60 to 90 days. Nikki Zapol, head of the sponsored-research office of Massachusetts General Hospital, estimates that 30 to 50 percent of contracts submitted by companies have unacceptable publication clauses that must be renegotiated.

In a survey of life-science faculty members, 27 percent of those with industry funding experienced delays of more than six months in the publication of their study results. Chalmers argues that the results of substantial numbers of clinical trials are never published at all.

In 1996, Canadian investigator Nancy Olivieri and colleagues found that deferiprone, used to treat thalassemia major, could worsen hepatic fibrosis. Apotex, the sponsoring company, threatened legal action if Olivieri published the findings. The contract between Apotex and Olivieri forbade disclosure of results for three years after the study without the company's consent. An article was eventually published.

In 1987, the manufacturer of Synthroid (levothyroxine) contracted with University of California researcher Betty Dong to study whether Synthroid was more effective than competing thyroid preparations. In 1990, Dong found Synthroid to be no more effective than other preparations, including generic preparations. The sponsoring company refused to allow the findings to be published; the contract with Dong stipulated that no information could be released without the consent of the manufacturer. An article was finally published in 1997.

Six investigators interviewed for this report cited cases of articles whose publication was stopped or whose content was altered by the funding company. In one case, according to Dr. Cummings, the company held up the prepublication review process for over half a year, then requested pages of detailed revisions that would have made the manuscript more favorable to the company's official marketing position. During the delay, the company secretly wrote a competing article on the same topic, which was favorable to the company's viewpoint.

In another case, the drug being investigated did not work. The investigator argued that scientific integrity required publishing the findings. The company never refused to publish, but it stalled until the investigator lost interest.

Another investigator, most of whose relations with industry have been without problems, related the case of two trials of the same drug, one more favorable to the company. Despite a protest from the investigator, the results of the less favorable trial were never published.

A fourth investigator found that a drug he was studying caused adverse reactions. He sent his manuscript to the sponsoring company for review. The company vowed never to fund his work again and published a competing article with scant mention of the adverse effects.

Dr. Curt Furberg, professor of public health sciences at Wake Forest University School of Medicine and principal investigator in a study whose results were unfavorable to the sponsoring company, refused to place his name on the published results of the study, because the sponsor was *"attempting to wield undue influence on the nature of the final paper. This effort was so oppressive that we felt it inhibited academic freedom."*

A sixth investigator recounted two examples of suppressed manuscripts regarding negative

> studies whose results were sufficiently important to publish.
> In scenarios such as these, the frequency of which is unknown, companies repeatedly delay publication, eventually exhausting investigators who are busy with other projects. One industry executive explained that such cases result from priority setting within the company; with limited personnel to produce publications, certain trials take precedence over others. However, as one investigator described it, *"when results favor the company, everything is great. But when results are disappointing, there is commonly an effort to spin, downplay, or change findings."* A CRO executive added that *"industry obstruction to publishing is a big problem. They are nervous if bad data comes out and gets into the mass media."* Investigators in the commercial sector may be less concerned than those in academia with contract clauses guaranteeing their right to publish, thereby giving industry greater control over publications.

However, the country with the least research on the toxicity of fluoroquinolones, is the USA, where the medical teams seem to work only on studies steered or controlled by the manufacturers, and do not dare to neither investigate honestly, nor to publish negative results for the interests of the industry. It is shame that the medical community that leads the world advances in other health issues, is just a servile community of doctors specialized in harvesting funds .

121.THE REAL COST OF A CIPRO PILL

For society as a whole, the real cost of a 500 mg pill of a quinolone, taking into account the damage inflicted on so many, measured by the working hours lost, diagnostic procedures, the expenses in palliative treatments and medical bills, is not less than 800 dollars per pill, for at least 20% of those that take quinolones.

In other words, every 500 mg pill of cipro or levaquin taken in Europe and the United States has a real cost of at least 160 dollars on average. The hi-tech drug system has released a toxin that circulates disguised and freely through the primary care offices, hospitals and specialized doctors, that momentarily saves some inconveniences to the patients but that requires a huge financial effort to fix its trail of damage, and also creates a lot of human suffering.

PART XV:
I NEED A DIAGNOSIS

122.DIFFERENTIAL DIAGNOSIS

It has been discussed in previous paragraphs that there are an array of illnesses that share common ground with the floxing syndrome (QTS) and that tend to baffle doctors. In all the cases we should consider the drug- induced version of each disorder:

- *Fibromyalgia*. We are not suffering from fibromyalgia, but receiving such a diagnosis is at least an acknowledgement that the floxed person has a physical problem. Conversely, many people diagnosed with fibromyalgia are really showing symptoms of a chronic intoxication caused by pharmaceutical drugs, environmental toxins or other factors.
- *Multiple sclerosis*, *Guilliam Barré Syndrome*. These two illnesses are so similar in many aspects to the QTS (quinolone toxicity syndrome) that many floxed persons are tested for them as well as for *myastenia gravis*. Almost all floxed persons are tested to rule out multiple sclerosis. Myasthenia gravis is less often investigated in floxed persons because only severe floxings present with muscle wasting and only after some months, and muscle paralysis is normally not present unless the wasting is too high.
- Other rheumatic diseases (*rheumatoid arthritis*, *reactive arthritis* like *Reiter's* or *spondylitis*). After a floxing, some blood tests can be abnormal, such as the sedimentation rate, the rheumatoid factor, the ANA titers, and others; inducing doctors to look deeper into these sets of illnesses.
- *Poly-myositis*, *dermatomyositis*, *inclusion body myositis*. They are investigated when the floxed person presents with muscle weakness, pain or inflammation, skin eruptions, rashes, scaly skin or similar abnormalities, all of them due to the floxing.
- *Steven's-Johnson syndrome*. Hallgren et al reported ciprofloxacin-induced SJS in young patients in Sweden. It is a well-known illness caused by fluoroquinolones, and it is very disabling.
- *Serum sickness*, *giant cell sickness*; it is well documented that cipro causes drug induced serum sickness.
- *Sjogren's* phenomena and syndrome; strikingly similar to floxing in so many aspects.
- *Raynaud's*, a localized vascular disorder. Floxing causes a form of Raynaud's.
- *Small vessel vasculitis*, because floxing exhibits a mixture of problems concerning small vessels and the intercelullar matrix.
- *Systemic lupus erythematosus*, which many floxed persons are tested for.
- *Poly-neuropathy*, *mono-neuritis multiplex*; in fact, many floxed persons have both during the evolution of their intoxication.
- *Sensory-motor neuropathies*, present in all the severe cases of floxing.
- *Rhabdomyolysis*, muscle destruction, with elevated CPK (creatine kinase) values. Mild forms of rhabdomyolysis are present in severe floxings, but tend to reverse at the 4-year mark or so.
- Toxic syndromes and neuromuscular disorders, depending on the doctors (there are extraordinary similarities with intoxications of many kinds like fluorosis, exposure to solvents and pesticides, toxic oil syndrome, or multiple chemical sensitivity, as well as other disorders like gulf war syndrome, etcetera).
- *Lyme* infection. Its symptoms are also very similar to those of a floxing.

In some cases, the quinolones do release true autoimmune responses, so they trigger or induce real rheumatic diseases, and do cause all the illnesses listed above (except lyme, obviously), as well as many others (see references at the end). But this report does not treat the quinolone induced rheumatic disorders.

Therefore, your doctor has to conduct an elimination process in order to discern and obtain a clear diagnosis. If you have a serious reaction, either bordering on clearly severe, and your body has withstood the aggression of the fluoroquinolones without launching a full blown rheumatic disease, your tests will probably show on some occasions:

- *That you have one or more autoimmune markers which are elevated, (ANA, rheumatoid factor, sedimentation rate ...) but only for some months.*
- *That you do not show any abnormality in the electromyographic tests and conductivity tests at the beginning, but that you do later on.*
- *That some of your blood tests show persistent alterations of liver and pancreas enzymes, elevated CPK or aldolase, bilirubin, etcetera.*
- *That your symptoms and your pains point to neuromuscular involvement.*

Then, it is likely that you end up being diagnosed as suffering from one or more of the following conditions:

- *Sensory-motor, autonomic, sensory peripheral neuropathy*
- *Mono-neuritis multiplex, focal poly-neuropathy, especially axonal*
- *Peripheral neuropathy, systemic neuropathy*
- *Vasculitic neuropathy*
- *Myositis, poly-myositis, myopathies of every sort*
- *Myasthenic syndrome*
- *Vasculitis, small vessel, reactive, toxic*
- *Vasculitic myositis*
- *Cardio-myopathy*
- *Optic nerve myopathy, ischemic neuropathy*
- *Connective tissue disorder*
- *Tendinitis, tenosynovitis, enthesitis*
- *Osteoarthritis, alteration in cartilages*
- *Fibromyalgia*
- *Leaky gut, malabsortion syndrome, candidiasis*

Your doctor will not be prone to diagnose a floxing syndrome.

123. MAY I HAVE A PROPER DIAGNOSIS?

No, you cannot have a proper diagnosis until the medical class recognizes the extensive toxicity of the quinolones. With almost all doctors ignorant of critical data, either because of lack of adequate education in medical school or because of later being misinformed and misguided by the advertising reports or published articles paid for by -and sometimes directly written by- the manufacturers, you will not get the proper conclusion from them. Some very highly educated floxed persons, having a very distinctive healthy

life prior to the floxing (which is well known to their doctors), are believed by their doctors. And, faced with the overwhelming evidence, their puzzled physicians admit that the antibiotic "*has released or created a dormant autoimmune disorder that you already had*". Actually, you have a true fluoroquinolone toxicity and only an infinitesimal chance of being recognized as such. The problem is that things will not likely be oriented in the right direction by your doctor.

First of all, your doctor should report your adverse reaction to the FDA in detail. Secondly, he should ask the medical associations to which he belongs to produce more unbiased research on the toxicity of the fluoroquinolone antibiotics, and finally he should study it deeply himself. But more than a person you are a statistic, and everyday he sees many people less physically fit than you and probably with a much worse condition, even though some of them can have minor health problems but very "visible" and recognized by the medical class.

You will probably never be properly diagnosed due to the efforts of the drug manufacturers to hide, conceal and dismiss all the widespread, common and devastating injuries caused by thefluoroquinolones, and the passivity of the Food and Drug Administration (FDA) agency, that blindly believes that these reactions really amount to less than 2% of prescriptions (paradoxically the FDA officials admit that only ONE PERCENT of all adverse effects are reported).

Deprived of an accurate diagnosis, you will be classified within one of the regular, mainstream, common illnesses that doctors have heard of. And it will undoubtedly be a connective tissue disorder for a trained physician with a closed mind, or a mental psychotic or half-paranoid state if your doctor is too dumb.

It is acceptable then to start a process of elimination to rule out the main known connective tissue illnesses, starting with the main ones that have a vasculitic factor: Rheumatoid arthritis, Reactive arthritis, Systemic lupus erithematosus, Sjögren's Syndrome, Small vessel vasculitis properly speaking and following with all the rest: Fibromyalgia, Multiple sclerosis, Guilliam Barré Syndrome, Poly-myositis, Inclusion body myositis, Stevens-Johnson Syndrome, Serum sickness, Poly-neuropathy, Mononeuritis multiplex, Sensorymotor neuropathies, Rhabdomyolysis low-range, Toxic syndromes and neuromuscular disorders of every kind.

According to some doctors, who become very impressed by the neurological symptoms, the real injury is a small fiber neuropathy, both motor (axons) and sensory. Behind the small fiber neuropathy would unfailingly be the fateful small vessel vasculitis. So, for all the neuromuscular disorders directly caused by the quinolone toxicity the precise diagnosis would be: small fiber neuropathy founded on an underlying small vessel vasculitis, plus a widespread connective tissue injury.

TABLE 21. SIMPLISTIC CLASSIFICATION OF NEURO-FLOX-PATHIES			
Focal	not associated with floxing		
Multifocal	Axonal	Fiber motor	**In SEVERE floxings only**
		Sensory motor	**INTERMEDIATE and SEVERE floxings**
		Sensory only	**Possible in all floxings**
		Small fiber / autonomic	**Possible in all floxings**
	Demyelinating		uncommon in floxing
NOTE: Multifocal axonal neuropathies are prevalent in floxings.			

However, taking into consideration the rest of symptoms that plague floxed persons, this diagnosis falls very short of the bigger picture.

By now we already know that after a floxing the nerves suffer many different pathologies. Although there are hundreds of more or less complex classifications of neuropathies, we are going to use this simple one for our purposes of arranging the information.

124. DIAGNOSING YOUR NEUROPATHIES

Basically, you have three ways to diagnose your neuropathies:

1. Clinically (symptoms, presentation, evolution, signs, responses). This is the preferred method for some autonomic and central nervous system neuropathies.
2. Non-invasive tests, which are especially useful for motor and sensory neuropathies.
3. Invasive tests, especially biopsies, which provide a very good evaluation of some neuropathies, either directly by evaluation or by extrapolation.

Severe floxed persons have deep autonomic, central nervous system and peripheral neuropathies. Diagnosing peripheral neuropathy is often difficult because the symptoms are highly variable. Tests of muscle strength, as well as evidence of cramps or fasciculations, indicate motor fiber involvement. Evaluation of a patient's ability to register vibration, light touch, body position, temperature, and pain reveals sensory nerve damage and may indicate whether small or large sensory nerve fibers are affected.

Based on the results of the neurological exam, physical exam, patient history, and any previous screening or testing, additional testing may be ordered to help determine the nature and extent of the neuropathy.

Electromyography (EMG) involves inserting a fine needle into a muscle to compare the amount of electrical activity present when muscles are at rest and when they contract. EMG tests can help differentiate between muscle and nerve disorders.

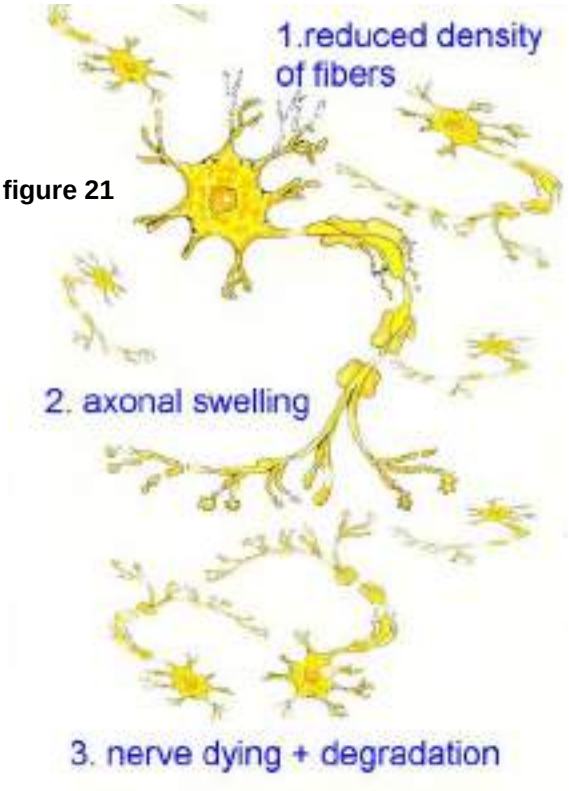


figure 21

Nerve conduction velocity (NCV) tests can precisely measure the degree of damage in larger nerve fibers, revealing whether symptoms are being caused by degeneration of the myelin sheath or the axon. During this test, a probe electrically stimulates a nerve fiber, which responds by generating its own electrical impulse. An electrode placed further along the nerve's pathway measures the speed of impulse transmission along the axon. Slow transmission rates and impulse blockage tend to indicate damage to the myelin sheath, while a reduction in the strength of impulses is a sign of axonal degeneration.

Nerve biopsy involves removing and examining a sample of nerve tissue, most often from the lower leg. Although this test can provide valuable information about the degree of nerve damage, it is an invasive procedure that is difficult to perform and may itself cause neuropathic side effects. Many experts do not believe that a biopsy is always needed for diagnosis.

Skin biopsy is a test in which doctors remove a thin skin sample and examine nerve fiber endings. This test offers some unique advantages over nerve conduction velocity tests and nerve biopsy. Unlike Nerve conduction velocity, it can reveal damage present in smaller fibers; in contrast to conventional nerve biopsy, skin biopsy is less invasive, has fewer side effects, and is easier to perform.

From the pathological perspective, the mass of neurons of a floxed person have suffered an impact that has rendered some of them dead, others dysfunctional, others swollen, and nearly all of them altered. See next figure 16 with the three main pathologies typically revealed by a biopsy made on

floxed persons: reduced density of nerve fibers, axonal swelling or inflammation, and nerve degradation.

There is a specialized type of biopsy called SMALL FIBER SKIN PUNCH BIOPSY that significantly aids in small fiber nerve etiologies. These biopsies are very useful to predict the progression, and to evaluate the evolution of floxings, because they can be repeated without significant sequela. These tests can confirm your 'neuro-flox-pathy' even in the case that your electrical tests are normal.

125. SMALL FIBER NEUROFLOXPATHIES

Many, many floxed persons have small fiber neuropathy. This neuropathy evolves towards axonal neuropathy in severe cases, causing muscle dysfunction, loss of muscle mass and lack of strength in quads, arms, hands, lower legs, etcetera. Skin punch biopsies of 3 mm can diagnose precisely the 'neuro-flox-pathy' and serve as an instrument for performing a follow up of the evolution.

A very well informed contributor to the report has submitted the following technical excerpts of articles. She has conducted thorough research on this issue. Only a brief summary is included here:

THE UTILITY OF SKIN BIOPSY FOR PREDICTION OF PROGRESSION IN SUSPECTED SMALL FIBER NEUROPATHY.

Gibbons CH et al. Beth Israel Deaconess Medical Center, Boston, MA 02215, USA.

Twenty-eight patients with sensory complaints of unknown etiology had repeated skin biopsies. Patients with large nerve fiber swellings on initial biopsy showed a decline in epidermal nerve fiber density on repeated biopsies. Patients without nerve fiber swellings did not have changes in nerve fiber density between biopsies. Patients with large nerve fiber swellings were most likely to present clinically with paresthesias [burning or prickling, numbness, tingling].

EFNS GUIDELINES ON THE USE OF SKIN BIOPSY IN THE DIAGNOSIS OF PERIPHERAL NEUROPATHY.

Lauria G, et al; European Federation of Neurological Societies. Immunology and Muscular Pathology Unit, Department of Clinical Neurosciences, National Neurological Institute Carlo Besta, Milan, Italy.

Skin biopsy has become a widely used tool to investigate small calibre sensory nerves including somatic unmyelinated intraepidermal nerve fibres (IENF), dermal myelinated nerve fibres, and autonomic nerve fibres in peripheral neuropathies and other conditions. Different techniques for tissue processing and nerve fibre evaluation have been used. In March 2004, a Task Force was set up under the auspices of the European Federation of Neurological Societies (EFNS) with the aim of developing guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathies. For diagnostic purposes in peripheral neuropathies, we recommend performing a **3-mm punch skin biopsy** at the distal leg and quantifying the linear density of IENF in at least three 50-mum thick sections per biopsy. Quantification of IENF density closely correlated with warm and heat-pain threshold, and appeared more sensitive than sensory nerve conduction study and sural nerve biopsy in diagnosing small-fibre sensory neuropathy. Diagnostic efficiency and predictive values of this technique were very high. Confocal microscopy may be particularly useful to investigate myelinated nerve fibres, dermal receptors and dermal annex innervation. In future, the diagnostic yield of dermal myelinated nerve fibre quantification and of sweat gland innervation should be addressed. Longitudinal studies of IENF density and regeneration rate are warranted to correlate neuropathological changes with **progression of neuropathy** and to assess the potential usefulness of skin biopsy as an outcome measure in peripheral neuropathy trials. In conclusion, punch skin biopsy is a safe and reliable technique.

THE ACUTE SENSORY NEURONOPATHY SYNDROME: A DISTINCT CLINICAL ENTITY.

Sterman AB,et al, Asbury AK.

Four to twelve days following initial **antibiotic** treatment for a febrile illness, three adults suddenly experienced numbness and pain over the face and entire body. Each had received a penicillin or a semisynthetic derivative, and two patients also received other antibiotics. Signs appeared rapidly and included profound sensory ataxia, areflexia, and widespread sensory loss, primarily of large fiber modalities (proprioceptive sensibility). Slowed or absent sensory conduction was found. There was no weakness, and electrical study of muscle and motor nerve conduction was normal in all. The cerebrospinal fluid was acellular, and protein levels were elevated to 126 and 175 mg/dl in two cases and were normal in the other. Presently, all have a severe, static, residual sensory deficit. During follow-up of **five years**, no evidence of neoplastic disease or immunological disorder has appeared.

Because of the rapid onset, widespread and pure sensory involvement, and poor recovery, the injury is most likely confined to the dorsal root and gasserian ganglia (**sensory neuronopathy**). This pattern resembles that of the experimental injuries induced by doxorubicin and pyridoxine. It appears likely that either the previously administered antibiotics or the illness for which they were administered were of pathogenetic importance. We designate this previously unrecognized disorder the acute sensory neuronopathy syndrome and suggest that it represents a distinct, readily identifiable clinical entity.

AXONAL SWELLINGS PREDICT THE DEGENERATION OF EPIDERMAL NERVE FIBERS IN PAINFUL NEUROPATHIES.

Lauria G, et al. Department of Clinical Neuroscience, National Neurological Institute Carlo Besta, Milan, Italy.

OBJECTIVE: To correlate the **density of swellings** in intraepidermal nerve fibers (IENF) with the longitudinal measurement of the epidermal innervation density in patients with **painful neuropathy** and to assess the predictive value of IENF swelling to progression of neuropathy. METHODS: Fifteen patients with persistent pain in the **feet** underwent neurologic examination, nerve conduction studies, quantitative sensory examination, and skin biopsies at proximal thigh and distal leg. In all patients and in 15 healthy subjects, IENF density and swelling ratio (no. swellings/no. IENF) were quantified at distal leg. Follow-up study, including IENF density and swelling ratio quantification, was performed a mean of 19.2 months later. Double staining confocal microscope studies using anti-human protein-gene-product 9.5, anti-tubule, anti-neurofilament, and anti-synaptophysin antibodies were performed to assess specific accumulation within swellings. Ultrastructural investigation of IENF was also carried out. RESULTS: Patients with neuropathy **had lower density** of IENF and **higher swelling** ratio than healthy subjects at distal leg. At follow-up, patients showed a parallel decrease in both IENF density and swelling ratio. However, swelling ratio remained higher than in controls. Progression of neuropathy was confirmed by the decay in sural nerve sensory nerve action potential amplitude. Double immunostaining studies suggest accumulation of tubules and ubiquitin-associated proteins within swellings. Swollen and vacuolated IENF were identified in patients with neuropathy by conventional and immuno-electron microscopy. **CONCLUSIONS**: Increased swelling ratio predicted the decrease in IENF density in patients with painful neuropathy. Its quantification could support earlier diagnosis of sensory axonopathy.

SMALL FIBER DYSFUNCTION IN PERIPHERAL NEUROPATHIES

Santiago S, et al. Laboratorio de SNA, Hospital La Paz, Madrid, Spain

INTRODUCTION: Disfunction of thin myelinated and unmyelinated fibers may appear isolated or in association with large-myelinated fibers injury. Small-fiber neuropathy includes autonomic and sensory symptoms, most prominent of them thermo-algesic deficits. DEVELOPMENT AND CONCLUSION: In some acute neuropathies, small-fiber injury is relatively pure, as in pandysautonomia, but it also appears in disorders with prominent somatic involvement, such as the Guillain-Barre syndrome, in which case autonomic symptoms worsens the prognosis. Small-fiber dysfunction is important in certain diseases that involve different components of the nervous system, like paraneoplastic syndromes and porphyria. Some drugs and toxic substances may damage thin myelinated and unmyelinated fibers. Nowadays, chronic idiopathic small-fiber neuropathy is diagnosed more frequently, because of the recent development of techniques that selectively evaluate this peripheral nerve component. Hereditary sensory and autonomic neuropathies can also be studied. Small-fiber dysfunction is very prominent in some diseases, e.g. diabetes mellitus and amyloidosis. In the pure autonomic failure, only the peripheral component of the autonomic nervous system is affected, and this feature is the key to make diagnosis versus multisystem atrophy. There are situations in which there is no clear deviation from normality, namely old age autonomic failure and orthostatic intolerance syndrome in which autonomic evaluation is mandatory.

INTRAEPIDERMAL NERVE FIBER DENSITY IN PATIENTS WITH PAINFUL SENSORY NEUROPATHY.

Holland NR, et al. Department of Neurology, Johns Hopkins University, Baltimore, MD, USA. Despite prominent symptoms of neuropathic pain, patients with small-fiber sensory neuropathies have **few objective abnormalities on clinical examination and routine electrodiagnostic studies**. We quantified intraepidermal nerve fiber (IENF) density in sections of skin obtained by punch skin biopsy, and found it to be **significantly reduced** in patients with painful sensory neuropathies compared with age-matched control subjects. In addition, IENF density correlated with clinical estimates of neuropathy severity, as judged by the extent of clinically identifiable sensory abnormalities. IENF density at the calf was lower than that obtained from skin at more proximal sites, indicating the length dependency of small-fiber loss in these neuropathies.

SKIN DENERVATION IN VASCULITIC NEUROPATHY.

Lee JE, Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan. BACKGROUND: Skin denervation in vasculitic neuropathy has rarely been documented despite frequent manifestations of small-fiber neuropathy including reduced sensitivity and neuropathic pain. Recently, skin biopsy

has been established as a new approach to diagnose small-fiber sensory neuropathy. OBJECTIVES: To investigate the pathologic features of cutaneous nerves and to evaluate inflammatory vasculopathy in the skin of patients with vasculitis. DESIGN: Case series. SETTING: National Taiwan University Hospital, Taipei.Patients Six patients with vasculitic neuropathy. INTERVENTIONS: Patients had 3-mm punch biopsy specimens taken from the distal part of the leg (without active vasculitic injuries) and a sural nerve biopsy specimen was taken in addition to detailed neurologic examinations, laboratory investigations, and nerve conduction studies. MAIN OUTCOME MEASURES: Results of nerve conduction studies, epidermal nerve fiber density studies, and immunohistochemistry. RESULTS: All 6 patients had combined large- and small-nerve-fiber involvement on the neurologic examinations. Nerve conduction studies showed a pattern of axonal neuropathy or mononeuropathy multiplex. Epidermal nerve fiber densities were significantly reduced in the skin of all patients, consistent with concomitant small-fiber neuropathies. Perivascular infiltration by T cells and macrophages was demonstrated by immunohistochemistry. All patients experienced neurologic improvement in muscle strength and alleviation of sensory symptoms after immunotherapy with **corticosteroids**, plasma exchange, or cyclophosphamide. CONCLUSIONS: Small-diameter sensory nerves are affected in vasculitis in addition to the well-known effect of vasculitis on large-diameter nerves. Significant inflammatory vasculopathy is present in the skin despite the absence of clinically active vasculitic injuries.

PAINFUL SMALL-FIBER NEUROPATHY IN SJOGREN SYNDROME.

Chai J, et al. Department of Neurology, University of Rochester, Rochester, NY, USA.

Of 20 consecutive patients with Sjogren neuropathy, 16 (80%) presented with burning feet and 12 (60%) with non-length-dependent sensory symptoms. Leg and thigh skin biopsies, performed in 13 patients, including 7 with normal electrophysiology, showed either reduced epidermal nerve fiber (ENF) density or abnormal morphology. ENF loss was frequently non length dependent, suggesting that patients with this disorder commonly have a small-fiber sensory neuronopathy rather than a "dying-back" axonopathy.

EVALUATION AND TREATMENT OF PAINFUL PERIPHERAL POLYNEUROPATHY.

Singleton JR. Department of Neurology, University of Utah, Salt Lake City, Utah 84132, USA.

Pain is a common component of sensory peripheral polyneuropathy and occurs primarily as a consequence of injury to small, unmyelinated C-fiber nerve axons. This class of fibers is particularly vulnerable to metabolic injury, and the neuropathy manifests in a length-dependent pattern. Diabetes mellitus, prediabetes associated with insulin resistance, toxins, and **drugs are common causes** of painful neuropathy, but a substantial percentage are idiopathic. Pathogenesis of neuropathic pain involves loss of peripheral axons and inappropriate peripheral and central adaptation of neuronal signaling to this loss. Treatment of painful neuropathy should be directed at removing the offending metabolic injury, if possible. Antiepileptic drugs, tricyclic antidepressants, opiates, and other treatments have shown efficacy in clinical trials for symptomatic relief of neuropathic pain.

SYMPTOM DURATION AND CLINICAL FEATURES IN PAINFUL SENSORY NEUROPATHY WITH AND WITHOUT NERVE CONDUCTION ABNORMALITIES.

Walk D, et al. , MMC 295, Minneapolis, MN 55455, USA.

BACKGROUND: The term "small fiber sensory neuropathy" (SFSN) refers to an axonal sensory polyneuropathy predominantly affecting cutaneous sensory modalities, often associated with pain and with no evidence of large fiber involvement. We hypothesized that, in most patients, SFSN is the earliest manifestation of a nonspecific axonal neuropathy and will **usually progress to involve larger, heavily myelinated sensory and motor fibers**. We sought indirect evidence of this through an analysis of the correlation between symptom duration and large fiber involvement in patients with painful sensory neuropathy (PSN). METHODS: A clinical diagnosis of PSN was supported by nerve conduction studies or measurement of epidermal nerve fiber (ENF) density in 43 patients. Symptom duration was correlated with the frequency of large fiber loss as measured by nerve conduction abnormalities. The severity and extent of clinical signs and symptoms were also evaluated in subjects with and without electrodiagnostic abnormalities. RESULTS: Patients with large sensory axon involvement had symptoms of longer duration than patients with SFSN. The frequency of electrodiagnostic abnormalities increased in direct proportion to disease duration. Patients with electrodiagnostic abnormalities also had more extensive pinprick sensory deficits, suggesting that small fiber loss was more advanced in this group as well. CONCLUSIONS: In PSN, the incidence of large fiber involvement appears to increase in proportion to symptom duration. This represents indirect evidence that SFSN usually progresses to involve both large and small fibers **within 2-10 years**.

REVIEW: SMALL-FIBER NEUROPATHY.

Al-Shekhlee A, et al, Preston DC. Department of Neurology, University Hospitals of Cleveland, Ohio, USA.

BACKGROUND: Most peripheral neuropathies involve large as well as small-fiber dysfunction. A small subset of neuropathies present with restricted or predominant small-fiber involvement. REVIEW SUMMARY: In this review,

we discuss the differential diagnosis, clinical presentation, evaluation, and treatment of small-fiber neuropathies. Although these neuropathies are rare, their differential diagnosis is broad, and includes many disorders, including metabolic, toxic, inflammatory, infectious, and genetic etiologies. As small fibers subserve pain and autonomic functions, these neuropathies usually present with pain and temperature loss, painful dysesthesias, autonomic dysfunction, or a combination. These neuropathies are especially challenging as nerve conductions and EMG, which help guide the evaluation of most peripheral neuropathies, may have **normal findings in patients with small-fiber neuropathies**. Other specialized studies, including tests of autonomic function, intraepidermal nerve fiber analysis, and quantitative sensory testing, are often required to confirm the presence of a small-fiber neuropathy. In some cases, the underlying etiology can be directly treated. In most, management is limited to symptomatic treatment of sensory and autonomic dysfunction. CONCLUSION: Small-fiber neuropathies are a heterogeneous group of disorders. They vary in etiologies and require special attention, as many disorders are rare and the differential diagnosis is broad. Evaluation is often extensive and may need pathologic specimen. Many patients respond to symptomatic therapy, but some are difficult to treat.

