Diagnosis and treatment of chronically active toxoplasmosis in immunocompetent patients in the practitioners´ surgery

27 case studies

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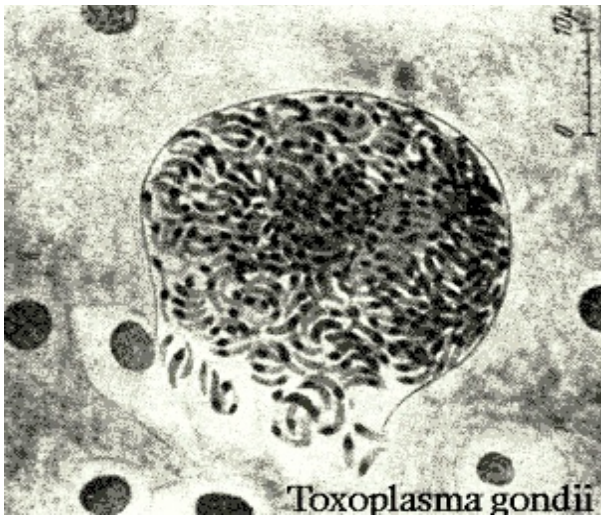

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Preface

Diseases sometimes develop over a longer period of time until a clear and conclusive diagnosis can be made. In these cases, general medicine has to consider several medical disciplines simultaneously, and this procedure is crucial in diagnosing the complex clinical picture described in this paper.

Isolated symptoms, as documented in the case studies, are frequent topics in anamnesis interviews, but the typical pattern of an active toxoplasmosis can only be detected if the practitioner uses an interdisciplinary approach during the anamnesis and includes relevant enquiries in the interview.

Today´s medicine does not cope well with the corresponding expenditure of time. Because of the enormous time pressure in hospitals and clinical surgeries, a fast diagnosis is necessary. Technical methods are indispensable measures here, but one unfortunately tends to believe that the problems of a patient are certainly “psychosomatic” if these technical procedures deliver clinically unremarkable results. Regrettably this mostly means the end of any further differential diagnostic investigation into the matter and the diagnosis remains stuck to the patient.

Sadly, the patient´s credibility – one of our best sources of information – is sometimes underrated, while the reliability of technical diagnostic methods tends to be overrated. In contrast to this it is vital for an anamnesis to cover the disease process as accurately as possible, taking into account the precise specifics and symptoms of multiple diseases, while asking a wide range of questions. As will be described in this paper in detail, an active toxoplasmosis should be taken in account in the clinical every days work, since it can cause severe illnesses also in immunocompetent patients.

I was very relieved when a patient, whose symptoms I had tried to diagnose for a long time, reacted favourably to a toxoplasmosis-specific treatment with a significant reduction in her muscular pains and other symptoms and I was even more surprised, when several of my patients, who suffered from combinations of fatigue, undefined muscular pains, concentration disorder and further symptoms, reacted equally well – up to complete remission of all symptoms – to this type of therapy. *The presumed key criterion for an active toxoplasmosis – a positive IgM detection in the clinical assay – was missing in all these patient´s records.* Based on a collection of these cases, a retrospective independent scientific study was assembled.

It turned out that the tachyzoite specific IgM can decrease surprisingly fast and it has already been proven by basic research that former presumed “inactive” Toxoplasma within the bradyzoite cysts can multiply and be highly active; it is presumed that they can trigger significant symptoms. It was possible to find scientific explanations and proof for almost all courses of this disease described in this study, which will be quoted accordingly.

Twenty Seven immunocompetent patients of a practitioner´s surgery, who showed hitherto unexplained combinations of symptoms as fatigue, undefined muscular pains and concentration disorder, exertional dyspnea up to a manifest cardiac insufficiency, rheumatoid - like symptoms and depression were diagnosed with an active toxoplasmosis and treated successfully in accordance with their therapeutic needs.

In the course of this study I became increasingly convinced that a reliable exclusion of an active toxoplasmosis is not possible based on laboratory results alone. The available lab tests are based on tachyzoite – specific antibodies and cannot reveal bradyzoite activitiy, because these undergo a near total “antigen shift” during their transformation from tachyzoites to bradyzoites. This will be discussed intensively with reference to the relevant sources. Until reliable laboratory parameters are made available, the diagnosis of an active toxoplasmosis that requires treatment must include a detailed anamnesis, taking the symptoms of an active toxoplasmosis into account. The relevant clinical presentation can be assessed by using the “toxoplasmosis checklist”, compiled and presented here and the therapeutic measures will be described in detail. The case studies and evaluations give an impression of the severe symptoms and the often lengthy progression of the disease – and of the efficacy of appropriate treatments.

This study has been compiled independently and without any help or support of a third party. The treatment follows the accepted guidelines for treatment with diagnose-based application of medication. The work has been written impartially and free of any conflicts of interest.

Dr Uwe Auf der Straße MD, April 2nd 2017

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Abstract

A high epidemic level of toxoplasmosis, a parasitic disease, can be observed globally. The negative impacts of toxoplasmosis especially on pregnant women, connatally infected children and immunodeficient patients are severe and have been researched thoroughly. Furthermore, there are by now numerous accounts for the persistency and the continuing activity of toxoplasmosis in immunocompetent hosts.

In a chronic active course of the disease, pronounced muscular pains, fatigue and concentration disorders occur, often along with profuse sweating and exertional dyspnea. Since the progression is slow in most cases, the clinical picture is less severe in the beginning than in an acute toxoplasmosis in e.g. immunosuppressed patients, therefore the disease is less conspicuous. It can be mistaken for diseases with different causes such as somatoform pain processing disorders, fibromyalgia, chronic fatigue, depressive moods, infectious mononucleosis, myopathy or exertional dyspnea of other origins. The study presented here will report cases of 27 patients suffering from an active toxoplasmosis, who were treated in a general practice in the northern Ruhr district of Germany.

Unfortunately, the serology referring to toxoplasmosis is unreliable. With a sensitivity of approximately 82%, the tests identify only tachyzoite - specific IgG; furthermore there are strong hints that the tests referring to the tachyzoite - specific IgM are unreliable. Bradyzoite – specific tests are not available. There is also abundant proof, that the toxoplasma located in the bradyzoite - cysts are not inactive. Recent research has found proof, that bradyzoites and tachyzoites exist in these cysts concomitant, and both are able to multiply themselves. The results of this study suggest that toxoplasma activity in these cysts can cause a severe disease, which remains undetectable to standard Lab procedures as long as no, or very few, cyst ruptures happen.

The tachyzoite - specific IgG can subside over longer periods of time, and thus it is very likely that an active toxoplasmosis can cause serious symptoms, while the lab results are completely negative. Another result of this study is that these cases neither differ with regards to their symptoms, nor with regards to the efficacy of the treatment from the seropositive cases.

Considering that the lab results referring to Toxoplasmosis are unreliable, a detailed anamnesis and clinical classification of symptoms are of crucial importance. After completion of a toxoplasmosis diagnosis the following orthodox treatment proved remarkably effective and good or very good recovery could be observed.

Unfortunately, no study on the prevalence and appearance of chronically active toxoplasmosis in immunocompetent patients in the practitioner´s surgery, the validity of laboratory parameters, especially the IgG and IgM assay, the duration of the infection and the effectivity of its´ treatment has been published so far. The case studies provided here permit conclusions on the subject for the first time.

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1.1. Introduction

Toxoplasmosis is caused by the protozoic, unicellular parasite Toxoplasma gondii. Cats which excrete large amounts of oocysts in initial infection, have been identified as its primary host. Oocysts are produced through sexual reproduction in the cat´s gut and contain infectious sporozoites. The oocysts can remain infectious for up to five years. After ingestion, the oocysts open; the sporo-zoites multiply through asexual reproduction (endodyogeny, Greek = internal budding) in the intestinal epithelium of the host, until the infected cells blast and the parasites are released as tachyzoites. A sexual reproduction only takes place in the intestinal epithelium of cats.

Almost all warm-blooded vertebrates, including humans, can serve as intermediary hosts. In the hosts, tachyzoites multiply through endodyogeny with a generation time of approximately six hours. The preferred target tissues of these parasites in humans are muscular and neuronal tissue, including the eye (Weiss & Dubey, 2010). A myocarditis (Montoya et al., 1997), a pulmonary involvement (Carme et al., 2002), a liver involvement (Dogan et al., 2007), a lymphadenitis mesenteralis (Kabelitz, 1959) and a stomach involvement (Ganji et al., 2003) have been documented.

Under pressure of an intact immune system, the development in an intermediary host is slowed down after some days – the parasites develop intracellular cysts, in which they can multiply slowly up to a count of several hundred per cyst in an asexual way as so-called bradyzoites. Bradyzoite cysts are potentially infectious. The surface structure of bradyzoites varies remarkably from that of tachyzoites, as Smith et al (1996) as well as Seon-Kyeong and Boothroyd (2005) have proven. Zhang et al. (1995) verified that the lgM- and lgG-response to bradyzoite cysts is very weak. The different antigen configuration of tachyzoites and bradyzoites and their intracellular existence, which is protected by a cystic membrane obviously helps the parasite to evade the immune system in the form of bradyzoites, as Fischer et al. (1997) stated.

Toxoplasma gondii is further able to modulate the immune response of the host, as several studies prove (Alibertini et al., 2004; Denkers and Butcher, 2005; Sinai and Joiner, 1997). For example, toxoplasma can prevent phagocyted bradyzoite cysts in macrophages from being merged with lysosomes. In this way the survival of bradyzoites is even enabled in Macrophages. The results of Courett et al (2005) suggest that toxoplasma can use CD11c and CD11b mouse leukocytes as a carrier. They found proof that CD11b leukocytes deliver Toxoplasma to the brain. Courett et al also investigated the distribution of Toxoplasma gondii in blood, lymphatic vessels and various organs in the course of the infection.

Considering the strategies of distrubution, camouflage, avoidance and control used by the parasite, it is understandable that antibodies only have a limited protective effect, as Frenkel already found out in 1967.

Ferguson et al. developed the hypothesis that in a chronic toxoplasmosis, bradyzoites can transform into faster proliferating tachyzoites, and that the influence of the immune system itself triggers a transformation of the bradyzoites back into tachyzoites, so that a type of dynamic equilibrium between the parasite and the host´s immune system could be established as a pattern of the chronic disease.

Cysts, which can contain a hundredfold of bradyzoites, can erupt periodically (Ferguson et al., 1989). Pavesio et al. (1992) found evidence that a “turnover” takes place in bradyzoit cysts and that they consequently are not inactive.

Ho-Yen et al. (1992) postulated that the phase of parasitaemia (in the shape of tachyzoites) might be only very brief in healthy, immunocompentent humans. After having changed into the shape of bradyzoites, the number of parasites in long-term cultivation of neurones increased further. Ho-Yen et al. concluded that this could be a mechanism specific to chronic toxoplasmosis. According to Weiss & Dubey (2009), bradyzoites can also persist for a lifetime. Watts et al. (2015) could finally prove in animal experiments that new bradyzoites can develop in the course of a chronic toxoplasmosis and that these bradyzoites were “surprisingly active” .Because of this, they question the orthodox opinion that bradyzoites are dormant stages of a toxoplasmosis. They conclude that bradyzoite activity can trigger a chronic phase of the infection.

A continuing activity of CD4 and CD8 T-helper cells, as well as interferon gamma is decisive for the control of the infection by the host (Suzuki et al in two work groups, 1988; Gigley et al, 2011). According to Badhra and Khan (2012), the CD8 T-helper cells are of vital significance. They show multifunctionality and express interferon gamma, the cytotoxic serine protease granzyme B, TNF alpha and interleukine-2. After a longer progression of a chronic toxoplasmosis, CD8 cells can increasingly lose the capacity to produce interferon gamma and TNF alpha. This loss of multifunctionality is described as “exhaustion of CD8 cells” and is supposed to lead to increased transformation of bradyzoites into tachyzoites, thus causing more and more symptoms of an active toxoplasmosis.

1.2. Immunocompetence does not rule out an active toxoplasmosis

Since the discovery of toxoplasmosis by Nicolle and Manceaux (1908), numerous clinical manifestations of the infection in humans have been described. Worth mentioning here among others are chorioretinitis, encephalitis, lymphadenopathy, myocarditis and polymyositis (Weiss and Dubey, 2009).

An infection in humans is most frequently caused by consumption of insufficiently cooked meat products, e.g. sheep, beef, lamb and pork, which contain cysts with bradyzoites (Cook et al., 2015). Vegetarians have a slightly lower risk of infection, even though an infection by contaminated water, which contains oocysts (Aramini et al., 1998) and contaminated vegetables is possible.

Remington found out as early as 1974 that 10-20 % of toxoplasmosis infections in immuno-competent adults and children can be symptomatic. The symptoms subsided mostly within one year, but in some cases they persisted for well over a year. Beverly & Beattie had discerned in 1958 that a persistence of toxoplasmosis was more frequent in patients with lymphadenopathy.

According to the study results of Greenlee et al. (1975), Behan et al. (1983) and Adams et al. (1984), myalgia is a frequent symptom of an acute infection or a reactivated toxoplasmosis. Behan et al. reported 1983 about a child with connatal toxoplasmosis as the source of a dermatomyositis.

Montoya et al. (1997) described an immunocompetent female patient, who developed a myocarditis with severe heart insufficiency because of a toxoplasmosis. In a study of Carme et al. (2002), 16 immunocompetent patients, who were infected with atypical strains of toxoplasmosis and had developed pulmonary symptoms, were observed.

1.3. Impacts of toxoplasmosis on the central nervous system

Townsend et al. (1975) discovered that 22 out of 45 patients suffering from a toxoplasmic encephalitis were immunocompetent. In a similar study of Luft & Remington (1985), 48 of 200 patients were rated immunocompetent.

Havlik et al. proved in a double-blind study in 2001 that a group of 60 patients with latent toxoplasmosis showed a remarkably longer response time (the patient had to react to a 1 x 1 cm light signal on a black screen) in comparison to a control group of 56 healthy patients. The remarkably longer response clearly correlated with the duration of the infection. Thus they concluded that a slowly increasing damaging effect of the toxoplasmosis on the human host exists.

Significant psychological changes with aggressive behaviour and increased impulsiveness in patients with a seropositive toxoplasmosis (Coccaro et al., 2015), frequent schizophrenia (Yolken et al., 1975; Torrey et al, 2012) and increased numbers of suicide attempts (Townsend et al., 1975; Yagmur et al., 2010; Dalimi and Abdoli, 2012) were also registered. Flegr (2007) intensively studied the behavioural changes and subsumed observed behavioural changes in a study in 2013.

Still measurable changes in the MRI of the brain are not necessarily observable. Assimakopoulous et al. (2015) reported about a patient suffering from toxoplasmic meningoencephalitis who presented an unobtrusive MRI result. Even considering the fact that the patient was immunosuppressed, it remains to be asked if negative MRI results of the brain are frequent in these types of infections.

1.4 Prevalence of seropositivity of toxoplasmosis

The prevalence of seropositivity with regards to toxoplasmosis for the global population is estimated to be about 30% (Montoya & Liesenfeld, 2004), with a deviation range of 10-60 % (Pappas et al., 2009). Mavin et al. (2000) as well as Jean et al. (2011) showed a decrease of seropositive test results in Scotland for the period of 1999-2000. Nevertheless, the prevalence of seropositivity increased significantly with age (20% in 11-20 year-olds, 90% in 71-80 year-olds). Seropositivity can persist after an infection, but there are indications for a decrease of the antibody titre, if the infection happened over an extended time (Jean et al., 2011).

Wilking et al investigated the seroprevalence of toxoplasmosis in Germany in 2016. The seroprevalence increased from 20% in the group of 18-29 year-olds to 77% in the group of 70-79 year-olds. Above the age of 79 years, a prevalence of 84% was ascertained. A male gender increased the risk by the factor 1.76. The keeping of cats and a BMI ≥ 30 were further risk factors. A vegetarian diet decreased the risk. In Eastern Germany, the prevalence was significantly higher than in Western Germany in all age groups; for the group of 40-69 year-olds the difference was up to 20%. A seropositivity of 50% of the entire adult population was ascertained. In the Netherlands, the complete seroprevalence in the period from 2006 – 2007 was significantly lower at 26%. Pappas et al wrote 2009 about the global prevalence of positive Toxoplasma results on the basis of Lab results from pregnant women. They found that the prevalence in Nothern Europe is significant lower than in Germany.

1.5 An active toxoplasmosis cannot be ruled out because of a negative IgG

The prevalence of seropositivity most likely does not represent the number of infected individuals. It has been ascertained early on in animal testing that not all infected individuals develop antibodies against toxoplasma (Jacobs, 1966). Later indications were found that the toxoplasmic IgG in humans can drop in time after the parasitaemic phase (Jean et al., 2011). Thus it is plausible that there are toxoplasmosis carriers, who are seronegative, but still develop significant symptoms because of a toxoplasma activitiy within the cysts (replication through endodyogeny, transformation of bradyzoites into tachyzoites, coexistence of bradyzoits and tachyzoits). Brady-zoites are only very moderately effective for the development of antibodies (Zhang et al, 1997; Smith et al., 1996 / See also Watts et al, 2015), and as far as I know, there are no bradyzoite specific tests for routine laboratory work available.

1.6 A seropositivity for toxoplasmosis often only exists for immunoglobuline G

Smith et al. (1996) pointed out that the immune response of the human immune system with regards to bradyzoites (the most commonly occurring type in immunocompetent patients after the completion of an acute infection phase) was very weak in most cases; they saw a reason in the rare presentation of antigens, which only occurred in connection with seldom happening rupture of cysts (Ferguson et al., 1989) and an almost complete lack of antigen-overlap between tachyzoites and bradyzoites. The organism´s stimulation to produce specific antibodies after the parasitaemic phase is possibly only very weak.

Ho-Yen et al. (1988) found out that a positive PCR detection (polymerase chain reaction) can be missing in immunocompetent patients; they attributed this to the brief phase of parasitaemia. The PCR assay proved to be sensitive, but only with regards to tachyzoites. This finding is in accordance with Bretagne (2003), who found out that negative results for IgM and PCR were frequent in toxoplasmosis patients.

In a study Yagmur et al. (2001) conducted with 200 participants, toxoplasmosis IgG was found in 41% of the cases of patients with an attempted suicide, as opposed to 28% in the healthy control group. Still the fact that the positive rate for IgM was only 5,5 % for the suicide group versus 5% in the control group received less attention. This could point to the assumption that a seropositivity for IgM might also be missing in clinical relevant toxoplasmosis.

Dubey et al (2002) examined the prevalence of viable Toxoplasma gondii in market weight pigs in Massachusetts by using Sabin–Feldman dye test, the modified agglutination test, and the Western blot as serological tests along with cats as bioindicators. Two of these cats were infected with toxoplasma gondii and shed oocysts, although the meat they had been fed with came from pigs which had been tested seronegative with the afore mentioned tests. This finding also supports the conclusion noted in 1.5 on the previous side.

On the grounds of the findings quoted in 1.5 and 1.6, the frequent conclusion that a missing IgG, IgM or Western blot detection or a negative PCR rules out a toxoplasmosis cannot longer be supported.

1.7 The virulency of toxoplasma can vary

It might become increasingly important that the virulency of toxoplasma can vary. Grigg et al. (2001) proved that a genetic recombination of different strains of toxoplasma gondii in cats is possible and that these strains show a different virulency. This way new, atypical strains with a high virulency might develop from the commonly known strains I, II and III.

Initially, type II was predominantly spread in Germany. In southern Europe, types I and III are also found. Schares et al., as well as Herrman et al. (2010) also detected atypical strains in their study on the distribution of toxoplasma genotypes in Germany. It cannot be evaluated which types of toxoplasma are involved in the presented cases.

1.8 Clinical courses of toxoplasmosis

In my report, I will distinguish a chronic toxoplasmosis, which remains without symptoms from a *chronic active toxoplasmosis*, which in contrast to the *simple chronic toxoplasmosis* produces symptoms and significant clinical impact. It can also occur in immunocompetent humans. Both clinical courses *can* be concomitant with an increase in immunoglobulins, as has been presented in 1.2 – 1.6., but cannot be excluded by using laboratory results alone.

Since a toxoplasmosis is per se always chronic - neither the human immune system nor therapeutics seem to be able to completely eradicate it – the term toxoplasmosis will be used in the following for cases with an asymptomatic course. The cases presented here all deal with patients, who analogously suffer from an *active*, symptomatic toxoplasmosis. It cannot be evaluated in this report if the presented cases were caused by initial infections or reactivation of prevailing toxoplasma infections.

Clinical courses in patients with an immune deficiency or receiving immunosuppressive or immunmodulating therapy, as well as cases of connatal toxoplasmosis are explicitly excluded from this report.

2. Clinical diagnostic of active toxoplasmosis in the practitioner´s surgery

The reported cases arose from the normal work during consultation hours over a period of approximately two years in a general practitioner´s surgery in the northern Ruhr district. Almost all patients came into the practice complaining about a triad of fatigue, pronounced muscular pains with partially reduced muscular performance and concentration disorders; common accompanying symptoms were profuse sweating, lethargy and exertional dyspnea. None of these patients suffered from a seropositive rheumatoid syndrome or a carcinoma. Swollen lymph nodes could only be detected in three cases.

In most cases, the clinical picture showed a slow but continuous progression over months up to years, but in some cases intermittent causes were described as well. To offer a first overview, the symptoms and percentage frequencies presented in greater detail in the results section will be mentioned here. **The order of the symptoms corresponds with the "checklist toxoplasmosis"(p 125). The first 6 symptoms are regarded as main criteria.** On page 124 there is an explanation how all these symptoms are weighed.

Fatigue: All patients claimed an uncommon, sometimes permanent fatigue, which resulted in a great need for sleep. Even after submitting to this need for sleep, a normal alertness and performance could not be attained. This symptom mostly occurred in advance or parallel to muscular pains.

Muscles: All patients reported muscular problems that mostly affected arm and leg muscles symmetrically and that were constant in their anatomical localization for weeks up to years. Often, a muscular pain was registered during or after a light physical strain, e.g. pains in the thigh muscles when climbing stairs. In some cases, the affected muscles were sensitive to pressure and the muscular performance was decreased, sometimes muscular cramps occurred more frequently.

Concentration disorders: 93% of the patients stated significant concentration disorders and disorders of the short-term memory; word finding disorders were a frequent symptom as well.

Profuse sweating: 78% of the patients reported unusual bouts of sweating; these often occurred after only light exertion and also frequently in rest, especially at night.

67% of all cases demonstrated an exertional dyspnea corresponding to NYHA I – III, in two cases even a manifest **cardiac insufficiency** was detected, which was followed up by extensive cardiac diagnostics including coronary angiography – all tests delivering normal results.

63% of the Patients complained about lethargy, which disturbed their abiltiy to work and their social life seriously.

In some cases either the patients themselves or their relatives registered a strong tendency towards an increased **irritability (59%),** which produced inappropriate aggressive reactions even to minor challenges or disturbancies.

Several patients described intermittent **disturbance of visual activity (44%)** in the sense of a disturbingly **blurred vision**; the ophtalmological test rendered normal results.

41% suffered from depressive moods, this lead to a **depression in two cases**, which required treatment. Many patients complained about **restlessness and insomnia (38%)**, which did not show a strong coincindence to sweating.

33% of the patients suffered from anxiety states and reported to have repeatedly experienced anxiety in non threatening situations; this decreased rapidly with treatment.

Several patients reported about **peripheral soft-tissue swelling and oedemas (33%)**, which decreased with treatment. In some cases, patients also reported about **morning stiffness (30%), warm-up pain** and **arthralgia**; a manifest arthritis with joint swelling and burning sensation was not observed.

Frequently, patients only mentioned some of these symptoms, mostly fatigue was mentioned first. Many patients seem to attribute some of the symptoms, e.g. muscular pains, concentration disorders, poor performance, sweating and further symptoms to age-related ailments and thus tend to leave them unmentioned. The indications for an active toxoplasmosis only emerge after detailed questioning and from the combination of symptoms (see the attachment "checklist toxoplasmosis"). A thorough exclusion of other diseases with similar symptoms is essential. As an active toxoplasmosis cannot be ruled out by using laboratory methods alone the diagnose is then verified through the effectivity of the treatment.

Personal note: *I am aware that this "ex juvantibus" approach is uncommon and in general not a preferable option in medicine, but as stated above – the disease is severe and the lab results are not reliable. I have become increasingly convinced, that a "non - treatment" of an active toxoplasmosis based on negative lab results alone is the worst option for these patients. The initial treatment is prescribed only if other diseases are excluded and if the "Toxoplasma Checklist" indicates a high risk for an active toxoplasmosis, and a combination therapy should only be performed if this initial treatment has been successful. The normal approach, which relies strictly on laboratory results, does not help here.*

3. Methodology

At the beginning of this treatment series I was not aware of the fact that an active toxoplasmosis is a frequent disease in immunocompetent patients. The described triad and its accompanying symptoms, the unaccountability of IgG and IgM assays and the decribed procedure only emerged in the course of time following the cited publications and my own observations.

In cases of highly suspected active toxoplasmosis following the Toxoplasma checklist, a thorough exclusion of other diseases was followed by toxoplasma antibody tests. IgM was used with a detection limit of 3 AU/ml, negative below 6 AU/ml, borderline 6 – 9.9 AU/ml, positive above 10 AU/ml. LgG was used with a detection limit 3 IU/ml, negative below 7.2 IU/ml, borderline 7.2 – 8.8 IU/ml, positive above 8.8 IU/ml. The test used here was directed against tachyzoite-specific antibodies. Prusa et al. (2012) determined a sensitivity of 81.8 % and a specificity of 100 % in an evaluation of the test in connection with congenital toxoplasmosis.

Clindamycine was used to start the therapy; in two cases with 3 x 300mg, in all other cases with 2 x 600 mg. If a significant reduction of the symptoms could be observed within a week (in single cases, the prescription of clindamycine was prolonged), patients received pyrimethamine (Daraprim®) 25mg 2x1, sulfadiazine 500mg 4x1 and folinic acid 15 mg (calcium folinate) 1x1 for 4-6 weeks. In some patients´ treatment, the combination had to be altered.

The details of these alterations can be found in the case studies and on page 90 under item 6 "overview of prescribed therapies".

In three cases with a very long persisting, extendedly symptomatic and positive IgG assay, I initiated a combination therapy even though the initial clindamycine treatment showed no clear effect. Unfortunately, this did not lead to a significant improvement of the clinical picture. Thus the essential criterion for the diagnose of an active toxoplasmosis in this study, the effectivity of the specific therapy, was missing. Because of this, these cases are not listed among the case studies. The IgG scores for these patients were 27.2, 118 and 208 IU/ml, the IgM scores were negative, the patients´ age was 64, 60 and 48 years and the symptoms had persisted for approximately 20 years.

These three cases lead to a decision for the further treatments: if the symptoms did not react to clindamycine administration, the prescription of a combination therapy was declined.

From 08/2016 onwards, a systematic interview of patients was done with the help of a questionnaire. The range of questions broadened with time, since the interviews delivered an increasingly comprehensive picture of the disease. The small number of patients, the personal knowledge of them and the individual courses of the disease made an anonymization impossible.

The questionnaire included questions on the duration of illness; furthermore, patients rated symptoms as muscular pains, fatigue, concentration disorders and profuse sweating on scales from 0-10 (0 = without symptoms / 10 = strongest symptoms) at three times. Prior to therapy, after treatment with clindamycine, and after completing 4 and 6 weeks of combination therapy.

In the course of the study, the questionnaire was supplemented by observation of further symptoms, such as: exertional dyspnea, lethargy, increased irritability, depressive moods, increased anxiety, visual disturbances, vertigo, peripheral oedemas, morning stiffness, sleeping disorders, abdominal pressure or pain, nausea, swelling of the lymph nodes and arthralgia.

Furthermore, patients were asked about side effects during therapy and whether they would – if needed – take the prescribed medication again. Additional symptoms could be added in handwriting. These results supplement the case studies; for some patients further intensities and reductions of symptoms are mentioned. The “checklist toxoplasmosis” that has been developed in the course of this study can be found in the appendix. The symptoms are arranged in the order of their frequency of occurrence.

To prevent inaccuracies, initial intensities of “0” and “1” and their symptom reductions were not accounted for in the final evaluation of all cases. Most patients described a remaining symptom intensity of “1” as negligible, thus the expression “free from symptoms” is used in the case evaluation of these patients. The expression “largely free from symptoms” equals the remaining symptom intensity of “2”.

Particulars on symptom reduction in %: this was determined from the symptom reduction on the VAS (Visual Analog Scale). **Examples:** a symptom reduction from “8” to “2” was accounted as 75% reduction, from “9” to “3” determined a 66% reduction. Intermediate values e.g. “6-7” were accounted as 6,5. The symptom reduction in % of all patients per group was summed up to the average symptom reduction in %, which therefore, cannot be the same as calculated by the average symptom intensities before and after treatment. Please keep that in mind when reading the survey of the results (p 126 and 127) in the appendices.

4. Case studies

For the sake of clarity, the anamneses listed below have been reduced to symptoms and results that are related to the active toxoplasmosis. The complete anamneses are in some cases significantly more extensive.

The first treatment started on 12th January 2015 (case 23), the treatment of the last case registered in this study (case 25) was completed at the end of January 2017.

Single symptoms might possibly be explained by other diseases, but the combination of symptoms with a recurring pattern point to a uniform reason, i.e. an active toxoplasmosis. The crucial diagnostic components are the anamneses and – since the results of the serology are uncertain – a thorough exclusion of other diseases and the effectivity of the toxoplasma - treatment. The specificity of the treatment is discussed in 7.5. For the sake of clarity, individual aspects and interpretations of a final discussion have been included in the case studies.

Cases 1 – 17 (group A, p. 19 - 56), include patients who showed the typical symptoms of an active toxoplasmosis and increased levels of the IgG against toxoplasmosis; none of them showed significant increased IgM. The differential diagnosis had either already been performed or was completed before the therapy was started. All of them improved very well under the toxoplasma specific treatment. They are arranged according to their levels of IgG.

Cases 18 – 27 (group B, p. 58 - 81), include patients with a completely negative toxoplasma serology, who also presented the clinical picture of an active toxoplasmosis, but who did not have a conclusive diagnosis and therefore no treatment for their disease, although most of them had undergone several diagnostic procedures due to serious complaints. They also responded very well to the specific treatment. These cases are arranged according to the intensity of the clinical picture, starting with the less severe cases.

4.1 Case 1, Mrs M.V., age 35

In 10/2009, Mrs M.V. was diagnosed with a borreliosis and treated accordingly. The treatment took about six weeks, an amelioration could only be achieved after treatment with ceftraxione 2.0g i.V. over a period of 23 days. Some weeks later, joint pains, morning stiffness of multiple joints (for approx. 15 minutes) and an increased fatigue gradually set in. No further moving arthritis was reported. In 1/2010 a rheumatologic evaluation was done, a fibromyalgia diagnosed. An appendectomy was done in 7/2010 because of a chronic appendicitis; afterwards the situation of the patient was ameliorated slightly. In 10/2010, an extensive dental restoration was done; due to a phobia of treatment this treatment was delayed. Still, the general condition of the patient did not improve any further; because of diffuse pains, she still needed tramadol 100mg 3x1.

In 1/2012, a general adynamia and a reduced cardiopulmonary resilience with exertional dyspnea that had been persisting for months was documented. A vitamin D deficiency was compensated with Dekristol® 20000, still her general condition showed only very little improvement. Discrete oedematous swelling of hands, feet and lower legs occurred along with an intermittent blurred vision.

ECG and ultrasound of the heart showed standard results, especially no sign of a myocarditis. In an ergometric assessment, the patient was able to achieve a load of 125 W, but at a heart rate of 162/min and a max. bloodpressure of 162/80 mmHg. Starting at the beginning of 2014, intermittent profuse sweating in the evening started, from 5/2014 joint pains were again documented.

In 7/2015, Mrs M.V. suffered from acne inversa on the groin, with a **latency period of about three months** a veritable decline in performance with adynamia, concentration disorders, muscular pains, fatigue and profuse sweating. From 3/2016, three surgeries had to be carried out on abscesses of the groin caused by acne inversa; an improvement of the general condition did not occur.

4/2016: leuko 10,300 / mcl, Hb 13.9 g/dl at an MCV of 100 fl, ferritin 39 µg/l, vitamin B12 950 pmol/l. A folic acid deficiency at 2.2 ng/mL was diagnosed (from 5.4); an according substitution for three months showed no improvement. In 7/2016 the BSG was 18/30 mm, the CPR rate 0.93 mg/l and the leukocytes 10,300 / mcl.

In 4/2016 toxoplasma IgG 17.5 IU/ml, IgM negative. Administration of folic acid was terminated. ***The symptomatic had been persisting for six years, for ten months a veritable decline in performance had been persisting.***

Therapy: a significant improvement of the mentioned symptoms could be registered after the one-week therapy with clindamycine 600mg 2x1; after four weeks of combination therapy with pyrimethamine 2 x 25 mg / calcium folinate 1 x 15mg / sulfadiazine 4 x 500 mg the patient felt considerably better. Since some symptoms still persisted, the therapy was prolonged for another two weeks. After six weeks of medication altogether, the patient was almost free from symptoms. As well, the initial lethargy was reduced from “6” to “0”. With reference to the exertional dyspnea an improvement from 6 to 2 occurred and the oedematous swelling of hands, feet and lower legs was reduced from 5 to 2.

Nota bene: an endocarditis lenta was considered because of differential diagnostics, still the inflammation parameters were only slightly increased and no auscultatory vitium was detected. The therapy mentioned above resulted in a fast and considerable recovery; the exertional dyspnea was amended considerably; further cardiological diagnostics were therefore unnecessary.

Mrs M.V. was still free from symptoms in 1/2017; the symptoms of fatigue as well as the profuse sweating were further reduced after the end of therapy. Mrs M.V. suffered from no side-effects and would repeat the therapy if necessary.

Comment: The medical history of the patient contained several factors, which affected the immune system of the generally healthy young woman: a borrelliosis, a chronic appendicitis, a bad tooth status, which was only restored delayed and finally an acne inversa. The patient suffered for at least six years from adynamia, lethargy, concentration disorders and exertional dyspnea. These were symptoms of an active toxoplasmosis, which had worsened considerably for about two months after the onset of the acne inversa.