QUANTITATIVE PATHOLOGY OF CUTANEOUS NERVE TERMINAL DEGENERATION IN THE HUMAN SKIN.

Chien HF, et al. Department of Anatomy and Cell Biology, National Taiwan University College of Medicine, Taipei. Pathological diagnosis of neuropathy has traditionally depended on ultrastructural examinations of nerve biopsy specimens, particularly for sensory neuropathies affecting unmyelinated and small-myelinated nociceptive nerves. These sensory nerves terminate in the epidermis of the skin, and the pathology of neuropathy usually begins from nerve terminals. We investigated the feasibility of diagnosing small-fiber sensory neuropathy by evaluating cutaneous innervation. Skin biopsy specimens of 3-mm in diameter were obtained from the distal leg and the distal forearm of 55 healthy controls and 35 patients with sensory neuropathy. In the healthy controls, conventional intraepidermal nerve fiber densities (IENF densities) as measured using the image analysis system in the distal forearm and in the distal leg were correlated (r=0.55, P<0.0001), with significantly higher values in the distal forearm than in the distal leg (17.07+/-6.51 vs 12.92+/-5.33 fibers/mm, P<0.001). Compared to IENF densities of healthy controls, these values of neuropathic patients were significantly reduced in the distal forearm (5.82+/-6.50 fibers/mm, P<0.01) and in the distal leg (2.40+/-2.30, P<0.001). We further explored the possibility of quantifying skin innervation by counting "ocular intraepidermal nerve fiber density" (ocular nerve fiber density) with no aid of an image analysis system. This was based on the fact that the epidermal length on specifically defined sections was very close to the predicted epidermal length of 3 mm, the diameter of skin punches (P=0.14). Ocular nerve fiber densities were significantly correlated with IENF densities as measured by the image analysis system (r=0.99, P<0.0001). Dermal nerve fibers of neuropathic patients either **disappeared or became degenerated.** These findings were consistent with the notion of early terminal degeneration in neuropathy, and will facilitate quantitative interpretation of epidermal innervation in human neuropathy.

Although fluoroquinolones have a wide spectrum of toxicity, if we had to summarize their toxicity we would just state NEUROTOXIC, specially DELAYED-ONSET-NEUROTOXICITY. Look in short how the neurotoxicity of fluoroquinolones translates its consequences to the victim (without including central nervous system issues):

Sensorimotor neuropathy	Muscular symptoms: muscle weakness (not fatigue), atrophy, balance problems, ataxic gait, fasciculations.
	Sensory symptoms: pain, paresthesia, numbness, paralysis, cramping, nighttime falls, antalgic gait
Autonomic neuropathy	Cardiovascular symptoms: exercise intolerance, fatigue, sustained heart rate, syncope, dizziness, lightheadedness, balance problems
	Gastrointestinal symptoms: dysphagia, bloating, nausea and vomiting, diarrhea, constipation, loss of bowel control
	Genitourinary symptoms: loss of bladder control, urinary tract infection, urinary frequency or dribbling, erectile dysfunction, loss of libido, dyspareunia, vaginal dryness, anorgasmia
	Sudomotor (sweat glands) symptoms: pruritus, dry skin, limb hair loss, calluses, reddened areas
	Endocrine symptoms: hypoglycemic unawareness
	Other symptoms: difficulty driving at night, depression, anxiety, sleep disorders, cognitive changes

The list of side effects that a severe reaction causes is simply brutal. A great deal of it implicates nerve damage. Even hypoglycemia (low sugar, sugar intolerance, vision abnormalities and pains associated to sugar consumption), dry mucous membranes, reddened areas and exercise intolerance are all nerve related. That is simply dramatic.

Fluoroquinolone neuropathy affects sensory, autonomic, and motor neurons of the peripheral nervous

system, which is to say that nearly every type of nerve fiber in the body is vulnerable. Moreover, every organ system in the body that relies on innervation for function is consequently subject to pathology.

PART XVI: TESTS

126.TESTS HABITUALLY PERFORMED IN FLOXED PERSONS

There are many tests indeed that could help you diagnose the floxing, and above all could help to rule out other illnesses.

This section is in preparation, and will cover blood and urine tests, physical examinations, electrical, magnetic or radiological devices, biopsies, and others. It is intended to be included in the next edition of the flox-report. It has been demanded by many readers.

PART XVII: THE END OF ANY ATHLETE'S CAREER

127. FOR ATHLETES ONLY

If you were an athlete or very active young or middle aged person, you will resume your trajectory only if you have experienced a mild reaction. Endurance will be severely curtailed by an intermediate reaction. After a severe reaction your athletic activities are completely wiped out for the next five to seven or more years, and only then will you be in the position to attempt very physically demanding activities depending on the level of permanent damage in joints and tissues that you have sustained. In any case a severe reaction means the abrupt end of an athletic existence.

If your activities prior to the floxing were endurance athletics or vigorous professional sports, you will likely not be able to resume them ever again without any joint pain at all if you experience an intermediate or severe reaction.

There are very characteristic musculoskeletal injuries caused by quinolones. Some times they are not the worst side effects, but are big limitations for sports/physical activity and cause enormous distress in young and healthy athletes.

Cartilage is always affected. In intermediate reactions it becomes softened and some get inflamed or start causing problems; for instance in the spine, hips and knees. In severe reactions cartilage becomes very eroded, and show up as different stages of osteoarthritis, from mild to advanced. Most affected areas are the shoulder joint, hips, knees (patella, meniscus specially), and ankles, but also neck and spine.

Look at some of the musculoskeletal injuries that young and athletic floxed persons developed after unnoticed reactions to short courses of quinolones. In all cases it has been demonstrated that they were quinolone-induced toxic reactions, because after re-exposure to quinolones they increased ten to a hundred times-fold in intensity, whereas no one had had any of them before.

- Epicondylitis in tennis or racquetball players. Diagnosed as an overuse syndrome or defective techniques or equipment. In fact is a toxic tendinitis. Can become permanent.
- Trochanteric bursitis (pain in the very tip of the hip bone). Diagnosed as tight belt syndrome or resting-on-the-side pressure. Another toxic bursitis (inflammation of the bursae, a sort of synovial bag present in most joints to help with the movements.
- Dull pain with stabbing pain episodes on the medial (inner side) or lateral (outer side) tibia, or ankle. Diagnosed as shin splints in runners and tennis players. In fact it is a neurologically rooted, tendon collapse due to the dysfunction of one or more of the tibialis muscle complexes. It is a motor nerve neuropathy (toxic).
- Very commonly athletes are diagnosed as having plantar fasciitis (pain in different sections of the sole of the foot), due to supposedly hyper- or over-pronation or supination, shoe defects, leg length discrepancies, overuse, etc... It is always a toxic degradation of the muscle-tendon complex of the fascia, especially caused by neuropathic dysfunction of the anterior and posterior tibialis tendon groups.
- Hamstrings pulls or sciatica are diagnosed when pain inside the hamstrings is present. This pain is not responsive to any conventional form of therapy. It is a toxic femoral neuritis (sensory-motor type). Frequently, femoral neuritis takes places in the same leg as the lower leg neuritis (ankle, tibialis). In intermediate reactions, hamstrings get involved, and to a lesser extent the antagonist

muscles of the thighs. But in more severe reactions, both hamstrings and quads are affected equally and profoundly.

- Posterior tibial and toe flexor tendon insufficiency is in reality a result of nerve dysfunction coupled with overuse and neuropathic lack of peroneal function. It is far more frequent than achilles tendinitis.
- The lack of flexing strength in some toe flexors is always a cause for concern, because it can indicate a partially irreversible injury in the peroneal and tibialis nerve (axonal).
- Achilles tendinitis is diagnosed hundreds of times. It is unnecessary to describe the real kind of injury this is, as it is a very, very distinctive class effect of all quinolones. It can cause ruptured tendons quite easily. In most cases of intermediate reactions, nodules along the tendon can be palpated and well-trained operators can diagnose scarring, tearing, engrosing and fibrosing of irregular tissue from MRI images. According to some doctors, less than one in ten tendon ruptures caused by quinolones are linked to the antibiotic, because most of the ruptures take place some months after completing the treatment. The floxed persons whose experiences have formed this report, met doctors that had treated four physicians with ruptured tendons caused by quinolones. Only one bothered to report it to the surveillance system, or MedWatch.
- A cause of total collapse of one or both legs with inability to walk in severe reactions is peroneal nerve toxic motor neuropathy, very difficult to detect on the electromyograms. The lack of function of the peroneal-tibial nerves causes the surrounding muscles to experience an underperformance of their tasks, and therefore submit the tibialis and flexors tendons to increased elongation and stress, ending up in very severe injuries that normally take more than 3 years to heal. They are incorrectly diagnosed as anterior tibialis tendinitis/atrophy.
- Knee pains: lateral, medial and backside. Pains in the knees caused by quinolones are of many different kinds. Neuropathic pains with a throbbing nature, increasing at night; more diffuse generalized pain due to cartilage deterioration and general tissue necrosis; localized and migrating pains due to enthesitis (tendon insertions), tendinitis and inflammation of bursaes and synovial membranes.
- Back problems are innumerable. The lack of strength in all muscles, the loss of cartilage integrity, and the nerve inflammations cause myriad symptoms and pains that can be confined to the back, shoulder and neck areas or radiate and refer to other parts of the body.
- Some of the most debilitating lateral upper leg pains are diagnosed as iliotibial band syndromes. In fact they are a truly mixed toxic condition that causes: enthesitis (irritation of the end attachments), neuropathy of the femoral nerve lateral branches and gluteus nerve that control the band, a fibrotic myositis with muscle damage that loses flexibility and a fascia disorder that causes the band to adhere to the adjacent muscles due to deterioration of connective tissue.
- Iliopsoas tendinitis is diagnosed as the result of overuse because it becomes weak in most upper leg motor neuropathies. It is perceived as pain in the anterior groin, and tenderness at touch, along with some gluteus atrophy- causes an abnormal gait of being bent forward at the waist.
- The damage to all the collagenous tissues of the body can also affect all the inner joints in hips, knees and ankles. Hips are targeted by quinolones in a lot of cases.
- For the same reason as stated above, many floxings end up with torn or ruptured rotator cuff tendinitis (shoulder) as well as osteoarthritis of the shoulder joint.
- At the presentation of the floxing symptoms and the uselessness of conventional protocols, the most well trained sport physicians will suspect that something abnormal is going on. Then the floxed person could be referred to a rheumatologist and diagnosed as suffering from myopathies of several types, myositis, polymyositis and other disorders that have already been mentioned before.
- The acute muscle pains and joint stiffness after exercise can lead to an incorrect diagnosis of lactic acid building up, that can be dismissed after the corresponding tests do not indicate this.

- The worst musculoskeletal reactions are always accompanied by muscle atrophy, difficult to see aparently, save for the sheer lack of strength that appears.
- A floxed person with an important intoxication cannot get muscle mass irrespectively of how much he/she works out at the gym.

If you have been a strong, endurance athlete and are in your thirties or forties, your doctors will not be prone to listen your complaints about this sudden and strange intolerance to exercise, lack of recovery, increased pains after exercise, loss of strenght, inabilitiy to gain muscle and will try to argue that it is due to the natural aging process--something that you clearly know is not the case.

128. FLUOROQUINOLONES AND SPORT ARE NOT COMPATIBLE

Every athlete with a tendinitis, multi-focal muscular or neuromuscular pains or overuse syndrome, should be asked whether he/she has taken quinolones at least during the last year, in order to assess the diagnosis properly.

With normal fluoroquinolone treatments of one-week's worth or so, the strongest athlete will only experience a progressive diminished capacity to recover after exercise. He will feel some soreness and stiffness some hours after his exertions. He will tend to think that it is normal since no other symptoms bother him and his soreness clears up in a day or so.

With a few such short treatments of quinolones over the years, the athlete will become markedly rigid, especially in his legs. Unless he practices stretching too, he will not pay much notice either and the problem will remain unnoticed.

If an athlete takes a prolonged course of fluoroquinolones, one of his main groups of nerves (mononeuritis) can become affected, for instance the tibialis anterior and the peroneal, or the whole sural nerve (please consult an anatomy text if you have difficulty in identifying some parts of the human body that are used in this report). Then, the corresponding muscle gets wasted in a matter of a few weeks. The athlete does not realize it but his plantarflexion and his ankle dorsiflexion, respectively, become impaired. So all the stress needed to stabilize the ankle is posed on a specific group of tendons (the tibialis posterior and flexor hallucis longus for the pronators), that suddenly become completely crippled and on the verge of rupturing. The athlete and their doctors become alarmed. The doctor orders some 3-phase scans and other diagnostic procedures and reaches the wrong conclusion that the athlete suffers from asymmetries, overuses, leg length discrepancies, structural flaws and/or others, that perhaps do exist, and have existed always in the floxed patient, but they are not the cause of his/her sudden pathologies. Conventional treatments are instated. The only thing that baffles everybody is the strange and disturbing long duration of the pains and limitations. Nobody has a clue about the real cause and the quinolones once again are not considered as the true cause of this toxic debilitating physical damage.

Notice that intermediate reactions predominantly affect distal motor neurons (the parts that are more distant from the trunk of the body) like ankles and wrists plus all the joints submitted to overuse, obviously. Severe reactions also affect proximal muscles and nerves (knees, hamstrings, quads, gluteus, biceps, triceps, shoulders, neck).

If an athlete has suffered a severe reaction, he loses the functionality of several joints or muscles. During the first months he can feel pains and the inability to exercise due to failure of one or two joints. But as the months pass by, more joints add to the list of incapacitating pains and limitations in range of motion. The athlete gets shocked because the list of joints involved is continuously increasing for up to 18 months and includes joints that he always had considered rock solid, without a single complaint of the slightest entity in the past. Normally, ankles, knees, hips, elbows, wrists, back, neck and shoulders are involved.

It is a tragedy for the athlete. All his joints snap and make a lot of noise when moving. Soon his knees

and/or hips start grinding, clicking and cranking, normally a sign of the erosion and destruction of the cartilages. MRI's prior to and post quinolones in several athletes have shown those changes clearly, even in athletes that have refrained from exercise post-floxing.

In severe reactions there is a marked weight loss, mainly muscle. Workouts can do nothing to help recover the muscle mass, nor can any supplement help, because the cause is neurological. If workouts are especially unable to recover or build up muscle mass as they were before, and this situation lasts for long, you can be facing permanent sequela in terms of physical damages.

In severe reactions sports in cold temperatures are not advised because most likely the athlete has some toes or fingers affected by a sort of occlusive vasculitis (non auto-immune issue in floxings, but rather a problem with vessels), and the tip of some of his fingers/toes become abnormally irrigated, so with temperatures hovering around freezing his tips can turn numb, pale, and blue and he risks losing some of them to frosbite (necrosis). Again, if the floxed person experiences some repetitive hits to his affected fingers, recovery can take a few additional years because of the superimposed damage to the vascular system caused by quinolones, and subsequent mechanical injuries.

After a severe reaction it takes between 3 years (for people in their thirties) and more than 4 years (for people in their forties) to feel that their body is starting to recover. For some others this time will never come. You will notice that the time has come when all your muscles gain strength when you exercise them. At the peak of neuropathic damage, exercise does not invigorate muscles because there is an axonal neuronal injury not yet re-enervated. But, if one is lucky enough, at around the third year, neurological pains in joints (hips, knees, gluteus, hamstrings, ankles) can be diminished if the athlete works out the antagonist muscles. Few people realize this key fact. Some times that can only be done by means of electrical stimulators at the beginning of the recovery, followed by isometrics and ending with full-scale workouts.

Only by then will the athlete be able to start a slowly progressive program of exercises as long as he feels that his flexibility returns and also his overall recovering capacity and level of pains are improving. The athlete will also have to fight to survive the rest of symptoms affecting the heart, eyes, sinus, digestive system, insomnia, neuropathies of all kinds, etc..., because as you have read above, nearly all the organs of the body suffer disabling toxic injuries.

Every trainer, orthopedist, coach, physiotherapist and professional whose activities are related with sports should be aware of these devastating effects of the quinolone antibiotics, and advise their pupils to ask doctors for safer, less toxic alternative antibiotics. Fortunately, there are already many coaches and sport professionals that avoid quinolones at all cost and it is common to encounter precautions about the risks of taking quinolones for people that practice sports frequently. This should become general practice now that popular fluoroquinolones like cipro are widely prescribed, because the generic form has already being released, after the expiration of the twenty year long exclusivity of manufacturing it by its discoverer (Bayer).

129. PHYSICAL DAMAGE TO MUSCLES AND JOINTS

If you were an athletic person and have taken quinolones with the end result of a floxing, then the scenario that your athletic body is facing is as devastating as described below:

- Joints with cartilages experiencing partial necrosis, therefore softened and with less mechanical loading capacity. Cartilages possibly eroded depending on the severity of the reaction.
- Tendons and ligaments floxed. A floxing of a tendon is a severe illness on its own. It is explained in detail throughout this paper.
- Muscles working abnormally because the neuromuscular junctions have been impaired due to the

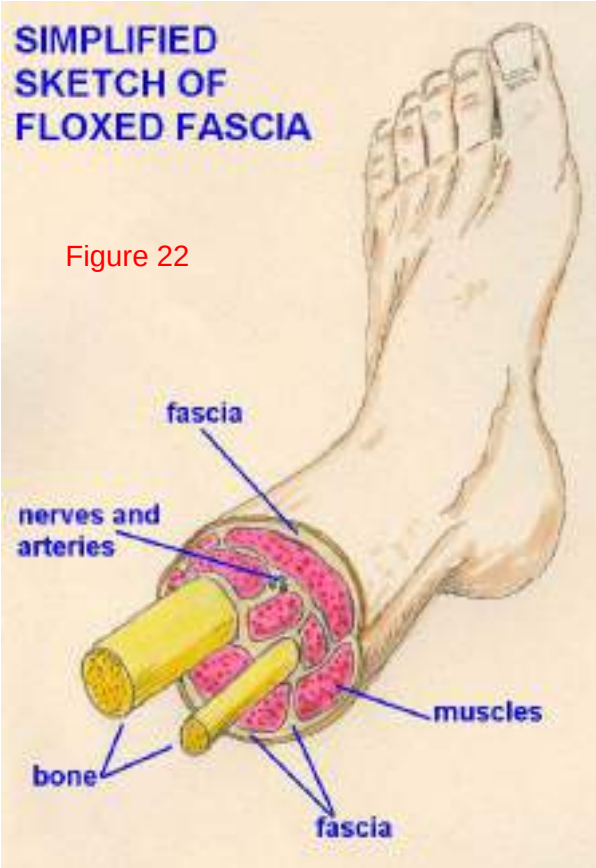
powerful neurotoxicity of fluoroquinolones. Lack of strength, weight loss and inability to create muscle mass after workouts are the proof of this injury. High levels of CPK and aldolase also reveal muscle destruction.

- Degraded muscle fascia. Your overall pains, stiffness, loss of range of motion and soreness are, above all, due to the damage caused to so many fascia layers.

Fascia surrounds and envelops everything from whole muscle groups and bones down to individual cells, including individual muscle fibres, tendons, ligaments, nerves, viscera and the circulatory system. All are degraded by a floxing. We insist on the fact that a floxing is toxic assault on the whole body, and not an anecdotal affliction of some isolated parts.

The meninges and the dural tube fascia play a vital role in the central nervous system. Superficial fascia is attached to the underside of the skin, much like a body stocking and is the outer layer of a three-dimensional continuous network that compartmentalizes the body, separating and surrounding each part. The fascia under the skin is inflamed and overloaded with toxic debris after a severe floxing, therefore we stress the importance of rolling-massage the skin (see a devoted photo here in the flox report).

Each muscle fiber has a fascial binding, and so muscle and fascia are functionally linked, giving rise to the term 'myofascia' (muscle-fascia). See the adjacent sketch. It is very simplified and not a technical representation (for instance, the relative size of the bones could lead an educated person to believe that tibia has been sketched smaller than fibula). All muscles are surrounded by fascia, which provides gliding and lubricated movement between muscles. When the fascia becomes floxed, it loses its properties and muscles do not move freely with respect to each other, initiating a cascade of problems that are all interconnected, which resolution from is difficult, hard, slow and disappointing.



Fascia is a connective tissue. A not so feeble floxing will be reflected in a degraded fascia, and it is often restrictions in fascia that give rise to 'muscle' pain. Circulatory and lymphatic vessels and nerves are placed through the body, wrapped in fascia membranes. If fascia is not moving freely nerves can be stretched, compressed or irritated and pain can be felt not only in the point of entrapment but all along the course of the nerve. One example is the nerve entrapments at the gluteus area that can elicit pains below the knee very frequently.

To say it in easy terms, floxing degrades the fascia tissue so that fascia loses its properties and gets stuck to surrounding issues. This leads to the collagen fibres shortening, thickening, and sticking together. Fascia is composed mainly of collagen (40%) and lubricating ground substance. Fascia that is shortened and hard compresses capillaries and nerves, causing pain, imbalance and discomfort, and resulting in decreased cardiovascular flow that further compromises healing capability.

Perhaps one of the most important pathologies of all those floxed persons that feel pains not just in joints but also in muscles and also a reduction in range of motion is myofascial degradation. For these people, myofascial release provides local and temporary relief. Unfortunately the problem is not mechanical and it tends to recreate itself for many years.

Releasing fascia makes the movement between muscle fibres and other structures possible. Myofascial pains disappear when the floxed person gets healed, what means that his/her fascias have recovered normalcy.

130. WATCH OUT FOR NEW PROBLEMS. YOUR BODY IS NOT THE SAME

A floxed person is prone to suffer increased problems because the severity of many common ailments is intensified very much by the quinolone intoxication.

For instance, any time you get a virus or bacterial infection, a relapse might be released, sometimes with extraordinary virulence. Your quinolone-induced pains will increase greatly, and this situation may last for many weeks after the clearance of the bug or infection.

The two worst sport traumas that a floxed person can suffer are:

- ¡¡ A BLOW ON OR NEAR A FLOXED NERVE !!
- ¡¡ A BLOW ON OR NEAR AN IMPORTANT MUSCLE FASCIA !!

As explained earlier, minor traumas take an abnormally long time to recover. Contact sports like soccer, football, boxing and karate are not advised during this stage of the illness. But a trauma on or near a floxed nerve is perhaps the worse accident that a floxed person can suffer. A floxed nerve is a nerve affected by a quinolone-induced mononeuritis, even if the floxed person had not noticed clearly that the nerve was damaged. For instance, the floxed person can have a quinolone-induced femoral neuritis but he thinks that his hip, gluteus and knee pains are just neurological pains from the antibiotic but not related to that specific nerve. If he suffers a blow on the quadricep that affects that nerve, the femoral neuritis will worsen sharply, and recovery of that part of the nervous system can take a few additional years of continuous dysfunction of the leg that can make him/she walk with a limp or the help of a cane for years. And sometimes the disability is accompanied by excruciating episodes of pain all along the upper leg when performing some movements and/or at night.

Also, a blow or trauma that affects a fascia between muscles may cause a scarring of fascia tissue that impedes a normal gliding between muscle bundles. If the point of impact is close to a fascia where nerves cross the muscles, the outcome can be devastating. These impacts close to powerful fascial tissues have a huge and long lasting repercussion on the floxed victim because he is deprived of all necessary healing abilities of a normal body.

As explained before, another difficulty that victims face is the wasting and loss of function of muscles. Precisely the inactivity of the first months of a floxing (acute phase) and above all, the quinolone neuritis that affects muscles causes them (in lean people) to atrophy a little and to lose function by a great degree. This makes things worse as our joints need as much strength as possible in order to avoid misalignments, overuse, and abuse of tendons.

For instance, without realizing it, some people, due to the severe neuropathic intoxication, and after taking it very easy with their Achilles tendons, experience atrophy of the tibialis anterior muscle, the calves, the soleus and the main ruling muscles of the lower leg and ankle. That submits the Achilles to further stress and the vicious circle starts again, leaving the Achilles or other parts of the ankle very disabled for years, for instance the flexors of the toes and the tibialis posterior tendon.

That is the reason why light weight work or isometric exercises are essential once the acute phase has passed (there is some controversy about this though). In severe reactions, some muscles fail to respond to strengthening exercises for at least 3 to 4 years or more, because the toxic neuritis that affects them makes any gain in mass or performance impossible, irrespective of the workouts that the floxed person undertakes.

Many people that suffer severe reactions develop a life-long intolerance to exercise (here we use intolerance in the sense that it is a lot of pain-soreness-stiffness, especially after exercise, whereas medical intolerance to exercise is basically used for those situations where the person cannot perform strenuous activities because of abnormal heart beats, or responses of the body). Any strenuous activity or sport causes their muscles to ache for a long time and their entire body becomes very stiff. It is a very common permanent aspect of internal injuries caused by quinolone antibiotics.

PART XVIII: TENDONS AND CARTILAGES

131.THE ACHILLES IS NOT THE MOST FREQUENTLY AFFECTED TENDON

Most young doctors know, because it is part of the current medical education, that fluoroquinolones may cause tendonitis, although rarely they think. For all floxed persons, it is extremely well known that quinolones destroy (necrose) tendons; not only in susceptible individuals but also in every human that takes them. And all tendons of the body are equally affected. By now, you have already learned that thousands of reports of ruptures plague the medical literature and the real clinical experience of many doctors and that those reported ruptures are less than the tip of the iceberg because nearly all ruptures take place months after completing the treatment, and nobody links them with the antibiotic. To become part of the statistics of tendons ruptured by quinolones, the rupture has to happen during the treatment, and without any other causative factor, otherwise it is very difficult if not impossible to link the rupture to the antibiotic. From the different studies done on the efficacy of reporting these kinds of injuries, it could be deducted that less than 5% of the ruptures of the tendons happen during the actual treatment with the fluoroquinolone.

We all know that some tendons become more painful than others, because in our personal physiques some tendons have less irrigation than others or because we tend to use them more than others because of our muscle balance and muscle activity.

So, for us the floxed persons, it is equally critical to assess the situation of all of our tendons, whether they are at the shoulder, hip, knee, ankle, wrist, fingers, neck, jaw, back or wherever.

But our doctors are grossly ignorant. In some countries they have been made to believe that the only tendon affected is the Achilles, and only in very rare instances. There are Eeuropean countries where the package insert only refers to the tenotoxicity (tendon toxicity) saying that "if you feel pain in the Achilles tendon, stop the treatment and consult your doctor". This seems to imply that you shouldn't watch out for any other tendon pain. So if you rupture your major shoulder tendons and become handicapped, do watch somewhere else (and take more quinolones and get injured for life). This way of explaining things in the package inserts also make doctors prone to think that if the drug only affects the Achilles tendon, that has to be a very odd reaction and odd reactions afflict only rare people. Some doctors with extremely great reputations in their fields, that match the cost of their bills, very used to prescribing quinolones, have been asked by their patients about "this sudden pain in my achilles area" while taking cipro, for instance, and their doctors have refused any possibility of the pain being caused by cipro because "that is an extremely rare event that cannot be your case" and because "if we paid attention to all warnings in the package inserts we would not take any medicine at all". There is no need to mention that some of those floxed persons developed extremely severe floxings soon after their courses of cipro ended. This demonstrates once again that a more honest approach to the toxicity of quinolones is warranted.

A honest description of the tenotoxicity of the quinolones in the package inserts should be described crudely like it is, as it has been demonstrated in hundreds of medical experiments, for instance like this:

> *"During the post marketing surveillance of this medicine, relatively unexpected tendinitis and ruptures of major and minor tendons have been reported in all kind of people. Ruptures reach disproportionate frequencies of up to 50% in persons that take this antibiotic with*

corticosteroids. In young, healthy and active people tendinitis becomes symptomatic in 5% of persons for low dose and short treatments, and in 100% of people with the highest doses approved and/or long treatments. The injuries of the tendons may appear months or a few years after exposure to the drug and tend to heal very slowly, and in many cases they become chronic or permanent. The injuries of the tendons are cumulative, so keep a record of the total amount of quinolones ingested in the life of the patient".

Finally, look at the distribution of the incidence of tendinitis of the foot-ankle provided in the next chart, and see that the achilles tendon does not lead the league of most affected tendons, very much to the contrary to the common (common in this context means 'ignorant') doctor's belief.

If you have read the account about tendinitis caused by quinolones compiled in this report, and browsed through the medical literature, you will wonder why the first question that a doctor asks his/her patients complaining of tendinitis is not whether they have taken quinolones in the past months. There are very few professions that are so indulgent with such a sheer incompetence.

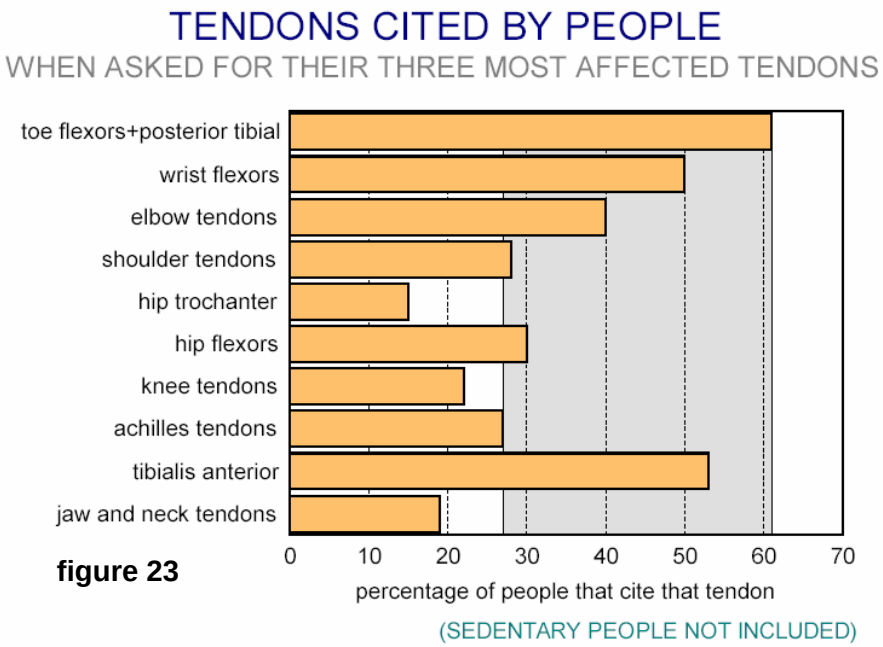


figure 23

Figure 17 shows how sedentary people are less symptomatic than active people in terms of average number of tendons noticeably affected.

When you suffer an intense intoxication by quinolones, there is an impact on virtually all the tendons of the body. Some will become more symptomatic and even will prostrate you. You can become temporarily crippled for some months. You can find hard to get up, to undress yourself, to walk small stretches at home, to lift things or to perform the minutest domestic tasks.