Mrs M.V., result of questionnaire:

muscular pains initially:	**7**		
after 1 week clindamycine:	**6**		
after 4 weeks combination therapy:	**2**		
after 6 weeks combination therapy:	**0**		
4 weeks after end of therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**4**		
after 6 weeks combination therapy:	**2**		
4 weeks after end of therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**8**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**2**		
after 6 weeks combination therapy:	**0**		
4 weeks after end of therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**7**		
after 1 week clindamycine:	**7**		
after 4 weeks combination therapy:	**6**		
after 6 weeks combination therapy:	**2**		
4 weeks after end of therapy:	**0**	**reduction of symptoms:**	**100%**
exertional dyspnea initially:	**6**		
after 1 week clindamycine:	**6**		
after 4 weeks combination therapy:	**4**		
after 6 weeks combination therapy:	**2**		
4 weeks after end of therapy:	**2**	**reduction of symptoms:**	**66%**

4.2 Case 2, Mr K.S., age 59

Mr K. suffered from multiple previous illnesses: multiple severe wear damages of the spine, condition after 6 surgeries altogether, a pronounced COPD, a coronary sclerosis, condition after boundary zone infarction approx. 2008 and a PAD, to mention just a few.

He explained that he has been constantly tired for eight years, slept frequently and could hardly concentrate, was bad - tempered and had severe muscular pains all over the body. The exertional dyspnea had even increased.

11/2016 toxoplasmosis IgG 24.4 IU/ml, IgM negative. ***The symptoms had been persisting for eight years.***

Therapy: initially clindamycine 2 x 600mg was prescribed, which decreased the symptoms slightly. Therefore, pyrimethamine 2 x 25 mg and calcium folinate 1 x 15 mg were additionally prescribed. After the patient developed diarrhea Clindamycine was substituted by sulfadiazine 4 X 500mg. Under this therapy, the symptoms were amended further. The rating of adynamia was reduced from 8 to 6, and also the dyspnea was improved from 10 to 8, which could be seen as a positive development, taking the severe and incurable COPD into account. The severe irritability was reduced from 10 to 8. After 4 weeks all symptoms had been reduced significantly and the combination therapy was ended.

Mr K.S., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**10**		
after 1 week clindamycine:	**7**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
concentration disorders initially:	**10**		
after 1 week clindamycine:	**9**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
profuse sweating initially:	**0**		
after 1 week clindamycine:	**0**		
after 4 weeks combination therapy:	**0**	**no reduction of symptoms**	

Comment: Despite the multiple severe previous illnesses, the life quality could be increased considerably by the toxoplasmosis therapy; in 1/2017, the physical complaints of Mr K.S. had lessened in the course of three months, he had very few side-effects and would repeat the therapy, if needed.

4.3 Case 3, Mr M.U., age 60

Mr M. complained about having strong muscular pains for a long time and about undefined fatigue; he suffered from being very bad tempered. He could not concentrate sufficiently anymore and had become very forgetful.

A MRT of the brain was negative. A hypothyreosis resulting from a thyreoditis was being substituted sufficiently to achieve an euthyreosis, a vitamin D deficit had been substituted; both therapies did not improve the clinical picture.

09/2016 toxoplasmosis antibodies were assessed: **toxoplasma IgG 26.7 IU/ml, IgM negative.** ***The symptoms had been persisting for approximately five years.***

Therapy: initially clindamycine 2 x 600mg was prescribed, which decreased the intensity of the muscular pains by half within the first week of therapy. Mr M. was significantly less irritated. The patient developed diarrhea, which improved quickly after he stopped taking clindamycine. Following, he received a combination of pyrimethamine 2 x 25 mg, calcium folinate 1x 15 mg and sulfadiazine 4 x 500mg for four weeks, which lead to another significant improvement. The irritability was also reduced further from 10 to 4.

Mr M.U., result of questionnaire:

muscular pains initially:	**9**		
after 1 week clindamycine:	**4**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**78%**
fatigue initially:	**9**		
after 1 week clindamycine:	**4**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**78%**
concentration disorders initially:	**5**		
after 1 week clindamycine:	**5**		
after 4 weeks combination therapy:	**3**	**reduction of symptoms:**	**40%**
profuse sweating initially:	**0**		
after 1 week clindamycine:	**0**		
after 4 weeks combination therapy:	**0**	**no reduction of symptoms**	

Comment: In 1/2017, Mr M.U. had been largely free from symptoms for four months; he has experienced minor side-effects and would repeat the therapy, if needed. Apart from the high efficiency of the therapy it was noticeable in this case that the patient´s emotional imbalance and the frequently aggressive behaviour improved quickly and considerably. This was also found in the following case.

4.4 Case 4, Mr P., age 54

Mr P. reported about a reduced resilience that has been decreasing slowly over the past years; he had been frequently exhausted since the beginning of 2011, had developed bouts of sweating from light physical exertion and suffered from constantly sore muscles. Since 2015 increasing concentration disorders with a loss of short-term memory developed, he was increasingly impatient and quick-tempered. Since 2016 this condition worsened further; an occasional dyspnea and slightly accelerated pulse could be observed. In addition to this, frequently stinging pains in the knees, finger joints and shoulders occurred from exertion. Fatigue, exhaustion and bouts of sweating increased, the short-term memory worsened and the concentration disorders intensified from 5/2016. In 9/2016 **toxoplasma IgG 27.9 IU/ml, IgM negative**. Blood count negative, euthyreosis, no increase in CK, GGT, CRP and uric acid levels.

At that time the symptoms had been persisting for approximately six years, in a stronger manifestation for approximately two years.

Therapy: initially clindamycine 600mg 2 x 1 was prescribed, which slightly decreased the intensity of all symptoms, including the concentration disorders and the irritability. The therapy was well-tolerated and continued for another two weeks; afterwards, the patient was largely free from symptoms.

Mr P., result of questionnaire:

muscular pains initially:	**6.5**		
after 10 days clindamycine 2 x 600mg:	**4.5**		
after 3 weeks clindamycine 2 x 600mg:	**1**	**reduction of symptoms:**	**85%**
fatigue initially:	**8**		
after 7 days clindamycine 2 x 600mg:	**2.5**		
after 3 weeks clindamycine 2 x 600mg:	**1.5**	**reduction of symptoms:**	**81%**
concentration disorders initially:	**7.5**		
after 7 days clindamycine 2 x 600mg:	**2.5**		
after 3 weeks clindamycine 2 x 600mg:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**8.5**		
after 7 days clindamycine 2 x 600mg:	**3.5**		
after 3 weeks clindamycine 2 x 600mg:	**0**	**reduction of symptoms:**	**100%**

Comment: In 1/2017, Mr P. had been free from symptoms for 3 ½ months; he suffered from no side-effects during treatment and would thus repeat the treatment if necessary. It was most striking that in this case the irritability disappeared in a very short time. Since Mr P.´s symptoms improved after treatment with clindamycine only, a positive effect on the CNS seems to have occurred.

4.5 Case 5, Mrs M.G., age 67

Mrs M.G. recalls having suffered from constant muscular pains and fatigue since she was a young woman, she “always” had difficulties with exercising intensively and even light exertion would lead to dyspnoea. Following a myocarditis in 1995, she developed an absolute arrhythmia. Since 1995 she suffered from multiple chronic pains from her joints and seronegative rheumatoid arthritis was diagnosed. She also showed pronounced and persistent anxieties of unknown etiology.

For at least 16 years, chronic pains of the spine, hand and finger joints, hips and knees because of multiple arthrosis have been recorded. She had undergone hip-TEP left and knee-TEP right. Painful swelling of hands and feet since 2001, morning stiffness 3-4 hours was evident. Inpatient treatment began in 2003 for a diagnosis of seronegative chronic polyarthritis and secondary tendomyopathy – therapy treated with Lanterel since 2006. Beginning in 2/2010, an increasing worsening of the general condition could be seen. In 3/2010 Mrs M.G. was admitted to hospital. Increasing arthralgia, day-long stiffness, back- and abdominal pains along with nausea and an exceptional fatigue were recorded. An exacerbation of rheumatoid arthritis was diagnosed; under therapy with 30mg/d prednisolone the condition improved slightly. In 2010 a pronounced exertional dyspnoea was seen alongside a severe 4-week infection; it improved well under clindamycine.

In 3/2013 a cardiological examination was done because of exceptional fatigue and dizziness; a mitral valve insufficiency I°, no enlargement of the left atrium were diagnosed, a very good ejection fraction of 70-80%, which the cardiologist found unusual considering the documented artrial fibrillation. In 6/2013 a renewed cariological examination was done because of exertional dyspnoea and lower leg edema. Ergometry was limited to only 75W. Mrs M.G. was very weak and a pronounced dizziness and intensive unsteadiness in walking could be seen. In 1/2014 30mg prednisolone was prescribed because of her pronounced joint pains; this led to an intermittent reduction of the symptoms. Borderline rheumatoid factor was examined, ANA was found to be negative. 9/2016 a phlebological examination was performed which resulted in the diagnosis “lipedema of the legs and an increasingly decompensated lymphatic drainage disorder”. **11/2016 toxoplasmosis IgG was found 32.5 IU/ml, IgM negative.**

At that time the symptoms had been persisting for about 50 years, for about 6 years the quality of life had been impaired severely.

Therapy: Since the patient suffered from severe tenderness of the muscles and an increase in muscular pains had been reported by some patients during the initial treatment phase, the initial dose was reduced to 3 x 300 mg clindamycine.

During the first two days Mrs M.G. experienced increased muscular pains; afterwards her overall condition improved continuously. After one week of treatment, her resilience had increased, the patient also reported an enhanced lucidity. The combination therapy with clindamycine 300mg 3 x 1, Daraprim® 2 x 25mg and calcium folinate 15 mg 1 x 1 was continued for six weeks altogether.

Almost all symptoms were reduced continuously, the pain medication was reduced. Torasemid could be stopped after an extensive decrease of the oedema (from “7” to “0”) and a significant improvement of the exertional dyspnea. The concentration capacity increased further. Fatigue and muscular pains were even reduced from “10” to “0”. Also the previously pronounced weakness decreased; Mrs M.G. could start a light physical training and her muscles were no longer tender to the touch. The profuse sweating decreased only slightly, however Mrs M.G. reported that these symptoms were greatly dependent on the hormone replacement therapy she received from her gynaecologist.

A recurrence occurred after a three-week interval free from symptoms, the renewed combination therapy yielded very good results after only two days. In 3/2017, the patient is still mostly free from symptoms but is treated with the combination therapy once a week for recurrence prophylaxis. Considering the very long disease duration of about 50 years, a recurrence prophylaxis will probably have to be kept up for a very long time. She doesn´t need any more pain medication.

Comment: It is difficult to put the clinical amelioration and improvement of life quality into words. Before the therapy, the patient was so weak that she “couldn´t even carry a litre of milk”, let alone take care of her household. The permanent pains, fatigue, loss of drive and concentration disorders made a regular life almost impossible. The disease duration is very high with about 50 years; this is the maximum duration in this study. I consider this as the main reason why the reduction of symptoms in part does not come up to the reduction achieved in other cases. Despite the strong manifestation of symptoms, the score of toxoplasmosis IgG antibodies is moderate at 32.5 IU/ml, the IgM is negative. This case can best be compared to case 14, but the IgG is more than thrice the score at 97.9 IU/ml there.

Mrs M.G., result of questionnaire:

muscular pains initially:	**10**		
after 10 days clindamycine 3 x 300mg:	**9**		
after 6 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 10 days clindamycine 3 x 300mg:	**7**		
after 6 weeks combination therapy:	**2**	**reduction of symptoms:**	**75%**
concentration disorders initially:	**8**		
after 10 days clindamycine 3 x 300mg:	**7**		
after 6 weeks combination therapy:	**5**	**reduction of symptoms:**	**47%**
profuse sweating initially:	**7**		
after 10 days clindamycine 3 x 300mg:	**6**		
after 6 weeks combination therapy:	**5**	**reduction of symptoms:**	**57%**
exertional dyspnea initially:	**9**		
after 10 days clindamycine 3 x 300mg:	**9**		
after 6 weeks combination therapy:	**3**	**reduction of symptoms:**	**66%**
dizziness initially:	**10**		
after 10 days clindamycine 3 x 300mg:	**10**		
after 6 weeks combination therapy:	**3**	**reduction of symptoms:**	**70%**
anxiety and depression initially:	**9**		
after 10 days clindamycine 3 x 300mg:	**7**		
after 6 weeks combination therapy:	**4**	**reduction of symptoms:**	**63%**

4.6 Case 6, Mrs S.I., age 68

Because of an exertional dyspnea, a coronary angiography was carried out in 1995 and coronary heart disease was ruled out. In 1999 a recurrent dizziness made an inpatient assessment necessary; a benign positional vertigo was diagnosed. The exertional dyspnea endured and in 9/2010 an echocardiogram found a normal left-ventricular systolic function, ergometry results were negative up to 75 W. In 5/2013 a second coronary angiography was carried out, relevant stenoses were ruled out. Left-ventricular systolic function was normal.

After a renewed boost of sigmoid diverticulitis in 9/2013, a laparoscopic sigma resection was performed. 2 months later post-op strictures had to be treated by balloon dilatation and a polyp was removed from the colon descendens. Mrs S.I. recovered only poorly from surgery and reported that she often felt very tired, her muscles hurt after only light exertion and she had significantly less strength. She could not get her housework accomplished, felt a lack of drive, was constantly tired and had frequent bouts of sweating; she suffered from severe insomnia and had become very forgetful.

In 6/2016 a knee-TEP was implanted; the symptoms mentioned above increased further, the thigh muscles hurt even when climbing stairs, the exertional dyspnea and the concentration disorders enhanced again. 10/2016 lab results: blood count and CK normal, CRP slightly increased at 0,58. **Toxoplasmosis IgG 35.7 IU7ml, IgM negative. At that time the symptoms had been persisting for about 38 months.**

Therapy: Clindamycine 600mg 2 x 1 was prescribed; the symptoms ameliorated within one week. With good tolerance and rapid action, clindamycine was prescribed for another three weeks, without resorting to a combination therapy.

Mrs S.I., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine	**5**		
after 4 weeks clindamycine	**3**	**reduction of symptoms:**	**62%**
fatigue initially:	**8**		
after 1 week clindamycine	**2**		
after 4 weeks clindamycine	**3**	**reduction of symptoms:**	**75%**
concentration disorders initially:	**6**		
after 1 week clindamycine	**4**		
after 4 weeks clindamycine	**3**	**reduction of symptoms:**	**50%**
profuse sweating initially:	**7**		
after 1 week clindamycine	**4**		
after 4 weeks clindamycine	**1**	**reduction of symptoms:**	**85%**
dizziness initially:	**7**		
after 1 week clindamycine	**7**		
after 4 weeks clindamycine	**2**	**reduction of symptoms:**	**71%**
exertional dyspnea initially:	**9**		
after 1 week clindamycine	**5**		
after 4 weeks clindamycine	**2**	**reduction of symptoms:**	**87%**

Futhermore, irritability, impatience and insomnia were reduced from 7 to 2. Mrs I.S. experienced no side-effects and would repeat the therapy if needed.

Comment: The symptoms became conspicuous after the sigmoid diverticulitis and the resulting sigma resection; a significant downturn was recorded after the second surgery (knee-TEP). Despite significant symptoms the therapy was effected only with clindamycine 600mg 2 x 1 for about one month. Mrs I.S. has been without symptoms for 2 ½ months.

4.7 Case 7, Mrs P.E., age 64

In 5/2012 a subtotal tyroid resection was carried out. A post-operative wound healing disorder with a chronical infection followed; 4 wound revisions had to be done from 2/2013 to 6/2015. In the course of 2015, concentration disorders along with unusual tiredness and fatigue, as well as dizziness and headaches occurred.

After a latency period of 2-3 months, progressive muscular pains set in. These muscular pains only occurred after strains at first, but got persistent and the strength of the proximal upper and lower arm muscles receded. Initially, profuse sweating without a clear cause occurred simultaneously, even without stressful triggers. Run-in pain, morning stiffness and joint pains occurred. The patient´s resilience was significantly reduced.

A tremor of unknown origin developed in the right hand. A neurologist suspected an essential tremor; an appropriate therapy did not yield any amelioration. A trial cortisol impact therapy with prednisolone 2 x 20 mg for one week was almost without effect. **1/2016 toxoplasmosis IgG 37.9 IU7ml; IgM low at 3.99 AU/ml, not significantly increased. At that time the symptoms had been persisting for about one year.**

Therapy: An initial clindamycine therapy yielded results after a few days but was stopped because of side effects. In 1/2016 a combination therapy with Daraprim 2 x 25mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500 mg was started. After 20 days the muscular and joint pains had decreased significantly, the muscles were no longer pressure sensitive and the resilience increased. Concentration and memory returned to normal, the tremor vanished, as did the headaches. The dizziness was reduced from 8 to 4. An increase in transaminases occurred in the course of the combination therapy, but this got back to normal after the end of the therapy. This is also the reason for the shorter time of combination therapy of only 20 days.

Mrs P.E., result of questionnaire:

muscular pains initially:	**8**		
after 3 weeks combination therapy:	**5**		
6 months after combination therapy:	**2**	**reduction of symptoms:**	**75%**
fatigue initially:	**8**		
after 3 weeks combination therapy:	**3**		
6 months after combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**9**		
after 3 weeks combination therapy:	**4**		
6 months after combination therapy:	**2**	**reduction of symptoms:**	**77%**
profuse sweating initially:	**7**		
after 3 weeks combination therapy:	**3**		
6 months after combination therapy:	**2**	**reduction of symptoms:**	**71%**

In 1/2017 Mrs P.E. had been free from symptoms for about 11 ½ months. She experienced no side-effects and would repeat the therapy if needed.

Comment: It is highly probable that a chronically infected wound and the four following wound revisions contributed to the activation of the toxoplasmosis.

Since the tremor decreased significantly and the headaches and concentration disorders found a complete remission during therapy, I identified these symptoms as toxoplasmosis-related symptoms with a CNS-involvement. Similar to case 1, further slight improvements could be recorded after finalizing the therapy.

4.8 Case 8, Mrs S.C., age 63

In 2003, a first suspected diagnosis of myopathy was made by a neurological outpatients´ department due to chronically persisting muscular pains. The clinical assay was virtually inconspicious, an electrophysiological examination remained without remarkable result. A muscle biopsy was considered, but not carried out. In 2004, an unclear decrease in performance, significant daytime sleepiness and lack of drive led to a cardiological examination. Ergometry was without result up to 125 W., then a rise in blood pressure and muscular exhaustion led to the termination of the ergometry. The flow-directed catheter showed moderately raised blood pressure under stress. The long-term ECG yielded an inconspicuous result, a cardiac reason for the symptoms could not be found.

A rheumatological examination was made due to run-in pain and stress-related pains in muscles and joints in early 2016. A basic therapy with MTX was not started initially. In 10/2016, the symptoms of unclear muscular pains, fatigue and concentration disorders were mentioned in the practitioner´s surgery. The symptoms had been persisting for about 15 years, including an abnormal muscle soreness after only light exertion. Furthermore, an exertional dyspnea (“6”) and oedematose swelling (up to “8”) of hands and lower legs was diagnosed. It was most noticeable that the development of the condition happened in intervals of 3-4 month-long periods with less symptoms, followed by up to 10 day-long intervals of worsening symptoms, including heavy muscular pains, morning stiffness, listlessness, concentration disorders, fatigue and word-finding disorders. Especially the word-finding disorders and the short-term memory loss had increased significantly within the last 2-3 years. 11/2016 CK 212 U/l**, toxoplasmosis IgG 38.4 IU/ml, IgM negative.**

Therapy: clindamycine 600 mg 2 x 1 was prescribed and the muscular pains and fatigue diminished slightly after the third day. After one week, the morning stiffness and muscular pains were gone, fatigue and concentration disorders had reduced from 10 to 2, listlessness had halved from 10 to 5. The dizziness had reduced from 5 to 3. A combination therapy with Daraprim 2 x 25 mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500mg reduced the symptoms even further, but after 14 days the impact of the drugs seemed to lessen. Clindamycine 600 mg 2 x 1 instead of sulfadiazine was prescribed, which led to a further amelioration of the symptoms.

Mrs S.C., result of questionnaire:

muscular pains initially:	**10**	
after 1 week clindamycine:	**0**	
after 4 weeks combination therapy:	**0**	**reduction of symptoms: 100%**
fatigue initially:	**10**	
after 1 week clindamycine:	**2**	
after 4 weeks combination therapy:	**0**	**reduction of symptoms: 100%**
concentration disorders initially:	**8**	
after 1 week clindamycine:	**2**	
after 4 weeks combination therapy:	**0**	**reduction of symptoms: 100%**
profuse sweating initially:	**0**	
after 1 week clindamycine:	**0**	
after 4 weeks combination therapy:	**0**	**no reduction of symptoms**
dizziness initially:	**5**	
after 1 week clindamycine:	**3**	
after 4 weeks combination therapy:	**0**	**reduction of symptoms: 100%**

Comment: Despite exhibiting intensive symptoms, Mrs S.C. never complained about profuse sweating. It was noticeable in this case that the impact of the combination therapy with sulfadiazine decreased after about 14 days; through the use of clindamycine instead of sulfadiazine, a positive effect could be reattained. The listlessness, the dizziness and the slightly intermittent visual disorders with blurry vision disappeared completely, the peripheral oedema receded from 8 to 1. The exertional dyspnea and the depressive moods were reduced from 6 to 3. The patient smokes and a COPD persists. For safety reasons, a further ergometry was done following the therapy in 1/2017; this was without result up to 100 W. Mrs S.C. experienced no side-effects and would repeat the therapy if needed. By the end of 1/2017, the patient had been free from symptoms for about 2 ½ months.

4.9 Case 9 Mrs G.A., age 57

For about 6 years, Mrs G.A. had been exceptionally tired and worn-out frequently; a condition that had worsened in the last 2-3 years. Sleeping disorders, concentration disorders, profuse sweating in the mornings and muscular pains developed. She was often short-tempered and could not increase her weak physical fitness despite frequent exercise; a pronounced exertional dyspnea persisted. For about one year frequent pains of the eyes and visual disorders occurred, the patient described “wafts of mist” in her visual field. **11/2016 toxoplasmosis IgG 40,6 IU/ml, IgM negative. BSG was increased to 28/44 mm, otherwise all recorded laboratory results were normal.**

Therapy: clindamycine 600 mg 2 x 1 was prescribed, but the symptoms diminished only slightly within one week. Nevertheless, a combination therapy with clindamycine 600 mg 2 x 1, Daraprim 2 x 25 mg and calcium folinate 1 x 15mg was prescribed, due to the typical symptoms. This also led to a merely slight reduction of symptoms; after 4 weeks clindamycine was exchanged to sulfadiazine 4 x 500mg. From then onwards the symptoms reduced significantly, so that the successful therapy could be stopped after 7 weeks.

Apart from the changes in symptoms listed on the following page, these changes could be recorded: morning stiffness reduced from 8 to 1, visual disorders from 7 to 1, listlessness from 9 to 5 and anxiety and depressive moods from 7 to 5.

Only very few side-effects occurred. In 1/2017 the patient´s symptoms had been mostly ameliorated.

Comment: The reduction of symptoms after the first week´s treatment with clindamycine was only minimal; it would have probably been more efficient to execute the follow-up combination therapy with a sulfadiazine / pyrimethamine combination right from the start.

Mrs G.A., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine:	**7**		
after 4 weeks clindamycine combination	**6**		
after 3 weeks sulfadiazine combination:	**1**	**reduction of symptoms:**	**87%**
fatigue initially:	**8**		
after 1 week clindamycine:	**6**		
after 4 weeks clindamycine combination:	**6**		
after 3 weeks sulfadiazine combination:	**2**	**reduction of symptoms:**	**75%**
concentration disorders initially:	**9**		
after 1 week clindamycine:	**9**		
after 4 weeks clindamycine combination:	**8**		
after 3 weeks sulfadiazine combination:	**3**	**reduction of symptoms:**	**76%**
profuse sweating initially:	**9**		
after 1 week clindamycine:	**7**		
after 4 weeks clindamycine combination:	**6**		
after 3 weeks sulfadiazine combination:	**1**	**reduction of symptoms:**	**89%**
exertional dyspnea initially:	**8**		
after 1 week clindamycine:	**8**		
after 4 weeks clindamycine combination:	**7**		
after 3 weeks sulfadiazine combination:	**0**	**reduction of symptoms:**	**100%**
visual disorders initially:	**7**		
after 1 week clindamycine:	**6**		
after 4 weeks clindamycine combination:	**6**		
after 3 weeks sulfadiazine combination:	**1**	**reduction of symptoms:**	**85%**

4.10 Case 10, Mrs S.M., age 53

A hypothyreosis, which was substituted with L-thyroxine 150 µg, had been persisting for years. Mrs S.M. now reported that she had been suffering from unclear muscular and joint pains, stiffness of the fingers and continuous fatigue since mid 2015. She furthermore felt very listless, generally weakened and experienced head pressure frequently. Laboratory results 6/2016: **toxoplasmosis IgG 61 IU/ml, IgG 6.21 AU/ml. At that time the symptoms had been persisting for about 12 months.**

Therapy: Treatment was started with 2 x 600 mg clindamycine. During this well-tolerated therapy, the overall symptoms decreased continuously, so that the treatment with clindamycine was only kept up for one month. A combination therapy was not considered.

After termination of the antibiotic treatment, a vitamin D deficiency of 9.6 ŋg was substituted with Dekristol 20000 and the L-thyroxine prescription was increased from daily 150 µg to 175 µg due to the still persisting fatigue; that explains the further amelioration of this symptom after termination of the therapy.

Mrs S.M., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine 2 x 600 mg	**5**		
after 4 weeks clindamycine 2 x 600 mg	**1**		
2 months after therapy:	**1**	**reduction of symptoms:**	**87%**
fatigue initially:	**10**		
after 1 week clindamycine 2 x 600 mg	**6**		
after 4 weeks clindamycine 2 x 600 mg	**5**		
2 months after therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**4**		
after 1 week clindamycine 2 x 600 mg	**2**		
after 4 weeks clindamycine 2 x 600 mg	**0**		
2 months after therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**1**		
after 1 week clindamycine 2 x 600 mg	**1**		
after 4 weeks clindamycine 2 x 600 mg	**0**		
2 months after therapy:	**0**	**reduction of symptoms:**	**100%**

Mrs S.M. experienced no side-effects and would repeat the therapy if needed. The reduction of profuse sweating can be statistically evaluated as 100% reduction of symptoms, but due to the minimal intensity at the beginning of the therapy it is not included in the final assessment of the whole group. In 1/2017, the patient had been free from symptoms for about 7 months.

Comment: The IgM was not significantly increased, despite the onset of the disease being in the recent past. Apart from cases 4 and 6, this is another case in which the concentration disorders, a CNS symptomatic, are in remittance only from being treated with clindamycine.

4.11 Case 11, Mrs K.M., age 39

Mrs K.M. reported that she had been suffering from pronounced fatigue, sleeping disorders with profuse sweating at night, all over muscle and joint pains for at least nine years. She often felt cold and was very exhausted. Since approx. 2012, diffuse abdominal pains and diarrhoea had been persisting, her fatigue was worsened by nocturnal restlessness, profuse sweating and an unusual forgetfulness; axillary swelling of the lymph nodes as well as discrete oedema of hands and lower legs occurred frequently. Mrs K.M. suffered from severe anxiety of unknown cause.

She explained that since the beginning of 2016 she felt cold in the evening, nevertheless her nocturnal sweating and further symptoms had worsened. The entire disease activity revolved around intervals of 2-3 weeks. In 3/2016, a coloskopy was carried out, which yielded a normal result.

An exertional dyspnea and tachycardia developed by 6/2016; in 10/2016 the blood count, CK and CRK were normal with increased **toxoplasmosis IgG at 68.5 IU/ml and IgM 3.32 AU/ml. At that time the symptoms had been persisting for about nine years.**

Therapy: Under treatment with 2 x 600 mg clindamycine the muscular pains increased within the first 4-5 days; palpable swelling in the muscles occurred, but exertional dyspnea and joint pains were reduced at the same time. After 9 days altogether, the swelling of the muscles had disappeared. Within the first week of treatment, the patient experienced increased anxiety, which had been reduced significantly after 9 days. A combination of daraprim 2 x 25 mg, sulfadiazine 4 x 500 mg and calcium folinate 1 x 15 mgwas prescribed. After the next 5 days of treatment, the muscular pains and anxiety had been reduced to 0 and the resilience had been increased. The abdominal symptoms were in complete remission, no further swelling of the lymph nodes occurred, the peripheral oedema had disappeared.

In a conclusive interview in 1/2017 Mrs K.M. had been free from symptoms for 6 weeks. She evaluated the side-effects as “marginal”, which can be explained with reference to the intensive symptoms she had suffered from for nine years. She would repeat the therapy if necessary.

Mrs K.M., result of questionnaire:

muscular pains initially:	**7**		
after 1 week clindamycine:	**3**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**10**		
after 1 week clindamycine:	**5**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**6**		
after 1 week clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**10**		
after 1 week clindamycine:	**9**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
anxiety initially:	**8**		
after 1 week clindamycine:	**0**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
exertional dyspnea initially:	**6**		
after 1 week clindamycine:	**0**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**

Comment: Some patients report about a slight increase of muscular symptoms during the first two days of clindamycine therapy. Only in these cases, a palpable swelling of the muscles and an increase in anxiety occurred prior to a significant amelioration. Due to these findings, I reduced the initial clindamycine dose to 3 x 300 mg in cases with equally intensive symptoms. Abdominal symptoms as part of the toxoplasmosis symptoms were recorded as well in cases 12, 20 and 21.

4.12 Case 12 Mrs F.H., age 61

For at least 15 years Mrs F.H. had suffered from muscular pains, multiple pains of the finger joints, both hip joints, knees, elbows and morning stiffness. An according examination in a specialist clinic yielded no crucial diagnose. A secondary hyperparathyroidism as a result of vitamin D deficiency was diagnosed in 2011 and normalised by vitamin D substitution, however the multiple symptoms did not decrease. Mrs F.H. explained that she had been continuously suffering from permanent fatigue, listlessness, pronounced exertional dyspnea (up to a self rating of 10) and strong bouts of profuse sweating (up to 6) for the last ten years. All female members of her family tended to develop profuse sweating after menopause, but her condition seemed to be exceptionally grave. Her legs were being tender to the touch and swollen (up to 10) for years. She furthermore suffered from concentration disorders, intermittent visual disturbances ("blurry sight" up to 8), was very easily irritated and impatient and had undefined anxieties and frequent tremors of unknown cause in the mornings. The joint symptoms slightly decreased in 2012 due to a prednisolone prescription. A basic therapy with sulfasalazine yielded little decrease in symptoms and was stopped due to side-effects.

Mrs F.H. described recurring abdominal symptoms of unknown cause that she had for years. These occurred periumbilical and in the epigastrium in the form of pressure and nausea. She graded the symptoms´ intensity at 7. For some months she also complainted about an undefined inflamed rash on the lower abdomen and proximal thigh (8).

11/2016 AMA, dsDNA antibodies negative, ANA 1:320 up to 1:80). **Toxoplasmosis IgG 74 IU/ml, IgM negative. At that time the symptoms had been persisting for about 15 years.**

Therapy: Initial prescription of clindamycine 2 x 600 mg; the overall symptoms – apart from the exertional dyspnea - were thus reduced slightly within the first week of therapy. Consequently, Daraprim 2 x 25mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500 mg were prescribed for the duration of one month.

Apart from the changes listed on the next page, the following ameliorations could be observed: dizziness and visual disturbances disappeared completely, the inflammatory lesions and swelling of the legs were reduced from 10 to 2, the abdominal symptoms decreased from 7 to 3. By the end of 1/2017, Mrs F.H. had been mostly free from symptoms for 2 months; she suffered from self described "average" side effects and would repeat the therapy if needed.

Mrs F.H., result of questionnaire:

muscular pains initially:	**9**		
after 1 week clindamycine:	**4**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 1 week clindamycine:	**2**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**7**		
after 1 week clindamycine:	**3**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
profuse sweating initially:	**8**		
after 1 week clindamycine:	**3**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**50%**
exertional dyspnea initially:	**10**		
after 1 week clindamycine:	**9**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**80%**
irritability initially:	**10**		
after 1 week clindamycine:	**5**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**80%**

Comment: It was most noticeable in this case that the pronounced swelling of the legs (phlebological classification: lipedema III, stage II-III with increasingly decompensated lymphatic drainage disorder) decreased significantly in the course of the therapy. A similar development could be observed in other cases also, but never as noticeable as in this case. The decrease in exertional dyspnea was also noteworthy. Post-therapy the patient is able to walk 6 km without any difficulty, which is a strong improvement. A lymphadenitis mesenterialis as a possible reason of abdominal symptoms due to toxoplasmosis has been known for some time (Kabelitz 1959); a gastric involvement due to toxoplasmosis has also been shown (Ganji et al. 2003). Please compare cases 11, 20, 21.

4.13 Case 13 Mrs A.H., age 82

Mrs A.H. reported to have increasing muscular pains all over, frequent bouts of sweating and “burning heat” since 5/2015 and she expressed concern about being very exhausted all the time. Her daughter also pointed out increasing concentration disorders and forgetfulness, as well as pronounced retardation, listlessness and depression of her mother. Temperature measurements were inconspicuous, no lymph node swelling was found. The symptoms showed a progression in intervals, whereas the length of intervals varied greatly between 1 and 10 days. Laboratory results: **toxoplasmosis IgG 84.7 IU/ml, IgM negative. At that time the symptoms had been persisting for at least one year.** She had undergone several examinations in a hospital and the general laboratory results (blood count, BSG, CK, GGT, AP, lipase) had been normal.

Therapy: Clindamycine 3 x 300 mg was prescribed and the symptoms descreased slightly, thus the therapy was prolonged to 3 weeks. Since a pronounced symptomatic still persisted after that time, a follow-up combination therapy with Daraprim 1 x 25 mg, calcium folinate 1 x 15 mg and sulfadiazine 1-0-1 was prescribed. Keeping in mind the patient´s age, the dosage was reduced for safety reasons. The symptoms were reduced significantly.

Mrs A.H., result of questionnaire:

muscular pains initially:	**9**		
after 7 days clindamycine 2 x 600 mg:	**6**		
after 3 weeks clindamycine 2 x 600 mg:	**2**		
after 1 month combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**9**		
after 7 days clindamycine 2 x 600 mg:	**5**		
after 3 weeks clindamycine 2 x 600 mg:	**5**		
after 1 month combination therapy:	**3**	**reduction of symptoms:**	**66%**
concentration disorders initially:	**6**		
after 7 days clindamycine 2 x 600 mg:	**5**		
after 3 weeks clindamycine 2 x 600 mg:	**5**		
after 1 month combination therapy:	**4**	**reduction of symptoms:**	**33%**
profuse sweating initially:	**9**		
after 7 days clindamycine 2 x 600 mg:	**5**		
after 3 weeks clindamycine 2 x 600 mg:	**2**		
after 1 month combination therapy:	**0**	**reduction of symptoms:**	**100%**

At the time of the interview, the symptoms had decreased significantly for 2 weeks; in 1/2017 that was 4 months. She experienced no side-effects and would repeat the therapy if needed.