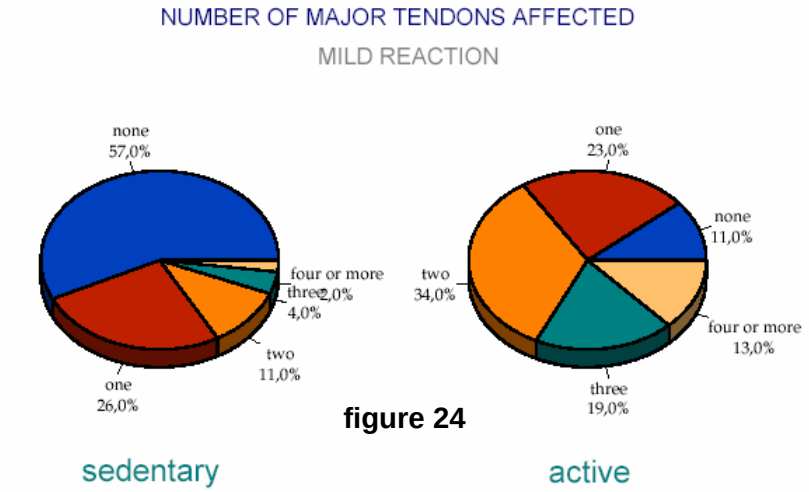


figure 24

More than half of the floxed persons most severely hit have reported resilient tendinitis in at least 6 places, some of which "migrated" along the body with time. We mean by "migration" in this context that some of the tendons more symptomatic vary along the timeline.

Some of the damage on the tendons is irreversible. Obviously, tendon necrosis and degeneration is the real pathology caused by quinolones. Symptoms are much less pronounced in sedentary people for obvious reasons. Figure 18

132.THE PERSISTENT TENDINITIS

Many floxed persons experience a recovery after some months or a few years of suffering. Some even come to believe that they feel pretty much normal. And then, when the nightmare seems over, a few months after the last bothering symptoms settled down, an intense bout of tendinitis and muscle pain develops, both in areas where previously tendinitis were present, and also in many new ones.

These new bouts of tendinitis and myopathies tend to last a few more months or years, depending on the severity of the renewed reaction.

If the healing has taken place in less than 18 months, then the bonus tendinitis can last for another 12 months or more. The intensity of the new tendinitis is comparable with the tendinitis at the onset.

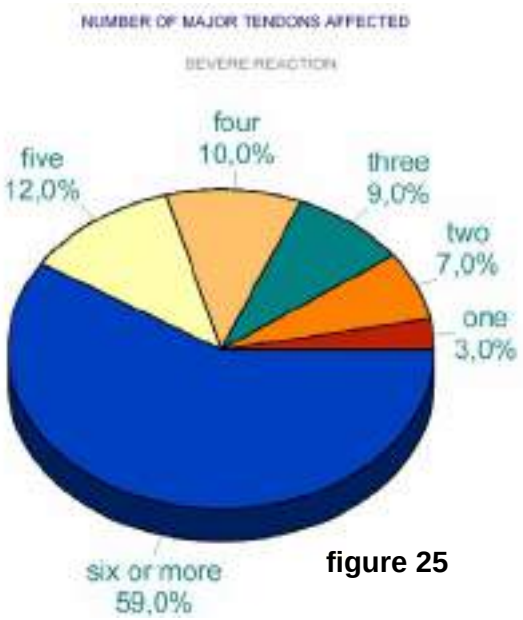


figure 25

If the time elapsed since the onset until a decent improvement is longer that 3 or 4 years, this rebounding and lingering tendinitis can last another 2 or 3 additional years, causing a great intensity of pains and limitations.

In many cases these tendinitis are bursitis or insertional tendinitis, but stenosing tendinitis and fluid accumulation is also observed.

This sort of bonus tendinitis has been detected in more than 80% of intermediate and severe floxed persons that met all this criteria:

-tendinitis at the beginning of the intoxication
-active people

Look to this report by some french researchers.

> [EPICONDYLITIS INDUCED BY FLUOROQUINOLONES IN ATHLETES. APROPOS OF 2 CASES]
> Le Huec JC, et al. Universite de Bordeaux II.
> Epicondylitis occurred in two leisure athletes who were taking fluoroquinolones. No similar cases have been reported in the literature. In both cases, pain occurred early after initiating drug therapy. Pain was intense and was not controlled by usual care. Echography demonstrated major inflammatory injuries with pseudo-necrosis. Magnetic resonance imaging confirmed the injuries and gave evidence of infraclinical injuries of the adjacent tendons. Surgical disinsertion of the epicondyles with biopsy was indicated due to the persistent pain. Histological examination revealed unspecific injuries of hyalin degeneration and a few giant cells in one case. Pain disappeared after surgery and the patients were able to return to their work, but neither was able to continue his sports activity. Injuries of the Achilles tendon have been observed in patients taking fluoroquinolone and the two cases reported here confirm the possibility of other localizations. Care must therefore be taken when prescribing these antibiotics in patients at risk (dialysis patients, those on corticosteroids, high-performance athletes).

The report says that no similar cases have been reported in the literature. Well, we are not "literature" after all, but we have recorded more than 90 epicondylitis induced by fluoroquinolones during the life of the present report. We also confirm that injuries can take place at localizations other than the Achilles tendons.

133. QUINOLONES AND FORGING, TWO INSEPARABLE COMPANIONS

Don't you think that it is quite strange that an antibiotic is toxic only for the achilles tendons and only to special (flawed) persons? That is the firm belief of most doctors. After more than 20 years of appalling evidence things have changed very little.

Fluoroquinolones have been tested in many mammals. No mammal has been found whose tendons remain undamaged after a treatment with fluoroquinolones. All animals tested in hundreds of trials suffered tendon and cartilage destruction. Still today, after 20 years of continuous research, some manufacturers are looking for a mammal that can withstand a quinolone treatment without getting their cartilages and tendons destroyed. You can make a brief search on the veterinarian literature and will see how fluoroquinolones destroy animal joints (cats, dogs, horses....). It is a very widespread fact much more honestly treated and admitted among veterinarians, than its counterpart for humans. In other words, veterinarians have openly researched quinolone-induced tendinitis and osteoarthritis in animals, which is widely acknowledged now. They have instated some restrictions for their use, and have also developed some protocols for treating floxed horses, cats, dogs and other species.

All in vitro tests with human specimens show tendon and cartilage destruction. But, wonder of wonders the manufacturers have convinced all doctors that cartilage and tendons of humans are different, and that tendon damage caused by quinolone therapy is an extremely rare event. For manufacturers, cartilage toxicity in humans has not yet been proven. For them, the thousands of injuries in the cartilages of victims of quinolones are caused by anything else or an extremely rare event of people already prone to it.

To forge simple mathematical calculations is easy. They divide the hundreds of millions of prescriptions of quinolones by the number of medically recorded ruptures of tendons attributed to them and conclude that the risk of rupturing a tendon is very low, so low in fact that it is similar to the risk of a person rupturing a tendon that has never taken a quinolone in his/her life. But the truth is different. The real ratio of people with injuries to the tendons for long and high dose treatments is 100%, so there is a clear toxicity. The injuries of the tendons of people that have taken small doses of quinolones are minimal and asymptomatic, so they do not appear in the statistics. And most tendon ruptures, perhaps 95% or more caused by quinolones are not linked to the antibiotic because they take place many months after ingesting the medicine and they are not the achilles tendon.

When immature animals are tested, the worst injuries are observed. Yet the manufacturers are fighting hard to get their quinolones approved for children, whereas currently they are not advised for people less than 18 years of age.

No matter how sad the immoral and greedy frivolity of the manufacturers may look to the eyes of decent people, the real tragedy is that tendon toxicity (tenotoxicity) and cartilage toxicity (chondrotoxicity) are guaranteed sequela of all quinolone treatments. When you take a quinolone antibiotic, all the tendons and cartilages of your body are exposed to this substance, and invariably get damaged. The damage, ranging from undetectable to a complete rupture, will show up in the months to come, and will depend on many factors, that have been discussed throughout this report.

Do not forget that the damage is cumulative. So, the more quinolones you take over the years, the deeper and more extensive damage they cause.

In the reference section, there are many works listed on quinolone tenotoxicity and chondrotoxicity. Sometimes it is hard to find the excerpts of the reports. Here we reproduced some passages of some of them.

QUINOLONES AND TENDON RUPTURES, FROM SOUTHERN MEDICAL JOURNAL
J. Michael Casparian, MD, et al, Department of Medicine, University of Kansas Medical Center, Kansas.
We report two cases of tendon rupture associated with ciprofloxacin that highlight unusual features of this association. One case involves a complete Achilles tendon rupture occurring **6 months after the medication** had been discontinued. In the second case, a partial rupture of the subscapularis tendon of the right shoulder occurred **during mild stretching exercises**. These cases provide insights into the broad nature of tendon ruptures that can be associated with fluoroquinolones. Because these antimicrobials are used commonly, clinicians need to be aware of the potential adverse effects that fluoroquinolones may have on tendons.

> Case 1. A 38-year-old **physician** was ...[prescribed] a 1-week course of ciprofloxacin (500 mg twice daily) because of a productive cough. The patient had no symptoms related to his legs until 6 months after discharge. At that time, he had sudden, severe pain while taking a short walk. Physical examination was consistent with a complete rupture of the Achilles tendon. He subsequently had surgical repair of the rupture, with an uneventful postoperative course.
> Case 2. A 54-year-old **physician** was given a 10-week course of ciprofloxacin (500 mg bid) for recurrent bacterial prostatitis. Two months into the course, he had marked right anterior shoulder pain associated with vertical "push-ups" done against a wall for the purpose of calf muscle stretching. Cessation of the activity and use of nonsteroidal anti-inflammatory drugs (NSAIDs) did not relieve the symptoms. Magnetic resonance imaging (MRI) of the right shoulder showed a partial tear of the subscapularis tendon. Discontinuing ciprofloxacin, along with starting physical therapy and NSAIDs, completely resolved the patient's symptoms in 5 weeks.

We know of at least 4 physicians that have had ruptures of tendons or suffered very severe tendinitis requiring crutches, caused by quinolones. Three of them did not report it to the MedWatch drug reaction reporting system.

Transplant recipients have an extremely high ratio of rupture of tendons if they take quinolones, not from the transplant but probably because they took steroids at the same time:

> ACHILLES TENDON DISEASE IN LUNG TRANSPLANT RECIPIENTS: ASSOCIATION WITH CIPROFLOXACIN
> P.N. Chhajed, et al. Heart Lung Transplant Unit, St. Vincent's Hospital, Sydney, NSW 2010, Australia.
> Achilles tendonitis or rupture are uncommon complications following the use of fluoroquinolones, with a reported incidence in the general population of 0.4%. The aims of the current study were to determine the incidence of Achilles tendon disease in lung transplant recipients and to identify risk factors.
> Only the use of ciprofloxacin was significantly associated with achilles tendon disease. Age, sex, underlying disease necessitating transplantation, serum creatinine and cyclosporine levels were not associated with achilles tendon disease. The association between ciprofloxacin and achilles tendon disease was not dose related. Of the 72 lung transplant recipients who had received ciprofloxacin, 20 (28%) developed achilles tendon disease (tendonitis 15, rupture five). In patients receiving ciprofloxacin, there was no association between the mean cumulative dose of prednisolone and achilles tendon disease. Tendon rupture occurred with a lower ciprofloxacin dosage than tendonitis and the mean recovery duration was significantly longer.
> To conclude, lung transplant recipients receiving ciprofloxacin are at significant risk of developing Achilles tendon disease. The association between ciprofloxacin and Achilles tendon disease appears to be idiosyncratic rather than dose-related.

Comments: It seems quite odd that according to the manufacturers the general population develop 0.4% cases of tendonitis after a treatment of ciprofloxacin and according to a detailed follow up in a hospital lung transplant recipients develop 28%. One big difference is the prednisolone that the transplant recipients took that the general population did not. But on the other hand, the transplant recipients were physically inactive in general, so their risk of rupturing a tendon was diminished in respect to the general population.

If the general population were prescribed the same doses and length of treatment of ciprofloxacin as the lung recipients, the occurrence of tendinitis would be roughly the same 28%. If, in addition, those patients started an active life, the ratio of tendinitis reported would be 100%. And if the dose was somewhat higher, the occurrence of tendinits would also be 100%, irrespectively of the activity level of the patient, as in table 3 of this report.

134. TENDIFLOXITIS

In summary, the main facts to remember about the toxicity of quinolones on the tendons and cartilages are:

1. The injuries are guaranteed, it is a class effect of these medicines.
2. Injuries normally show up some months after completing the treatment. Ruptures can occur up

to 2 years post-treatment.

3. The general theory that we propose is an ischemic factor (due to vascular and extracellular matrix degradation) plus an overall tissue toxicity (and more specifically connective tissue) fits well with all the characteristics of the fluoroquinolone tenotoxicity (tendon toxicity) and chondrotoxicity (cartilage toxicity). Some injuries seem to be beyond repair.
4. Active people take the worst hit. Sedentary people can sustain a great deal of damage in tendons and cartilages without becoming very symptomatic and therefore without realising it.
5. Recovery from tendinitis and joint problems can take some years, typically 5, 6, 7 or more years. In many cases tendinitis becomes chronic, widespread, and permanent.
6. Early osteoarthtritis is a sure aftermath of any serious reaction to a fluoroquinolone treatment, manifested as cartilage softening and erosion. All of this damage is irreversible in nature.
7. There is no known cure at all for quinolone tenotoxicity and chondrotoxicity. All conventional treatments are useless, and no efficacy has been shown by top-end therapies (i.e. autoplasma injections) that show a high efficacy ratio for normal cases.
8. Although the achilles tendon gets the fame, it is far from being the tendon most affected. No tendon of the body is spared, but the tendons of the knee, ankle, hip, neck, back, elbow, wrist and shoulder take the biggest assault.
9. All claims of manufacturers about tendon and cartilage safety are plain fraud.

Doctors live happily prescribing quinolones because they have been made to believe that disabling tendon injuries are extremely rare and only occur to people prone to them. Warnings do exist but are not listened to:

> FLUOROQUINOLONE THERAPY AND ACHILLES TENDON RUPTURE
> Diane Vanek, et al. California School of Podiatric Medicine. Palo Alto Medical Foundation, Palo Alto, CA. (J Am Podiatr Med Assoc 93(4): 333-335, 2003)
> Fluoroquinolones have been associated with tendinopathies. The authors present three cases of Achilles tendinopathy in which the patients' symptoms were preceded by treatment for unrelated bacterial infections with ciprofloxacin. Although the exact mechanism of the relationship is not understood, those who engage in sports or exercise should be advised of the risk of quinolone-induced tendinopathy.

When a floxed person starts to get well in respect with tendinitis, he usually enters cycles of alternating normalcy and periods of tendinitis that are strong and debilitating.

Well, many many of us (almost all persons related to the flox report) were permanently engaged in sports and exercise before being floxed and were not advised of the risk of getting the crippling, prostrating tendinopathies that are keeping us handicapped for years or perhaps forever.

135. THE CONNECTIVE TISSUE AGAIN

In other sections of the flox-report you have read arguments explaining how after the floxing basically your body is not the same because the fluoroquinolones substantially degrade all the matter that surrounds the cells and serves for transmission of all the vital exchanges between the cells and the arteries that supply them, and the veins that remove the wastes. And you also know that among the most affected is the specialized connective tissue.

Connective tissue contains cells and metabolites important in immune function, such as inflammation, and in tissue repair after injury. Blood vessels, a connective tissue, transport substances throughout the body. Components in connective tissue regulate movement of nutrients between cells. Adipose tissue is a unique connective tissue, providing storage of energy and insulation. Various drugs, among them the fluoroquinolones, disrupt the regulation of connective tissue synthesis and degradation.

Connective tissue trauma is a major source of physical discomfort, especially in athletes. This is not surprising, considering that connective tissue is one of the most abundant and widely distributed tissues in the body. It forms our bones, surrounds our organs, holds our teeth in place, cushions and lubricates

our joints, and connects the muscles to our skeleton (extracted from a paper by Elzi Volk).

Connective tissue is metabolically active and serves many structural functions. The tissue consists of three basic components: fibers, extracellular matrix and cells. Mixed populations of cells with various functions interact with the extracellular matrix contributing to the various mechanisms in tissue physiology. Except for cartilage, connective tissue is innervated (has a nerve supply). Vascularity (blood supply) in tendons and ligaments is sparse, whereas cartilage is avascular (has no blood supply). Both nerves and blood ducts are injured by quinolones.

The extent and depth of the injury of the connective tissue that all fluoroquinolones cause to everybody, determines the symptoms, the evolution of the intoxication and the final outcome.

The extracellular matrix fills the spaces in-between the cells and fibers. Its viscosity acts as a lubricant due to the high water content. Soluble precursors of the fibrous proteins, proteoglycans, glycoproteins and other molecules secreted by cells are abundant in this ground substance.

The two major components of the extracellular matrix are the proteoglycans and structural glycoproteins, which trap water molecules and lend strength, rigidity and resiliency to the extracellular matrix.

The various cells in connective tissue store vital metabolites and synthesize fibrous proteins and other components of the extracellular matrix. They play important roles in immune and inflammatory responses as well as in tissue repair. Many cells are indigenous to connective tissue. Some originate in bone marrow, but are constantly present in the tissue. Other cells migrate from blood vessels in response to tissue injury, inflammation and repair, but cannot reach the cells in floxed states. They tend to disappear as healing progresses and inflammation subsides. These cells include plasma cells, neutrophils, monocytes and basophils.

LEVOFLOXACIN-INDUCED TENDON RUPTURE: A CASE REPORT AND REVIEW OF THE LITERATURE. Liana Gold, ARNP, MSN; Helena Igra, MD

The deleterious effects of fluoroquinolones on tendons have been documented since the 1980s. A concomitant rise in tendon rupture incidence has been observed during this same time span. With the increasing use of levofloxacin and other quinolone antibiotics, we should expect to encounter a growing number of patients experiencing tendonopathy. Patients presenting with joint tenderness and swelling, especially those in a high-risk category, should be questioned as to quinolone use dating **as far back as 6 months or more**. Discontinuation of the medication and immobilization of the affected joint should be foremost. Preventative measures include avoiding indiscriminate use of quinolones, recognition of risk factors, and adherence to renal dosing. Finally, an emphasis on patient awareness can further reduce the morbidity associated with quinolone-induced tendonitis and/or rupture by prompting earlier presentation, evaluation, and intervention.

THE EFFECTS OF ENROFLOXACIN ON DECORIN AND GLYCOSAMINOGLYCANS IN AVIAN TENDON CELL CULTURES.

Yoon JH,et al. Department of Pathology, College of Veterinary Medicine, The University of Georgia, Athens, GA 30602, USA.

Tendonitis and tendon rupture have been reported to occur during or following therapy with fluoroquinolone antibiotics. Though the pathogenesis is unknown, several studies suggest that fluoroquinolone antibiotics alter proteoglycan content in soft tissues, including tendons, and thereby alter collagen fibrillogenesis. To better understand the mechanism of action of fluoroquinolones, we studied the effects of enrofloxacin, a widely used fluoroquinolone in veterinary medicine, on avian tendon cell cultures established from gastrocnemius tendons from 18-day-old chicken embryos. We found that cell proliferation was progressively inhibited with increasing concentrations of enrofloxacin. This was accompanied by changes in morphology, extracellular matrix content and collagen fibril formation as detected by electron microscopy. We also observed a 35% decrease in the content of total monosaccharides in enrofloxacin-treated cells. The ratio of individual monosaccharides was also altered in enrofloxacin-treated cells. Enrofloxacin also induced the synthesis of small amounts of keratan sulfate in tendon cells. Moreover we observed enrofloxacin-induced changes in glycosylation of decorin, the most abundant tendon proteoglycan, resulting in the emergence

of multiple lower molecular bands that were identifiable as decorin after chondroitinase ABC and N-glycanase treatment of extracts from enrofloxacin-treated cells. Medium conditioned by enrofloxacin-treated cells contained less decorin than did medium conditioned by control cells. We hypothesize that enrofloxacin induces either changes in the number of N-linked oligosaccharides attached to the core protein of decorin or changes in decorin degradation process. **In conclusion, our data suggest that enrofloxacin affects cell proliferation and extracellular matrix through changes in glycosylation.**

PEFLOXACIN-INDUCED ACHILLES TENDON TOXICITY IN RODENTS: BIOCHEMICAL CHANGES IN PROTEOGLYCAN SYNTHESIS AND OXIDATIVE DAMAGE TO COLLAGEN
Marie-Agnes Simonin, et al. Department of Pharmacology, Faculté de Médecine, Vandoeuvre-lès-Nancy, France.
Despite a relatively low incidence of serious side effects, fluoroquinolones and the fluoroquinolone pefloxacin have been reported to occasionally promote tendinopathy that might result in the complication of spontaneous rupture of tendons. In the present study, we investigated in rodents the intrinsic deleterious effect of pefloxacin (400 mg/kg of body weight) on Achilles tendon proteoglycans and collagen. Proteoglycan synthesis was determined by measurement of in vivo and ex vivo radiosulfate incorporation in mice. Collagen oxidative modifications were measured by carbonyl derivative detection by Western blotting. An experimental model of tendinous ischemia (2 h) and reperfusion (3 days) was achieved in rats. Biphasic changes in proteoglycan synthesis were observed after a single administration of pefloxacin, consisting of an early inhibition followed by a repair-like phase. The depletion phase was accompanied by a marked decrease in the endogenous serum sulfate level and a concomitant increase in the level of sulfate excretion in urine. Studies of ex vivo proteoglycan synthesis confirmed the in vivo results that were obtained. The decrease in proteoglycan anabolism seemed to be a direct effect of pefloxacin on tissue metabolism rather than a consequence of the low concentration of sulfate. Pefloxacin treatment for several days induced **oxidative damage of type I collagen**, with the alterations being identical to those observed in the experimental tendinous **ischemia** and reperfusion model. Oxidative damage was prevented by coadministration of N-acetylcysteine (150 mg/kg) to the mice. **These results provide the first experimental evidence of a pefloxacin-induced oxidative stress in the Achilles tendon that altered proteoglycan anabolism and oxidized collagen**.

THE EFFECT OF ENROFLOXACIN ON CELL PROLIFERATION AND PROTEOGLYCANS IN HORSE TENDON CELLS.
Yoon JH,et al. Department of Pathology, College of Veterinary Medicine, The University of Georgia, Athens, GA 30602, USA
Fluoroquinolone antibiotics have been used widely in humans and domestic animals, including horses, because of their broad-spectrum bactericidal activity, and relative safety. The use of fluoroquinolones, however, is not without risk. Tendonitis and spontaneous tendon rupture have been reported in people during or following therapy with fluoroquinolones. We have studied the effects of enrofloxacin, a fluoroquinolone antibiotic used commonly in domestic animals, on tendon cell cultures established from equine superficial digital flexor tendons. Effects on cell proliferation and morphology were studied using cell counting and scanning electron microscopy. Monosaccharide content and composition was determined by gas chromatography-mass spectrometry analysis. Western and Northern blot analyses were utilized to evaluate the synthesis and expression of two proteoglycans, biglycan and decorin. Our data **demonstrate** that enrofloxacin inhibits cell proliferation, induces morphological changes, decreases total monosacharide content and alters small proteoglycan synthesis at the glycosylation level in equine tendon cell cultures. These effects are more pronounced in juvenile tendon cells than in adult equine tendon cells. We hypothesize that **morphological changes** and **inhibition of cell proliferation** are a result of impaired production of biglycan and decorin, proteoglycans involved in fibrillogenesis of collagen, the most important structural component of the tendon of enrofloxacin-treated tendon cells. Our findings suggest that fluoroquinolones should be used with caution in horses, especially in foals.

136.WITH FLUOROQUINOLONES DEGRADATION EXCEEDS REPARATION

Following mainly the explanation of Elzi Volk for connective tissue, we can say that synthesis (creation)

and degradation (destruction) of connective tissues is a continual process and that many modulators like drugs can affect these processes. Remodeling of tissues is the process of changing and replacing tissue components with others. Normal remodeling during growth or repair requires a proper balance of synthesis and degradation of tissue components. Proteoglycans in the extracellular matrix appear to regulate remodeling of connective tissue by influencing collagen formation during the repair process. As you can read in hundreds of medical reports, among them the cited above, this process is completely altered, sometimes beyond repair, by any fluoroquinolone treatment. Remodeling is also regulated by mechanical stimulation (mechanical tension and compression modify bone and cartilage remodeling).

Unfortunately for floxed persons, there are many tissues, especially connective tissue that depend on diffusion of nutrients through the extracellular matrix for maintenance since they have no direct blood supply. With the extracellular matrix damaged, little by little, the tissues become injured, at the same rate as the loss of healthy exchanges through the matrix build up to a point of becoming symptomatic, typically some months after the treatment with fluoroquinolones has been completed.

Turnover of connective tissue is the net balance between synthesis and degradation of the macromolecules. A turnover negative balance is characteristic of several inflammatory and joint diseases where degradation occurs at a higher rate than synthesis. We have deducted clearly that quinolones impede the normal synthesis of new tissues, and also degrade other tissues, so they act in both aspects. A healthy repair process implies a turnover so that synthesis equals degradation. Fluoroquinolones cause dis-equilibrium between degradation and repair that lasts for years in many cases.

Turnover rate of various connective tissue components varies. Elastin may take months to years for renewal. This might be the reason why floxed tendons tend to heal so slowly and help to explain why so many floxed persons suffer from tendinitis 7 or 10 years post floxing. Collagen is also a stable protein and renewal is slow. Replacement of mature collagen can require weeks to several months. Collagen turnover rates vary in different structures. Tendon collagen renewal is very slow, whereas the collagen of loose connective tissue that surrounds our organs is renewed more rapidly.

137. PURELY FLOXED TENDONS

Skeletal muscle and tendons are distinct tissues. However, they function as one unit: the musculo-tendon unit. Tendons attach the muscle to bones and transmit force from the muscle to the bone. Connective tissue forms a network throughout the muscle. It surrounds the fibers, the bundles of fibers and wraps around the whole muscle. This connective tissue network is continuous through the muscle and into the tendon that inserts the bone.

Tendons primarily consist of collagen – up to 85% of the dry weight –, which imparts the mechanical and physiological properties of this tissue. Type I collagen predominates with small amounts (approximately 5%) of Type III and Type V collagen. Smaller amounts of elastin exist in the extracellular matrix. The type and quality of cross-linking varies in tendon fibers and is associated with the degree of mechanical loading experienced by the musculo-tendon unit. The regulation of the cross-link quality in new collagen is established by the mechanical loading during growth and development. Tendons that transmit the highest forces have the highest degree of cross-linking. Mechanical forces also determine morphology of collagen. The distal end of human tibialis posterior tendon, which receives compressive forces as well as tensional forces, exhibited less linear and more swirled collagen formation than seen in the proximal end (which receives mostly tensional forces), no wonder that this specific tendon is the most affected by floxings, followed at a distance by the flexors of the toes and the achilles' tendons.

NOTE: After a high level reaction, tendons become permanently damaged forever.

Closely packed fibers are bundled together and run parallel to the long axis of the tendon. Fibroblasts are few and located in the spaces between the collagen bundles. Many collagen bundles grouped together form the fascicle, and a synovial-like membrane, the epitenon, surrounds several fascicles to form the

tendon unit. This membrane contains blood and lymphatic vessels and nerves. Several layers of elastic connective tissue sheaths enclose the tendon unit. The properties of these layers vary depending on site. Some tendons (such as the flexor tendons in forearm) are enclosed by a synovial sheath, which carries many blood vessels.

The nerve supply to tendons and ligaments originates from the nerves of the muscles. Degree of vascularity of tendons differs depending on structure and site of the tendon. Blood vessels within the tendinous tissue are relatively sparse. Altered blood flow and exchange caused by fluoroquinolones and consequent production or accumulation of soluble factors may modulate the type and amounts of proteoglycans and collagen. The more vascularized tendons have blood vessels that infiltrate throughout the tendon from the outer connective sheath. The less vascular tendons have outer membranes that act as conduits of blood supply for the tendon fibers within. The other source of nutrition is diffusion from the synovial fluid, which provides a significant supply of nutrients for many tendons. The tissues enclosing and surrounding the tendon provide a cellular and vascular component for healing and providing nutrition to the tissue within.

By now you already know that all these nourishing vital mechanisms are modified by any treatment with fluoroquinolones. How much and how negatively it will affect you during the years to come is the only thing that has to be elucidated in each case.

138. INCURABLE FLOXED LIGAMENTS

Ligaments are bands of connective tissue that bind bones to each other, crossing joints with wide ranges of motion as well as joints with little motion. Unlike tendons, both ends of ligaments insert into bone. The tissue may exist as fibrous bands, sheets or short thickened strips in joint capsules. Unlike previous assumptions, ligaments and tendons differ from each other in several ways. Collagen content is generally similar in tendons and ligaments. Type I collagen predominates (90%) with small amounts of type III (10%), which is more than tendons. Ligamentous collagen has more reducible cross-linking. The tightly packed bundles of collagen with many fibroblasts are aligned along the axis of tension.

> QUINOLONES AND TENDON RUPTURES; from Southern Medical Journal
> There have been three reports of patients with fluoroquinolone-associated disruption of the Achilles tendon in which histopathology was obtained..../... Histopathology in a second case of ruptured Achilles tendon showed necrosis and cystic changes that are not found in non-drug-associated tendinopathies. Another patient had pain and swelling of one Achilles tendon 9 months after only a 1-week course of ciprofloxacin (500 mg bid). Biopsy of the tendon was done 4 months after the onset of symptoms. Histologic examination revealed **abnormal fiber arrangement** and structure with **fibrotic areas**, hypercellularity with some nuclei being more rounded, **neovascularization**, and increased **glycosaminoglycans in the extracellular matrix**. These histologic findings are similar to those in tendon overuse injuries in athletes.

As in tendons, site-specific structural and biochemical differences exist in ligaments due to different mechanical demands and the nutritional environment. The elastin content in ligaments varies depending on function. Most ligaments have less than 5% elastin. However, others have higher concentrations (up to 75%) imparting more elastic properties. Intraligamentous blood vessels are sparse. Therefore, mid-tissue nutrition relies greatly on diffusion from nearby blood vessels, which lie parallel to the tissue and synovial fluid.

139. IRREVERSIBLE CARTILAGE DAMAGE

All floxed persons fear and dislike all data that demonstrates that fluoroquinolones cause irreversible damage to all the cartilages of the body. However we cannot deny the evidence.

A joint is a junction of two bones, holding them together while allowing for smooth movement against one

another. The joint capsule and fibrous lining holds many components where the bone-ends meet. The synovial cavity, which is surrounded by a membrane, contains fluid that lubricates and nourishes the articular cartilage, the tissue that caps the ends of the bones.

In addition to supplying nutrients to cartilage, synovial fluid contains phygocytic cells that remove debris resulting from wear and tear in the joint capsule. The amount of fluid in the synovium varies depending on the size of the joint. The fluid is normally viscous when there is no joint movement; as movement increases, the fluid becomes less viscous.

Cartilage is a resilient material that absorbs shock and provides an elastic surface for smooth gliding of joints. Chondrocytes are embedded in the extracellular matrix comprised of type II collagen, proteoglycans and water. Cartilage lacks blood vessels, nerves and a lymphatic system. The cells must therefore rely on diffusion of nutrients through the extracellular matrix from the underlying bone or the synovial fluid. Damage to articular cartilage may be present long before it is noticed since these joints are non-innervated. Peripheral activation and sensitization of nerves during inflammation may elicit pain well after degenerative processes are stimulated. That is a reason that partly explains why joint pains start some time after the treatment with fluoroquinolones has been completed.

The extracellular matrix is of great importance to the cartilage. Collagen fibers and the ground substance make up the extracellular matrix. Collagen fibers and the glycoproteins comprise the fibrous web that anchors the chondrocytes within the matrix and provide tensile strength to cartilage. The fundamental component in the ground substance is the glycosaminoglycans. The large proteoglycan aggregates described in Part I play an important role in maintaining optimal function of our joints. In cartilage, the predominant glycosaminoglycans are chondroitin sulfate and keratan sulfate.

Note: A floxed cartilage looses many of its mechanical and structural properties and it is prone to degradation and osteoarthritis, if not directly destroyed by the quinolone.

Considering the importance of the extracellular matrix to normal physiology and function of articular joints, any factor that increases the ratio of degradation to loss of matrix components will cause cartilage health to deteriorate. Alterations in cellular activity may also affect the turnover rate and remodeling process. This may be the key component of fluoroquinolone toxicity to human cartilage.

PART XIX: MUSCULOSKELETAL INJURIES

140. PATHOPHYSIOLOGY OF THE CHEMICAL TOXICITY CAUSED BY FLUOROQUINOLONES

Most connective tissue injuries involve damage to the structural components of the tissue. Metabolic states, such as a floxing, may also affect connective tissue health.

Degradation of the extracellular matrix is also responsible for the pathogenesis of osteoarthritis. Chondrocytes in articular cartilage with osteoarthritis may be unresponsive to local growth factors resulting in decreased synthesis of matrix components. According to several doctors that are treating some floxed persons, the fluoroquinolone reaction activates a cascade of inflammatory events, and chemical degradation of cells and metabolism, that ends up in a given state of osteoarthritis, more or less symptomatic.

> PROF. DR. RALF STAHLMAN. CHARITÉ - UNIVERSITÄTSMEDIZIN BERLIN. INSTITUTE OF CLINICAL PHARMACOLOGY AND TOXICOLOGY CBF
> Fluoroquinolones can cause tendon disorders as an adverse reaction associated with this class of antimicrobials. We investigated aspects of the pathomechanism of quinolone-induced tendotoxicity in human tenocytes focussing mainly on the question whether fluoroquinolones induce apoptosis. Monolayers of human tenocytes were incubated with ciprofloxacin or levofloxacin at different concentrations (0, 3, 11, 30, 100 mg/L medium) for up to 4 days. Alterations in synthesis of specific proteins were determined using immmunoblotting. At concentrations which are achievable during quinolone therapy, 3 mg ciprofloxacin or 10 mg levofloxacin/L medium significantly decreased type I collagen; similar changes were observed for the 1-chain of the integrin receptor. Effects were intensified at higher concentrations and longer incubation periods. Furthermore, time- and concentration-dependent increases of the apoptosis marker activated caspase-3 were found. Our results provide evidence that apoptosis has to be considered as a final event in the pathogenesis of fluoroquinolone-induced tendopathies. As a follow up to this project we will study the effects of glucocorticoids alone and in combination with fluoroquinolones on human tendon cells. In this part of the project, we hope to provide biochemical evidence for the clinical observation that a treatment with steroids has been recognized as a risk factor for quinolone-induced tendopathies.

Apoptosis means programmed cell death. Cells commit suicide when receive given signals, for example signals emitted by quinolones.

141. REPAIR OF FLOXED CONNECTIVE TISSUE

Injury to connective tissue involves damage to the cells and structural components of the tissue. Several responses are triggered and a sequence of events begins to repair the tissue. The reaction to injury includes vascular, cellular and biochemical responses. (The explanations concerning connective tissue have been obtained from the work of Elzi Volk and others).

Three phases of the repair process can be applied to the general healing of connective tissue. These phases, however, may overlap. These responses prevent the spread of damaging agents to nearby tissues, dispose of damaged cells, and replace damaged tissue with newly synthesized components.

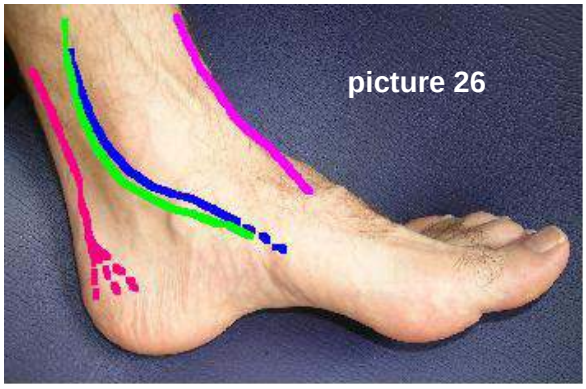
Acute inflammation phase: Immediately after the chemical (floxing) injury, several vascular and cellular reactions initiate the response known as inflammation. The primary purpose of inflammation is to rid the site of damaged tissue cells and set the stage for tissue repair. Many of the events that

occur during this time initiate tissue repair. Leukocytes (white blood cells), such as neutrophils and monocytes, accumulate within the damaged tissue along with resident macrophages. Enzymes released from these cells help digest necrotic cells and degrade matrix molecules; neutrophils and macrophages engulf cell debris. Blood platelets release growth factors that stimulate new fiber and matrix molecule synthesis.

Matrix and cellular proliferation phase: Chemical mediators released by inflammatory cells stimulate migration and proliferation of fibroblasts, which participate in the repair process. As you have seen this phase is profoundly impaired by quinolones by means of many mechanisms among which there is fibroblast metabolism impairment. Fibroblasts secrete fibronectin, proteoglycans and small diameter Type III collagen fibers. In addition to these fibers, newly formed capillary channels, clotting proteins, platelets and freshly synthesized matrix molecules form granulation tissue. A floxed person is deprived from this phase, up to an extent that defines the severity of his/her floxing.

Remodeling phase: Remodeling reshapes and strengthens damaged tissue by removing and reforming the matrix and replacing cells. As repair progresses, inflammatory cells disappear, the number of blood vessels and the density of fibroblasts decrease. The proportion of Type I collagen to Type III collagen and the matrix organization increases. Collagen fibers are reoriented in the direction of loading, especially in ligament repair. As you know, there are many medical reports that indicate that quinolones cause a faulty, disoriented remodeling of collagen fibers. Collagen matures and elastin forms; tensile strength increases in normal people but not much in floxed persons, who end up with very weak tendons. The remodeled tissue does not completely resemble the original and thus the mechanical capabilities of that tissue may be altered.

142. THE ANKLES: AN EXAMPLE OF TENDONS SEVERELY HIT BY QUINOLONES



As an example of the implications of a floxing over a joint, in the present edition of this paper, we deal briefly only with the ankle joint and surrounding tissues, although the quinolones also target any other joint in the body.

This picture 26 of the ankle area shows the main tendons that are so commonly damaged by quinolones. It is a class effect, that is to say, a direct injury, irrespective of one's build.

- Red: achilles tendon.
- Green: flexor digitorum longus
- Blue: posterior tibial tendon
- Purple: tibialis anterior

As stated before, the achilles tendon is not the one most affected by fluoroquinolones. The posterior tibial tendon and the flexors of the toes are much more frequently affected, and more severely, but contrary to the achilles, these tendons do not tend to rupture so easily.

This picture 27 shows a dorsiflexion movement (forcing the toes upwards). This manoeuver stretches the achilles tendon and stresses the posterior tibial tendon and forces the flexor digitorum longus to work.

In severe reactions, this movement performed against resistance on the tip of the toes, can cause extremely incapacitating injuries in the posterior tibial and flexor digitorum group of tendons, that require months to resolve.

This same gesture plus some pronation is done during the contact phase of a normal running activity, which from repetition can cause a devastating damage to the floxed athlete.

According to the studies of the mainstream, industry-prone, researchers, *"tendon disorders associated with fluoroquinolones have been estimated to occur at a rate of approximately 15 to 20 per 100,000 patients."* The real figures are those stated in table 3 of this paper, that account for 100,000 patients per 100,000 patients if they are given a high, yet approved, therapeutic dose. This is so because of a direct toxic effect.

According to the most widespread manufacturer's version of this problem, out of 100 cases of Achilles disorders, *"tendon rupture occurred in 31% and tendinitis in 69%."* That is again an incorrect figure because ruptures are much less common than that. They also tell us *"the average time between the start of treatment to the onset of symptoms was 13 days, with a range of 1 to 90 days"*. This means that they have only studied report of ruptures associated with quinolones up to 90 days after the start of treatment, whereas in reality they occur up to many months later.

One of their studies found that 50% of patients with fluoroquinolone-induced tendinitis recovered in 1 month. In another study, 25% of the patients had symptoms that persisted for at least 2 months. So they conclude, *"even with early diagnosis and management, discontinuance of the fluoroquinolone, and placement of the tendons at rest, tendinitis heals slowly".* **We would like to know how slow would they rate the healing of many athletes with unremitting and incapacitating tendinitis after 4, 5 or 7 years of suffering from quinolone toxicity.**

There have been reports of patients with fluoroquinolone-associated ruptures of the Achilles tendon in which histopathology was obtained. In one patient who had a rupture, the histopathology showed necrosis along with neovascularization, multiple fissures, and interstitial edema, but no inflammatory cell infiltrate. Histopathology in a second case of ruptured Achilles tendon showed necrosis and cystic changes that are not found in non-drug-associated tendinopathies.

Another patient had pain and swelling of one Achilles tendon 9 months after only a 1-week course of ciprofloxacin (500 mg bid). Biopsy of the tendon was done 4 months after the onset of symptoms. Histologic examination revealed abnormal fiber arrangement and structure with fibrotic areas, hypercellularity with some nuclei being more rounded, neovascularization, and increased glycosaminoglycans in the extracellular matrix. These histologic findings are similar to those in tendon overuse injuries in athletes.

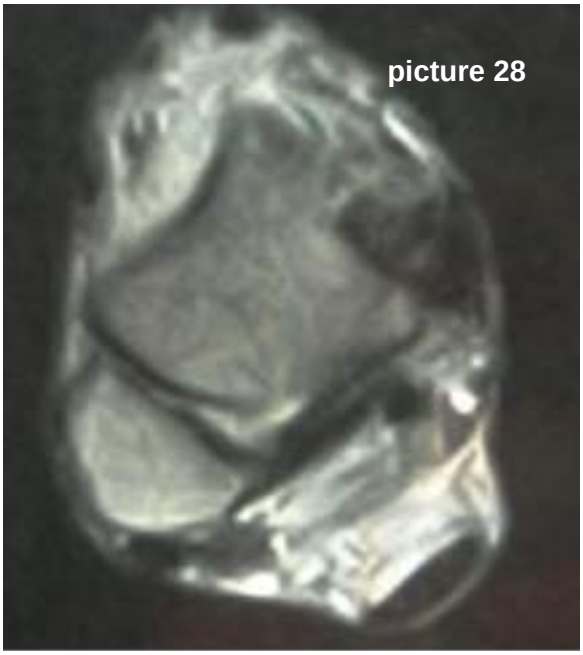
In summary, the damage is extensive and deep on tissues that have very little capacity to regenerate, so the injuries linger on for a long time or become chronic or permanent.

But again, for the industry and their well paid or brainwashed doctors, our group of 42 floxed persons, mostly young healthy athletes with zero previous health problems, is a group of people with special risk factors prone to rupture their tendons. Read what they always add to any report on side effects of quinolones: *".....effects such as tendon ruptures, which may occur in the absence of any medication, particularly since the reported cases frequently had coexisting risk factors. However, clinical reports, histopathologic findings, and an experimental model support a causal relationship between fluoroquinolone use and tendon ruptures". ../.. "Since it is often difficult to establish causality for individual cases, efforts to quantify the risk of tendon ruptures should be viewed as only estimates. There may be a bias in over reporting an association between tendon rupture and fluoroquinolone use, involving cases that might have spontaneously occurred without the medication. On the other hand, the association may be unrecognized, and therefore some cases may be underreported".* **This sort of disqualification of every study makes doctors not pay attention to ADVERSE EFFECTS at all.**

Some researchers are more independent from industry: A case report described an individual who had 9 months of symptoms after a 1-week course of fluoroquinolones: "*The histopathology in this patient is particularly noteworthy. Abnormal biopsy findings, consistent with a reactive healing process, were found at 4 months, suggesting these medications may have prolonged effects on tendons. The presence of a cystic change in another patient suggests the pathophysiologic changes associated with fluoroquinolones may not be completely reversible, at least in some cases. The prolonged symptoms associated with increased glycosaminoglycans of the tendon in one patient who had only a 1-week course of antibiotics and the cystic changes in another patient support mechanisms for ruptures to occur long after the antibiotic therapy has been discontinued. An abnormal reactive healing response, or cystic degeneration, may be responsible for our case of the rupture that occurred 6 months after ciprofloxacin therapy was discontinued*".

It follows: "*Our cases add to the anecdotal evidence suggesting a causal relationship between fluoroquinolones and tendon rupture. Additionally, these cases highlight the broad nature of tendon ruptures that may be associated with this class of medications. Tendons other than the Achilles may be affected by the use of fluoroquinolones. Furthermore, a considerable delay may exist between the administration of a fluoroquinolone and the spontaneous rupture of a tendon. In one of our cases, the delay was 6 months after completion of a course of ciprofloxacin. However, evidence from previous reports suggests that such a delay is possible. The rat model shows that fluoroquinolones may produce inflammation of the tendon within 1 day after their administration. An abnormal healing response to fluoroquinolone-associated inflammation, or cystic degeneration may produce effects months after completion of even a short course of a fluoroquinolone*".

The conclusions were: "*Fluoroquinolone-associated tendon disruption, including rupture, is well described in the literature. Although the Achilles tendon is the most susceptible site, other tendons may be affected. Typically, spontaneous tendon rupture occurs during or shortly after a course of therapy, but symptoms may occur months after taking fluoroquinolones. Whether fluoroquinolones should be used in patients with a history of tendon problems or with risk factors for the development of tendon ruptures depends on the seriousness of the infection and the alternatives available. Awareness of the association between tendon disorders and fluoroquinolones may lead to enhanced surveillance, which should be extended to sites beyond the Achilles tendon and to periods of months after a course of these antibiotics*".

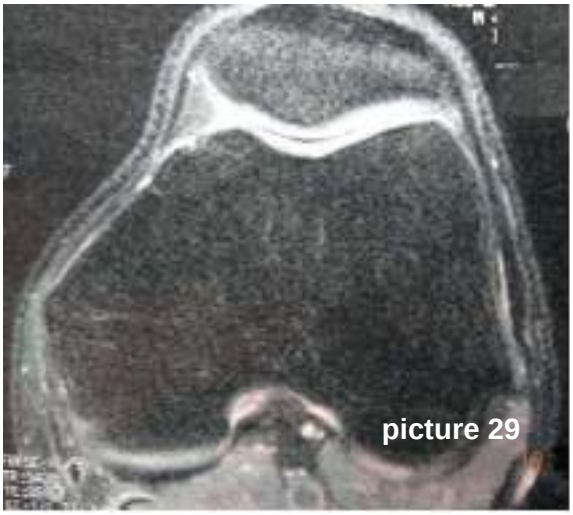


Other problems diagnosed by means of MRI's to the floxed persons that participated in the creation of this flox paper include (for the ankle):

- tendinitis of the achilles
- tendinitis of the posterior tibial tendon, flexor digitorum and tibialis anterior
- tenosynovitis with inflammation of the tendons sheath
- synovial infiltrate on tendons
- stenosing tenosynovitis in one or more major tendons
- partial ruptures of one or more of the major tendons
- tendon cysts

Figure 28 (with permission; sorry for the low quality of the file received). Look what "*mild*" tendinitis and tenosynovitis look like in a young healthy athlete three years and three months after unnecesary exposure to quinolones for a minor suspected bladder infection. Here, you (or your doctor) can see some fluid accumulation and paratendon engorssment in the posterior tibialis

tendon and flexor digitorum longus. It is a cross section of the ankle, with the achilles tendon in the lower right side of the picture.



And in the following sequence of a MRI plane of a knee, you can see the irreversible injury caused by ciprofloxacin to a young and previously healthy young man.

This is a cross (figure 29) *(with permission)* section of the knee of a floxed athlete 41 years old, that have never had any problem before, completely attributable to ciprofloxacin. He also has a MRI taken one year before the intoxication with quinolones, taken as a volunteer for a rutinary study for leg alignments and gait analysis. So there is proof that no problem existed before.

In this image, the central dark item is the femur close to the knee. The upper oval shape is the patella. The two white stripes that appear in the contact between the patella and the femur are the cartilages of both bones. The signal of the cartilage of the patella is engrossed and diffuse, indicating that a first grade osteoarthritis has developed.

143.CLASSIFICATION CRITERIA FOR THE LOWER LEG

(As an example, for classification purposes, we have established a scale of severity of the tendinitis and joint problems, used to make entries in the research diaries).

The severity of the physiological performance of any given part of a floxed body is graded according to its functionality. For instance, Grade 1 corresponds to the normal state, and Grade 9 to the pre-rupture of tendons.

TABLE 22. CIPRO INDUCED TENDINITIS	
SCALE OF GRADES OF SEVERITY FOR THE LOWER LEG	
GRADE	ACTIVITY RESTRICTIONS (expressed as the maximum activity tolerated)
G1	No limitations. Full sports intensity. (Normal state). There is a limited endurance in comparison with normal levels previous to the floxing.
G2	There are limitations of intensity or duration of athletic activities. Maximum of 2-3 times per week for no more than 45 minutes each time.
G3	Only isometric, symmetric (no lateral displacements) and non-impact sports. Avoid sudden starts and stops. Avoid especially eversion and inversion movements of the ankle. Need for a good warm up before exercising.
G4	Sports play very restricted. Jogging in straight line only, no hard surfaces and level ground. Only short periods of activity allowed very few times per week.
G5	Brisk walk with no limitations, including uneven ground. No uphill downhill hiking. Only real sports possible = swimming and stationary bicycle. No sports with weight bearing.
G6	Sports forbidden at all. Not even stationary bicycle. It is not possible to walk briskly. Can walk for up to two hours but not fast.
G7	Sharp and intense pain with many movements of the leg. Difficult or impossible driving. Daily activity very limited. Walk with a limp. Pains of different sorts with or without activity.
G8	Claudication. Normal activities impeded. No driving. Very painful walking. Limitation of any foot movement. Pain palpable. Possible dark areas in skin. Limping.
G9	Bearing weight impossible. Crutches in both arms mandatory. Foot immobilization. Pain with the smallest movement, stabbing, cutting, tearing, unbearable. Pain under pressure. Hematomas.
G10	Tendon rupture or partial tear.

NOTE: "it is not possible" really means that perhaps it is physically possible but the consequences afterwards would be a sharp worsening of symptoms, or moving to a scale higher in grade.

A floxed athlete is constantly moving from one grade to another, depending on the ingestion of more

quinolones, activity level and time elapsed since last ingestion of quinolone antibiotics. Cycling of symptoms keeps floxed persons moving up and down the scale. In many cases, grade 1 is never recovered again, but instead a low, functional grade is maintained.

In intermediate reactions, the floxed person moves up and down the scale many times, with a clear tendency towards recovery. For severe reactions the floxed person is always between grades 3 and 9 for many years, reaching rapidly grades G6 and G7 after limited strenous exercises, even 4 and 5 years postfloxing.

We have used other similar tables for neurological issues when preparing this report. Similar tables can help you to trace your evolution.

144. MUSCULAR DYSFUNCTION: A TREACHEROUS SEQUELAE

As repeated before, all severe reactions come with a neurological damage and many small axons and neuromuscular connections are destroyed, so many muscles do not function properly. The damages are not so profound as to cause very visible wasting of the muscles, but instead there is a marked loss of function, lack of strength, loss of muscular mass and maybe muscle destruction (cases with high blood's CPK and aldolase). This damage tends to be fairly asymmetrical.

The inability of some muscles to perform their tasks causes great neurological pains when tendons, joints and nerves themselves are forced to do a job for which they have become too weak. Many doctors are unable to detect this lack of stength manually and by exploration only. But athletes know their bodies too well and it is easy for them to point out the areas of disability. Special mechanical tests can measure the drop in strength of many muscles, but they are often not necessary because many physical therapists can diagnose the disorder quite well.

For instance, a severe floxed athlete can have one weak vastus medialis plus the gluteus minimus, and perhaps the central hamstrings. This condition will increase his knee pains a lot, and also his neurological, shooting pains, when attempting movements with leg abduction, and running and walking in general will be much impaired.

Electrical stimulation from the 3rd year on is advisable for those muscular groups that are weak. The electrical stimulation can do nothing in terms of reversing the necrosis or dying off of the axon ends that cause muscular dysfunction, but it can increase the strength of the surrounding fibers a lot, and thus the overall muscular area regains some functionality that causes the pain levels to drop a lot, which allows the floxed person to regain some functionality, sleep better, perhaps have less fasciculations and live with less disability. Nevertheless, not even the most agressive electrostimulating therapies are able to bring floxed muscles back to normal condition, so they remain atrophied. As mentioned before, for a person with a strong intoxication by quinolones, it is not possible to build up muscle no matter how hard they try to exercise. Unfortunately there are some disadvantages and too many electrical discharges on the muscles can cause some breakdown and increase the CPK levels for several days.

In severe reactions, one of the best and most sensitive indicators of recovery is regaining muscle normalcy, which means normal strength and volume gain in response to exercise training.

The advantages of physical therapy are controversial for the general floxed population, but have to be seriously considered by all former athletes. It could aim for the following targets:

- removal of toxins under the skin (gritty, bumpy epidermis)
- release the adherences of the fascial layers of connective tissue between muscles
- alignment of tendon fibers
- smoothing of tendon sheaths and relieving stenosing points

- increasing or maintaining the range of motion of joints
- inactivating the myofascial trigger points
- increasing muscular tone

Stretching has to be done carefully. Some stretches pose a lot of stress on the cartilage of joints and normally it is already softened by the intoxication, so scars, grooves, ruptures and deep erosions can occur, whereas that would be impossible to happen in your body prior to the floxing.

PART XX: THERAPEUTICAL APPROACH TO FLOXED TENDONS

We refer here to the potential treatments for floxed tendons, ligaments and cartilages. In fact, nobody knows any therapy with proven eficcacy. So we only make a survey of different supportive measures that can be of some help in very specific cases only.

While it is true that tendinitis is among the group of permanent injuries caused by fluoroquinolones, it is also certain that most people do not take the doses needed to get severely hit and do recover, as it has been discused before.

145. SURGICAL APPROACH TO THE FLOXED TENDONS

We know people that have been suffering from very debilitating quinolone-induced elbow epicondylitis for 7 years. It is a tendon for which quinolones show a predilection. Some doctors are for a surgical intervention. We believe than in severe cases there are so many tendons so much affected that surgery had to be performed on several tendons of almost every joint, rendering the method virtually inviable. The following report, as it corresponds to a french translation, uses the term "lesion" as a synonim of injury.

> EPICONDYLITIS AFTER TREATMENT WITH FLUOROQUINOLONE ANTIBIOTICS
> JC Le Huec, T Schaeverbeke, D Chauveaux, J Rivel, J Dehais, and A Le Rebeller
> We report two cases of epicondylitis of the elbow occurring after treatment with fluoroquinolone antibiotics. Both patients had intense pain which appeared very shortly after the first dose of the drug and was not relieved by conservative treatment. Ultrasonography revealed extensive inflammatory lesions with **pseudonecrotic** areas. MRI confirmed the lesions and also showed a subclinical abnormality of the adjoining tendons. The persistent nature of the pain was the indication for surgical release of the extensor mechanism. After operation pain disappeared completely and the patients were able to return to their normal activities. Injuries of the tendo Achillis are a well-known side-effect of treatment with fluoroquinolone. Our two cases show that such lesions may occur elsewhere. They also indicate the need for caution when prescribing these antibiotics to patients at risk of tendon lesions, such as top-level sportsmen or patients on dialysis or steroid treatment.

146. NUTRITIONAL APPROACH TO FLOXED TENDONS AND CARTILAGES

There are some authors (Olzi and others), that have compiled proposals to approach the healing of the connective tissue of normal people through nutrition (foods and supplements).

For floxed persons things are different, because the damage is chemical and antinatural, but probably for mild reactions the following tips could constitute a program that would aid in healing. For severe floxed persons, none of the following advices has made any difference, and might even have a negative impact on symptoms.

146.1 Calories

Many studies demonstrate that collagen production is sensitive to changes in short and long-term food intake. Within 24 hours of fasting of some animal models, collagen synthesis in articular cartilage decreases to 50% of normal. Specific effects of malnutrition on connective tissue turnover are dependant

on many factors such as exercise activities, injuries, and disease. Replacement of tissue pools of macronutrients requires weeks to months and certainly affects turnover rates of tissue components.

Calories provide the body with cellular energy for normal metabolism, building and repairing tissues and stimulate hormonal responses. Individuals with injuries or other trauma should avoid a decrease in calories below maintenance or slightly above, thereby providing the nutrients and energy needed for healing and repair.

146.2 Protein

Muscle tissue provides a steady source amino acids for general body needs. Connective tissue is the second source, which is reflective of the relative rate of turnover to muscle tissue. Many studies have demonstrated that a protein deficient diet results in a reduction of growth and development of the organism as well as delay in wound healing and repairs.

All of the essential aminoacids are required for synthesis of proteins and other components and growth factors in the extracellular matrix. Some studies show that supplementing certain individual aminoacids (methionine, lysine, arginine, and proline) to a protein deficient diet may inhibit prolongation of the inflammation phase of connective tissue healing and aid in fiber cross-linking mechanisms during repair.

Unfortunately, as it is discussed later, supplementation of floxed persons with arginine or lysine is controversial with at least as many negative reports as positive ones.

Although countless studies demonstrate that protein malnutrition is significantly detrimental to normal turnover and healing of connective tissues, floxed persons do not normally restrict protein intake, unless they are strictly vegetarian and consume incorrect proteins like the one derived from soy.

146.3 Carbohydrates

Aside from protein, carbohydrates are a major component of an athlete's diet and supply quick energy for the body in the form of glucose. Although little information exits on the direct effects of glucose deficiencies on connective tissues, it is well known that glucose is an energy source for several components and growth mediators. Tissue cells such as fibroblasts and chondroblasts require glucose for synthesis of various macromolecules. Glucose is a building block of glycosaminoglycans and glycoproteins in the ground substance of the matrix. Arguably, hypoglycemia (abnormally low level of plasma glucose caused very frequently by quinolones) impairs normal cell function and delays wound healing. As well, production and release of several hormones, such as insulin and growth hormone, decline with low levels of plasma glucose further delaying tissue growth and repair. There is a suspicion that treating floxed persons with controlled combinations of growth hormone and anabolic steroids, could contribute to a quick healing process.

Conversely, high levels of plasma glucose (hyperglycemia, also caused frequenly by quinolones) may also be detrimental. Decreased insulin function may lead to hyperglycemia which also impairs wound healing. This is consistent with the high intolerance that many floxed persons develop to sugar and all kind of sweet foods.

High levels of plasma glucose reportedly may inhibit the stimulatory action of ascorbic acid on proteoglycan and collagen production. Furthermore, chronic high plasma and tissue glucose levels produce advanced glycation products that affect the physical, chemical and mechanical properties of collagen and elastin protein.

Diets low in carbohydrates typically cause body water loss. For athletes, the resultant dehydration may compromise integrity of connective tissues subject to mechanical loading. Considering that many connective tissues such as in articular joints require a relatively high water content for optimal functioning under stress, dehydration may increase incidence of injury or jeopardize healing and repair of injured

tissue. Hence the importance for floxed persons of taking a lot of good quality water, but avoiding all sort of excesses in order to avoid the negative effects of too much water intake that for a floxed person can mean an increase in central nervous system symptoms, among other unwanted effects.

146.4 Fats

Saturated fats are commonly found in animal foods and in some vegetable plants and have little direct import in the physiology of connective tissue. However there are influences of polyunsaturated fatty acids on injured connective tissue.

The major polyunsaturated fatty acids are classified as two types: n-3 and n-6 polyunsaturated fatty acids. The n-6 family is the major polyunsaturated fatty acids in cell membranes and is derived from vegetable oils. Low levels of n-3 polyunsaturated fatty acids exist in most individual cell membranes because diets are generally low in fish oils which are the source of this polyunsaturated fatty acids family. Polyunsaturated fatty acids are precursors for a family of hormones called eicosanoids, which are released by macrophages and other cells and mediate many cellular functions. The major role of eicosanoids is in the inflammatory response; therefore, dietary polyunsaturated fatty acids may moderate the length of the inflammatory phase.

A relative excess of n-6 polyunsaturated fatty acids stimulates production of prostaglandin E2 which may prolong the inflammatory response. Although increasing intake of n-3 polyunsaturated fatty acids may not impact acute inflammation, such nutritional support quite possibly moderate long-term inflammation related to excessive prostaglandin E2 production and cytokine release from activated macrophages.

146.5 Vitamins

VITAMIN C (ascorbic acid)
Of all the vitamins, ascorbic acid probably has the most influence on connective tissue metabolism and has been the most studied.

In connective tissue, ascorbic acid is involved in several metabolic reactions. Iron is necessary for a variety of enzymatic reactions, and ascorbic acid protects iron from oxidation. Vitamin C preserves the enzyme-iron complex that catalyzes the reaction for intracellular assembly of collagen. Increased intake of dietary Vitamin C may prevent inhibition induced by high glucose (as seen in quinolone induced hyperglucemia) on collagen and proteoglycan synthesis.
In addition to collagen, the influence of Vitamin C extends to proteoglycans. The most commonly known role of Vitamin C is as an antioxidant. Vitamin C supplementation in surgical and non-surgical patients resulted in improved wound healing, reduced inflammation and improved recovery.

Always be aware of the toxic effects or large quantitites of any vitamin. In particular, Vitamin C excess can cause, among other disturbances, kidney stones, increased iron absortion leading to iron overload and liver problems, erosion of dental enamel, increased oxygen demand and pro-oxidant effects.

VITAMIN B COMPLEX
The B vitamin complex is a large group of compounds with different structure and biological activity. They are usually found within the same food sources. The primary role of the B vitamins is cellular energy metabolism. Any deficit in cellular energy will have adverse effects on cellular function. Therefore, the B vitamins are essential in connective tissue metabolism.

Many of the B complex serve as cofactors in process of collagen and elastin cross-linking. Deficiencies in several of the B vitamins influence expression of collagen genes and induce decreased mechanical strength of repaired and remodeled tissue.

Since most all B vitamins are found together in similar food groups, deficiencies of one singular vitamin is uncommon. However, deficiencies may exist if overall dietary intake is reduced. A mixture of all B vitamins

should adequately provide for daily needs.

Always be aware of the toxic effects or large quantitites of any vitamin. In particular, Vitamin B1 excess can cause, among other disturbances. Niacin excess can be hepatotoxic (liver toxicity). Vitamin B6 excess causes NEUROPATHY. Vitamin B12 excess may cause insomnia, leukemia, kidney damage and also hypertiroidysm.

VITAMIN A

Retinoids are a group of compounds of which some have vitamin A activity and others do not. Vitamin A is often referred to as retinol in much of the literature and will be used interchangeably here. Although carotenoids are commonly mistaken for vitamin A, only a fraction of them have any vitamin A activity. b - Carotene is the most significant because in the body it can be broken down into two retinol molecules and therefore supply vitamin A when needed. Retinol is stored in the liver and distributed to peripheral tissues by strict regulatory mechanisms and metabolized in several pathways.

Retinol is converted to retinoic acid inside cells and both are potent regulators of specific genes, including expression of fibronectin and type I procollagen. Other metabolites of retinol regulate cell differentiation and are associated with glycosaminoglycan, glycoprotein and proteoglycan synthesis. Although still unclear, the role of vitamin A in proteoglycan synthesis may be involved in sulfation of glycosaminoglycan s. Tissue from animals deficient in vitamin A typically displays decreased synthesis of highly sulfated glycosaminoglycan.