Comment: The concentration capacity increased only slightly with therapy, thus the concentration disorder was probably only partially caused by an active toxoplasmosis. The patient´s age, an ischemic insult in her medical history and a medication with transdermal fentanyl are most likely additional factors that impede her ability to concentrate. The other symptoms decreased very well and despite the patient´s age the therapy could achieve a significant increase in life quality.

4.14 Case 14 Mrs H.A., age 47

Mrs H.A. visited our surgery in 2008 for the first time. Since 1998, she had been suffering from pronounced muscular pains of the arms and back, a fibromyalgia had been diagnosed in 2004. After several intervertebral disc surgeries dorsal fixation surgery in 2006 was performed to stiffen L5/S1. After several knee surgeries she had a preveiling depressive state. Gastroscopy and colonoscopy were performed in 2009 without result. In 1/2012 reflux esophagitis I° - II° with hiatus hernia was diagnosed. In 1/2012 sleep apnoea syndrome was excluded. 7/2012 a laparoscopic cholecystectomy and adhesiolysis were conducted due to a chronic cholecystitis. Since 6/2015 considerable pressure and pain in the upper abdomen (up to as self rating of "10") was repeatedly experienced, as well as intermittent occurrences of suspiciously light stools. A bacterial cholangitis was suspected and treated with ciprofloxacine 500 mg for 20 days. This caused a significant, but only short-term decrease of symptoms. An ERCP was not carried out.

In mid-2016, the patient´s general condition worsened significantly; diffuse muscular pains all over, general weakness and fatigue increased considerably. On closer examination the patient had suffered from increasing listlessness, unusual tiredness and muscular pains in the last 9 years, concentration and sleep disorders had been persisting for 6-7 years and for 3 years a significant exertional dyspnea (up to a self rating of "10") had developed.

Since approximately 2016, the seeing with the right eye was "blurry", even though the ophtalmological examination was inconspicuous. **9/2016 toxoplasmosis IgG 97.9 IU/ml, IgM 3.06 AU/ml, the general laboratory results (blood count, BSG, CK, GGT, AP, lipase) were normal. At that time, the symptoms had been persisting for about 18 years.** Mrs H.A. had to undergo a hysterectomy prior to the toxoplasmosis therapy, hence the following convalescence was slow.

Therapy: 10/2016 clindamycine 600 mg 2 x 1 was taken. After 16 days of taking a significant improvement could be seen, so that Daraprim 2 x 25 mg and calcium folinate 1 x 15 mg were prescribed additionally. Since no sufficient further improvement could be diagnosed after 7 weeks of combination therapy, clindamycine was exchanged for cotrimoxazole forte 2 x 1. After another 20 days there was a good success and the therapy was stopped. In 1/2017 the symptoms had improved for 2 months. Apart from the symptoms mentioned below, other symptoms also improved: irritability from 10 to 5, right-sided upper abdominal pains from 10 to 2 (compare case 25); discoloured stools did not occur any more. The vertigo was reduced from 4 to 2, sleeping disorders and morning stiffness from 9 to 2, the listlessness from 8 to 3.

Mrs H.A., result of questionnaire:

muscular pains initially:	**9**		
after 16 days clindamycine:	**7**		
after 7 weeks combination therapy:	**4**		
after 10 weeks combination therapy :	**2**	**reduction of symptoms:**	**88%**
fatigue initially:	**9**		
after 16 days clindamycine:	**6**		
after 7 weeks combination therapy:	**6**		
after 10 weeks combination therapy:	**2**	**reduction of symptoms:**	**88%**
concentration disorders initially:	**10**		
after 16 days clindamycine:	**9**		
after 7 weeks combination therapy:	**7**		
after 10 weeks combination therapy:	**3**	**reduction of symptoms:**	**70%**
profuse sweating initially:	**9**		
after 16 days clindamycine:	**8**		
after 7 weeks combination therapy:	**5**		
after 10 weeks combination therapy:	**3**	**reduction of symptoms:**	**66%**
exertional dyspnea initially:	**10**		
after 16 days clindamycine:	**10**		
after 7 weeks combination therapy:	**5**		
after 10 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
anxiety initially:	**9**		
after 16 days clindamycine:	**9**		
after 7 weeks combination therapy:	**7**		
after 10 weeks combination therapy:	**3**	**reduction of symptoms:**	**66%**

Comment: The slow recovery had probably been caused by the long duration of the disease, the convalescence after hysterectomy and the low effectivity of the first combination therapy. This was the case with the longest duration of therapy. A weekly relapse prevention is still taken.

4.15 Case 15 Mrs H.G., age 59

Mrs H.G. first complained about muscular pains and arthralgia in 2010. A conclusive rheumatological examination was initiated, but yielded no sufficient indication for a PcP. In about 2013 joint and muscular pains increased gradually and herpes reactivations cumulated. A pronounced fatigue, along with concentration disorders and listlessness caused significant impairment on the job. In 5/2014 the laboratory results for antibodies to borrelia, electrophoresis and vitamin D were inconspicuous. CCP antibodies were positive at 16 U/ml (up to 7). Discrete swelling of the hands and lower legs were found. A repeated out-patient examination in a specialized clinic showed no proof of a rheumatoid disorder. Laboratory results in 2/2015: antibodies to borrelia negative, **toxoplasmosis IgG 99 IU/ml. IgM negative. At that time the symptoms had been persisting for about 6 years**; for 2 years a significant worsening of the condition had occurred.

Therapy: Initially, the patient was treated with clindamycine 3 x 300 mg for a period of 20 days. After a improvement could be seen, the therapy was continued with Daraprim 2 x 25mg, calcium folinate 1 x 15 mg and sulfdiazine 4 x 500mg, which resulted in a remission of all symptoms.

Mrs H.G., result of questionnaire:

muscular pains initially:	**8**		
after 20 days clindamycine:	**6**		
after 20 days combination therapy:	**0**		
15 months after therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 20 days clindamycine:	**7**		
after 20 days combination therapy:	**0**		
15 months after therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**6**		
after 20 days clindamycine:	**3**		
after 20 days combination therapy:	**2**		
15 months after therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**5**		
after 20 days clindamycine:	**3**		
after 20 days combination therapy:	**1**		
15 months after therapy:	**1**	**reduction of symptoms:**	**80%**

Mrs H.G. suffered from light nausea and head pressure during combination therapy; she graded these symptoms as moderate side-effects. At the same time, she felt a significant decrease of her symptoms and thus wanted to continue the therapy. In 1/2017 she had been free from symptoms for 21 months. She would repeat the therapy if needed.

4.16 Case 16 Mrs D., age 44

From age 13 on (1983) Mrs D. suffered from chronic multiple pains; because of these complaints several inpatient treatments had been necessary already during childhood. She reported that she had been examined for rheumatism several times, but the results had always been negative. First bouts of profuse sweating along with unclear fatigue and swallowing disorders were documented in 2002.

It only turned out a lot later that these were recurring phases with multiple joint pains, unusual physical weakness, episodes of tachycardia from stress along with fatigue and muscular pains; in addition, recurring swelling of the axillary lymph nodes from age 15 were also noteworthy. Mrs D. has two healthy children aged 14 and 17.

In 3/2015, Mrs D. had to undergo an adhesiolysis and ablation of an ovarian cyst. The post-surgical development was unconspicious at first, but about one month later an increase in exertional dyspnea and inadequate quickening of the pulse after light exertion occurred. Since I suspected a septic process with a momentary unknown focus, I prescribed ciprofloxacine 500 mg 2 x 1, which led to a slight improvement.

Mrs D. was admitted to hospital to rule out an endocarditis lenta. A transoesophagal ultrasound examination of the heart (TEE) as well as a spirometry yielded inconspicuous results. In ergometry a load of 100 W could be achieved, but only at a heart rate of 178/min. Blood cultures were carried out once, but the laboratory results yielded no decisive result. Mrs D. was advised to undergo psychotherapy, then she was discharged.

The condition of Mrs D. deteriorated excessively within the next days, but a repeated prescription of ciprofloxacine did not improve her condition.

She was re-admitted to another cardiologic department; the TEE was again negative, but ergometry could only be executed up to 75 W there. Mrs D. became increasingly weakened and she had very intensive bouts of profuse sweating. The long-term ECG was inconspicuous. An exertional dyspnea NYHA II was diagnosed and a depressive episode suspected. The patient was discharged and consulted the practice. Clinical findings: pale, cold-sweated patient in condition of complete exhaustion, minimal findings in pulmonal auscultation, corresponding with a slight infection. Abdomen without finding and blood sedimentation rate slightly increased at 38 / 58 mm.

Therapy: Since a septic process had not been completely ruled out from my point of view and due to the patient´s very critical health at that time, I decided to administer Ceftriaxone 2.0 g infusions daily. During that treatment her condition improved continuously; after 30 infusions only very minimal symptoms remained and the treatment was stopped.

In 9/2015, about 4 months later, her resilience decreased very slowly at first, now also multiple joint pains came into focus. Mid 11/2015 Mrs D. explained upon request, that she had suffered from migrant joint pains since her youth; this made me suspect a chronic borreliosis as source of her joint pains and a resulting cardiac involvement for the first time. The CCP rate and the count for borreliosis antibodies were negative, thus making a borreliosis less likely, but not excluding it. In 2/2016, due to the intensively increasing symptoms, Ceftiaxone infusions were started again and proved effective. This time, a relapse prevention of one Ceftiaxone infusion per week was used as follow-up after the therapy with 30 infusions was completed. 9/2016 it transpired that the patient had had “severe muscular pains, an unusual fatigue and decreased physical resilience for “as long as she could think”. She complained about strong fluctuations of the eyesight; she often felt very dizzy. MRT head negative.

She told that she had grown up in the countryside and had eaten fresh meat very frequently. **Toxoplasmosis antibodies IgG 106 IU/ml, IgM negative. At that time the symptoms had been persisting for over 30 years.**

The Ceftriaxone infusions were stopped and clindamycine 2 x 600 mg was prescribed. During that treatment the joint pains increased quickly and the patient observed no positive development of her condition.

After a few days, the Ceftriaxone infusions were started again and at the same time a combination therapy with Daraprim 2 x 25 mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500 mg was prescribed. From then on a simultaneous decrease of all symptoms could be observed for the first time; after six weeks combination therapy the following changes apart from the ones listed below had been recorded: listlessness from 9 to 3, irritability from 8 to 1, loss of hair from 10 to 1, sleeping disorders from 8 to 3, anxiety and depressive moods from 10 to 0. A slight peripheral swelling of hands and feet was reduced from 4 to 2. The simultaneously described unclear visual disturbances (strong fluctuations, up to 10) were not improved.

Mrs D., result of questionnaire:

muscular pains initially:	**8**		
after 1 week combination therapy:	**6**		
after 6 weeks combination therapy:	**2**	**reduction of symptoms:**	**75%**
fatigue initially:	**10**		
after 1 week combination therapy:	**6**		
after 6 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
concentration disorders initially:	**10**		
after 1 week combination therapy:	**7**		
after 6 weeks combination therapy:	**5**	**reduction of symptoms:**	**50%**
profuse sweating initially:	**4**		
after 1 week combination therapy:	**0**		
after 6 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
exertional dyspnea initially:	**10**		
after 1 week combination therapy:	**4**		
after 6 weeks combination therapy:	**2**	**reduction of symptoms:**	**80%**
dizziness initially:	**8**		
after 1 week combination therapy:	**5**		
after 6 weeks combination therapy:	**3**	**reduction of symptoms:**	**62%**

Comment: A second disease – possibly a seronegative borreliosis – that had caused pronounced multiple migrant joint pains from age 13 onwards, could be treated effectively with Ceftriaxone. From my point of view the active toxoplasmosis with according symptoms, which had persisted from youth and which had weakened the patient was the likely reason for the relapse of the borreliosis. The ineffectivity of clindamycine might be explained by the simultaneous pausing of Ceftriaxone infusions. Only a combined treatment of both diseases at the same time could in the end lead to an elimination of most symptoms. A one-day weekly relapse prevention with Daraprim, calcium folinate and sulfadiazine is still kept up.

4.17 Case 17 Mrs S.V., age 37

The patient reported that she had had several grave flu-like infections since 4/2016, including a pronounced submandibular lymph node swelling since 5/2016. She claimed not having recovered completely afterwards; she felt very tired, had concentration disorders and pains in the shoulders, elbows and wrists.

After about 3 months her condition worsened further. In 8/2016, severe generalized muscle and joint pains, word-finding disorders, very strong bouts of profuse sweating, flushing and exertional dyspnea came to the fore and a swelling of the paracervical lymph nodes increased. Mrs S.V. experienced unpleasant episodes of tachycardia from exertion. She felt very exhausted all the time and had impairments of her sight frequently, which she described as “blurry vision”. An ophtalmological examination was negative. She was exceptionally irritable. Laboratory results: blood count and BSG normal, ASL below detection level, euthyreosis, folic acid 19 ng/ml. **Toxoplasmosis IgG above 400 IU/ml, IgM 4.75 IU/ml. At that time the symptoms had been persisting for about 7 months.**

Clindamycine 600 mg 2 x1 was prescribed; after 10 days the symptoms had decreased slightly, a combination therapy with Daraprim 2 x 25 mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500mg was carried out for one month. Meanwhile, the complete clinical picture improved. The word-finding disorders and swelling of the lymph nodes decreased significantly and episodes of tachycardia were reduced from 7 to 2. Irritability, visual disorders and listlessness disappeared completely.

By the end of 12/2016, Mrs S.V. had been free from symptoms for 6 weeks, but by the beginning of 2017 she had suffered from a relapse, which was initially marked by fatigue (4), listlessness (5), muscular pains (3) as well as morning stiffness (1). A combination therapy was started immediately, which led to a complete remission within one week; the therapy was stopped after three weeks. By the end of 1/2017 Mrs S.V. was free from symptoms.

Mrs S.V., result of questionnaire:

muscular pains initially:	**7**		
after 10 days clindamycine:	**2**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
relapse after 3 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 10 days clindamycine:	**6**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**87%**
relapse after 3 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**7**		
after 10 days clindamycine:	**7**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
relapse after 3 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**7**		
after 10 days clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
relapse after 3 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**

Comment: This patient had – including typical symptoms – by far the highest IgG count for toxoplasmosis, even exceeding the measuring range. Judging by the quite specific information she provided, we can assume a short span of disease duration of approximately 7 months. Possibly the initial toxoplasma-ingestion was very significant or a weakened condition of the patient had made frequent and intensive parasitaemic phases possible, which also accounted for the strong increase of IgG. Nevertheless, the IgM count was not significantly increased.

Even only 7 months after the occurance of first symptoms, the IgM count can be negative and can thus not be used as an exclusion criterion for an active toxoplasmosis. A relapse after only 6 weeks is unusual, but could be treated very well. In case of a further relapse, an alternative combination therapy and a relapse prevention therapy would have to be considered.

The following **Cases 18 – 27 (**group B), present patients with a completely negative toxoplasma serology, who also suffered from the clinical pattern of an active toxoplasmosis. All of them had undergone several diagnostic procedures, but until the toxoplasma check up and treatment, a conclusive diagnose and effective treatment had not been found. They also responded very well to the specific treatment, even slightly better than the patients of group A. The cases are arranged according to the intensity of the clinical picture, starting with the less severe cases.

4.18 Case 18 Mrs R.H., age 56

Mrs R.H. came to see me in 4/2016 for the first time. Apart from several other problems she had been suffering from fatigue for a long time. She also experienced weakness and pains in the leg and shoulder muscles, which were also very tender to the touch. Despite regular physical activity, the muscles´ strength would not increase; her resilience was also decreased significantly. **Toxoplasmosis IgG and IgM negative. At that time the symptoms had been persisting for 18 months.**

Therapy: An exclusion of other diseases had already been performed, so with a typical constellation of symptoms for an active toxoplasmosis, appropriate information was given and a therapy trial with clindamycine 600 mg 2 x 1 was undertaken. This led to a significant reduction of muscular pains and fatigue after only 4 days of treatment, so that the therapy was continued. After taking clindamycine for 3 weeks, the patient was free from symptoms.

Mrs R.H., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine 2 x 600 mg	**0**		
after 3 weeks clindamycine 2 x 600 mg	**0**		
2 months after therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**6**		
after 1 week clindamycine 2 x 600 mg	**2**		
after 3 weeks clindamycine 2 x 600 mg	**1**		
2 months after therapy:	**1**	**reduction of symptoms:**	**83%**
concentration disorders initially:	**1**		
after 1 week clindamycine 2 x 600 mg	**1**		
after 3 weeks clindamycine 2 x 600 mg	**1**		
2 months after therapy:	**1**	**no reduction of symptoms**	
profuse sweating initially:	**1**		
after 1 week clindamycine 2 x 600 mg	**1**		
after 3 weeks clindamycine 2 x 600 mg	**1**		
2 months after therapy:	**1**	**no reduction of symptoms**	

Mrs R.H. only experienced few side-effects and would repeat the therapy if needed. In 1/2017 she had been free from symptoms for 6 months.

Comment: This case shows clearly, as does case 24, that concentration disorders and profuse sweating are no obligatory symptoms.

4.19 Case 19 Mrs S.J., age 25

In mid-2014 slowly increasing bouts of profuse sweating occurred for the first time, thus Mrs S.J. came to see me about them in 1/2015. The laboratory results including electrophoresis were inconspicuous and further examinations were not carried out on the otherwise fit and resilient athletics student.

In 1/2016 Mrs S.J. came to the surgery with a significantly reduced general condition, intensive bouts of profuse sweating, episodes of tachycardia and paracervical swelling of the lymph nodes. BSG was increased at 46/66 mm, with spleen slightly sonographically enlarged, EBV IgM increased to 159 E/ml (positive above 40), EBV IgG increased to 89 E/ml (positive above 20), in conclusion, an acute mononucleosis was diagnosed. The general condition improved after physical rest and the laboratory results returned to normal, so that the patient was fully resilient again in 3/2016. From 9/2016 onwards, the patient suffered from 3 successive severe infections within a few weeks and thus consulted me in 11/2016.

Upon enquiry it turned out that she had not only been suffering from increasing sweats within the last 2 years, but also from a large number of other continuously increasing symptoms, such as muscular pains, fatigue, concentration disorders, joint pains, overall physical weakness, morning stiffness, exertional dyspnea and exercise-related tachycardia (6), as well as frequently occurring intensive vertigo. She had been observing frequent paracervical swelling of the lymph nodes for years. 12/2016 blood count, BSG, GGT, GOT, GPT, vitamin D, ferritin level were normal. EBV IgG 433 E/ml, EBV IgM below detection level. **Toxoplasmosis IgG negative, IgM 3.7 AU/l. At that time the symptoms had been persisting with increasing intensity for about 2 years**, a significant worsening had occurred within the last 2 months

Therapy: Clindamycine 300 mg 3 x 1 was prescribed; this led to a decrease of muscular pains, fatigue, concentration disorder, exertional dyspnea and dizziness within 11 days of treatment, but the profuse sweating, morning stiffness, listlessness and irritability remained unaffected. Daraprim 2 x 25 mg, calcium folinate 1 x 15mg and sulfadiazine 4 x 500mg were prescribed. After 20 days, clindamycine 300 mg 3 x 1 was prescribed instead of sulfadiazine due to a decreasing effectivity. This led to a complete elimination of the hitherto unaffected symptoms, so that the therapy could be stopped after 30 days altogether.

Mrs S.J., result of questionnaire:

muscular pains initially:	**4**		
after 11 days clindamycine:	**0**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**8**		
after 11 days clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**2**		
after 11 days clindamycine:	**1**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**10**		
after 11 days clindamycine:	**10**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
exertional dyspnea initially:	**6**		
after 11 days clindamycine:	**3**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
dizziness initially:	**8**		
after 11 days clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**

Comment: The mononucleosis lasted from 1/2016 until approximately 3/2016 and weakened the patient considerably. From 9/2016 onwards infections and symptoms of an active toxoplasmosis occurred more frequently, which probably had been persisting in a milder form for about 2 years already. A Chronic Fatigue Syndrome (CFS) with abnormal fatigue, muscular pains and concentration disorders is a well-known complication of a mononucleosis – and strongly resembles symptoms of an active toxoplasmosis. Possibly, a mononucleosis can be the precursor of an active toxoplasmosis – the CFS would then be caused by the active toxoplasmosis rather than by a viral persistence in these cases and thus could be treated. In 1/2017 the patient had been free from symptoms for 6 weeks.

4.20 Case 20 Mr B., age 27

Mr. B., an athletic young man reported that his quality of life had greatly decreased within the previous three years. His resilience had lowered considerably, he needed more rest and was often quite irritable. He often felt a kind of unpleasant periumbilical pressure and nausea. He had been experiencing unexplainable sleeping disorders of increasing frequency and nocturnal sweating. He had muscle pains in the mornings, also without having worked the day before and his heart rate already started to accelerate at light exertion. His ability to concentrate had lessened considerably, from time to time he experienced visual disturbances in terms of “blurry” sight.

Laboratory results: euthyreosis, blood count normal, BSG 7/9 mm, CK 68 U/l, GGT 50 U/l, **toxoplasmosis IgG and IgM negative. At that time the symptoms had been persisting for about 3 years.**

Therapy: Clindamycine 2 x 600 mg was prescribed; within one week the symptoms were reduced considerably and thus a follow-up therapy with Daraprim 2 x 25mg, calcium folinate 1 x 15mg and sulfadiazine 4 x 500mg was started. In the course of this therapy, the overall symptoms receded continuously. Among other things, the listlessness was reduced from 8 to 2, visual disturbances with “blurry” sight and irritability were both reduced from 5 to 2.

The abdominal symptoms (pressure and nausea) were reduced from 7 at the beginning to a complete remission, the episodes of exertional tachycardia were reduced from 5 to complete remission, so that no further diagnostic was necessary.

Mr B., result of questionnaire:

muscular pains initially:	**6**		
after 1 week clindamycine:	**2**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**7**		
after 1 week clindamycine:	**1**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
concentration disorders initially:	**7**		
after 1 week clindamycine:	**3**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**71%**
profuse sweating initially:	**5**		
after 1 week clindamycine:	**1**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**80%**
exertional dyspnea initially:	**8**		
after 1 week clindamycine:	**7**		
after 4 weeks combination therapy:	**3**	**reduction of symptoms:**	**62%**

Mr B. had been mostly free from symptoms in 1/2017. He did not experience any side-effects and would repeat the therapy if needed.

Comment: A toxoplasma-triggered mesenteric lymphadenitis as a possible correlation to the mentioned abdominal symptomatic has been known for a long time (Kabelitz 1959). An involvement of the stomach in the course of a toxoplasmosis (Ganji et al. 2003) as well as a liver involvement (Dogan et al: 2007) have already been proven. Compare also cases 11, 12, 14 and 21 where patients suffered from similar abdominal complaints.

4.21 Case 21 Mrs H.I., age 37

Mrs H.I. gave birth to a healthy daughter in 2009 and in 2012 to a healthy son. After the second birth she suffered from post-natal depression and recovered only slowly. She was often tired and exhausted, had occasional nocturnal sweating and got nervous and impatient. She slowly developed an increasing exertional dyspnea, lower leg oedema, as well as morning stiffness and muscular pains; she sometimes felt very weak. Light visual disturbances in terms of “blurry” sight developed. These symptoms showed a slow progression over the complete time and **had been persisting for about 3 ½ years. 12/2016 toxoplasmosis IgG and IgM negative.**

Therapy: with a typical constellation of symptoms for an active toxoplasmosis, a therapy trial with clindamycine 600 mg 2 x 1 was undertaken. This led to a slight reduction especially of muscular pains and fatigue, so that a follow-up combination therapy with clindamycine 2 x 600mg, Daraprim 2 x 25 mg and calcium folinate 1 x 15 mg was prescribed. This led to a continuous decrease of symptoms and the therapy could be succesfully stopped after one month.

Apart from the changes mentioned on the next page, the following improvements could be recorded: A listlessness of 10, depressive moods of 7, visual disturbances of 3, lower leg oedema of 10 and periumbilical pressure and abdominal symptoms of 10 disappeared completely.

Mrs H.I., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine:	**3**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**10**		
after 1 week clindamycine:	**5**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**90%**
concentration disorders initially:	**8**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**10**		
after 1 week clindamycine:	**10**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
exertional dyspnea initially:	**8**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**87%**
sleep disorders initially:	**10**		
after 1 week clindamycine:	**7**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
irritability initially:	**8**		
after 1 week clindamycine:	**6**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**

Comment: Here a post-natal depression seamlessly merged into an active toxoplasmosis. In case 23 a comparable development was observed, and it seems worthwhile to take an active toxoplasmosis as a cause for an unusually long postnatal depression into consideration, especially when the depression is accompanied by muscle pains, concentration disorder profuse sweating et cetera. **After the treatment all symptoms including the depression had completely vanished**.

4.22 Case 22 Mr Z., age 53

Mr Z. presented himself in the practice in 10/2016. He is slim, non-smoker, has been vegetarian for three years and reported that his physical resilience had decreased considerably within the last months. He got out of breath quickly when climbing stairs and was very tired. His concentration was impaired severely; even though being an experienced musician, he could no longer play at sight; also playing his wind instrument was limited to some minutes due to his weakness as opposed to well over 45 minutes before.

While on holiday he had recently experienced a two-hour episode of tachycardia after physical exertion and the exertional dyspnea had increased further and he had to undergo inpatient cardiological treatment after his holiday.

A coronary ischaemia was ruled out, a mitral valve prolapse was diagnosed. A cardio-CT and stress echo were negative. 9/2016 **toxoplasmosis IgG and IgM showed negative results. At that time, the symptoms were persisting for 3 months.**

Therapy: Clindamycine 600 mg 2 x 1 was prescribed; after 3-4 days an increase in physical resilience set in, also the concentration capacity started to increase. Due to the positive development, no combination therapy was prescribed and the clindamycine therapy was prolonged for 14 days, when the therapy could be stopped because of the positive results. Exertional dyspnea had subsided completely and there had been no more episodes of tachycardia. Mr Z. could restart his professional activities.

Mr Z., result of questionnaire:

muscular pains initially:		**5**		
after 1 week clindamycine	2 x 600 mg	**1**		
after 2 weeks clindamycine	2 x 600 mg	**0**	**reduction of symptoms:**	**100%**
fatigue initially:		**6**		
after 1 week clindamycine	2 x 600 mg	**2**		
after 2 weeks clindamycine	2 x 600 mg	**1**	**reduction of symptoms:**	**83%**
concentration disorders initially:		**6**		
after 1 week clindamycine	2 x 600 mg	**4**		
after 2 weeks clindamycine	2 x 600 mg	**1**	**reduction of symptoms:**	**83%**
profuse sweating initially:		**0**		
after 1 week clindamycine	2 x 600 mg	**0**		
after 2 weeks clindamycine	2 x 600 mg	**0**	**no reduction of symptoms**	
exertional dyspnea initially:		**6**		
after 1 week clindamycine	2 x 600 mg	**2**		
after 2 weeks clindamycine	2 x 600 mg	**0**	**reduction of symptoms:**	**100%**

Mr Z. had been free from symptoms for 7 weeks in 1/2017; he experienced no side-effects and would repeat the therapy if needed.

Comment: The negative serology referring to toxoplasmosis points towards an infection a long time ago, possibly still in the stage of meat consumption. Since the symptoms decreased very rapidly, the treatment was stopped after 2 weeks. The patient did not suffer from profuse sweating, so this is no obligatory symptom. The sweating has also been missing in cases 2, 3, 8, 23 and 27.

The concentration disorders were reduced significantly under therapy, which points to an effectivity of clindamycine even in the CNS, as seen in cases 4, 6 and 10.

4.23 Case 23 Mrs G.N., age 40

Mrs G.N. had been permanently tired since at least 1998 with known and substituted thyreoditis. 3/2006 she gave birth to a healthy son, the toxoplasmosis testing during pregnancy remained inconspicuous. She reported that she had felt herself becoming increasingly forgetful during pregnancy. She had been very listless since 2008 and often had gloomy moods. Since then she also suffered from slow-healing lesions of the fingertips. 11/2009 she underwent rehabilitation due to chronic fatigue. In 5/2010 she gave birth to a healthy daughter. The fatigue still continued to persist and unclear vertigo was added. In 2011 a gynaecological laboratory examination showed normal results for FSH, LH, estradiol and prolactin. A comprehensive ORL examination was negative. 5/2011 and again in 3/2014 sleep apnea was excluded. A Colonoscopy 8/2011and MRI head were both negative.

In the beginning of 2014 several 3-day episodes of fever, chills and sweating of unclear cause took place. 10/2014 intermittent myalgic pains of both legs and exertional dyspnea with strong rise in heart frequency with slight exertion and severe concentration disorders were documented. Cefuroxime 500 mg 2 x 1 was administered due to a severe pharyngitis and the muscular pains receded slightly. A Lumbar puncture in 2014 excluded neuroborreliosis. In 1/2015, Mrs G.N. was examined neurologically because of her abnormal fatigue, listlessness and concentration disorders. No formal mental disturbances, paranoia or psychotic experiences were diagnosed. A possible depressive episode was discussed. **1/2015 laboratory results:** TSH 0.06 mU/l under thyroxin substitution, all other results including **toxoplasmosis IgG and IgM negative. At that time, the symptoms had been persisting for about 15 years.**

Therapy: In the course of a combination therapy with daraprim 2 x 25 mg, calciumfolinate 1 x 15 mg and sulfadiazine 4 x 500 mg, the sulfadiazine had to be exchanged for clindamycine 3 x 300mg due to side-effects; from then onwards the condition improved rapidly. After one month, the therapy had to be stopped in 3/2015 due to an increase in transaminases and leukopenia and afterwards the laboratory results returned to normal. Starting about 12/2015 the symptoms of a toxoplasmosis slowly started to reappear (1st relapse) alongside a severe infection; after 4 more months a 10-day treatment with clindamycine 3 x 300 mg saw some improvement, but no complete remission. After another 4 months, a 2nd relapse occurred. The laboratory results remained negative, the clindamycine / daraprim / calciumfolinate combination therapy resulted in a fast remission and seemed be more effective than during the first therapy cycle.

Mrs G.N., result of questionnaire:

muscular pains initially (1/2015):	**8**		
after 10 days combination therapy:	**2**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
during 2nd relapse (9/2016):	**4**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially (1/2015):	**10**		
after 10 days combination therapy:	**6**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
during 2nd relapse (9/2016):	**10**		
after 4 weeks combination therapy:	**3**	**reduction of symptoms:**	**70%**
concentration disorders initially (1/2015):	**10**		
after 10 days combination therapy:	**6**		
after 4 weeks combination therapy:	**5**	**reduction of symptoms:**	**60%**
during 2nd relapse (9/2016):	**10**		
after 4 weeks combination therapy:	**3**	**reduction of symptoms:**	**70%**
profuse sweating initially (1/2015):	**0**	**no changes**	

Comment: pre-existing symptoms, which probably had been pointing to a toxoplasmosis, worsened following a pregnancy as also happened in case 21. All in all, the life quality of the patient has increased considerably after the toxoplasmosis treatment, nevertheless her mental resilience has remained impaired and she had to reduce her professional workload. She is less resilient towards tasks that require a permanently high level of concentration than before her illness. Apart from this case, relapses also occurred in cases 5, 17, 25 and 27. The onset of effect and general effectivity of the relapse – treatment was similar in these cases. For details about relapses and relapse - prevention see also pages 91, 107/108 and 111.

The 4-month delay from the 1st relapse until treatment was caused by a lack in contact with the practitioner´s surgery. Thus, I conclude that the possibility of a relapse should be clearly pointed out to the patient, to enable a prompt treatment of an eventual relapse. In 1/2017 the patient had been free from symptoms for about 5 months.

4.24 Case 24 Mrs H.R., age 45

Mrs H.R. suffered from a severe case of pneumonia in 9/2012. In 10/2012 an exertional dyspnea even at the slightest exertion was documented. A cardiological examination showed a left ventricular dysfunction with generalized moderate left ventricular hypokinesia. A coronary angiography yielded no conspicuous results. In 7/2013, cardiological examination was repeated with no changes in preliminary finding recorded. 12/2013 an examination by an lung specialist showed a normal result. 10/2014 a cardiologic examination was repeated due to exertional dyspnea and profuse sweating and there were no changes compared to preliminary findings.

Mrs H.R. explained that from mid-2015, she had been experiencing increasing concentration disorders and from the beginning of 2015, she had suffered from a full-blown depression. Her husband independently told that she had been jittery and unfocused, sometimes crying without an obvious reason. According to her personal assessment, Mrs H.R. lacked all vital energy and interest in life. From about 3/2016 generalized muscular pains and profuse sweating started and increased continuously. 9/2016 **toxoplasmosis IgG and IgM negative. At that time, the symptoms had been persisting and increasing for about 4 years.**

Therapy: Due to the typical constellation of reported symptoms and a high degree of suffering, clindamycine 600 mg 2 x 1 was prescribed. Within one week, the muscular pains and fatigue were reduced significantly and concentration disorders and sweating were decreased slightly. A combination therapy of Daraprim 2 x 25 mg , calcium folinate 1 x 15 mg and sulfadiazine 4 x 500mg was prescribed, which led to a very good reduction of all symptoms. The therapy could be stopped after 4 weeks.

Mrs H.R. experienced very few side-effects and would repeat the therapy, if needed. In 1/2017 she had been experiencing significantly fewer symptoms for 3 months.

Mrs H.R., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine:	**2**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**75%**
fatigue initially:	**10**		
after 1 week clindamycine:	**5**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**80%**
concentration disorders initially:	**10**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
profuse sweating initially:	**10**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
depression initially:	**10**		
after 1 week clindamycine:	**8**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**
exertional dyspnea initially:	**10**		
after 1 week clindamycine:	**9**		
after 4 weeks combination therapy:	**4**	**reduction of symptoms:**	**60%**

Comment: a severe case of pneumonia in 9/2012 might have triggered the activation of a toxoplasmosis; the exertional dyspnea starting in 10/2012 possibly was a first symptom. This is the only case in which exertional dyspnea and later concentration disorders in combination with depression preceded muscular pains.

A prolonged therapy might have yielded slightly increased results altogether but the patient was very content with the results so far, so that the treatment was stopped at that point.