Few in vivo studies exist documenting specific roles of retinoids in connective tissue, except for those studying wound healing in animal models. That rapidly growing tissues are sensitive to vitamin A deficiency is well known. Deficiency of other nutrients, such as zinc and protein, that assist in transport and metabolism of retinol may induce deficiency symptoms. Therefore, since retinol distribution from the liver is tightly regulated, functional deficiencies may result with normal vitamin A intake and stores. Additionally, extra-physiological doses of vitamin A may counteract the inhibitory effects of systemic corticosteroids on plasma retinol transport.

Because vitamin A is fat-soluble, toxicity is also a concern in connective tissue metabolism. High levels may inhibit collagen synthesis, as seen in the skin, and increase catabolism of cartilage. This may be concentration dependent since excessively high levels affect ascorbate induced lipid peroxidation, which in turn inhibits vitamin C-induced collagen synthesis.

Always be aware of the toxic effects or large quantitites of any vitamin. In particular, Vitamin A excess causes liver abnormalities and is teratogenic for the foetus. It also causes blurred vision, muscular incoordination, nervous system changes anb bone and skin abnormalities. In fact we recommend you to avoid any kind of supplementation with vitamin A above the daily recomendation of just one milligram (1 mg).

VITAMIN E

Vitamin E is a group of compounds comprising of two major classes: tocopherols and tocotrienols. The basic chemical structure in each class is similar with variations of substituents and confirmation resulting in different relative activity. We use the term vitamin E as a reference primarily to the tocopherols, as they have the greatest activity in the body.

Literature information on the role of vitamin E in connective tissue metabolism is controversial. The major function of vitamin E is as an antioxidant and in the maintenance of cell membrane integrity. Its role as an antioxidant is thought to require vitamin C and selenium. Although no specific disease of connective tissue can be attributed to vitamin E deficiency, it is no doubt needed for life and cell processes.

Animal model studies have shown that severe deficiency in vitamin E influence collagen cross-linking and an increase in susceptibility of insoluble collagen to degradation by proteinases. Conversely, excessive doses of vitamin E elicit effects similar to those of corticosteroids: inhibition of collagen synthesis and

wound repair. Rats given supra-physiological doses of vitamin E exhibited less tensile strength in skin of healed wounds. Indeed, vitamin E may potentiate adverse effects of corticosteroids. We do not recommend to take supplemented vitamin E to treat a floxing because some floxed persons have reported increased hemorrhages probably due to the injuries of the small blood vessels caused by cipro and levaquin.

Vitamin E has exhibited anti-inflammatory effects in some animal models. As an antioxidant, vitamin E may protect lysosome membranes leading to a decrease in histamine and serotonin from mast cells during inflammation. However, studies show that the vitamin E has a preventative role rather than therapeutic. If sufficient vitamin E is present before inflammation response is initiated, the inflammatory phase may be shortened. Apparently, therapeutic administration (i.e. administration after the induction of inflammation) did not affect duration or progress of the inflammation phase. Thus perhaps optimal results may be seen only in individuals with degenerative joint conditions or with chronic inflammation.

Always be aware of the toxic effects or large quantitites of any vitamin. In particular, Vitamin E excess causes an increased tendency to hemorrhage.

The role of vitamins as an aid during the recovery of a floxing is treated again later on the report.

146.6 Minerals

Minerals are required for normal cell function and several serve as cofactors in the many enzymatic processes involved in synthesis connective tissue macromolecules. Copper and manganese are critical cofactors for collagen and glycosaminoglycan synthesis and metabolism. Some recent research alludes to an increased role of manganese in synthesis of glycosaminoglycans. However, a deficiency in these minerals is extremely rare. Some pharmaceuticals are known to negatively interact with some minerals. Nonetheless, defects in collagen synthesis are generally observed only at the lowest levels of dietary intake of most minerals. An athlete eating a diet with adequate protein and calories is likely to have normal levels of minerals.

Clinical evidence is largely lacking for effects of mineral deficiencies on connective tissue except for zinc. This mineral primarily acts as cofactor in many enzyme systems that regulate cell proliferation and growth and in immune integrity. Diminution of collagen synthesis and strength as well as impaired healing is seen in animal tissues with zinc deficiencies.

Controversy exists in whether supplemental zinc can accelerate healing above the normal rate. Several supplement companies in the sports marketing arena claim that most athletes are deficient in this mineral. However, total body assessment of zinc is not easily obtained and many published studies have erroneously relied on data interpretation from zinc plasma concentrations in humans. As well, most studies do not measure plasma concentration versus time to assess fluctuations.

Zinc exists in intracellular and extracellular pools and its exchange in the body is tightly regulated. Many factors influence tissue pool concentrations, such as absorption, oral contraceptives, and steroid therapy. Nonetheless, a well-nourished athlete with a healthy intake of animal protein, fruit, vegetables and a vitamin/mineral supplement is unlikely to be deficient in zinc. Populations who may exhibit deficiencies are the elderly, those with malabsorption, and lactovegetarians who consume large amounts of foods with phytates.

Zinc excess may cause impairment in the inmune responses and neuropathy. Selenium excess is noticed primarily by the loss of hair and by nail brittelness; it also disturbs the nervous system. High doses of manganese are neurotoxic.

Magnesium, the big icon of floxing treatments, taken in high doses may cause serious cardiac and neurological symptoms.

The role of minerals as an aid during the recovery of a floxing is treated again later on the report.

146.7 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, such as aspirin and ibuprofen, are routinely administered to treat connective tissue injuries. The anti-inflammatory and analgesic properties of these drugs are effectively employed for short-term relief. The immediate action of NSAIDs is due to decreased prostaglandin E2 synthesis by inhibition of cyclooxygenase (the rate-limiting enzyme involved in prostaglandin E2 synthesis).

Despite the efficacy of NSAIDs to reduce inflammation and pain, several in vitro and in vivo animal studies suggest that chronic use of some NSAIDs may promote degradation of articular cartilage. In vitro studies with several NSAIDs, such as aspirin, fenoprofen, and ibuprofen, reported inhibited net proteoglycan synthesis by chondrocytes in normal and osteoarthritic cartilage. Inhibition was concentration-dependant; however, effects were more profound in cartilage from osteoarthritic subjects. This suggests that cartilage degeneration in arthritic patients could be accelerated with NSAID treatment.
Consequently, avoidance or short-term use of NSAIDs is increasingly favored by care-providers in connective tissue injuries. Less-hazardous use of acetaminophen may be effective, although long-term use can be hepatotoxic. Most NSAID research has focused on articular cartilage with few studies examining effects on dense connective tissue (i.e. tendons and ligaments). NSAIDs may have an effect on early stages of dense tissue repair, although significant inhibition of healing has not been documented.

This is the influence of NSAIDs on the healing of connective tissue, but there is another aspect to be taken into account and it is the increased chance of having central nervous system abnormalities if NSAIDs are used during a quinolone treatment, and also for a period afterwards. Small doses of NSAIDs are not fully contraindicated in not severe floxings.

146.8 Corticosteroids

Anti-inflammatory steroids, such as cortisone, hydrocortisone and prednisone, may be administered systemically or by injection into connective tissue such as in the synovial cavity of a joint. They act by suppressing the immune response: preventing the migration of inflammatory cells and stabilizing the lysosomal membranes in cells thereby inhibiting the production of prostaglandins. This suppresion of the inmune response is considered by most doctors as crucial in order to stop a reaction to a quinolone. There are many medical records that show how -apparently- acute reactions to quinolones were stopped by a corticosteroid. We do not know whether those positive effects would also work in insidious delayed reactions.

In addition, corticosteroids also inhibit fibroblast proliferation and collagen and glycosaminoglycan synthesis resulting in compromised wound healing. Short-term intra- and periarticular administration of low-dose steroids has not been documented to cause serious complications in normal individuals. However, reports of tendon ruptures, bone necrosis, accelerated joint destruction, impaired wound healing and metabolic disturbances have been reported with prolonged usage.

Lymphocytes and neutrophils (inflammatory cells) may directly influence macromolecule turnover and promote collagen deposition and proteogycan synthesis. Arguably, inflammation is an integral part of the healing process. Thus, by their very actions as anti-inflammatories, corticosteroids and NSAIDs may delay or impair the repair and remodeling process. Instead, treatment of inflammation during injuries should be considered as "managed inflammation": relying on alternative means for pain relief (acetaminophen, ice packs and reduced activity) during the acute inflammation phase, and proper subsequent treatment depending on the nature of the injury.

For quinolone-induced injuries NSAIDs and corticoids are not a good choice. Corticoids are always a bad choice once the acute phase has ended, save if other inmunological illnesses coexist.

146.9 Anabolic Steroids and Growth Hormone

To take anabolic (build-up) androgenic (pro masculine) steroids is a therapy that has been reported by a few cases of floxed persons with positive effects according to their account. Anabolic steriods have to be taken in very precise amounts, with a well studied combination of different hormones, that may include Human Growth Hormone and for short periods of time. They are not free from risks, so a close surveillance of body functions is essential.

A lot of research is missing in this area, and we are looking forward to hearing of more experiences of this kind supervised by a doctor.

146.10 Chondroprotective Agents

Although claims that chondroprotectors alone may cure joint diseases or completely prevent injury are surely misguided, they may indeed prove worthy as adjunct therapy. Nearly all of the human research focuses on osteoarthritis, with little, if any, addressing other connective tissue such as ligament and tendon maladies.

Several classes of compounds are referred to as chondroprotectors, with varied chemical structure and effectiveness. The osteoarthritis research focuses mostly on delayed cartilage breakdown and stimulation of cartilage regeneration, with concomitant alleviation of symptoms such as pain, stiffness, etc. These compounds may be administered by injecting into the articular joint (intra-articular), like hyaluronate, intramuscularly (into the muscle), or orally (MSM and others).

None have been still proved useful in quinolone mediated reactions, but we included here some excerpts of the work of Olzi for basic reference of not so strongly hit victims of quinolone intoxication.

HYALURONATE

Sodium hyaluronate is a high-molecular-weight polysaccharide manufactured from bacterial fermentation. Synovial fluid contains hyaluronic acid as a natural lubricating and cushioning substance. It is also a very integral component of articular cartilage proteoglycans.

Because hyaluronate is not well absorbed orally, intra-articular injections of highly-purified hyaluronate aim to restore the fluid properties of the extracellular matrix in arthritic joints. Although the mechanisms of action are not clear, scientists posit that hyaluronate modulates several cellular functions thereby reducing inflammation and pain response.

The floxed athletes that have tried it reported some relief, rated as moderate to high, that lasted some 4 to 6 months on average. Some underwent repetitive treatments for 18 months or so (up to four treatments).

GLUCOSAMINE

Until recently physicians have relied mostly on symptom alleviation to restore a degree of normal mobility and function to patients with osteoarthritis and other joint degenerative diseases. Search for new treatments has focused on substances that might enhance synthesis and inhibit catabolism of matrix components.

Glucosamine is a naturally occurring amino-sugar synthesized by chondrocytes from glucose. Most glycosaminoglycans contain glucosamine: heparin, hyaluronate, keratan sulfates. Results from human trials demonstrate that glucosamine may produce a gradual and progressive reduction in joint pain as well as an increase in joint mobility and function with no toxicity. There is increasing evidence suggesting that glucosamine may provide therapeutic benefits for individuals with osteoarthritis.

CHONDROITIN SULFATE

Chondroitin sulfate ("chondroitin") is found in many tissues in the body such as tendon, bone, and eye

cornea. Additionally, chondroitin is the most abundant glycosaminoglycan in articular cartilage. chondroitin has been demonstrated in vitro to inhibit several degradative enzymes that destroy cartilage and exhibit anti-inflammatory activity. Therefore, authors postulate that chondroitin has a protective effect rather than an anabolic effect as seen in glucosamin.

Similar to glucosamin studies, chondroitin has been demonstrated in clinical trials to increase movement as well as decrease pain and use of NSAIDs in human oestoarthritis patients. As in the case of glucosamine, the therapeutic response to chondroitin is gradual, appearing weeks after beginning of therapy. Exogenous glycosaminoglycans require prolonged periods of treatment because the compounds must enter into the metabolism of the joint cartilage. Nevertheless, the clinical improvements persist after stopping treatment. As well, patients report few side effects.

GLUCOSAMIN AND CHONDROITIN

Although studies report beneficial results from using the two glycosaminoglycans singly, some authors speculate that combining the two glycosaminoglycans are synergistic.

Although no short-term toxicity has been reported, long-term safety of glycosaminoglycans needs to be investigated. Although few side-effects in humans have been reported, glycosaminoglycan effects on patients with underlying diseases should be examined, especially diseases affecting coagulation. Thirdly, no studies have examined their use in other forms of arthritis or other connective tissue maladies.

The standard daily dosage for glucosamine is 1000-1500 mg and 800-1200 mg of chondroitin sulfate divided into 2-3 dosages. A loading dose is recommended for a minimum of two months. Most individuals should see an improvement in eight weeks or less. Thereafter, daily maintenance dosages may be reduced to 500 mg GA and 400 mg of CS or more, depending on disease status. Two other compounds that are frequently used with glycosaminoglycans are manganese and vitamin C. Manganese is a mineral that serves as a cofactor in biochemical reactions in joint connective tissue metabolism, such as glycosaminoglycan synthesis. Deficiencies of manganese result in formation of abnormal bone and cartilage. However, evidence of efficacy of manganese in osteoarthritis is lacking.

Questions raised by individuals with diabetes address the safety of glycosaminoglycan use. Abnormal glucose metabolism is a very common side effect of fluoroquinolones, and not few symptoms of diabetes are also shared by the Quinolone-Toxicity-Syndrome (for instance the vision disturbances, sugar intolerance, and all kind of neuropathies, specially peripheral neuropathies). As a result, there is som concern too that glucosamine may harm floxed people. Although glucosamine and chondroitin are classed as carbohydrates, the body does not break them down into glucose. Consequently, they will not raise blood sugar levels by providing a source of glucose. However, since many factors can affect insulin secretion and blood glucose levels in QTS (quinolone toxicity syndrome) patients, those who use glycosaminoglycans should be alert and watch our for worsening of symptoms or new or increased side effects.

147. RECOMMENDATIONS FOR FLUOROQUINOLONE TENDINITIS

It is very difficult to try to give any advice for a lost case, as a severe quinolone-induced tendinitis is. Nevertheless, the following tips may help some people to lay a plan of recovery.

The only way out of a strong quinolone induced tendinitis is:

AVOID REEXPOSURE THROUGH FOOD.

It is an obvious measure. If you have suffered a severe reaction and still get some quinolones through food, your tendinits are going to be your companions forever.

CONSERVATIVE THERAPIES.

The preferred are skin rolling, self-massage, range of motion exercises, ice at acute episodes, some restriction of activities but not inmobilization save ruptures, alignement of

fibers with steel hook, myofascial release, Graston techique and stretching,, sometimes up to the point of agressive progressive stretching. It also has a high ratio of efficacy the watertherapy (exercises in water). Additionally you might consider taking some of the vitamins and supplements explained above.

STRENGTHENING OF MUSCLES.

This is the key to healing a floxed tendon or at least to recover its functionality and stop most of the pain, because a truly floxed tendon is degraded for many years. All antagonist muscles have to be strengthened to relieve stress of the affected tendons. For each tendon affected, you have to find out which muscles have become neurologically unable, forcing the tendon to be overloaded, and correct the situation. There is no way round. Few floxed persons realize this fact.

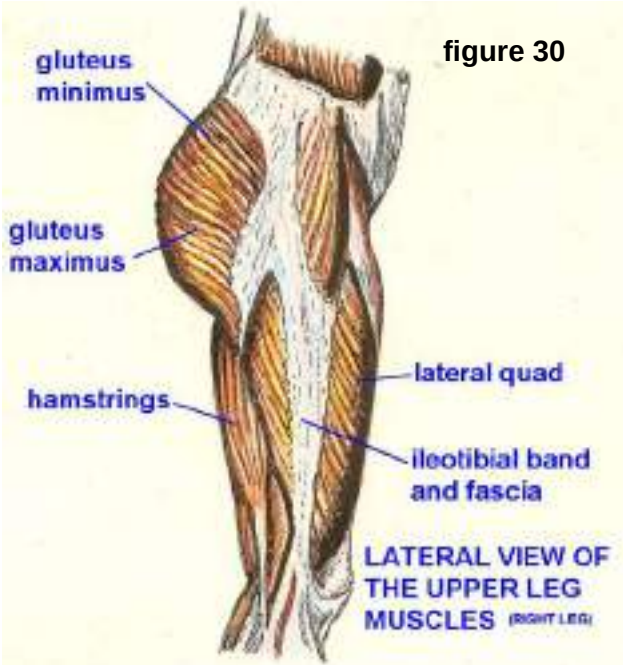


figure 30

TIME.

The only real quinolone healing. Allow a couple of years for specific reactions (reactions that affect almost exclusively tendons); three or four years for more general intoxications and six, seven or more years for severe reactions.

As you will read somewhere else in this paper, fish oil seems to increase a lot every kind of joint pain. We do not know how much the vitamin E that is normally added to the oil contributes to this unwanted effect, but surely is the cause because fatty fish (organic salmon, wild sardines) does not cause this problem. As for nutraceuticals, glucosamine and condroitin sulphate seem to be useless in severe cases, as well as hyaluronic acid. For less strong reactions they decrease pains and might be considered among the supplements to take. Anetholtrithione has not shown efficacy yet for long term floxed persons, although a proper trial is still pending. But in general, this drug helps a lot with the range of motion, lessens the pains, and decreases anxiety, so it can be of help for some QTS (Quinolone-Toxicity-Syndrome) victims.

Once you have overcome the acute phase of any tendinitis, inactivity can help you to get a fictional but very nice feeling of being rid of tendinitis. Hoewer, once you have reached an state in which you do not feel tendinits when you are inactive for long periods, you may be still three years away from a real healing.

Future editions of this report probably will profundize on this issues:

-Some notions on joint anatomy and pathophysiolology of the musculoskeletal system.
-Specific exercises for the most commonly affected tendons.
-Images of professional therapies being performed.
-Stretches for specific tendons.
-Other areas of interest that are demanded by readers and fall within our aim and reach.

The following article would suggest that exercise, after all, can play a positive role in the healing process of a flox-degraded extracellular matrix:

ROLE OF EXTRACELLULAR MATRIX IN ADAPTATION OF TENDON AND SKELETAL MUSCLE TO MECHANICAL LOADING. Kjær, Michael. *Physiol Rev* 84: 649–698, 2004;
The extracellular matrix (ECM), and especially the connective tissue with its collagen, links tissues of the body together and plays an important role in the force transmission and tissue

structure maintenance especially in tendons, ligaments, bone, and muscle. The extracellular matrix turnover is influenced by physical activity, and both collagen synthesis and degrading metalloprotease enzymes increase with mechanical loading. Both transcription and posttranslational modifications, as well as local and systemic release of growth factors, are enhanced following exercise. For tendons, metabolic activity, circulatory responses, and collagen turnover are demonstrated to be more pronounced in humans than hitherto thought. Conversely, inactivity markedly decreases collagen turnover in both tendon and muscle. Chronic loading in the form of physical training leads both to increased collagen turnover as well as, dependent on the type of collagen in question, some degree of net collagen synthesis. These changes will modify the mechanical properties and the viscoelastic characteristics of the tissue, decrease its stress, and likely make it more load resistant. Cross-linking in connective tissue involves an intimate, enzymatical interplay between collagen synthesis and extracellular matrix proteoglycan components during growth and maturation and influences the collagen-derived functional properties of the tissue. With aging, glycation contributes to additional cross-linking which modifies tissue stiffness. Physiological signaling pathways from mechanical loading to changes in extracellular matrix most likely involve feedback signaling that results in rapid alterations in the mechanical properties of the extracellular matrix. In developing skeletal muscle, an important interplay between muscle cells and the extracellular matrix is present, and some evidence from adult human muscle suggests common signaling pathways to stimulate contractile and extracellular matrix components. Unaccostumed overloading responses suggest an important role of extracellular matrix in the adaptation of myofibrillar structures in adult muscle. Development of overuse injury in tendons involve morphological and biochemical changes including altered collagen typing and fibril size, hypervascularization zones, accumulation of nociceptive substances, and impaired collagen degradation activity. Counteracting these phenomena requires adjusted loading rather than absence of loading in the form of immobilization. Full understanding of these physiological processes will provide the physiological basis for understanding of tissue overloading and injury seen in both tendons and muscle with repetitive work and leisure time physical activity.

148. DELAYED TENDON RUPTURES

You will not find any doctor that acknowledges that your symptoms are still present or developping some months after the cessation of a quinolone treatment. That is plain ignorance. For one of the many fluoroquinolone toxicities (tendon rupture) it is already admitted that it can take place months after the treatment. One day, this will become common knowledge for all the pathologies caused by fluoroquinolones.

RUPTURE OF THE PATELLAR LIGAMENT ONE MONTH AFTER TREATMENT WITH FLUOROQUINOLONE

SAINT F. and others; Lille, FRANCE [translation from french done by us]

The tendinopathies are complications common to all fluoroquinolones. A case of spontaenous rupture of the patellar ligament of a 37 year old athletic man one month after a treatment of 3 weeks with ciprofloxacin is reported by the authors. Several cases of tendon ruptures have been described in the literature, however the reported case is characterized by the long delay of rupture happening after finishing the treatment and the absence of initial pains. The autors describe the physiopathological mechanisms and the risk factors involved in this pathology. They remind that it can be the loads and above all that this treatment needs the avoidance of counterindications and a long term supervision.

PART XXI: PHYSICAL THERAPIES AND ADITIONAL METHODS

Although we suffer a chemically induced damage, and there is no known cure for it, some supportive physical therapies have been proposed by different people. Like with everything else, no consistent results have been recorded, and all therapies have shown beneficial effects for some, nothing for others, and unwanted consequences for the rest.

But not all are so controversial, and certain physical therapies are mandatory for given conditions, like for instance myofascial release for entrapments of nerves within the fascia layers of the muscles.

In this chapter we list some of the most debated therapies, without describing them in detail. For some of them we venture an opinion but it is only you, as always, who has to get all the information, and professional medical help, before starting any program or before rejecting any avaliable treatment.

149. MASSAGE

As said, there are no magic silver bullet treatments and no total agreement about how to treat pains and disabilities. Test the ones that help you most in maintaining your fitness, sanity and well-being. If you were very athletic prior to the floxing, your drama will probably multiply, because all your physical activities will come to an abrupt end for many years. Probably some of the following will help:

- MECHANICAL: ultrasound; massage, especially deep massage and with the aid of steel tools by a specialized practitioner; stretching. They help with the regeneration, realignment of scar tissue and removal of by-products of the reactions. Releasing of the trigger points (entrapment of nerves in muscle bundles) that neurological deficits cause also can bring some temporary relief. Aggressive stretching of limbs affected with neuritis exacerbates neurological pains, and for some 18 hours or so, throbbing stabbing pains can be felt.
- SUPPORTIVE: acupuncture; relaxation, meditation, occasional dry saunas, homeopathy, mesotherapy, gentle yoga. Hyperbaric oxygen can be of help for the first stages of acute musculoskeletal collapses, when people become bedridden.
- EXERCISE: Especially controversial. For some it is positive only after you feel you are getting out of the acute phase: biking and swimming are preferred. Strengthening, especially isometric exercises, and several sports and exercises, should be introduced progressively. Somehow there is scattered evidence that excessive exercise can induce new relapses, which needs future clarification.

Later on in the report, see the section devoted to athletes.

150. STRENGTHENING AND STRETCHING

Is a critical part of any recovery program. They have to be adapted to the specific needs of the areas of the body that are treated. It is not covered in this version of the Flox Report. Most tendon deficits and nerve pains are much increased by weak muscles (due to neuromuscular junction injury), so the need for muscle strength becomes critical.

151. PHYSIOTHERAPY

If the reaction has been strong and the floxed person has many physical limitations as a consequence of the floxing, physical therapy by a good technician, can be of great help. The following case explains the professional approach to a possibly mild case of achilles tendinitis.

> PHYSICAL THERAPIST MANAGEMENT OF FLUOROQUINOLONE-INDUCED ACHILLES TENDINOPATHY. Brenda L Greene
> Probably you can find the whole article at this address:
> http://www.ptjournal.org/cgi/content/full/82/12/1224
> ../..This case report described a patient whose Achilles tendinopathy was an adverse side effect of short-term antibiotic use. It illustrates the importance of awareness of relationships between adverse drug effects and musculoskeletal conditions. This case report also describes a patient's recovery from fluoroquinolone-induced tendinopathy. Decreased load-bearing ability of the tendon suggests that the first phase of rehabilitation should be a protective one. During the first month of rehabilitation with his first physical therapist, this patient's tendon was not protected and his symptoms worsened. Later, the heel lifts, counterforce bracing, and crutch use were all intervention strategies designed to decrease the tensile load transmitted to the Achilles tendon during walking. Although little is known about connective tissue healing subsequent to drug-induced toxicity, the literature does provide insight into connective tissue mutability and response to mechanical stress, in general. Too great a load results in microfailure and potentially macrofailure of the connective tissue, but lack of loading results in connective tissue atrophy and weakness. For this reason, it was necessary to find a balance between loading and unloading the tendon and to progressively stress the tendon over time in an attempt to increase the tendon's ability to tolerate greater stresses. The progressive exercise program was designed to gradually load the Achilles tendon in a controlled fashion. During the first 6 weeks, the patient was able to tolerate minimal progression of the exercise program, but during the last 5 weeks, his ability to resist loading increased weekly.
> ../...By understanding the nature of connective tissue remodeling, the intervention was designed to first protect the tendon and then to progressively load the tendon. During the initial 6 weeks of protection, however, when the tendon was structurally and mechanically altered from the toxic effects of the fluoroquinolone antibiotic, the progression was slow in comparison with the relatively faster initial recovery from acute overuse injuries that I have observed. The patient's improvement was nonlinear in that he made little progress in the first 7 weeks and made rapid progress in the last 4 weeks. In fluoroquinolone-induced tendinopathy, the tendon has the potential to rupture even after the cessation of medication usage.6 Adequate protection of the healing tendon, which lasts until the tendon regains its tension-bearing capacity, probably is important. The time frame for this patient's recovery was consistent with the range stated in Pattern 4D of the Guide to Physical Therapist Practice—2 weeks to 6 months and 3 to 36 visits. His entire recovery process took 5.5 months and a total of 24 physical therapy visits. He had 10 visits with his first physical therapist and 14 visits with me.
> Case reports are a good approach to describe relatively infrequent pathologies, such as Achilles tendinopathy secondary to fluoroquinolone antibiotic use. However, due to the lack of controls in case reports, the experiences with this patient may not be generalizable to other patients and the patient's recovery could have resulted from factors other than the physical therapy intervention.

152. MYOFASCIAL RELEASE

It is not a massage technique properly speaking, If you have suffered a floxing with big musculoskeletal involvement and keep on attempting to exercise vigorously, you are a firm candidate to develop almost intractable trigger points (bundles of muscles, fascia and nerves) if as a consequence of the floxing:

- you have some atrophy, or lack of strength and have problems to increase your muscular mass.
- you have some stiffness and muscle pain specially after exercise (fascia degradation).
- you are lean and fibrous in nature.

Floxed persons develop multiple trigger points, specially if they exercise to be active physically. The trigger poinst develop thanks to two mechanisms:

A. Local injury to tissues causes tearing in the fibers of muscle, tendon, ligaments, and tissue

lining the bone called periosteum. These injuries are caused because muscles have lost part of their strength due to defects at the neuromuscular junction, because connective tissues, specially fascias are degraded and cause stiffness, and because the muscle cells are not served properly due to the degradation of vessels and extracellular matrix. Such tears do not heal due to continuing stress and impaired healing caused by the toxicity of quinolones.

B.Systemic toxicity (accumulation of toxins in all tissues) that creates painful tender points in areas of chronic mechanical stress, such as the back of upper neck, shoulders, lower back, knees, buttocks, legs, and other tissues. Systemic toxicity also causes the formation in the blood of micro-curdles which clog tiny vessels and further impede blood flow and healing.

In many patients these trigger-points (muscles) contain highly palpable ropy cords and are prone to suffer from pain referred from trigger points in the matrix of these cords. The cords behave not as muscle, but as dense fibrotic tissue. The pain referred from trigger points in these cords can best be stopped with ultrasound or negative galvanism. But the relief is brief unless the muscles are stretched what some times is difficult or impossible. So, cross-friction technique with hooks is used to stretch and loosen these muscles (cord bundles).

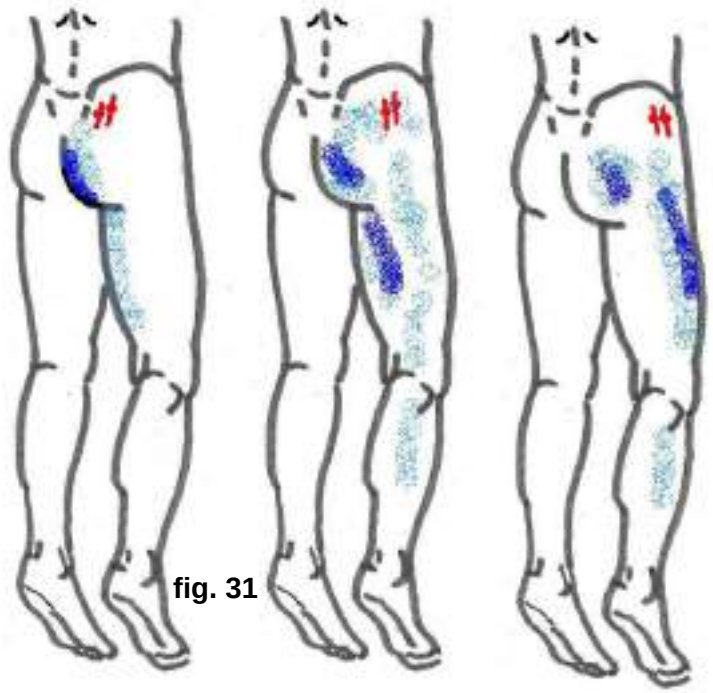


fig. 31

Your trigger points can develop anywhere, but we are to mention only some common ones that are located at the upper buttocks area, specially in the gluteus minimus muscles. Trigger points in these muscles frequently result in well-defined patterns of pain referral that may be variously experienced as “sciatica” pain. This pain can be intolerably persistent and excruciatingly severe. The trigger point source of the pain is deep in the gluteal musculature and almost all of the pain becomes apparent in a remote structure along the leg.

Figure 31 depicted by a therapist that has been treating floxed persons for seven years, based on a drawing by Myosymmetries International Inc.. Red knots are the locations of typical trigger points, and blue areas are the zones where the pain is felt.

An exercise that can help to strengthen the gluteus minimus is to stand on one leg on a Boheler's plate because the primary function of the gluteus minimus is as an abductor (opening the leg) of the thigh, helping to keep the pelvis level during single-limb weight-bearing.

As common as gluteus minimus trigger points in floxed persons are lower back, piriformis and abdominal trigger points.

The treatment for these trigger points is myofascial release, using blunted steel hooks. A severely floxed person may need this therapy for many years.

If your fascias have become degraded by the floxing, it is possible that they also get stuck at some points. If muscles do not move freely with respect to each other, or if a nerve passes through the area where the fascia is not doing its job, it will be compressed, or stretched, or irritated and then very high pains will develop all along the length of the nerve.