4.25 Case 25 Mr T., age 57

Mr T. is a younger looking, athletic patient, who has been living exclusively vegan for about 3 years. Starting from 1990, he had been taking care of diseased cats for some years, from 1992 on he suffered from exceptional fatigue, as well as unclear sweating, joint pains and an exceptional sensitivity to cold. All laboratory results, antibodies against anaplasma bacteria, borreliosis, CCP, ANA, AMA, Waaler-Rose test and electrophoresis were negative. Also inconspicuous were CEA, Ca 19-9 and PSA. Hepatitis B and C as well as HIV testing was negative while hepatitis A IgG was slightly elevated. A Cholecystectomy was performed in 1/2007, an ERCP in 1/2010, and a double-sided subtotal thyroidectomy in 3/2011 due to cold nodes.

An 11/2016 toxoplasmosis check showed a high probability of toxoplasmosis with **negative laboratory results for toxoplasmosis**, borreliosis, CCP, unconspicious blood count and normal ESR. **Symptoms were persisting for about 24 years.**

Initial prescription of a combination therapy with Daraprim 2 x 25 mg, calcium folinate 1 x 15mg and sulfadiazine 4 x 500mg led to a very significant reduction of symptoms within 10 days in 12/2016. Immediate cessation of therapy was needed due to suspected strong side-effects and taking of laboratory results. Apart from a slight increase of GGT and leukopenia (3,400 / mcl) all results inconspicuous. After stopping the therapy Mr T. felt significantly better; after approximately 3-4 days he was almost free from symptoms.

Due to the very good therapeutic result, a therapy-free period was arranged, but within the span of about 14 days, all previous symptoms reoccurred. Now a combination therapy with clindamycine 600 mg 2 x 1 instead of sulfadiazine was prescribed. With a better tolerability, this caused the patient to be free from symptoms after three days. The therapy could be continued for 1 month and was ended successfully.

Mr T., result of questionnaire:

muscular pains initially:	**1**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
fatigue initially:	**10**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**8**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
profuse sweating initially:	**10**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
irritability initially:	**10**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
dizziness initially:	**4**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
anxieties initially:	**10**		
after 7 and 30 days combination therapy:	**0**	**reduction of symptoms:**	**100%**
depression initially:	**10**		
after 7 and 30 days combination therapy:	**5**	**reduction of symptoms:**	**50%**

Comment: The initial therapy had to be stopped despite very good therapeutic results due to side-effects. The symptoms reoccurred quickly and a continued therapy with an altered medication became necessary after 2 weeks. This combination therapy was again very successful. **This shows, that especially in case of long-time persisting infections, a therapy interval of at least one month is necessary, regardless of a quick onset of effect.**

By the end of 1/2017, Mr T. had been free from symptoms for about 3 weeks. He has recorded his experiences before and after therapy. Excerpts of these records can be found on the next two pages.

Toxoplasmosis-diary of Mr T. 12/2016:

Muscle rigidity, chronic fatigue with very little recreational sleep, scary nightmares, anxieties in the morning, depressive moods, aggression and overreaction, sometimes provocative risk-taking behaviour for the last 20 years.

Loss of olfactory sense, extreme afternoon fatigue, disorders of fast grasping and coordinative movements with significant loss of hand-eye coordination. Strong (mostly nocturnal) sweating, up to 6 times urination per night with dripping of urine afterwards, dry mouth in the morning. Extreme impairment of the short-term memory and word-finding disorders, names cannot be remembered, forgetting of appointments and the like. Painful loss of drive, intermittent joint pains, for safety reasons because of muscular weakness turning around when descending stairs. Feeling of weakness despite ability to carry out heavy workload, rarely muscular pains. Significantly longer recreational intervals needed. In sporadic intervals slightly pulling pain in the region of the liver, also parallel pulling pains in the region of the heart (independent from exertion, alcohol consumption etc.)

Initial therapy with Daraprim 2 x 2, calcium folinate 1 x 1, sulfadiazine 4 x 1

19.12.2016: first ingestion of medication in the evening at 19.00 hours. At about 22.00 hours slight change in visual acuity (peripheral areas more pronounced), sleep at night deeper than usual.

20.12.2016: largely missing of muscle rigidity after getting up; activity can be attained faster, no mid-afternoon slump

21.12.2016: almost instant accessibility to all names at workplace; night´s sleep deep and dreamless, significantly less night phases and visits to the toilet.

22.12.2016: night calmer, getting-up almost without difficulties, no mid-afternoon slump, improvement of memory for names continues. Flickering in front of the eyes during lengthy reading is reduced, hearing more precise.

23.12.2016: first completely undisturbed night´s sleep for years! Deep sleep without nightmares, no visit to the toilet. The grasping movements have become much more precise.

24.12.2016: undisturbed night´s sleep as before, no more nightmares, anxieties in the morning reduced to a minimum and decreasing. Walking on the forefoot returned to normal, numbness of the toes decreasing. Work efficiency better.

25.12.2016: midday-sleep is no longer possible, due to lack of tiredness. Playing the guitar and darts can be done much more easily.

26.12.16: a strange day. All earlier symptoms seem to be reoccurring in reverse order – deep slumber at midday. Inner turmoil. It feels as if the body goes through all stages of the disease in fast forward.

27.12.2016: slept well. No urological symptoms any more, smell of urine now back to normal. Immense backlog for recreation and sleep.

28.12.2016: sleep has been deep. Dexterity and planning competence have increased, work assignments are being approached with consequence and are completed accordingly. Less forgetfulness; little irritability and verbal attacks.

29.12.2016: a very successful day regarding manual skills, but also very tiring, but the tiredness feels pleasant. The day seems to last longer, there is "more time for everything".

From the 30.12.2016 increasing side-effects: joint pains, strong nocturnal sweating, nausea, light headaches, occasional vertigo, pulling pain round the kidneys, weakness, chills.

3.1.2017: Therapy was stopped after visit to the doctor, blood count is being checked.

4.1.2017: The side-effects decrease. Positive changes that have remained: uninterrupted sleep without nocturnal visits to the toilet, no more morning rigidity or joints or joint pains, no more anxiety in the morning, depression clearly decreasing. I can laugh again! Almost no mid-afternoon slumber, sleep is a lot more restful, but an immense backlog remains; I can sleep for 10-12 hours without interruption. Motor skills are improving considerably, muscles strength is rising, no more muscular pains. Pains close to liver and heart do not occur any more. No more attacks of ravenous hunger, the appetite for an alcohol-sweets combination has disappeared. Better sensitivity in the balls of the feet and toes.

4.26 Case 26 Mrs U., age 42

Mrs U. reported that she had been feeling weak and less resilient for years and she had been feeling dizzy frequently. A vestibular cause could be eliminated. Neurological examination and MRT head were negative. In 11/2011 high-grade vitamin D deficiency with still normal PTH was noted, after substitution with Dekristol 20000 1 x 1 gradual improvement of the symptoms was seen. Since mid-2015 increase of dizziness; episodes of cephalgia at the back of the head with pronounced sensitivity to light and visual disorders occurred within several days. Profuse sweating had occurred since autumn 2015 and since 1/2016 Mrs U. felt increasingly tired and exhausted, with a strong need for sleep. In 3/2016 she had an significant weight gain which could not be explained, as well as increased loss of hair, feeling cold, increasing vertigo (up to 9) and sleeping disorders (8). A hypothyroidism and a thyroiditis were excluded and the CRP , blood count and electrophoresis was inconspicuous. In 4/2016 development of an additional exertional dyspnea and episodes of tachycardia with light physical exertion ocurred, as well as explicit peripheral oedema. These symptoms were reduced under prescription of diuretics.

Mrs U. was admitted to a cardiological unit for further examination. A low degree thickening of the heartmuscle, with normal contractility and without diastolic dysfunction was diagnosed, as well as a minor pericardial effusion. There were no indications for an endocarditis. Ergometry load was attainable up to 75 W with a heart rate of 160 beats per minute and an exertional dyspnea with minor ST-line deviation in V5 and V6. A coronary angiography and laboratory results yielded no findings. A heart insufficiency II-III° as well as a chronic pericarditis were diagnosed. In **9/2016 toxoplasmosis IgG and IgM were negative. At that time, the symptoms had been persisting for 20 years altogether, with a significant worsening within the last 5 years.**

Therapy: In 9/2016 clindamycine 600 mg 2 x1 was prescribed. Within 1 week, the symptoms decreased significantly, but the therapy was not continued by the patient due to problems within the family. In the course of 3 days the symptoms were back at full strength. On 10/2016, clindamycine 600 mg 2 x 1 was prescribed again. After 3 weeks the symptoms had decreased very well, but the patient started to feel a slight increase in muscular pains and profuse sweating again. She was successfully treated with a combination therapy of Daraprim 2 x 25 mg, calcium folinate 1 x 15 mg and sulfadiazine 4 x 500mg for 4 weeks. The diuretics were no longer necessary and therefore discontinued.

Comment: This is the toxoplasmosis patient with the most severe cardiopulmonary disabilities. Carme et al. found pulmonary involvement in a group of patients with active toxoplasmosis in 2001. It is therefore imaginable that the exertional dyspnea in cases of toxoplasmosis can be caused by pulmonary or cardial involvement, or a combination of both. All other symptoms of Mrs U. improved as well, among them also significant anxiety states, which had been treated with Duloxetin 30 mg for some time. A persisting vertigo was reduced from 9 to 0, which also helped to improve the patient´s quality of life.

Mrs U., result of questionnaire:

muscular pains initially:	**8**		
after 1 week clindamycine:	**8**		
after 3 weeks clindamycine:	**4**		
after 4 weeks combination therapy:	**2**	**reduction of symptoms:**	**75%**
fatigue initially:	**10**		
after 1 week clindamycine:	**9**		
after 3 weeks clindamycine:	**5**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**
concentration disorders initially:	**7**		
after 1 week clindamycine:	**3**		
after 3 weeks clindamycine:	**1**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
profuse sweating initially:	**8**		
after 1 week clindamycine:	**8**		
after 3 weeks clindamycine:	**5**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**87%**
anxiety initially:	**7**		
after 1 week clindamycine:	**4**		
after 3 weeks clindamycine:	**4**		
after 4 weeks combination therapy:	**1**	**reduction of symptoms:**	**85%**
exertional dyspnea initially:	**8**		
after 1 week clindamycine:	**8**		
after 3 weeks clindamycine:	**4**		
after 4 weeks combination therapy:	**0**	**reduction of symptoms:**	**100%**

Mrs U. had been almost free from symptoms for 2 months in 1/2017. She experienced very few side-effects and would repeat the therapy if needed.

4.27 Case 27 Mrs K.M., age 46

In 5/2010 a hysterectomy was performed due to continuous abdominal pains. A cardiological examination in 11/2010 offered no findings. During 2012, recurrent cystitis with normal laboratory results occurred, and in 12/2012 a minor alpha-2-increase with negative immunofixation in immunoelectrophoresis was seen. In the course of 2012 Mrs K.M. suffered from an increase in pronounced fatigue, unclear pains of the neck and shoulder muscles, and also pains in several joints. The resilience decreased significantly and a weakness in the leg muscles impeded her walking. Additionally, she would be clearly weakened after 5-10 minutes of walking with need for a break.

Due to a suspected polymyalgia rheumatica a cortisone impact therapy was prescribed, but yielded only very slight and short-term improvement of the symptoms. In 2/2013, incipiet seronegative rheumatoid arthritis was diagnosed. Etoricoxib and Meloxicam were not tolerated well and yielded no relevant improvements. 3 x 1 g novaminsulfone reduced the pains to some degree, but not the unusual weakness and fatigue.

At the beginning of 2013 the weakening of the muscles increased to such a degree, that the patient had to hold on to something constantly while standing, tremendously reducing the possible walking distance. To exclude an inflammatory CNS-disease, an MRT of the head was arranged, but yielded no results. 7/2013 saw a slight, short-term decrease of the pains under prednisolone 20 mg 1-0-0, but the pronounced fatigue was still uninfluenced. A renewed therapy with prednisolone 20 mg/d in 2/2014 caused only very little improvement. An extensive laboratory exploration in a specialised clinic was performed in 7/2014. Excluded among others were autoimmune deficiencies, thyreoiditis and myasthenia. Since 7/2014 a basic therapy with sulfadiazine was prescribed, but yielded no significant improvement.

By then the abnormal weakening of the muscles had progressed so far that the patient could only stand with help (lamppost, bus stop) for 5 minutes, then her legs started to shake uncontrolledly due to the progressive weakness. Risk of falling was always present. **In 12/2014 borreliosis and toxoplasmosis serology were negative. At that time the symptoms had been persisting for about 4 years.**

Therapy: I n 1/2015 therapy with clindamycine 300 mg 3 x 1 for 16 days led to significant improvement of the general condition and decrease of muscular pains was seen. Oral thrush had developed by the end of the therapy. A few days after the therapy was ended, the muscular pains increased again. From 4/2015 renewed therapy, this time with Daraprim 2 x 25mg, calcium folinate 1 x 15mg and sulfadiazine 4 x 500mg was undertaken. A clear improvement could be observed, but there were also side-effects like head pressure and headaches, which could be attributed to the sulfadiazine. Clindamycine 2 x 600 mg was again prescribed instead of sulfadiazine along with Ampho-Moronal (Amphotericine B 10 mg) 5 x 1 as thrush prophylaxis.

In the course of this therapy a significant reduction of muscular pains and an increase of overall physical resilience occurred. The remaining symptoms improved noticeably under prednisolone 5 mg daily. Walks of 45 minutes and riding a bicycle were again possible without problems.

At the beginning of 11/2016 the patient had been almost free from symptoms for 16 months, while being treated with 5 mg prednisolone/d and sulfasalazine 2g/d. Due to the thrush she developed during clindamycine therapy, she rated the side-effects as average to severe, but was still open for an eventual repetition of the therapy.

Unfortunately, she stopped taking prednisolone and developed a relapse very quickly. The muscular pains and fatigue increased notably, although other symptoms of an active toxoplasmosis did not (yet) show.

12/2016 prednisolone 20 mg/d was prescribed again, but within one week no effect could be observed. Therefore, a combination therapy with clindamycine 2 x 600mg, Daraprim 2 x 25 mg and calcium folinate 1 x 15mg with a simultaneous prescription of Ampho-Moronal (Amphotericine B 10mg) 5 x 1 was started. During the first 3 days of combination therapy stress-related muscular pains self rated up to 10 occurred, followed by a continuous improvement. After 10 days, the fatigue had decreased from 8 to 2 and the muscular pains were reduced from 8 to 1. Mrs K.M. was free from symptoms after 20 days and the combination therapy could be stopped and prednisolone was again reduced to 5 mg/d. As in case 23, the treatment of the relapse with combination therapy was slightly more effective than the first treatment. Mrs K.M. was free from symptoms in 1/2017 and the prednisolone therapy (5 mg daily) was continued.

Mrs K.M., result of questionnaire:

muscular pains initially:	**9**		
after 16 days clindamycine 3 x 300 mg:	**5**		
after 4 weeks combination therapy (s.a.):	**2**		
11/2016 14 months after end of therapy:	**1**		
12/2016 relapse:	**6**		
after 20 days combination therapy:	**0**	**reduction of symptoms:**	**100%**

fatigue initially:	**9**		
after 16 days clindamycine 3 x 300 mg:	**6**		
after 4 weeks combination therapy (s.a.):	**5**		
11/2016 14 months after end of therapy:	**2**		
12/2016 relapse:	**8**		
after 20 days combination therapy:	**0**	**reduction of symptoms:**	**100%**

concentration disorders initially:	**0**		
after 16 days clindamycine 3 x 300 mg:	**0**		
after 4 weeks combination therapy (s.a.):	**0**		
11/2016 14 months after end of therapy:	**0**		
12/2016 relapse:	**0**		
after 20 days combination therapy:	**0**	**reduction of symptoms:**	**0%**

profuse sweating initially:	**0**		
after 16 days clindamycine 3 x 300 mg:	**0**		
after 4 weeks combination therapy (s.a.):	**0**		
11/2016 14 months after end of therapy:	**0**		
12/2016 relapse:	**0**		
after 20 days combination therapy:	**0**	**reduction of symptoms:**	**0%**

Comment: earlier therapy trials with prednisolone only led to very insignificant and short-term improvements of the symptom, thus a “simple” polymyositis could not be the cause. The clinical picture resembled among others a seronegative polyarthritis, but a therapy with sulfasalazine and 5 mg prednisolone/d alone did not yield significant effects.

An overlap of toxoplasmosis and polymyositis has been observed before. Behan et al. (1983) reported about a case, in which a toxoplasmosis treatment could improve the clinical picture of a disorder resembling polymyositis significantly. In this case also the need for a corticoid treatment continued. Paspalakis et al. reported in 2001 about a case, in which an active toxoplasmosis preceded a polymyositis. They concluded that toxoplasma may have had caused antigen-changes in the muscles, which then induced a polymyositis.

Cuturic et al. (1997) also postulated due to the specific development of a toxoplasma-induced polymyositis that one might be able to identify 2 stages of a toxoplasma-polymyositis: an acute stage that responds to a therapy directed against protozoa and a chronic stage caused by immunological changes that requires treatment with steroids. They demanded that toxoplasma antibodies should be determined for all patients with polymyositis.

Mrs K.M. never suffered from concentration disorders or profuse sweating. Especially the missing concentration disorder points to the fact that even in long duration of an active toxoplasmosis a CNS involvement is not inevitably in any case.