CASE REPORT (Real example). One floxed person developed cipro-induced neurotoxicity of the crural nerve (main nerve of the leg), that was also reflected in the conductivity tests. As a result, his quads and hamstrings atrophied and the ileotibial band (tight and narrow muscle band that runs along the outer side of the leg from the hip to the knee) got overloaded. The fascia between quads and ileotibial band was in bad shape too due to the floxing, as many other fascia layers of his body, with a lot of adhesions, scar tissue formation and deposition of abnormal material. The femoral cutaneous nerve passes through that fascia, and it got altered causing very high pains along the buttock, outer side of the leg, outer side of the knee and proximal (upper) tibiais muscle end. These pains still last after 5 years and are constant at times, causing a limp, preventing the victim from sleeping and causing much misery. The victim only gets some temporary relief when he takes a deep fascia release at the layer between ileotibial band and quads. Take into account that the deep fascia of the leg forms a complete investment to the muscles, and is fused with the periosteum (sheath of bones) over the subcutaneous surfaces of the bones. It is continuous above with the fascia lata (ileotibial band), and is attached around the knee to the patella, the ligamentum patellæ, the tuberosity and condyles of the tibia, and the head of the tibula. Behind, it forms the popliteal fascia, covering in the popliteal fossa; here it is strengthened by transverse fibers, and perforated by the small saphenous vein. It receives an expansion from the tendon of the Biceps femoris laterally, and from the tendons of the Sartorius, Gracilis, Semitendinosus, and Semimembranosus medially; in front, it blends with the periosteum covering the subcutaneous surface of the tibia, and with that covering the head and malleolus of the fibula; below, it is continuous with the transverse crural and laciniate ligaments. It is thick and dense in the upper and anterior part of the leg, and gives attachment, by its deep surface, to the Tibialis anterior and Extensor digitorum longus; but thinner behind, where it covers the Gastrocnemius and Soleus. It gives off from its deep surface, on the lateral side of the leg, two strong intermuscular septa, the anterior and posterior peroneal septa, which enclose the Peronæi longus and brevis, and separate them from the muscles of the anterior and posterior crural regions, and several more slender processes which enclose the individual muscles in each region. A broad transverse intermuscular septum, called the deep transverse fascia of the leg, intervenes between the superficial and deep posterior crural muscles.

The following information has been adapted from a document of Myosymmetries International Inc. Myofascial Release (Muscle-Fascia-Release) is used for recovery from all types of physical injuries such as sporting injuries, back and neck pain, whiplash, stress-related muscular tension and repetitive strain injuries. Myofascial Release is also used in the treatment of immune system dysfunctions such as Fibromyalgia, Chronic Fatigue Syndrome, and others, and is mandatory in floxed persons with the symptoms and conditions listed above.

As you know by now, fascia is specially targeted by the toxicity of quinolones. Fascia is the most pervasive tissue in the body, surrounding and enveloping everything from whole muscle groups and bones down to individual cells, including individual muscle fibres, tendons, ligaments, nerves, viscera and the circulatory system in all its guises. Through the meninges and the dural tube fascia plays an enormous role in the central nervous system. Superficial fascia is attached to the underside of the skin, much like a body stocking and is the outer layer of a three-dimensional continous network which compartmentalises the body separating and surrounding each part. Fascia is entirely continuous throughout the body, therefore, if there is restriction in any part it will affect other parts, sometimes at a distant point from the origin.

Each muscle fibre has a fascial binding, and so muscle and fascia are functionally linked, giving rise to the term 'myofascia' (muscle - fascia). Injuries or imbalances in the muscular system will be reflected in the fascia, and it is often restrictions in fascia which give rise to 'muscle' pain. Releasing fascia provides lubrication for the movement between muscle fibres and other structures. Circulatory and lymphatic vessels and nerves move through the body in fascial membranes providing feedback to the central nervous system. If fascia is not moving freely all other structures will experience painful restriction in movement. This phenomenon is behind those stiffness and soreness caused by physical activity in floxed persons.

Fascia is composed mainly of collagen (40%) and lubricating ground substance. Both muscle with its fascial sheaths and ground substance are 70% water - fascia acts like a sponge. With physical and emotional trauma it dehydrates - water is pushed out - rendering it hard and gel-like, thus reducing the lubricant qualities of the ground substance between the collagen fibres and decreasing the distance between the fibres. This leads to the collagen fibres shortening, thickening, and sticking together. Fascia

which is shortened and hard compresses capilleries and nerves, causing pain, imbalance and discomfort, and resulting in decreased cardiovascular flow which further compromises healing capability. Myofascial Release brings about an increase of hydration of the ground substance, the collagen fibres and the whole of the fascial system. It increases the distance between the collagen fibres, allowing for further hydration and a decrease in compression around other structures.

It follows then that myofascial restrictions play a large part in pain syndromes. Fascia which is restricted can be extremely painful itself and cause surrounding fascia to stiffen protectively. Structures around restricted fascia cannot move without friction, compounding the problem. Continuous overload of an area can then lead to total fascial restriction in which movement is almost impossible without extreme pain. This will not show up in any orthodox medical tests, neither need the muscles themselves be directly involved or responsible. The pain resulting from myofascial restriction is often described as deep, sharp, dull, burning, diffuse, heavy, or 'like toothache'. Often it is difficult to pinpoint the exact location of the centre of pain and very often, if the cause is not treated and wider areas of fascia become affected, the pain can become generalized. Pain in the myofascial system is often referred pain, that is, the origin is in a seemingly unrelated, unaffected area. A myofascial practitioner will seek to treat the problem where it arises rather than where the symptoms emerge.

Myofascial Release is the term referring to a collection of techniques for separating layers of fascia, releasing restrictions, restoring elasticity, conductivity and hydration. A Myofascial Release practitioner will use a variety of techniques including gross or 'cross-hand' stretches, focused stretches, skin rolling, 'windmill' or J-stretches, fascial glide, deep 3-dimensional stretches, following fascia layers in their direction of ease, pulls, focused rebounding, shaking or rocking, tender point treatment and trigger point release. Other muscle release techniques may well be used during the same session and tendons, ligaments, muscle tissue and fascia will all be treated where necessary, either concurrently or separately.

Myofascial restrictions can lead to muscle imbalances as individual muscles and whole muscle groups are prevented from functioning fully because of myofascial pain, resulting in some becoming short and tight and others long and tight or atrophied. Weakness will occur in any case. It is therefore important to reestablish muscle balance when myofascial release has taken place. A specifically devised Pilates exercise programme, focusing on maintaining biomechanical balance and myofascial release, is excellent for reeducating the brain in correct muscle recruitment for each movement or postural hold.

QUINOLONE INDUCED MYOTENDINOPATHY

Vasuki Narayanasamy M.D, Harsha Vyas M.D, Guha Krishnaswamy M.D.

The Fluoroquinolones is a popular class of antibiotics due to its wide spectrum of activity, favorable pharmokokinetics and relative lack of side effects. They act by inhibiting DNA gyrase and topoisomerase IV resulting in ineffective bacterial DNA synthesis. Myotendinopathy is a major concerning side effect associated with the use of Fluoroquinolones. We are reporting cases of sartorius muscle and achilles tendon ruptures secondary to the use of quinolones.

Case report #1: This is an 82 year old female patient who presented to the clinic with left lower

extremity pain and swelling after being treated for bronchitis with levofloxacin in her prior visit. On examination, the calf and dorsum of the left foot was associated with moderate swelling and ecchymosis around the insertion of Achilles tendon. Full range of motion at the ankle was limited due to pain. The pulses were intact. A MRI was performed since a tendon rupture was suspected due to the acute nature of presentation and a history of fluroquinolone use. The MRI showed a near full thickness of the Achilles tendon around 3 cm proximal to the calcaneal insertion. Patient chose the non surgical approach and was treated by non weight bearing cast.
Case report #2: This is a 72 year old male who presented to the clinic with ecchymosis of right lower extremity and intense edema. He was treated with Gatifloxacin 10 days prior to this presentation for COPD exacerbation. Deep vein thrombosis was ruled out by Doppler U/S of the Lower Extremity. Further investigation by MRI showed rupture of the right Sartorius tendon at the insertion to knee. This is the first case to be reported for Gatifloxacin induced tendon rupture. He was treated initially by phonopheresis and continued conservative non surgical management since he was not a surgical candidate.
Conclusion: FQ induced myotendinopathy has been reported extensively in the literature since the 80's, due to the concern associated with the widespread use of antibiotics in modern medicine. It has been associated with numerous risk factors of which concurrent steroid use and age>60 play a very important role. The exact mechanism by which it occurs is still unclear. There has been data showing an ischemic/vascular insult predisposing the rupture. Also, Quinolones upregulate the expression of Matrix metalloproteinases which are involved in the rapid turn over of the cells thereby causing tendon injury. A thorough physical exam and history is helpful in the diagnosis of most cases. MRI is a sensitive and a specific tool to assess the severity of rupture. Management can be either conservative or involve an aggressive surgical approach based on the age, comorbidities and life style of the patient.

153. WATER EXERCISES

Water (aquatic) therapy is kind of the joints and helps to strengthen almost all muscles. It avoids joint impact,and therefore is gentler on the musculoskeletal system.

154. DRY SAUNA

Dry sauna provides some comfort, increases circulation and dilates tissues and vessels, but there is no clear evidence that it helps with recovery from a floxing.

155. FLOXING, CONNECTIVE TISSUE AND EXERCISE

Excessive or high-intensity exercise may be traumatic to the body's skeletal system and result in acute or overuse injurie. Low-intensity exercise is not considered to be injurious to a healthy normal individual. In fact, immobilization can impair normal metabolism and remodeling of connective tissue. When a joint is immobilized, the diminished mechanical loading and unloading of cartilage and surrounding tissues interferes with normal turnover of cells and matrix components. Decreased stimulation of cells results in decreased proteoglycan synthesis. Consequently, matrix loss leads to increased vulnerability of the tissue to injury when normal activities are resumed.

Studies in animal models have shown exercise to be beneficial to healthy metabolism of connective tissues. Eccentric exercise may disrupt skeletal muscle and connective tissue structures. The delay (two days after exercise bout) in increased biomarker levels suggest that breakdown is not immediate and does not result directly from mechanical damage to connective tissue. It is suggested that connective tissue breakdown results from the localized inflammatory response to exercise-induced musculo-tendon trauma. Inflammatory mediators from inflammation in the musculo-tendon unit may promote collagen breakdown and subsequent synthesis in surrounding connective tissues.

Exercise may contribute to long- and short-term stimulation of cartilage metabolism by mechanical loading of the joints. Compression of the joint capsule induced by mechanical loading changes joint

fluid and pressure, osmotic pressure, cell-matrix interactions and cell activities. In animal models, post-exercise proteoglycan synthesis was enhanced and breakdown was reduced in the carpel joint synovial fluid. Cartilage degradation was impaired and the extracellular matrix was more stable. Several studies suggest that the effects of mechanical loading on articular cartilage metabolism is mediated by changes in composition and humoral factors released into the synovial fluid.

156. OTHER TREATMENTS

Out of real neccesity, many floxed persons undertake thorough research of a method of speeding healing. Some of the proposed aids for recovery have been:

- TESTOSTERONE PLUS GROWTH HORMONE. Delicate treatment that has to be carefully planned, preferably with the aid of a qualified doctor, and monitored for liver, pancreas and kidney function. Probably may help with strong floxings. Much research is warranted.
- AUTOHEMOTRANSFUSION OF OZONATED BLOOD. Relatively common in Europe, and less used in America. It would help to decrease pain.
- AUTOINJECTION OF PLASMA GROWTH FACTORS. It concentrates the growth factors of your own blood in some points of your body, around a tendon for instance, to speed healing. There are anecdotical reports of two cases where it was applied to floxed persons, without any difference.
- HYPERBARIC OXYGEN. A dangerous therapy that has to be used judiciously.
- LIPID EXCHANGE. DETOXIFICATION. Not covered by this report at all.

157. REAL LIFE CASES THAT SUMMARIZE IT ALL

The following personal case says it all.

> (REPRODUCED WITH PERMISSION.)
> My husband was in better physical shape than most teenagers and had so much muscle tone in his body. He was given Cipro 500mg in August, 1998. One month later in September, it was like a bomb went off in his body. His muscles and joints became so painful. He was in so much pain that it became difficult for him to sleep at night. Insomnia along with pain, then when he did sleep, he developed this weird symptom. Some might call it restless leg syndrome, but I called it restless leg and arm syndrome. I have never seen a person's arms and legs shake like his did in his sleep. His limbs flopped around so widly that it always woke me up. It was like watching only arms and legs being electrocuted. I don't know if this is really restless leg syndrome, but I have no other name to call it. In January, 1999, He was being treated for depression but had never tried to harm himself before. He told me often before and after he shot himself that he just wanted to stop hurting in his body. The first tendon rupture occurred about 12 months after taking Cipro in July 1999 in his left calf area where he now has a permanent limp. 13 months, August 2000, after taking Cipro the second rupture of a tendon occurred in the right knee quadriceps. After an operation to repair that rupture, the quadriceps muscle tore in half on the right thigh April 2001. Pain was always constant, but the tearing seemed to have stopped after April 2001. April 2004, CiproXr 1,000 mg given for congestion from cold. 11 months, February, 2005, after taking CiproXR tearing starts again. This time it's the right elbow tendon. It tears almost completely loose. The tear is started from turning a screwdriver. An operation is done, but tears again in August 2005 during physical therapy. Another rupture occurs in October 2005 in the left arm elbow using very little effort. Here is a list of all the things happening in his body since he took Cipro: Tendon ruptures in both legs and both arms, tendonitis daily in both arms, daily muscle & joint pain all over body being treated with 75mcg fentanyl pain patch, weakness & no strength in muscles, rectal bleeding daily, acid reflux daily, restless leg & arm syndrome nightly being treated with neurotin, migraines occasionally, back spasms occasionally, permanent limp in left leg from rupture, severe rash with unusual swelling of left corner bottom lip that occurred twice, hot flashes, lack of blood in tissue observed by doctor during operation on right arm, suicide attempt once with .38 in mouth (shot self but lived), depression daily, back pain often, diarrhea occasionally, chest pain occasionally, anxiety attacks daily & being treated with medicine, insomnia, definite hearing loss of high frequency, numbness or tingling in hands occasionally and ringing in ears occasionally. Now our

5 year old grandchild is stronger than he is. In 7 years time this once strong man has been reduced to completely disabled. This medicine didn't affect me like this, but for those who do have reactions to it, it is devastating. I have done some research on stories of different people suffering from side effects of Cipro and Levaquin. As for our own experience compared to some I have read about, I believe your current physical shape may have something to do with the timeline. I have read about some people in their 70's taking only 1 pill, then getting up from a chair and instantly having a rupture of the calf tendon. The first rupture my husband had didn't occur until almost 12 months after taking a full prescribed dose of Cipro 500mg. His first dose of Cipro was taken August 1998. The ruptures didn't stop until after the last tear in April 2001. Then in April 2004 he was prescribed CiproXR 1,000mg and he took the 15 day supply prescribed. 11 months later in February 2005 the ruptures started again. He is still in danger of ruptures. My personal opinion is that his ruptures took longer to appear because of his physical condition. He was a very active person and his muscles were more like that of an athlete. These last ruptures combined with the earlier ones have affected both his legs and arms. He has lost all the muscle tone he used to have last year. It appears from the ruptures he has gone through that the loss of muscle tone left him more vulnerable to rupturing to occur. When he still had muscle tone, he ruptured a tendon from picking up something heavy, then with the last rupture when his muscle tone had changed greatly, it took the amount of pressure a person would apply to squeeze a blood pressure bulb. Also, the ruptures were closer together in happening as his muscle tone decreased.

158. EMERGENCY CARE FOR YOUR FEET

This section has been asked for by many readers and is in preparation.

159.TREAT YOUR SELF FAIRLY

Allow yourself some treats. Do not blame your bad luck. Try to keep a positive attitude. Do not submit yourself to excessively strict diets, programs or schedules.

In every phase, whenever you feel strong enough or able to, try to get in contact again with those activities that you enjoyed most before being floxed.

PART XXII: ANTIBIOTICS IN THE LIFE OF A FLOXED PERSON, AND OTHER DRUGS

160. I NEED TO TAKE AN ANTIBIOTIC. WHAT SHOULD I TAKE?

You are scared to death. But there is no other choice because you have a proven infection and the mild all-natural antibiotics will not clear it. This time you search frantically for a class with no adverse effects, but you do not find any. An allergic reaction to any food or drug is always possible but we do not discuss it here.

When you are floxed, any virus or bacteria that you catch will release a relapse. The infection will cause you to deteriorate rapidly and in a couple of days you will find yourself months behind in your recovery. Perhaps the release of white cells into the bloodstream or other mediators alters the status of the mechanisms of inflammation, cell metabolism and all the complex equilibriums of the body. So it is important to get as few infections as possible.

You have to discuss it together with your doctor and choose a class of antibiotic that is both effective against the bacteria and has as safe a profile as possible. Your search should be directed to avoid antibiotics with a high record of neurological or vasculitic adverse reactions. Medical literature has established that well: beta-lactams and the quinolones are the drugs most commonly associated with seizures and encephalopathy; the aminoglycosides, tetracyclines, clindamycin, erythromycin, polymyxins, and possibly ampicillin have the potential to aggravate neuromuscular disease; ethambutol, isoniazid, and chloramphenicol are toxic to the optic nerve; bismuth can cause a myoclonic encephalopathy, macrolids are linked especially with vasculitic events and also quinolone-wise with prolongation of the QT interval of the heart. Beta lactams have also been implicated with serum-like sickness, a condition very similar to floxing in some aspects. Sulfonamides can also release lupus, another illness that shares many similarities with the floxing syndrome. Penicillin is much studied and therefore many adverse effects have been found but it is still a choice. Some antibiotics cause total hearing loss or severe injuries to kidneys and other organs for certain dosages and to susceptible people.

Never use a quinolone eye drop if another antibiotic can do the job. The quinolone will kill the bacteria for certain, but at the same time it might damage your eyes irreversibly. And if the quinolone drop has been prescribed to you for avoiding infection after eye surgery, then remember that it will delay and impair healing.

After some study you conclude that some antibiotics seem quite benign like amoxicillin and others like chloramphenicol and nitrofurantoin (macrobid) seem equally if not more terrific than fluoroquinolones, but considering your battered state and the potential adverse effects there is not much to choose from, so in the end you have to take a risk. It is unlikely that a new antibiotic of a different class will give you so much damage as the damage you are sustaining from the quinolones. Hopefully, through careful selection or by means of a couple of attempts you will find one that works well for you with no more adverse consequences.

If you have had an intermediate or severe reaction, you should put a lot of emphasis on informing doctors, nurses, emergency rooms, medical offices, and hospitals that no other quinolone antibiotic should be administered to you for the rest of your life. Indicate in your medical records that you are unable to take any fluoroquinolone antibiotics under any circumstances, as you have endured a toxic reaction and must never be exposed to them again.

161. AVOID RE-EXPOSURE TO PRESCRIPTION QUINOLONES

Even if you have not been exposed to quinolones, do not take any quinolone antibiotic unless strictly necessary. Of course, do not ignore the possibility of suffering from a floxing syndrome if you have experienced the symptoms listed above and have taken quinolones in the past. One thing is clear: the effects of the quinolones are cumulative and once the reaction has been released, any rechallenge initiates an amplified response. The re-exposure will bring you devastating and possibly permanent damage that could become a life-long condition.

Do not allow yourself to be prescribed anymore quinolone antibiotics. Quinolones are also the active agent in many non-oral formulations like eardrops, nose ointments and eyedrops.

REMEMBER:
After any kind of reaction, if you ever take another quinolone, the side effects can be tragic and unmanageable.

Do not accept your doctor's prescription for a quinolone antibiotic without having checked for other alternatives and/or safer, less toxic drugs; and never take a quinolone on the grounds that *"according to his experience"* quinolones are effective, well tolerated, with minimal side effects as antibiotics. His experience is reduced to prescribing quinolones in the *"fire and forget"* manner (handing them out like candy), and not caring for the patient's adverse effects caused over time.

In general, and save very rare exceptions, the problems caused by quinolones are not properly identified, therefore the victims are potentially exposed to new and inmensely devastating toxicities. In this real example, reproduced with permission, a strong man was severely crippled by a second round of cipro.

> [Original written in 2006] *My husband took Cipro 500mg in 1998. The rupturing itself seemed to have stopped in the year 2001. He had a very athletic build. He still had all the other side effects such as tendonitis. They never did cease. Then in 2004, he was given a higher dose of CiproXR 1000. He took that full dose also. We had no idea at that time that he was allergic to Cipro. It took about a year both times before the ruptures began after taking Cipro. The first round of Cipro in 1998 damaged both his legs. The second round of CiproXR in 2004 damaged his arms. There are tears present as of this day in both his arms and legs. Operations that he had failed. By that, I mean that tearing occured afterwards involving the same tendon that had been operated on such as his right quadriceps that was reattached to his knee the tore midway up his thigh shortly afterwards. He has lost all his muscle tone he once had. He can barely get out of bed each day. He has no strength in his body. He still suffers the other side effects daily. It has crippled him in more ways that one. It's hard for a man who remembers how strong he once was and to see how weak he has become. At this point, seeing all the damage in his body, I don't think he will be safe from rupturing for many many years to come. I am not quite sure if he will ever be safe from rupturing again.*

We have recorded more than six hundred testimonies of this kind, corresponding to a not so long period.

162. RE-EXPOSURE THROUGH FOOD

All persons are currently being exposed to quinolones through the food chain. The inmense majority will not get any measurable adverse effects through their lifes. Very few, namely those that are sensitive to quinolones and would get a violent reaction to a single pill, but that have never taken quinolones as a medicine, will react to the quinolones ingested through food, that are a constant low dose exposure. These hypersensitive people will be diagnosed as having fibromyalgia, chronic pain syndrome, and other illnesses depending on what symptoms are more prominent on them.

All floxed persons after taking cipro, levaquin or their counterparts, and that were not hypersensitive to quinolones can heal more or less adequately eventhough they may be constantly rechallenged through food. Only two groups of people will have to check carefully what they eat:

- Severe floxed persons through the medicine form.
- Hypersensitive floxed persons (those that have a violent reaction after the first pill, without reaching the level of allergy).

Obviously, all floxed persons will benefit from a quinolone-free diet. The problem is that quinolones can potentially be almost everywhere: farmed fish, poultry, cattle, eggs, dairy and other products. The animal versions of fluoroquinolones and other antibiotics are widely used to help raise animals for human consumption. In almost all farms, antibiotics are used permanently as part of the diet of the animals because they keep the herd or flock "healthy", promote growth and have a little cost, allowing to put the final product on the market at a real low price.

Quinolones are extensively used in the farming of shrimps, fish and other seafood, and raising poultry. They are also used in all kinds of meat, and therefore are present in butter, milk, cheese, yogurt, eggs, and many prepared foods. Some years ago other antibiotics were preferred for mammals, due to the high cost of quinolones, but now quinolones are produced massively in Asia, at negligible costs.

The quinolones approved for animals are thought to be unusable for people because of their toxicity for humans, so taking those quinolones for animals through the diet of a floxed person, is a bad bet. Almost all information on the inadequacy of the use of quinolones in poultry comes from the concern of creating strains of bacteria quinolone-resistant:

QUINOLONE RESISTANCE IN CAMPYLOBACTER ISOLATED FROM MAN AND POULTRY FOLLOWING THE INTRODUCTION OF FLUOROQUINOLONES IN VETERINARY MEDICINE
Endtz HP, et Al. University Hospital, Leiden, The Netherlands. J Antimicrob Chemother. 1991
The rapid emergence of resistant campylobacter may also have important implications for the treatment and prophylaxis of diarrhoeal disease. The increase of quinolone resistance coincides with the increasing use of fluoroquinolones in human and veterinary medicine. Extensive use of enrofloxacin in poultry and the almost exclusive transmission route of campylobacter from chicken to man, in The Netherlands, suggests that the resistance observed is mainly due to the use of **enrofloxacin** in the poultry industry.

Table 2 Quinolones licensed for use in food animals by region of the world

Region	Livestock	Poultry	Pet animals	Fish
Europe	enrofloxacin, flumequine, marbofloxacin, danofloxacin	enrofloxacin, difloxacin, flumequine, oxolinic acid	enrofloxacin, difloxacin, marbofloxacin	sarafloxacin, (oxolinic acid) [a]
USA	none	enrofloxacin, sarafloxacin	enrofloxacin, difloxacin, orbifloxacin	none
Japan	enrofloxacin, danofloxacin, orbifloxacin, difloxacin, oxolinic acid	enrofloxacin, danofloxacin, ofloxacin, vebufloxacin, oxolinic acid	enrofloxacin, orbifloxacin	oxolinic acid
Asia	enrofloxacin, danofloxacin, ciprofloxacin	enrofloxacin, ciprofloxacin, danofloxacin, ofloxacin, flumequine, norfloxacin, oxolinic acid, (sarafloxacin)	enrofloxacin	oxolinic acid enrofloxacin, flumequine
Latin America	enrofloxacin, ciprofloxacin, danofloxacin, norfloxacin, (flumequine)	enrofloxacin, ciprofloxacin, danofloxacin, norfloxacin, (flumequine, oxolinic acid)	enrofloxacin	oxolinic acid
Canada		enrofloxacin [b]	enrofloxacin	
Australia	none	none	enrofloxacin	none
South Africa	enrofloxacin, danofloxacin	enrofloxacin, danofloxacin, norfloxacin	enrofloxacin	

[a] Substances in parentheses are in limited use.
[b] Voluntarily withdrawn from the market in 1998.

table 23

Recently, fluoroquinolones have been banned in the USA for treating poultry, in order to avoid the proliferation of quinolone-resistant bacteria, not because any authority is concerned with the toxicity of the meat produced.

Here you have the list of quinolones licensed for use in food animals all over the world (table 23). Take into consideration that most fish in western countries comes from other parts of the world.

© World Health Organization 1998

"Currently, several quinolones are available for treatment of animals, poultry and fish in many countries in the world. Available data indicate that they are also used for disease prevention in some regions. Quinolone production and usage is estimated to be about 50 tonnes for proprietary products (mainly USA, European Union, Japan, South Korea in 1998) and, because of their lower prices, about 70 tonnes for generic quinolones. However, available usage data, particularly for non-proprietary quinolones, are known to be grossly incomplete. For instance, data from China estimate annual quinolone consumption in animals in China alone to be in the range of 470 tonnes (annual consumption in human medicine in China: about 1,350 tonnes). "

According to some other studies consulted, the consumption of quinolones by the legal market has quadrupled in 2005 with respect to 1998. The illegal market is at least as big as the legal one, if one looks to the seizings of quinolones used illegally in animal farming that take place in Europe.

There are very few warnings about the toxic effects of antibiotics used in aminal farming.

FAO (FOOD AND AGRICULTURE ORGANIZATION. UNITED NATIONS)

5.2.2.1 Antibiotic residues

With the increased use of veterinary drugs in food production, there is global concern about the consumption of low levels of antimicrobial residues in aquatic foods and the effects of these residues on human health. This concern is not limited to only aquaculture products but to all foods of animal origin where the use of antibiotics has become an integral part of intensive animal husbandry.

The potential hazards associated with the presence of antimicrobial drug residues in edible tissues of products from aquaculture include allergies, toxic effects, changes in the colonisation patterns of human-gut flora and acquisition of drug resistance in pathogens in the human body (WHO, 1999).

Table 24. Examples of antibiotics used in aquaculture.

Group	Compound	Comments
Sulphonamides	Sulphamerazine Sulphaimidine Sulfadimethoxine[1]	Bacteriostatic agents (trout and salmon).
Potentiated Sulphonamide	Co-trimazine/Sulfatrim	Used for treating diseases in salmon and trout.
Tetracyclines	Chlortetracycline Oxytetracycline[1,2,3,4]	Wide use in aquaculture. Used in salmon, trout, turbot and shrimp farming. Approved for prevention in lobsters in Canada.
Penicillins (Beta-lactams)	Ampicillin[4] Amoxycillin[2,4]	Used to treat furunculosis in salmon and rainbow trout fry syndrome (RTFS) in Europe.
	Benzyl penicillin[3]	Used for yellowtail and sea bream in Japan
Quinolones	Ciprofloxacin	Used in shrimp farms in Asia
	Enrofloxacin	Used in shrimp farms in Asia
	Norfloxacin Oxolinic acid[2,3,4] Perfloxacin Flumequine[3,4]	Used in shrimp farms in Asia
	Sarafloxacin[2]	EU MRL 150ug/kg fish muscle
Nitrofurans	Furazolidone	Broad-spectrum antimicrobial agent. Used in shrimp farms in Asia. Use discouraged as it is a potential carcinogen.
Macrolides	Erthromycin[4] Spiramycin	
Aminoglycosides	Gentamycin	
Other antibiotics	Chloramphenicol	Residues in foods may cause aplastic anaemia in man[5]. Use banned in the European Union.
	Florfenicol[1,3,4] Thiamephenicol[4] Tiamulin Nalidixic acid Milozacin	Used to treat RTFS and furunculosis in salmon.

1. Use permitted in Canada
2. Licensed for use in the UK (Alderman and Hastings 1998)
3. Use permitted in Norway (Alderman and Hastings 1998)
4. Use permitted in Japan (Okamoto 1992)
5. Tan (1999).

Antibiotics are used in aquaculture as prophylactics, as growth promoters and in the treatment of diseases. Prophylactic use of antibiotics is defined as the administration of antibiotics in advance of disease occurrence and this is a common practice in shrimp hatcheries in Asia to reduce the incidence of diseases (GESAMP, 1997). A recent review (Graslund and Bengtsson, 2001) report the widespread prophylactic use of antibiotics in both shrimp hatcheries and in shrimp ponds in Southeast Asia. Antibiotics are usually administered in aquatic feeds and most commercial shrimp feeds contain antibiotics (Flaherty *et al*., 2000). In contrast, antibiotics are not used either as prophylactic agents or as growth promoters in temperate water aquaculture production in Europe and North America (Alderman and Hastings, 1998).

> Control over the sale and use of antibiotics in some shrimp producing countries is limited which has led to problems in overseas markets. The occurrence of antibiotic residues in cultured shrimp from Asia has led to the rejection of products in export markets (Saitanu *et al.,* 1994) and more recently, the European Union has introduced new legislation requiring the testing of all shipments of farmed shrimp from China, Vietnam and Indonesia for residues of chloramphenicol (EC, 2001b,c).

We have very detailed records of a floxed person that had two violent relapses, both of them causing him complete temporary blindness and symptoms of extraordinary severity. He is a severe floxed person but not hypersensitive to quinolones previously to his current reaction. Fortunately he kept a daily diary that allowed him to discover that he had reacted both times to a meal of roasted quails brought home by his uncle that run a farm. Once relatively functional after the second massive intoxication he discovered that his uncle was watering the birds permanently with very elevated concentrations of enrofloxacin (fluoroquinolone for animal raising). Avoiding commercially produced poultry, the floxed person has avoided those life-threatening relapses up to now, more than two years after the last one.

Antibiotics are fed to raised animals both legally and illegally. We have several reports of very big seizings of banned fluoroquinolones at farms across Europe.

In the USA fluoroquinolones have been banned to raise poultry since end of 2004, due to concerns about quinolone resistant strains of avian bacteria. That is good news for the general population.

163. OTHER QUINOLONES

We have seen hundreds of times how a doctor changes the prescription of a fluoroquinolone, for instance cipro, to another fluoroquinolone, for instance levaquin, once his patient has complained about nasty side effects like central nervous system abnormalities, tendinitis or the like. This appalling ignorance is causing most of the severe reactions that we have encountered, with the end result of permanent injuries.

Remember that all fluoroquinolones are nearly identical and their toxic profile is so similar that after being intoxicated by one of them, the whole class of antibiotic has to be avoided for life.

164. OTHER DRUGS

If you are suffering a pretty severe reaction to a fluoroquinolone, remember that you have been intoxicated and that your whole body is affected, eventhough you can only feel symptoms generated by certain organs and systems of the body.

So, most drugs will have from now on different influences over you with respect to what would otherwise be normally expected. In many cases, some unwanted effects will appear.

Drugs that are have a negative influence in a severe floxed person are all statins, all neuroleptics, all drugs that modify or alter the inmune system, many blood thinners and anti-inflammatories, and many more. If you need to take them, watch out for side effects, adjust the dosage and talk to your doctor (just in the improbable case he wants to listen to you). Avoid if possible all other drugs with a clear toxic profile.

You should also take into account that the impairment caused by quinolones, of some of the P450 liver pathways, may also impede the normal metabolization of some of the drugs that you have to take, or may cause another intoxication on you because of the undue levels that the new drug can reach in your body fluids.

165. QUINOLONES CAN MAKE YOU LOOSE YOUR JOB

If you suffer an intense reaction you will have a lot of difficulties to keep up with your job, but just for taking a quinolone you can risk your employment if you are screened for opiates' consumption.

> FALSE-POSITIVE URINE OPIATE SCREENING ASSOCIATED WITH FLUOROQUINOLONE USE
> Zacher JL, Givone DM. PharmD Student, University of Illinois at Chicago, Chicago, IL. Ann Pharmacother. 2004 Jul 13
> OBJECTIVE: To review the literature regarding false-positive urine opiate screens associated with the use of fluoroquinolones. ../..... DATA SYNTHESIS: Various settings utilize the practice of screening for drugs of abuse, such as opiates. These screening procedures can impact aspects of one's life, such as employment; therefore, accuracy is of the utmost importance. Two clinical trials were evaluated which showed that certain fluoroquinolone antibiotics cross-react with some of the commonly used urine opiate screening immunoassays. This suggests the importance of verifying positive results in instances where one's livelihood can be affected. CONCLUSIONS: Fluoroquinolones can cause false-positive urine opiate screens. Clinicians should be aware of this potential interaction and may need to verify positive results.
> Here is an expanded list of antibiotcs that can cause a false-positive opiate screen, it is not a complete list: CIPRO (ciprofloxacin), PENETREX (enoxacin), MAXAQUIN (lomefloxacin), CINOBAC (cinoxacin), ZAGAM (sparfloxacin), LEVAQUIN and QUIXIN (levofloxacin), FLOXIN (ofloxacin), NEGRAM (nalidixic acid), AVELOX (moxifloxacin), TEQUIN (gatifloxacin), FACTIVE (gemifloxacin), RAXAR (grepafloxacin), NOROXIN (norfloxacin), CHIBROXIN (norfloxacin), TROVAN (trovafloxacin).

166. ANESTHESIA

Some therapies also exert very abnormal influences on the floxed person. For instance, most general anesthesia procedures are highly toxic for the already altered nerves of the severe floxed persons. While normal dosages of general anesthesia would not cause any significant side effect on a normal person, this same person, once floxed, will probably suffer a sharp increase or worsening of the following symptoms:

- Brain fog, unability to read an understand fully the content of any newspaper sheet for instance. It lasts some days on average.
- Aberrant perception of colors, specially noticeable while reading because each word of a normal black lettering writting looks of a different color. It lasts some days on average. This disorder is called chromatopsia and seems to be due to retinal intoxication and optical nerve alterations.
- Trembling of whole limbs and/or trunk, very noticeable at night, this can last more than a year or become permanent.
- Increase in musculoskeletal problems, with increased wasting due to the increased toxic load of the nerves that control the muscles, and increase in tendinitis due to the lack of functionnality of the muscles.

The above information is based in the anecdotical evidence of only five cases, so, as with the rest of the information provided in the Flox Report, do not take it as a general rule for all cases, because there is an acute shortage of data.

Local anesthetics like procaine (novocaine) are toxic if the floxed person is currently taking anticholinesterase agents or is taking large doses of acetylcholine supplements. The toxicity affects nerves primarily and the impairement caused in the neuromuscular connections can cause high muscle and joint pains in a few hours after getting the anesthethic.

In the next section, we profundize a little on a handful of products and treatments that have been postulated by victims, including us in some cases, in their search for some relief.

PART XXIII: IS THERE ANY THING THAT HELPS?

Unfortunately, no cure has been found for a floxing, neither any medicine or supplement that makes a difference in the evolution of a recovery.

People little affected can find relief or help in drugs and suupplements with known properties, but a person strongly affected by a floxing, will not get any benefit from them, but on the contrary she/he will sometimes experience the opposite effect with respect to a normal person, because the alteration of many of his/her body systems is very deep and because of the chemical sensitivities developed.

It is depressing and very dispairing for severely floxed victims to check that supplements do not have on them now the same effect than on normal people or than on themselves before, but instead they get now negative repercusions.

During the reading of the whole Flox Report keep up a critical analysis, and specially in sections like this one where a lot of recommendations based on average experiences, are made.

167. GENERAL RECOMMENDATIONS FOR A FLOXING

There is a good site (www.medicationsense.com) , that belongs to Dr. Cohen. The site has an honest approach to the world of misprescription, overmedication and conflicting interests in the drug use. We recommend to have a look at it. It also contains a section on fluoroquinolones. There, Dr. Cohen describes what some floxed persons have reported to him, as to what supplements have helped them most. You can assess whether these proposals seem adequate for your case.

> ALTERNATIVE POSSIBILITIES. Dr. Cohen.
> Magnesium in doses of 400-1000 mg/day may be useful for reducing neuropathic pain or muscle spasms in some people. Feedback from quinolone sufferers about magnesium has been mixed. The U.S. recommended daily amount of magnesium is 320 mg for women and 400 mg for men. Use of higher dosages should always be done with the supervision of a healthcare practitioner. Seniors, people with kidney disorders, and those taking medications for cardiovascular or neurological disorders should have medical supervision even for RDA doses of magnesium. Interestingly, Dr. David Flockhart also recommends magnesium for quinolone reactions. Dr. Flockhart recommends low doses of milk of magnesia (1 or 2 teaspoons twice-daily), to be taken for several months. His theory is that because of the affinity of minerals for quinolone antibiotics, magnesium might help leech some remaining fluoroquinolone molecules from the tissues.
> I am not a fan of milk of magnesia, which is a laxative. If the goal is to absorb magnesium in order to get it into the tissues, chelated magnesium (e.g., magnesium aspartate, magnesium glycinate) or a magnesium solution (e.g., magnesium chloride) are absorbed better than milk of magnesium or cheap magnesium supplements. It has also been suggested that magnesium could be used with calcium and other minerals. The fact is, no one knows. There's little solid science, so it is trial and error. (For more information on magnesium, please go to the other magnesium sections of this website.)
> B-vitamins have been reported to reduce tingling. Pyrodoxine (vitamin B6) and pantethine (a derivative of pantothenic acid) have been reported to improve some types of nerve pain. One person wrote to me that high doses of lecithin had helped with memory problems. This is not farfetched. Lecithin contains several substances essential for normal nerve functioning. One of these is phosphatidylcholine.
> For anxiety or agitation, or to increase GABA in the nervous system, many alternative doctors recommend taking GABA, which is an amino acid. GABA has some similar qualities to Valium and Xanax, and it may be helpful for anxiety, nervousness, or insomnia. Too much

GABA can cause sedation. Inositol is also used for treating anxiety.
There are several alternative methods for reducing inflammation. Omega-3 fatty acids (fish or flax oils) increase the anti-inflammatory prostaglandins (PGE3) in cell membranes. GLA, found in primrose or borage seed oil, increases PGE1, which is also anti-inflammatory. Studies have shown that high doses of omega-3 fatty acids and of GLA reduce the pain of arthritis. This method takes time, several months, because it requires a rebalancing of the prostaglandins in the membranes of trillions of cells, but the ultimate reduction in inflammation is better, in my experience, than with prescription anti-inflammatory drugs. Omega-3 fatty acids and GLA are just two of many alternative methods for reducing inflammation.
If you are interested in alternative supplement and diet possibilities, I would suggest consulting with a knowledgeable alternative practitioner. Many doctors have adopted alternative methods because they became dissatisfied with the drug-oriented mindset of mainstream medicine. In my experience, alternative doctors are much more receptive to patients' concerns about medication side effects. Good alternative practitioners are also far more knowledgeable about the biochemical systems of the body. They have tests to measure people's levels of fatty acids, amino acid, antioxidants, minerals (including toxic minerals), and many other factors that may explain why some people are more vulnerable to certain diseases or reactions. Good alternative doctors are knowledgeable about magnesium and other minerals, GABA, omega-3 fatty acids, and many other human-compatible therapies. For example, alternative practitioners use alpha lipoic acid for treating neuropathies. Alpha lipoic acid has long been used in Europe, and there is a considerable medical literature on this substance. Few mainstream doctors are aware of alpha lipoic acid, magnesium, or the other natural remedies I have discussed above. I cannot say that alternative doctors have the answer to quinolone reactions. I can only say that it is another option worth considering.
If you run out of options with your mainstream doctors and would like to consult with an alternative practitioner, ask your friends whom they have seen and recommend. Half of the population has consulted with an alternative practitioner at one time or another. You can also find practitioners via the websites of the American College for the Advancement of Medicine (www.ACAM.org) or the American Holistic Medical Association (www.AHMA.org). One caveat: many alternative practitioners do not accept insurance and many of their tests are not covered by health insurance plans. Another caveat: different alternative practitioners use different methods; ask questions, ask for written information; many offices will send brochures or other information about practitioners' methods.

Our records do not match entirely with the above recommendations (in fact some are plainly contradictory like the suggestion about magnesium that we postulate that severely floxed persons should not take and we also "discovered" long ago that lecithin is one of the worst natural substances for a floxed person) but surely it is due to the fact that our data reflect mainly the responses of people strongly affected.

168. PROTOCOLS FOR NEUROPATHIES

There are many protocols of supplements and selfcare for neuropathies, specially peripheral neuropathies, some well founded and that can be of some help in those floxings that present with neuropathies predominantly.

We have found it innecesary to reproduce them here because you can find them in many reliable internet sites.

169. ADEQUATE EATING

Mild and intermediate reactions do not request a specific recovery program. They can more or less heal on their own. For severe reactions, healthy conduct and healthy foods are all part of a recovery plan. Each of us reacts differently, and there is a lot of controversy about this issue, but on average, there is a very common core of reactions that allows us to establish some recommendations. Stick to your already healthy diet. If you develop intolerances or bad reactions to some foods (very typical), avoid them during the years to come.

Obviously, it is strongly advised to avoid any quinolone or fluoroquinolone antibiotic; and to also avoid any meat, fish, dairy, eggs or animal product that has been treated with quinolones. Some contain concentrations of quinolones that are up to 50 times higher than concentrations in human tissues during a standard treatment, and can release relapses that range from mild to very severe. Do not believe food producers or health protection agencies if they tell you that is safe to consume meat or poultry that has been kept off antibiotics for 3 days before slaughter. It is not safe, the quinolones are not fully excreted, and enough of the drug remains in the animal's tissues to bring you a very severe relapse.

> AUTHORITY: SEC. 512 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (21 U.S.C. 360B). SEC. 20.813 ENROFLOXACIN [QUINOLONE] ORAL SOLUTION.
> Conditions of use. It is used in drinking water as follows: (1) Chickens and turkeys--(i) Amount. 25 to 50 parts per million of enrofloxacin in drinking water. (ii) Indications. Chickens: Control of mortality associated with Escherichia coli susceptible to enrofloxacin. Turkeys: Control of mortality associated with E. coli and Pasteurella multocida (fowl cholera) susceptible to enrofloxacin. (iii) Limitations. Do not use in laying hens producing eggs for human consumption. Administer medicated water continuously as sole source of drinking ater for 3 to 7 days. Prepare fresh stock solution daily. Treated animals must not be slaughtered for food within 2 days of the last treatment. **Individuals with a history of hypersensitivity to quinolones should avoid exposure to this product**.

FASTING

During the acute phase of a severe reaction (first two years), it is quite common to feel much better when fasting for 18 hours or more. The same applies if during the fasting some probiotic cultures are taken. The improvement is felt in terms of less stiffness, less pains and less overall soreness. The original achy state returns as soon as the floxed person consumes any food. This fact, discovered by chance by some floxed persons, happens to be common knowledge among rheumatoid arthritis sufferers.

WATER

A common mistake in the early stages of any floxing is to take an excessive amount of water daily. Perhaps it is not as relevant for mild or intermediate floxings, but it is not recommended for severe reactions. Too much water increases the overall feeling of sickness and can deplete the body of essential minerals, which are difficult to get through an intoxicated intestine. The water ingested by floxed persons should be of good quality and balanced mineral composition, with low sulphate load and of course not fluorinated, and not chlorinated if possible. The amount of water has to be adjusted for body weight, activity needs, and climate, and also considering the rest of the sources of water (fruits, vegetables, juices). Cases of chronic hyponatremia have been reported in floxed persons that take water compulsively. In winter and for sedentary activities one and a half liters should suffice for a body weight of 70 kilograms (150 pounds). In summer, exposed to heat and sunshine, and being active three liters is normal. Many floxed persons develop diabetes insipidus as a side effect, and large amounts of water increase their discomfort.

SUGAR

Sugar has an adverse influence increasing insomnia, restlessness and neurological pains. If a floxed person should have to choose a single food to avoid, that would be sugar. Sugar worsens all symptoms of QTS (Quinolone-Toxicity-Syndrome). Fluoroquinolones impair the glucose metabolism. We do not know if a worsening of symptoms after consuming sugar (or honey or any sweets) means that the glucose metoblism is injured. In severe floxings, this intolerance to sugar lasts more than five years on average.

> ***QUICK RECOMMENDATION:***
> ***In severe reactions, the three foods to avoid above all are SUGAR, SOY and OMEGA-3 oils.***

ALCOHOL

Alcohol is also vaso-constrictive and a toxin for the neurological system, so it is better to avoid it, although clearly some wine or beer has an immediate soothing effect. The definitive experience of most severe floxed persons is that more than two or three glasses of wine weekly is always paid in

terms of high pains but only in the most affected nerves.

CAFFEINE AND GRAPEFRUIT

The floxed body does not metabolize caffeine so it can increase your insomnia problems. According to many reports, the floxed person cannot properly metabolize caffeine because the quinolones have damaged (extraordinarily impaired) the cytochrome P450 system that is in charge of the clearance of many drugs in the body. This explains why so many foods, additives and products cause problems to floxed persons, and why a severely affected floxed person cannot metabolize caffeine properly for at least 5 years post-floxing. Grapefruit juice has the same inhibitory effect on the cytochrome P450 system as quinolones, so it is better to avoid it now and forever as a healthy measure.

CHOLESTEROL

Do not allow your cholesterol to drop too low. Some floxed persons have reported improvements with organic food high in cholesterol. However, scientific research shows that the toxic effects from these drugs on the muscle tissue acts mainly on the endogenous synthesis of cholesterol (the one produced by the body) rather than cellular uptake of preformed cholesterol (the one ingested). Maintain it a bit higher than your normal level, assuming that your normal level is ok, obviously. Note: on the short term, right after the treatment, quinolones cause a sharp increase in the cholesterol levels (up to three fold) that tend to normalize in the first months.

OMEGA-3

This is one of the paradoxes of floxing. Omega-3 oils are virtually side-effects-free for the general population, and are a healthy food. The same can be said for non strongly affected floxed persons. Omega 3 oils help to overcome the stiffness and the reduction in range of motion of every joint and help to keep a balanced diet.But for a severely floxed person and some other floxed persons, the effect is just the contrary. Fish oil (we do not know which section of the oil: CLA or others) releases strong relapses in neuropathies (pains), fasciculations all over the body, and joint pains after some days of ingesting it. This has been tested many times. We have observed this kind of contradictory effects with many supplements.

PARADOXES:
Many supplements with healthy properties and safe records, are very detrimental for severely floxed persons, for unknown reasons.

DILATORS

It is also beneficial to take some red peppers, and some nuts. Dilators help with insomnia, but increase some of the dryness symptoms. They have, as many other supplements and foods, a contradictory effect. Sometimes you will wish to take advantage of the vasodilating properties, and others you will try to avoid dry mucous membranes.

THINNERS

Garlic and onion might help the exchanges at cellular level and movement along the small damaged blood vessels, but do not mix large amounts of these with other supplements that they could interact negatively with or could amplify their actions. Garlic, in particular, taken in large doses (4 cloves a day) increases insomnia problems according to several well-documented reports from floxed individuals. All thinners increase the risk of internal bleeding in a severely floxed person. They promote movement of fluids within the body, but also increase some central and peripheral nervous systems symptoms.

In the first instance it might be considered wise to order a test for food and supplement tolerance for every floxed person. It consists of an analysis of the IgG reactions to a hundred common foods and additives, so that the floxed person could know which ones release an IgG reaction, because such reactions could exacerbate the floxing symptoms as they would add more immune complexes to the already burdened blood vessels with the IgG and IgM complexes liberated after the toxicity. However, trials done with a few floxed persons do not show dramatic improvements if they avoid foods to which they are

intolerant (IgG reactive), indicating that the drug induced immune reaction is of another order of magnitude with respect to food intolerances.

In the section with information for athletes you can find more information on the effects of certain foods, vitamins and supplements on the rebuilding of connective tissue.

170. EXPERIENCES WITH SUPPLEMENTS

Out of despair, floxed persons tend to think that if an approved and hi-tech drug has brought them such a tragedy why shouldn't they look for an antidote. However, before discussing the issue of supplements, we should emphasize that after so many years of research, if we had to handle a single piece of advice, we would just recommend to stay away of all supplements, no matter how interesting properties they may have. The deeper the intoxication, the more important becomes this recommendation.

Having said that, in severe reactions the miserable quality of life for months on end exerts a lot of pressure on the search for a drug or supplement that would help in healing or to promote and expedite recovery, but it is almost guaranteed that none helps at all with any symptom. For mild and intermediate reactions it is also wiser not to take anything, although some supplements may have a positive potential because the body of a not severely affected person can respond to supplements closer to normal.

In any case, either by the influence of others, or by own initiative, many floxed persons have the determination of taking supplements and ask for information about the experiences of others. This is what we try to include here.

Unfortunately there are not miracle substances for us; but according to numerous floxed persons there are some products that may help to overcome pain, chronic insomnia and disability. Supplements can be harmful too, if taken in excessive doses, if they interact with other substances or drugs you are currently taking, or simply if you are intolerant to them. You will have to avoid temptations of overdosing with vitamins and supplements, trying desperately to speed up your recovery. However, therapeutic and medically controlled doses of vitamins and supplements plus time are the only treatment advisable to date according to many doctors and former victims. Adjusting the dosages is a real challenge. Sometimes we stick to a very low dose and end up believing that the supplement is useless when in reality can be very helpful in higher doses. Other times we tend to take really high doses without any need for them. Always remember that twice the normal dosage of a good thing does not double its effect and in fact can turn it in to a poison. Normally supplements should be taken one or a few at a time, for some weeks and then shifting to other combinations.

Very often the floxed person that has not been sufficiently informed starts taking a lot of supplements together not aware of the dangers of interactions or increased action of some combinations. Probably, the best action to start with could be to get a blood test panel of the main ions, electrolytes, minerals and vitamins periodically, and to supplement only those that are out of balance. For everything you plan to take, you should first consult your doctor or health practicioner and do a research on your own.

Take also into account that many floxed persons are sure that the best choice is to stay away from any supplement irrespective of the severity of the reaction. Unfortunately there are contradictory experiences. To make things more difficult, floxed persons report different results with supplements. What works fine for some is counter indicated for others. Normally those differences are seen between floxed persons that belong to different groups of severity of the reaction. People with the same degree of damage seem to coincide more. Anyway, based on personal experiences of some floxed persons, the following are some comments on supplements.

Central nervous system (insomnia, restlessness) and vision problems tend to benefit from foods and supplements that have vaso-dilatory properties. Do not take them during acute phases of inflammation (for instance after a trauma or surgery), otherwise your pains will increase. Supplements with a thinning

action seem to be slightly detrimental for muscular pains and taken above safe doses cause small internal bleedings, of which you can easily detect kidney bleeding through an urine dipstick.

VITAMIN B

Many doctors prescribe vitamins of the group B because of our neuropathies, specially if the person is deficient in B12 for example. For the neurological problems, long-term treatments with vitamins B1, B12, benfothiamine and vit B coenzymes may help. There is some scientific evidence that citidine plus uridine (sodium salts CMP, UTP, UDP and UMP) may help to restore the myelin sheath, but do nothing to help the motor dysfunctions (more prevalent in floxings). Some floxed persons have taken this combination -prescribed by their neurologists- for up to three months straight without noticeable improvement. Some preparations of vitamins B can be also neurotoxic (vitamin B6 for instance), so it is especially important not to surpass the daily-recommended doses. The typical potency of a pill of vitamin B is 20,000 times the recommended daily intake. We all know that some water-soluble vitamins cannot be stored and their surpluses are excreted, but we also should be aware of the potential risks of overdosing for long periods of time. As a consequence, there is no wonder that many floxed persons report increased pains after taking vitamins of the group B (not enough data on the detailed composition of the exact brand and composition of the supplement that they took). See other parts of the report that include some hints on the toxicity of vitamins. We believe that some of the unexplained symptoms of some floxed persons are actually a side effect of overdosing with vitamins and supplements. We consider important to mention here that there are real risks in overdosing vitamins. For the vitamins of group B, widely used by many floxed persons, the main risks of exceedingly large doses are:

Vitamin B1: Heart palpitation, insomnia, agitation, high blood pressure, skin eruptions, hypersensitivity.
Vitamin B2: Nausea, vomiting, fatigue, anemia, low blood pressure, [yellow urine].
Vitamin B3/4: Flushing (Vit B3), nausea, vomiting, headaches, high blood sugar, high uric acid, jaundice, sweating, skin rash, raised stomach acid, insomnia, joint pains, calcium loss, increased choline requirements.
Vitamin B5: Edema, severe fatigue, joint pains, reduced protein metabolism, gastrointestinal symptoms, raised VLDL triglycerides, calcification, dehydration, depression.
Vitamin B6: Numbness in hands and/or feet (from high intake of pyridoxine, *not* pyridoxal-5-phosphate), depression, suicidal tendencies, severe fatigue, low blood sugar, mood swings, migraine-headaches, heart palpitations, hyperthyroid, hypothyroid (long-term supplementation), spinal / nerve degeneration (all forms of Vitamin B6), muscle spasms / cramps, osteoporosis, arthritis, higher blood pressure (short-term supplementation), lower blood pressure (long-term supplementation), abnormally high phosphorus-sodium ratio (low pH), abnormally high magnesium-calcium ratio, severe calcium deficiency, severe manganese deficiency, decreased estrogen, decreased prolactin, restlessness, increased dream activity, insomnia.
Biotin: Reduced / slowed insulin release, increased Vitamin C requirements, increased Vitamin B6 requirements, skin eruptions, increased blood sugar,
Folic Acid: Kidney damage, abdominal bloating / distention, nausea, loss of appetite, increased cholesterol LDL / HDL ratio, increased zinc and potassium requirements, may mask pernicious anemia from Vitamin B12 deficiency
Vitamin B12: Can cause folic acid-related anemia if low, numbness or tingling in right arm or right side of face, anxieties, panic-anxiety attacks, heart palpitations, hyperthyroid, optic nerve atrophy (in someone with Leber's disease), insomnia, some types of leukemia, liver, kidney diseases, may worsen symptoms of mitral valve prolapse, may increase tumor / cancer cell division,
Inositol / Choline: Nausea, vomiting, dizziness, high blood pressure, liver disease, kidney disease, cardiovascular disease, increased magnesium requirements, may increase potassium requirements, acne-like skin rash,
Lecithin: Gout, kidney disease, nausea, high blood pressure, dizziness, kidney stones, insomnia, osteporosis, joint pains, edema, burning feet, increased zinc andincreased calcium requirements, acne-like skin rash,

OTHER VITAMINS

Some vitamins are especially helpful, like vitamins C and E, but never in mega-dose preparations that are sold over the counter. As an example, vitamin E shouldn't be taken along with any blood thinner (bilberry, gingko, garlic) because of the risk of hemorrhage, more marked in severe floxings. A floxing creates a tendency to get hemorrhages more easily than before the intoxication so one has to be careful with all supplements with thinning effects. If you take thinners test your urine with a dipstick frequently to see if there are blood cells (normally not enough to stain the

urine, that still can look cristal clear). Excess vitamin E can also cause proximal weakness, myalgia, high serum CK and muscle necrosis, all extremely incompatible with a floxing. We do not yet know whether some of the myalgias and joint pains that many floxed people have after ingesting fish oil is due to the vitamin E that they have as antioxidant. In previous parts of this report we have profundized on the role of some vitamins on floxings.

BERRIES

Berry (cranberry, bilberry) extract seems to be especially effective in advanced stages of the floxing because of its modulatory effect on the smooth muscle of the blood vessels, and also its blood thinning and vasodilation capabilities. High doses can induce internal bleeding because of alterations in the quinolone-battered thinnest walls of the vasa vasorum. Other blood thinners have shown some promising therapeutic effects for floxed persons like ginkgo biloba, for instance. It would be interesting to find out whether a combination of one of these thinners plus magnesium taken in the early stages of a severe floxing (months 1 to 6 or so) could halt or limit the evolution of the injuries. Long term berries consumption can cause kidney and liver damage.

Grapes (seeds) taken raw have positive effects in some mild and intermediate cases. For decreasing the symptoms of stiffness, soreness and an antioxidant, grape seed extract has a good consideration among floxed persons.

COMBINATIONS FOR VISION

For vision problems, there are some combination of vitamins A and E, plus zinc, manganese, copper and lutein. Bilberry has on its own also a very noticeable effect in making floaters less noticeable and suppressing ziggies and flashies, but tends to increase myalgias and perhaps neuropathic pains. For vision problems it is also essential to control sugar levels because quinolones cause an abnormal functioning of the adrenal glands. Sugar increases flashers, ziggies and dark flies and also insomnia.

COENZYME Q10

Coenzyme Q10 seems to be low in serum samples of some long-term floxed persons (not enough data yet). Perhaps quinolones cause the coenzyme concentrations to lower, as statins do (agents to diminish cholesterol). Then supplementation with coenzyme Q10 to maintain normal levels could be beneficial but those floxed persons that have tried it have not noticed any measurable positive effect, but an increase in neuropathy symptoms. Statins have many common characteristics with quinolones. They are regarded as safe drugs too, with only a 1% to 2% rate of adverse effects, mainly musculoskeletal pains-myalgias, myopathies, neuropathies and even rhabdomyolysis (fatal muscle destruction that causes a fulminant renal collapse). But like quinolones, statins cause guaranteed damage to everybody when taken for long periods or high doses. It seems that quinolones may have a mechanism similar to the one through which statins cause their damage: decreasing the serum level of coenzyme Q10, inhibiting the conversion of HMG-CoA to mevalonic acid, both of which impair cellular integrity and reconstruction, that in turn cause destruction of muscle fibers.

Some doctors denied to some floxed persons the possibility that Q10 supplementation would increase their neuropathies (tremors, palpitations, peripheral neuropathy pains) because that is contradictory with all their knowledge. Nevertheless it is true. For instance, the following information reports unwanted nerve symptoms in HIV patients that take Q10. In our opinion, something similar must be happening with floxed persons.

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CoQ10 might also interact with reverse transcriptase inhibitors used for treatment of HIV (e.g., lamivudine and zidovudine). These medications can cause damage to the mitochondria, the energy-producing subunits of cells, leading in turn to a variety of side effects, including lactic acidosis (a dangerous metabolic derangement), peripheral neuropathy (injury to nerves in the extremities) and lipodystrophy (cosmetically undesirable rearrangement of fat in the body) . **The supplement CoQ10 has been tried for minimizing these side effects, but unexpected results occurred**. In a double-blind, placebo-controlled study, use of CoQ10 improved general sense of well being in people with HIV-infection using

reverse transcriptase inhibitors; however, for reasons that are unclear, it actually **worsened symptoms of peripheral neuropathy**. For this reason, people with HIV who have peripheral neuropathy symptoms should use CoQ10 only with caution.
The maximum safe dosages of CoQ10 for young children, pregnant or nursing women, or those with severe liver or kidney disease have not been determined.

AMINOACIDS

To break some acute reactions, special supplementations with simple amino acids can help. Amino acids like arginine, glutathione and carnitine are usually effective in limiting some pains or progression of the symptoms. Apparently acetyl-L-carnitine can help in the restoration of nerve endings in the long run (see aditional comments later). Alpha lipoic acid is used for the neurological pains with mixed results and its role seems more related to its antioxidant activity with little adverse effects.
Although many medical trials with aminoacids involve very large doses and sometimes long periods, it is recommended by most judicious doctors not to take large doses neither longer than one month.

PROBIOTICS

In many cases, quinolones create and additional problem killing the friendly bacteria of the gut, and allowing fungi to proliferate (candidiasis) as well as releasing a mal-absorption syndrome or leaky gut (damage of the lining of the intestine, impeding the normal breaking down and filtering of food elements). This syndrome poses a lot of problems in terms of lack of absorption of nutrients, toxicities and reactions to foods. It seems that the enormous net of vessels and nerves around the intestines gets damaged in severe reactions and consequently many foods provoke toxic-like reactions that are felt like exacerbations of the floxing. The injuries to the gut vessels can take a long time to heal and cause people to be in a permanent state of malaise. For this problem, some multi-minerals and multivitamins preparations (never in mega doses, avoiding "potency" products) will be helpful to replenish the normal levels of critical elements. In order to regain the natural balance of the intestinal flora, you may add some friendly lactobacillus, acidophilus or other strains to your diet.

Remember:
These recommendations on supplements are only comments about other's experiences. Do not use them for planning your recovery.

JOINT SUPPORT

On the other hand, insomnia, floaters and flashies increase a lot with natural anti-inflammatories or vasoconstrictors like lecithin, pineapple, sugar and substances that are good for the joints for instance. Floxed persons seem to have a need for some nutritional joint support to help with the deterioration and the pain. Substances like MSM, glucosamine, chondroitin and others are helpful in that sense but their anti-inflammatory activity increases vision problems (floaters and ziggies), the neuropatic pains, the twitchings and the heart arrhythmias and also seems to delay some kind of recovery. In previous sections of the report we have treated the supplements for joint support (connective tissue section), from the point of view of their potential role in helping with the restoration of the integrity of the damaged connective tissue.

NAC (N-acetylcysteine)

Recently, N-acetylcysteine, a mucolytic agent, seems to be providing good results among some floxed persons, especially among those recently intoxicated. It must be due to its effects as promotor of fluids in the mucous membranes as it is indicated for treatments of ischemic of vasculitic toxicities. It has a low toxic profile. It is also used as a liver protector against the toxicity of some anti-inflammatories.

SOY AND ACETYLCHOLINE

Oddly enough, it has been explained before that there are very few severely floxed persons that do not react badly to soy and its derivatives, especially if they are concentrated. Only sugar is so detrimental for floxed persons. We don't know for sure why soy (lecithin) is so bad for severely

floxed persons. Probably behind this fact there is some important clue to understand one of the mechanisms of damage caused by quinolones. We have theorised in previous sections about the imbalance caused by any ingestion of lecithin in the nerve connections where acethylcholine plays a dominant role as neurotransmitter, for instance at the neuromuscular junctions. One of our doctors has pointed to research reports that show that phosphatidylcholine binds to bilirubin (liver wasteproduct) creating a neurotoxic compound that has an affinity for the nerve endings. According to this doctor, floxed persons with normal-high or above normal levels of serum bilirubin should react worse to soy. Up to now not enough evidence has been collected among us as to confirm this theory.

GLUTATHIONE

It is a powerful antioxidant that plays a role in the healing of all cells after an intoxication. It is uncertain that supplemental glutathione can be absorbed and transported into the cells, so there are some doubts about the efficacy of glutathione supplementation. N-acetyl-cysteine is a precursor of glutathione and can work better in that sense.

CHLORELLA

Chlorella is an algae with a high content of chlorophyll and that supposedly has a detoxing effect binding to toxins. For us it is important because it helps with insomnia.

MAGNESIUM

It is well assumed that magnesium can help because of its vasodilator effect and its soothing capabilities on the nervous system. According to that, it seems important not to become magnesium deficient. There are many medical articles that show that a deficiency in magnesium levels prior to taking quinolones aggravates the floxing symptoms and injuries. Some floxed persons do have low serum magnesium levels, as confirmed by their blood tests. A combination of calcium and magnesium seems to work more efficiently. Most doctors aware of the injuries of a floxing recommend magnesium. Avoid high doses of magnesium for long periods in order to elude hypermagnesemia (see next paragraph entitled "SOME NOTES ON THE UNJUSTIFIED POSITIVE ROLE OF MAGNESIUM"). Besides hypermagnesemia, high doses of magnesium can have a laxative effect and for many floxed persons can exacerbate joint pains, cranks and noises, especially after some months of continued use. Be aware that some floxed persons have their joint pains and fasciculations increase when they take magnesium (normally this is the case of all severely affected persons).

SELENIUM

Selenium is a trace mineral that is essential to good health but required only in small amounts. Selenium is incorporated into proteins to make selenoproteins, which are important antioxidant enzymes. The antioxidant properties of selenoproteins help prevent cellular damage from free radicals. Free radicals are natural by-products of oxygen metabolism that may contribute to the development of chronic diseases such as cancer and heart disease. Other selenoproteins help regulate thyroid function and play a role in the immune system. Surveys indicate that individuals with rheumatoid arthritis, a chronic disease that causes pain, stiffness, swelling, and loss of function in joints, have reduced selenium levels in their blood. In addition, some individuals with arthritis have a low selenium intake. Further research is needed before selenium supplements can be recommended for individuals with arthritis, not to mention people with floxing. Doctors with a knowledge on floxings, also recommended selenium because it helps equilibrate the sulphur molecules of the body, so much needed after an intoxication. It is toxic to the nervous system in megadoses.Selenium has both beneficial and harmful effects.

Low doses of selenium are needed to maintain good health. However, exposure to high levels can cause adverse health effects. Short-term oral exposure to high concentrations of selenium may cause nausea, vomiting, and diarrhea. Chronic oral exposure to high concentrations of selenium compounds can produce a disease called selenosis. The major signs of selenosis are hair loss, nail brittleness, and neurological abnormalities (such as numbness and other odd sensations in the extremities). High blood levels of selenium (greater than 100 µg/dL) can result in a condition

called selenosis. Symptoms of selenosis include gastrointestinal upsets, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability, and mild nerve damage.

There are reports of people that have died because an acute intoxication after ingesting large doses of over the counter supplements of selenium.

CLINICAL CASE. After a single test showing a raised level of prostate-specific antigen (PSA), a 75-year-old man became concerned about prostate cancer. Without confirmation of the diagnosis, he researched prostate cancer on the Internet and discovered that selenium may have a role in its prevention and treatment. He purchased sodium selenite powder and tablets from two separate pharmacies for supplementation. He died in 24 hours due to acute selenium toxicity.

All said, not few victims of a floxing report diminished pains after exercise when they take small doses of selenium.

MANGANESE

Apart from its uses in rare overt deficiency disorders, manganese might have some efficacy in osteoporosis and osteoarthritis. Manganese ascorbate, in combination with glucosamine hydrochloride and chondroitin sulfate, was helpful in treating knee osteoarthritis pain in a recent randomized, double-blind, placebo-controlled pilot study. Oral manganese, however, may be neurotoxic in those with liver failure. Manganese is primarily eliminated via the biliary route, and hepatic dysfunction with biliar involvement (relatively common in floxings) leads to depressed manganese excretion. Manganese may accumulate in the basal ganglia of those with liver failure and may exacerbate hepatic encephalopathy and/or cause Parkinson's disease-like symptoms.

HAWTHORN

Is a vasodilator that helps a lot with insomnia issues, although its main drawback is an increase in dryness symptoms.

HERBAL PREPARATIONS

They are too risky to try, so is better to stay away of them. Some have a very toxic profile.

TABLE 25. POSITIVE AND NEGATIVE EFFECTS OF SUPPLEMENTS REPORTED BY FLOXED PERSONS

SUBSTANCE	POSITIVE	NEGATIVE	SUBSTANCE	POSITIVE	NEGATIVE
Lysine	↑	↓↓	*Magnesium*	↑↑↑	↓↓
Gaba	↑↑	↓↓↓↓	*Calcium*	↑↑↑	↓
Carnitine	↑↑↑	↓	*Vitamin C*	↑↑↑	
Hawthorn	↑↑↑↑	↓	*Vitamin E*	↑↑↑	↓↓
Gingko biloba	↑↑↑↑	↓	*Vitamins group B*	↑↑↑↑	↓↓ (B6)
Alpha lipoic acid	↑↑↑		*Folate (folic acid)*	↑↑↑	
Grape seed	↑↑↑	↓	*Soy (phosphatidylcholine)*	↑	↓↓↓↓
Friendly bacteria (probiotics)	↑↑↑	↓	*Bilberry, Cranberry*	↑↑↑↑	↓
Fish oils	↑↑↑	↓↓↓	*Bromelain*	↑	↓↓↓
Gamma linolenic oil (GLA)	↑↑↑	↓↓	*Serotonin promoters*		↓↓↓↓
N-acetylcysteine	↑↑↑		*Glutamine*	↑↑	↓↓↓
Glutahione	↑↑↑		*Quercetin*	↑	↓↓↓
Chlorella	↑↑↑↑		*Coenzyme Q10*	--	--
Olive leaf	↑↑	↓	*Tryptophan-5HTP*		↓↓↓↓

↑ : means positive effect; ↓ : means negative effect; The more arrows, the more pronounced the effect

The contents of table 25 are based in the experiences of less than a hundred persons. Not all of them have tested every one. Do not use it as a fixed frame of reference for yourself. They are only average experiences. This is only a brief list of some of the most well known ones. There are many other substances that could be rated based on our statistics, including minerals, all the rest of vitamins, all amino acids and many other herbal supplements, but it is beyond the scope of the current version of this report. Each substance has its own therapeutic effects. Some should not be taken together. In a future revision of this report an appendix on details about these and other supplements could be added with the point of view of the experiences of the floxed persons.

The suitability of taking supplements may vary along the course of the recovery. It does not seem wise to use the doses of the acute phase for long-term chronic treatments.

Detoxifying, chelating and cleansing treatments will not be discussed here. This report also does not cover any treatment by means of chemical drugs, metal compounds or the like. None of the people that have collaborated in this report has undertaken any of them. We believe that the risks of detoxifying programs is too high for floxed persons to be worthwhile.

In short, is best to avoid any supplement, and adhere to a healthy diet. In any case, only people with mild and intermediate reactions can benefit from supplements, because they can choose the ones with a given effect over a specific disorder. Severely floxed people have problems with several disorders that need opposite actions. Some of the problems of a severely floxed person will exacerbate if he/she takes supplements for another group of alterations. So there is no other way out but time.

As a rule of thumb vasodilators help with insomnia and some symptoms, but increase dryness. Thinners increase nerve pains, and sialoges have a good positive effect.

171. SOME NOTES ON THE UNJUSTIFIED POSITIVE ROLE OF MAGNESIUM

While it is true that a quinolone reaction reaches far worse consequences in people that are defficient in magnesium, there is not a single evidence that magnesium helps at all once the treatment and the acute phase of the reaction have ended, save the testimonies of floxed persons. There are many floxed persons that rush to "chelate", to "flush", to "bind" the remaining quinolones of the body with megadoses of magnesium, to get rid of the cipro or levaquin stuck to our cells as soon as possible. On top of that there are thousands of internet sites and health stores promoting wonderful stories about the properties of magnesium. Logically it is frequent to see how many people take enormous amounts of magnesium "maximum doses up to bowel tolerance" for treating a floxing.

Our rational search only supports slightly the supplementation of magnesium and only in low to moderate doses (never more than 300mg a day). For severe reactions it is better to stay away of magnesium if you somehow manage to have a normal and varied diet.

Please, notice that the doctors with the best knowledge in the treatment of quinolones' toxicities do recommend taking magnesium supplements in large amounts, so our opinion could be wrong, no matter how sound it might look to us.

In our experience, it seems that not few floxed people that overdose with magnesium supplements enter a state of hypermagnesemia after some weeks of taking high doses. Therefore the importance of having regular blood tests of magnesium, calcium, potassium and thyroid hormones if one takes high potency magnesium supplements.

Neuromuscular toxicity is the most consistently observed complication of hypermagnesemia. That is the lead reason that we have warned about magnesium supplementation. Increased magnesium decreases impulse transmission across the neuromuscular junction producing a curare-like effect. Hypermagnesemia causes blockage of neuromuscular transmission by preventing presynaptic acetylcholine release and by competitively inhibiting calcium influx into the presynaptic nerve channels via the voltage-dependent calcium channel. The initial clinical manifestation of this problem is diminished deep tendon reflexes that is usually first noted when the plasma magnesium concentration reaches 4.8 to 7.2 mg/dL. More severe hypermagnesemia can result in somnolence, loss of deep tendon reflexes, and muscle paralysis, potentially leading to flaccid quadriplegia and, since smooth muscle function is also impaired, decreased respiration and eventual apnea. Facial paresthesias also may occur at moderate serum levels.

Magnesium also is cardiotoxic and, in high concentrations, can cause bradycardia. Magnesium is an effective calcium channel blocker both extracellularly and intracellularly; in addition, intracellular magnesium profoundly blocks several cardiac potassium channels. These changes can combine to impair cardiovascular function. Bradycardia and hypotension begin to appear at a plasma magnesium concentration above 4.8 to 6 mg/dL. A variety of electrocardiogram changes can be seen at a concentration of 6 to 12 mg/dL, including an increase in Q-T interval (the most dreaded cardiac complication of a floxing).

Moderate hypermagnesemia can inhibit the secretion of parathyroid hormone, leading to a reduction in the plasma calcium concentration. This effect has been described after magnesium infusion in normal subjects. The fall in the plasma calcium concentration is usually transient and produces no symptoms, but many floxed people are prompted to believe that they are hypothyroid.

Hypermagnesemia may be associated with non-specific symptoms such as nausea, vomiting, and flushing. In addition, hyperkalemia has been described following parenteral magnesium administration. The mechanism responsible for the hyperkalemia is unclear, but decreased urinary potassium excretion due to magnesium-induced blockade of renal potassium channels may be involved. Although we have not yet managed to sort out and classify the vast amount of data pertaining to blood tests of floxed persons, it looks as if high dose magnesium supplementation tended to unbalance the potassium and calcium concentrations and thus inducing kidney and thyroid problems.

Hypermagnesemia may interfere with blood clotting through interference with platelet adhesiveness, thrombin generation time, and clotting time.

Fatal overdoses are also present in the literature (but not among the experiences known by us):

> FATAL HYPERMAGNESEMIA IN A CHILD TREATED WITH MEGAVITAMIN-MEGAMINERAL THERAPY
> John K. McGuire, et al. Pediatric Pulmonary and Critical Care Medicine, Children's Memorial Hospital and Northwestern University Medical School, Chicago, Illinois.
> We report a case of fatal hypermagnesemia resulting from the unsupervised use of high doses of magnesium oxide administered as part of a regimen of megavitamin and megamineral therapy to a child with mental retardation, spastic quadriplegia, and seizures. The treatment regimen was given at the recommendation of a dietician working as a private nutritional consultant without the involvement or notification of the child's pediatrician. Hypermagnesemia is an uncommon but serious side effect of the use of magnesium containing compounds. These compounds are widely used as laxatives and dietary supplements, and serious side effects are uncommon when used in appropriate dosages and with adequate supervision.
> The use of alternative medical therapies, including megavitamin/megamineral therapy, is widespread. Many patients use alternative medicine or seek care from alternative medicine practitioners without the recommendation or knowledge of their primary physicians. Despite unproved benefit, many alternative therapies may be safe. However, unsupervised use of generally safe treatments can result in serious side effects. This case report serves to illustrate the characteristic pathophysiologic changes of severe hypermagnesemia, an entity rarely seen in pediatric practice, and more importantly, it alerts primary care and subspecialty pediatricians to be aware of and monitor the use of alternative medical therapies in their patients.

172. ACETYL-L-CARNITINE

A number of floxed persons reported improved neurological symptoms after taking actetyl-l-carnitine (carnitine in short) for some weeks. After researching the possible link with an intoxication by fluoroquinolones, we have concluded that this report may help to explain the relationship.

> ACETYL-L-CARNITINE: A PATHOGENESIS BASED TREATMENT FOR HIV-ASSOCIATED ANTIRETROVIRAL TOXIC NEUROPATHY.
> AIDS: July 2004. Hart, Andrew et al; Royal Free and University College Medical School, London.
> "...acetyl-l-carnitine treatment improves symptoms, causes peripheral nerve regeneration and is proposed as a pathogenesis-based treatment for neuropathy (distal symmetrical polyneuropathy)... In

> this patient cohort, NRTI-induced distal symmetrical polyneuropathy (Antiretroviral toxic neuropathy) was diagnosed by a neurologist. All patients had stable antiretroviral toxic neuropathy prior to recruitment, making spontaneous resolution unlikely to have accounted for the changes in symptoms and innervation reported here...
> ...Six months of oral acetyl-l-carnitine treatment resulted in significant increases in the innervation (the amount or degree of stimulation of a muscle or organ by nerves) in epidermis, dermis and sweat glands, an improvement maintained throughout the treatment for all patients. The results demonstrate that dermal PGP-immunostaining nerve fibres regenerated sufficiently to reach the range found in normal skin. Intraepidermal fibres also regenerated, although more gradually. This difference in regrowth rate in separate skin areas is unsurprising as reinnervation occurs more slowly in epidermis than in other tissues..."
> Conclusions: acetyl-l-carnitine treatment improves symptoms, causes peripheral nerve regeneration and is proposed as a pathogenesis-based treatment for distal symmetrical polyneuropathy.

The whole report is very interesting and can be consulted freely on the internet.

173. DRUGS THAT HELP

Save one exception, we do not consider taking any drug and if you need or plan to do so, then ask your doctor. Many people take drugs for neuropathic pains (Neurontin and others), normally with good or no results. Other people get benefits from heparin for its profound effects on capillary permeability and anticoagulant properties, as it increases the traffic of substrates and waste products across the interstitial compartment between cells and vessels, but the risks of internal unnoticed bleeding are too high.

Every drug that uses the P450 liver cytochrome pathway for its metabolism will probably have an exaggerated effect on the floxed person because that mechanism is damaged by the quinolones and the concentrations of the drug can be much higher than expected.

It is better to avoid any medication that causes vasoconstriction, like anti-inflammatories (NSAIDS). If taken during months 0 to 5 they exacerbate the neurological symptoms (central nervous system) and joint pains (throbbing pains). There seems to be no problems with them from then on except in the event of severe floxings. In fact, NSAIDS, as many other drugs or supplements, can have a beneficial effect on mild floxings but very detrimental in severe floxings. This tends to baffle people but the reason could be simple. NSAIDS are anti-inflammatories and therefore their effect should be beneficial to all floxed persons alike. In mild and intermediate floxings, the ischemia (narrowing, flood depriving) of the blood vessels and the degradation of the extracellular matrix has not reached its critical point and still can take up some more narrowing and the extracellular still can do its job before more nerves and tissues start to dye massively. However in severe floxings the critical point of ischemia and degradation has been surpassed and there is not any margin left for further vasoconstriction and degradation, and therefore small amounts of NSAIDS cause immediate pains in nerves, an exacerbation of vision issues and many more relapsing symptoms.

Inversely, floxed persons that can take some NSAIDS, soy, pineapple, or other vasoconstrictors without relapsing or worsening their conditions are far from their critical ischemia point and can expect an easier and quicker recovery.

Cortico-steroids may help in the first stages. They can modulate, reduce or suppress the autoimmune reaction, so they could be a treatment of choice but not for severe cases. There are medical reports indicating complete and prompt healing of quinolone reactions after some days of administration of cortisone. Many people have stated that their symptoms returned amplified once the corticoid treatment was stopped. Long-term consumption of corticoids is associated with greater risks of rupturing major tendons for floxed persons.

After the acute phases, when a severe reaction has become chronic, it is not advised to undertake any treatment for your quinolone pains based on the use of corticoids. They will exacerbate the problem, and will make tendons much more prone to rupture. Avoid anti-inflammatories as much as possible. In severe reactions anti-inflammatories always exacerbate pains in the most affected areas, while in mild reactions

these negative effects might not be felt and therefore provide some relief for the pain.

Many of the commonly prescribed drugs for treating the floxing syndrome interact negatively with many natural supplements, so you should pay special attention to this fact and not mix drugs and supplements unless you are absolutely certain of their compatibility.

There is good site, created by Dr. J. Cohen, that has some recommendations about possible treatments for floxings. We recommend that you visit his page. In any case, here you have a summary of the treatment possibilities pointed there.

> TREATMENT POSSIBILITIES (www.medicationsense.com) . Dr. Cohen.
> ....However, please realize that these are simply suggestions. There are no known specific antidotes to quickly reverse a quinolone reaction. By necessity, people have tried many different treatment methods, and results are spotty. I do not know if any of the suggestions below are highly effective, but having experienced a severe, years-long disability myself in the mid-1990s (not a quinolone reaction) and now having improved considerably, I encourage people to keep asking questions and trying things.
> Many people sustaining quinolone reactions turn to their regular doctors and specialists. Some doctors try to be helpful, but many are uninformed about quinolone reactions or uninterested. Some doctors just cannot conceive that quinolones could cause such serious, long-term reactions. Doctors are taught that drug companies and the FDA conduct intensive research to ensure the safety of new drugs. This is untrue. According to an article in JAMA: "Discovery of new dangers of drugs after marketing is common. Overall, 51% of approved drugs have serious adverse effects not detected prior to approval2." Many doctors are not aware of this.
> In any event, doctors may suggest a variety of medications. For nerve or neuropathic pain (tingling, burning or electrical sensations), drugs such as Neurontin (gabapentin) or anti-seizure drugs may be recommended. Tricyclic antidepressants are known to help some neuropathies. The best-known tricyclic is amitriptyline (Elavil), which is sedating, so it might also be helpful for people also experiencing insomnia. For others, it will be too sedating. Nortriptyline is as effective as amitriptyline for neuropathies, and nortriptyline generally causes less sedation or other side effects. Desipramine is similar to nortriptyline and may actually increase energy in people who are fatigued. In others, desipramine can cause anxiety. Avoid tricyclics in people with cardiac conditions or symptoms.
> Muscle spasms, twitching, tremors, and seizures may be helped with long-acting anti-anxiety benzodiazepines such as clonazepam (Klonopin) or diazepam (Valium). Some doctors may recommend Xanax, which is a poor muscle relaxant but effective for reducing anxiety. Xanax is fine for PRN (intermittent) use. Xanax works fast and is not usually sedating, but when taken three or four times every day, it can quickly cause dependency with severe withdrawal reactions. The long-acting benzodiazepines can also cause dependency, but in my experience, less frequently than Xanax does. With any of these drugs, the lowest dosage that works should be used.
> SSRI antidepressants (Zoloft, Paxil, Prozac, Effexor, etc.) may be helpful for depression. Because some people's nervous systems are very sensitive to these drugs, they should be started at very low doses and increased very gradually, if necessary. By "lower doses," I mean doses that are lower than the lowest doses recommended by manufacturers. For example, although the usual starting dosage of Prozac is 20 mg/day, 5 mg/day has been effective in clinical studies and works for many people.
> Anti-inflammatory drugs are controversial: some people have written to me that they have been helped with anti-inflammatory drugs, especially for muscle/joint/tendon pain, but others have written that these drugs have worsened their conditions. Corticosteroids (cortisone, etc.) are very controversial. Doctors sometimes prescribe steroids in the hope of reducing the reactions, but many people have written that steroids actually made their reactions worse. Steroids can increase the risk of tendon ruptures with quinolones.
> There may be other medications used for quinolone reactions that I have not listed here. This list is not intended to be comprehensive. It merely reflects my knowledge, which is limited. For more complete, updated information, please ask your doctor or pharmacist. Also, check the websites listed at the bottom of this article.

Exceptionally, we have researched a little on one enzyme and one medicine, as explained herein below.

174. SERRAPEPTASE

This natural enzyme is known for its anti-inflammatory effect, blood thinning properties and its ability to block the amines that transmit the pain signals of the inflammed tissues, hence its capacity to

decrease the pain levels. It is used in Europe with relative frequency. There is no surprise that it is a thinner that facilitates the exchanges at the extracellular matrix and through the small veins and arteries.

The enzyme has been tested in a very limited trial with a core of floxed persons, with not very relevant conclusions. The conditions under which it has been surveyed, and the results are:

- Floxed persons with intermediate and severe reactions. None with mild floxing.
- Floxed persons in their 3rd, 4th and 5th years; none recently floxed person.
- Doses of about 30 mg a day divided in three 10 mg units in empty stomachs, with water.
- It seems clear that it diminishes overall pains (neuromuscular myalgias) by a variable degree.
- The improvement is noticeable by the second day.
- The people have taken it for up to two weeks.
- Improves pains after vigorous activity.
- No ill effects perceived, not even increased tendency to bleeding common in other thinners, as nose bleeding and kidney bleeding.

That does not mean that the enzyme does not have adverse effects. It is a very little studied enzyme, what has its risks.

The conclusion is that more studies are needed before it could be recommended for long term floxings. No data avalaible on how can help floxed persons on their acute phase or shortly after being floxed.

175. ANETHOLTRITHIONE

During our research, we came across this report:

> ANETHOLE DITHIOLETHIONE: AN ANTIOXIDANT AGENT AGAINST TENOTOXICITY INDUCED BY FLUOROQUINOLONES]
> SIALOR OR SULFARLEM. F POUZAUD, M-O CHRISTEN, J-M WARNET, P RAT
> Tendinopathy and tendon rupture are the adverse effects observed with fluoroquinolone antibiotics in old patients. The aim of this study was to investigate the effect of anethole dithiolethione (5-[p-methoxyphenyl]3H-1,2-dithiole-3-thione) on the oxidative stress induced by three fluoroquinolones (pefloxacin, ofloxacin, ciprofloxacin) incubated with rabbit tenocyte cell line. Anethole dithiolethione is a well known antioxidant and glutathione inducer. Anethole dithiolethione is widely used in human therapy for its choleretic, sialogogic properties and recently proposed as cytoprotective agent in lung precancerous injuries prevention in smokers. In this purpose, protection against oxidative stress induced by fluoroquinolones has been assessed using cytofluorimetric probes to quantify cytotoxicity and reactive oxygen species production. Fluorescence signal was quantified in 96-well microplates, using cold light cytofluorometer. Significant reactive oxygen species production was detected after 45 minutes for all fluoroquinolones tested. Anethole dithiolethione has been evaluated on this parameter. Anethole dithiolethione significantly (*: $P<0.05$) reduces and normalizes reactive oxygen species induced by fluoroquinolones. So, anethole dithiolethione (Sulfarlem), well known for its antioxidant and glutathione inducing properties, good tissue diffusion and good tolerance in humans, could be beneficially associated to fluoroquinolones, and be proposed as a therapeutic adjuvant to prevent oxidative stress and tendinous adverse effects induced by xenobiotics and more precisely by fluoroquinolones.

If you have read the previous sections of the report, you will have learnt that we postulate that besides direct toxicity, the main mechanism of fluoroquinolone damage is a degradation of the extracellular matrix and a malfunction of all the microvessels that vehiculate the end exchange of vital functions, causing a standstill in many functions, for lack of proper fluid exchanges. This drug seems to be basically a secretions inducer, what would push ahead the fluid exchanges, so this kind of researchs make us to believe that some of the deductions that we have made about the floxing syndrome may have some ground.

The drug has been tested in a very limited trial with floxed persons (7 initially and only 5 ended the

treatment, the other 2 stopping it for lack of interest), with not very relevant conclusions. The conditions under which it has been surveyed, and the results are:

- Floxed persons with intermediate and severe reactions. None with mild floxing.
- Floxed persons in their 3rd, 4th and 5th years; none recently floxed person.
- Doses as directed on the package insert (3x25 mg/day). Body weights between 140 and 182 lb.
- The people have taken it for up to two weeks, with an average of 10 days.
- No improvement noted on tendons, as could be expected because such a long time had elapsed in all cases after the floxing.
- Some persons reported improvement in the central nervous system, specially brain conditions (awareness, clear thinking, better mood, less brain fog, less insomnia, much less anxiety) that could be real consequences of the better fluids exchange at the brain level or either attributable to a placebo effect.
- Less pains in joints and muscles, specially after exercise. The level of pain improvement is normally described as "half the pain". The pain and soreness after exercise did not disappear in any of the patients.
- No ill effects perceived.That does not mean that the drug does not have adverse effects.

A better controlled, more scientifical and more complete study is needed before any accurate conclusion for floxed persons can be withdrawn.

The compound taken is called commercially SULFARLEM in many countries. From the package insert, in french, we translate this:

Ingredients: anetholtrithione, monohydrated lactose, gum guar, wheat starch, sacharose, colloidal silica, magnesium stearate. [The size of the pill is minute]. *The covering has gelatin, sacharose, talc, titanium dioxide (E171), colouring (E110, E124).*
This drug is intented to treat the dry mouth symptoms caused by:
-neuroleptics (drugs used to treat some mental illnesses), caused by drugs used to treat depression, painkillers and drugs for treating Parkinson's.
-raditherapy of the neck, ears or jaw.
-alteration of the salival glands caused by Sjogren's.
Do not use Sulfarlem if:
-you have one or more biliar stones.
-you have an obstruction of the biliar ducts.
-you have severe jaundice.
-you are hypersensitive to one of the ingredients.
Sulfarlem may cause diarrhea [did not happen to any of the floxed volunteers].
Urine can become yellower as is not a cause of concern [happened to all volunteers].
Consult the potential interactions with other medicines.
Side effects:
-Excessive saliva production.
-Potential diarrhea and loose stools.
-Yellower urine.

176. ADEQUATE HABITS

The main points to address are the sensitization reaction and the vascular-matrix degradation. Many flare-ups are clearly linked by floxed persons with the ingestion of quinolone-containing food, but other relapses that seem to come out of the blue. As a rule of thumb we should limit new releases of immune compounds and clogging-constrictive actions. It seems that it may be wiser to avoid as many toxical compounds as possible. So a floxed person has to avoid exposure to toxics throuhg his/her leisure or at work.

As for food and supplements, one could rate them as IgG producer, thinner, thickeners, vasodilator, vasoconstrictor or neutral ant take decissions based on that properties.

In general, avoid cold in the extremities. It slows recovery if you are cold for long periods. Take a natural, dry sauna occasionally, if you can. Avoid stressful situations and especially those that release strong emotions and feelings of anger and hate because they naturally raise cortisol levels and other hormones that target the nerves and a number of vasoactive autocoids and hormones that exert dilatory and constrictive effects resulting in negative consequences for the floxed person.

Remember:
Massive residues of quinolones are found in industrially raised poultry, fish and cattle; enough to cause a strong relapse.

PART XXIV: SPECIALIZED READING

177.MEDICAL EXCERPTS

In the next edition of the report we will include here the excerpts of about one hundred of medical papers with relevant information.

PART XXV: REFERENCES

178.BIBLIOGRAPHY-REFERENCES

We have consulted nearly 5,500 abstracts, summaries and full articles about quinolones' adverse effects. We have purchased the right to access some medical reports. For a more complete list of references, visit www.fqresearch.org. Here you can find some references.

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179.TYPICAL MISSPELINGS FOR "FLUOROQUINOLONES"

fluoroquinolones, lfuoroquinolones, fuloroquinolones, flouroquinolones, flurooquinolones, fluoorquinolones, fluorqouinolones, fluorouqinolones, fluoroqiunolones, fluoroquniolones, fluoroquionlones, fluoroquinloones, fluoroquinoolnes, fluoroquinolnoes, fluoroquinoloens, fluoroquinolonse, luoroquinolones, fuoroquinolones, floroquinolones, fluroquinolones, fluooquinolones, fluorquinolones, fluorouinolones, fluoroqinolones, fluoroqunolones, fluoroquiolones, fluoroquinlones, fluoroquinoones, fluoroquinolnes, fluoroquinoloes, fluoroquinolons, fluoroquinolone, ffluoroquinolones, flluoroquinolones, fluuoroquinolones, fluooroquinolones, fluorroquinolones, fluorooquinolones, fluoroqquinolones, fluoroquuinolones, fluoroquiinolones, fluoroquinnolones, fluoroquinoolones, fluoroquinollones, fluoroquinoloones, fluoroquinolonnes, fluoroquinolonees, fluoroquinoloness, cluoroquinolones, vluoroquinolones, dluoroquinolones, gluoroquinolones, eluoroquinolones, rluoroquinolones, tluoroquinolones, fkuoroquinolones, fiuoroquinolones, fouoroquinolones, fpuoroquinolones, flhoroquinolones, fljoroquinolones, flkoroquinolones, flyoroquinolones, flioroquinolones, fl7oroquinolones, fl8oroquinolones, flukroquinolones, flulroquinolones, fluiroquinolones, fluproquinolones, flu9roquinolones, flu0roquinolones, fluodoquinolones, fluofoquinolones, fluogoquinolones, fluoeoquinolones, fluotoquinolones, fluo4oquinolones, fluo5oquinolones, fluorkquinolones, fluorlquinolones, fluoriquinolones, fluorpquinolones, fluor9quinolones, fluor0quinolones, fluorowuinolones, fluorosuinolones, fluoroauinolones, fluoro1uinolones, fluoro2uinolones, fluoroqhinolones, fluoroqjinolones, fluoroqkinolones, fluoroqyinolones, fluoroqiinolones, fluoroq7inolones, fluoroq8inolones, fluoroqujnolones, fluoroquknolones, fluoroqulnolones, fluoroquunolones, fluoroquonolones, fluoroqu8nolones, fluoroqu9nolones, fluoroquibolones, fluoroquimolones, fluoroquiholones, fluoroquijolones, fluoroquinklones, fluoroquinllones, fluoroquinilones, fluoroquinplones, fluoroquin9lones, fluoroquin0lones, fluoroquinokones, fluoroquinoiones, fluoroquinooones, fluoroquinopones, fluoroquinolknes, fluoroquinollnes, fluoroquinolines, fluoroquinolpnes, fluoroquinol9nes, fluoroquinol0nes, fluoroquinolobes, fluoroquinolomes, fluoroquinolohes, fluoroquinolojes, fluoroquinolonss, fluoroquinolonds, fluoroquinolonfs, fluoroquinolonws, fluoroquinolonrs, fluoroquinolon3s, fluoroquinolon4s, fluoroquinolonez, fluoroquinolonex, fluoroquinolonea, fluoroquinoloned, fluoroquinoloneq, fluoroquinolonew, fluoroquinolonee