This case also points out that the frequently mentioned fatigue does not necessarily mean a CNS involvement due to toxoplasmosis, since the symptoms “fatigue” and “concentration disorders” show a clear distinction here.

It is quite probable that the weaning of prednisolone has played a role in the development of the relapse, especially since the relapse occurred immediately afterwards. A hypothesis might be that without the prednisolone an activation of the polymyositic component of the illness was triggered, which in itself disturbed the immune control and thus started the relapse.

5. Results

In my - unselected – patient population of about 1250 patients, 27 cases of active toxoplasmosis that required treatment were found within 3 years until the end of 1/2017; this demonstrated a prevalence rate of approximately 2.1%. 5 of these cases, namely cases 7, 10, 13, 17 and 22 could be classified as new cases with a disease duration of one year or less.

In **group A** (toxoplasmosis IgG positive), 17 patients (63% of the overall group) can be found, among them 14 women and 3 men. The **average age** in this group was **56 years** with a standard deviation (SD) of +- 12 years. The **disease duration** varied from 7 months to 50 years; a value of **10 years**, SD +-12.6 years could be accepted as an average estimated disease duration.

The **toxoplasmosis IgG** had been increased from 20 up to over 400 IU/ml with an **average count 74.9** +- 86 IU/ml. If one disregards the exceedingly high count in case 17, of which it is only known that it was above the measuring range of 400 IU/ml, an average count of 54.5 +- 28.9 IU/ml can be determined. This said, Case 17 is not left out and the IgG average of 74.9 is used in the further calculations. The IgM was only slightly increased to an average 4.3 +- 1.26 IU/ml in cases 10, 11, 14, 17. The average disease duration in these cases was 7.1 years. **No significant increase of IgM was registered in any of these cases** (borderline from 6, positive from 10 AU/ml).

In **group B** (toxoplasmosis IgG negative), 10 patients (37% of the overall group) can be found, among them 7 women and 3 men. The **average age** in this group was **42.8 years** with a standard deviation (SD) of +- 12 years. The **disease duration** varied from 3 months to 24 years; with an average of **5.8 years**, SD +- 7.2 . Without taking case 25 into account, which showed the longest disease duration in this group, the average estimated disease duration would be 3.8 +- 4.1 years. This said, case 25 is not left out and the average of 5.8 years is used in further calculations.

Only case 19 shows a slightly increased IgM at 3.7 AU/ml. The disease duration of this case was 2 years. **A significant IgM increase was not registered in any case.**

In 2 cases (11 and 23), symptoms started to increase after pregnancies; in one case (6), symptoms occurred after two surgical interventions.

In 4 cases, latency times of 3 – 6 months after initially weakening incidents (e.g. repeated infections or surgeries) could be observed prior to the onset of symptoms of an active toxoplasmosis (compare cases 1, 7, 17 and 19).

Intensity of symptoms and their percentage reduction

Fatigue was often the earliest symptom for an active toxoplasmosis and was shown **by all patients of both groups.** The intensity of fatigue varied in group A from 8 – 10, in group B from 6 – 10. In **group A** the average symptom intensity amounted to **8.8**, with a **symptom reduction of 85%**; the average symptom intensity for **group B** was marginally lower at **8.6** with a slightly higher **symptom reduction of 89 %**.

average symptom intensity	**group A**	**group B**
fatigue at beginning of the therapy:	**8.8** +- 0.9	**8.6** +- 1.6
after 1 week of therapy:	**4.9** +- 2.0	**4.2** +- 2.7
at termination of therapy:	**1.4** +- 1.4	**0.9** +- 0.9
average symptom reduction in %:	**85** +- 15	**89** +- 10

Muscular pains were also reported **by all patients of both groups. The** intensity varied in group A from 6.5 – 10, in group B from 1 – 9. In **group A** the average pain intensity was **8.2** with a **symptom reduction of 90%**; the average pain intensity for **group B** was lower at **6.7** with a **symptom reduction of 94 %**

average symptom intensity	**group A**	**group B**
muscular pains at beginning of the therapy:	**8.2** +- 1.0	**6.5** +- 2.4
after 1 week of therapy:	**4.7** +- 2.2	**2.3** +- 2.4
at termination of therapy:	**0.9** +- 0.9	**0.4** +- 0.8
average symptom reduction in %:	**90** +- 11	**94** +- 10

The following symptoms were not observed in all patients respectively. **To avoid false low values, the next readings will only mention those patients who showed a respective symptom intensity of at least "2" prior to therapy.**

Concentration disorders affected all patients apart from cases 10 and 27. This amounted to **16 patients (94%) of group A and 9 patients (90%) of group B.** The intensity varied from 3-10 in group A and 0-10 in group B. The initial intensity of **7.8** in **group A** was higher than that of **6.5** in **group B.** Group A achieved a **symptom reduction of 75%** and group B achieved a **symptom reduction of 84%.**

average symptom intensity	**group A**	**group B**
concentration disorders at the beginning:	**7.8** +- 1.6	**6.5** +- 3.0
after 1 week of therapy:	**5.5** +- 2.2	**4.2** +- 2.6
at termination of therapy:	**2.2** +- 1.7	**1.3** +- 1.3
average symptom reduction in %:	**74** +- 23	**84** +- 15

Profuse sweating affected 14 patients (**82%) of group A** and 7 patients (**70 %) of group B**. Cases 2, 3, 8 as well as 22, 23 and 27 were not affected. The sweating varied in both groups from 0-10; the average intensity in group B was slightly higher than in group B, but showed a significantly higher standard deviation. The initial intensity in **group A** at **7.5** (with a **symptom reduction of 84%**) was lower than in **group B** at **8.8**, whith a **symptom reduction of 88%**.

average symptom intensity	**group A**	**group B**
profuse sweating at beginning of the therapy:	**7.5** +- 1.6	**8.8** +- 1.9
after 1 week of therapy:	**5.0** +- 2.4	**6.2** +- 4.1
at termination of therapy:	**1.3** +- 1.6	**1.0** +- 1.4
average symptom reduction in %:	**84** +- 18	**88** +- 15

The following symptoms will only be discussed with reference to their initial and final symptom intensity, since not all three values were recorded for all patients. As mentioned before, the readings will only mention those patients, who showed a respective symptom intensity of at least 2 prior to therapy.

Exertional dyspnea was seen in 11 patients of **group A (65%)** and 7 patients of **group B (70%)**. Here, cases 1, 2, 5, 6, 8, 9, 11, 12, 14, 16 and 17 as well as 19, 20, 21, 22, 23, 24 and 26 were affected. An exertional dyspnea was also reduced under therapy in cases 2 and 17 but these cases are not included in the count, since both patients suffered from pulmonary diseases also, so that it was difficult to evaluate the effectivity of the toxoplasmosis therapy with regards to dyspnea. The initial intensity was between 6-10 in group A and between 5-10 in group B.

average symptom intensity	**group A**	**group B**
exertional dyspnea at beginning of the therapy:	**8.4** +- 1.5	**7.4** +- 1.4
at termination of therapy:	**1.8** +- 1.4	**1.4** +- 1.5
average symptom reduction in %:	**80** +- 17	**82** +- 17

Listlessness had been described as an early symptom by most patients and was registered by 12 patients **(70%) in group A** and 5 patients **(50%) in group B.** Here, cases 1, 2, 5, 8, 9, 11, 12, 13, 14 and 16 as well as 19, 20, 21, 23 and 25 were affected. The initial intensity ranged from 6-10 (group A) to 8-10 (group B); 3 out of 6 men (50%), as well as 9 out of 21 women (42%) were affected.

average symptom intensity	**group A**	**group B**
listlessness at beginning of the therapy:	**8.1** +- 1.1	**8.8** +- 1.0
at termination of therapy:	**2.1** +- 2.1	**0.8** +- 1.0
average symptom reduction in %:	**76** +- 25	**90** +- 12

A significantly increased irritability was seen in 9 patients of group A (53%) and 4 patients of group B (40%); cases 2, 3, 4, 7, 11, 12, 14, 16 and 17 as well as 19, 20, 21 and 25. The initial intensity varied from 6-10 (A) and from 5-10 (B); the symptom reduction was 67% (A) and 90% (B).

5 out of 6 **men** were affected (cases 2, 3, 4, 20 and 25 = **83%**). The one unaffected man (case 22) was the patient with the shortest disease duration in this study (3 months). 8 out of 21 **women** were affected (cases 7, 11, 12, 14, 16, 17, 19 and 21 = **38%**). The initial average intensity in men was 8.2 with a reduction to 3.6, equalling a **56% reduction**. The initial average intensity in women was 8 with a reduction to 1,25 equalling a **86% reduction**. The average disease duration was 9.8 years (+- 9.8 years) for women, which was 1.2 years higher than the men´s average disease duration of 8.4 years (+- 8.1).

average symptom intensity	**group A**	**group B**
irritability at beginning of the therapy:	**8.6** +- 1.7	**7.0** +- 2.1
at termination of therapy:	**3.6** +- 2,9	**0.5** +- 0.9
average symptom reduction in %:	**67** +- 24	**90** +- 41

Depressive moods could be observed in 7 patients of group A (41%) and 4 patients of group B (40%), namely in cases 5, 8, 9, 11, 12, 14 and 16 as well as 21, 23, 24 and 25. **Only 1 out of 6 men (17%) was affected, compared to 10 out of 21 women (48%)**. The male case (case 25) presented a disease duration of 24 years at an age of 57 years. The female patients are recorded in cases 5, 8, 9, 11, 12, 14, 16, 21, 23 and 24 with an average disease duration of 16.2 years and an average age of 49.9 years. The initial symptom intensity for the male patient was reduced by half from 10 to 5; the average initial intensity for the female patients was reduced from 7.6 to 2.4, with an average symptom reduction of 72%.

average symptom intensity	**group A**	**group B**
depressive moods at the beginning of therapy:	**8.0** +- 1.5	**7.5** +- 2.8
at termination of therapy:	**2.9** +- 2.5	**2.25** +- 2,3
average symptom reduction in %:	**65** +- 28	**78** +- 23

Anxieties without a clear cause burdened 6 patients in **group A (35%)** and 2 patients in **group B (20%).** These were cases 5, 9, 11, 12, 14 and 15 as well as cases 25 and 26. The intensity varied from 6-10 (A) and 7-10 (B). Only patient 25 with a disease duration of 24 years is male. **29% women and 17% men across both groups exhibited this symptom.** The calculation for the two patients of group B only serves to compare this to group A. It is understood, that a calculation based on only two cases is questionable.

average symptom intensity	**group A**	**group B**
anxieties at the beginning of therapy:	**8.3** +- 1.4	**8.5** +- 0.5
at termination of therapy:	**2.0** +- 2.1	**0.5** +- 0.5
average symptom reduction in %:	**76** +- 20	**92** +- 8.0

Visual disturbances, meaning an intermittent blurry sight occurred in 9 patients of **group A (53%)** and 3 patients of **group B (30%)**; these were cases 1, 2, 6, 8, 9, 12, 14, 16, 17 as well as 20, 21, 25. The initial intensity ranged from 4-10 in group A and 5-8 in group B.

5 patients from group A (cases 1, 2, 6, 14 and 16) did not experience a reduction of their visual disturbances. The average disease duration was 12.8 years (+- 10 years) for these patients and thus higher than the overall disease duration of group A (10 years +- 12.6 years). The average disease intensity in these patients of 7.6 (+- 2.3) is higher than the intensity of group B. Both patients with intensive visual disorders of 10, who experienced no improvement in their visual disturbances under therapy had disease durations of 18 years (case 14) and 30 years (case 16). Among the patients of group A with improvement in their visual disturbances, there are 2 cases with a disease duration of 15 years (cases 8 and 12).

average symptom intensity	**group A**	**group B**
visual disturbances at the beginning of therapy:	**6.6** +- 2.6	**4.0** +- 0.8
at termination of therapy:	**4.3** +- 4.0	**0.67** +- 0.9
average symptom reduction in %:	**42** +- 48	**80** +- 28

A **non-systemic vertigo** was experienced by 7 patients of **group A (41%)** as well as in 3 cases of **group B (30%)**; these were cases 6, 7, 8, 11, 12, 14, 16 and 19, 25 26. The intensity varied from 4-8 (A) and 4-9 (B).

average symptom intensity	**group A**	**group B**
vertigo at the beginning of therapy:	**6.4** +- 1.4	**7.0** +- 2.2
at termination of therapy:	**1.7** +- 1.6	**0.0** +- 0.0
average symptom reduction in %:	**74** +- 22	**100** +- 0,0

Peripheral oedema, often associated with an exertional dyspnea, were diagnosed in 6 patients of **group A (35%)** and 3 patients of **group B (30%)**; cases 1, 5, 8, 12, 14 and 16 as well as 21, 25 and 26 were affected. Only patient 25 is male. **Thus, 8 out of 21 women (38%) and 1 out of 6 men (17%) were affected across both groups.**

average symptom intensity	**group A**	**group B**
peripheral oedema at the beginning of therapy:	**6.6** +- 2.0	**7.6** +- 2.0
at termination of therapy:	**2.0** +- 1.0	**0.0** +- 0.0
average symptom reduction in %:	**65** +- 20	**100** +- 0,0

Morning stiffness ranging from some minutes up to approximately an hour occurred in 5 patients of **group A (29%)** and 3 patients **(30%) of group B**; cases 5, 8, 9, 11, 14 as well as 19, 21 and 25 were affected. The initial intensity ranged from 6-10 in both groups.

average symptom intensity	**group A**	**group B**
morning stiffness at the beginning of therapy:	**8.0** +- 0.6	**8.0** +- 1.6
at termination of therapy:	**0.6** +- 0.8	**0.0** +- 0.0
average symptom reduction in %:	**95** +- 6,4	**100** +- 0,0

Sleep disorders, predominantly a sleep maintenance insomnia with frequent and lengthy nocturnal alertness and difficulties in falling asleep again**,** occurred in 5 patients of **group A (29%)** and 3 patients **(30%) of group B**; cases 6, 9, 11, 14, 16 as well as 19, 21 and 25 were affected. The initial intensity ranged from 6-9 (A) and 5-10 (B).

average symptom intensity	**group A**	**group B**
sleep disorders at beginning of the therapy:	**7.8** +- 1.2	**8.0** +- 0.0
at termination of therapy:	**2.2** +- 1.3	**0.0** +- 0.0
average symptom reduction in %:	**72** +- 20	**100** +- 0.0

Further symptoms that were reduced in the course of the therapy:

5 patients of group A and 2 patients of group B reported about **hot flushes** that were reduced significantly under therapy (cases 6, 8, 13, 14, 16 / 19 and 25).

3 patients of group A (11, 12 and 14) and 2 patients of group B (20 and 21) complained about **unspecified abdominal pressure and nausea** that was reduced significantly under therapy (in case 11 intensity 10 and reduction to 1, in case 12 intensity 7 and reduction to 3, in case 20 intensity 8 and reduction to 3, in case 21 intensity 10 and reduction to 5).

3 patients reported **swelling of the lymph nodes** in their medical history; in case 11 they occurred axillary, in cases 17 and 19 paracervical.

2 patients described that their **ravenous cravings for "sweets"** had disappeared completely due to the therapy (cases 12 and 25).

2 patients reported about a significant **loss of hair** that had been reduced quickly during therapy (cases 16 and 26).

Patient 7 suffered from a massive **tremor of unknown cause**, which was reduced from 10 to 5 during therapy.

6 Overview of prescribed therapies

Here, it will be reported about both groups together. I did't find differencies in the effectivitiy of the treatment between both groups, nor are there clear differencies concerning the disease itself. So a seperated examination of both groups is not useful in this chapter. It might be of interest in a far larger collective.

In 5 cases (18%) no combination therapy was prescribed due to the efficacy of clindamycine; thus a monotherapy with clindamycine was carried out for 2 – 4 weeks. These were the cases 4, 6 and 10 (average disease duration 2 years) and the cases 18 and 22 (average disease duration 8.3 months). **In these cases the concentration disorders, which were observed in all 5 cases, were reduced during therapy.**

In 2 cases a monotherapy with clindamycine had to be replaced by a combination therapy with sulfadiazine. In case 13 (disease duration 1 year), the therapy had to be replaced after 3 weeks, because the effectivity of the therapy was still not optimal. A loss of effectiveness of the monotherapy with clindamycine could be observed after 3 weeks in case 26 (disease duration 20 years), so that the therapy had to be altered.

In 2 cases, the treatment was effected initially by a combination therapy, without prior treatment with clindamycine-monotherapy (cases 23 and 25).

12 patients (44%) receieved a combination therapy with Daraprim, calciumfolinate and sulfadiazine only (cases 1, 3, 7, 12, 13, 15, 17, 20, 24, 26). The duration of the treatment varied from 20 days (case 8) up to 6 weeks (case 15).

In 5 cases (18%), sulfadiazine had to be replaced by clindamycine in the course of the combination therapy; these were cases 8, 19, 23, 25 and 27. This was done due to a decreasing or insufficient effectiveness in cases 8, 9 and 19; in cases 23, 25 and 27, the replacement was necessary due to side effects (nausea, headaches).

A combination therapy with Daraprim, calcium folinate and clindamycine alone was prescribed in 2 cases (7%); these were cases 5 and 21.

Clindamycine 2 x 600 mg had to be replaced in three cases during combination therapy (11%). The change to sulfadiazine was done due to side-effects in **case 2** and due to a decreasing effectiveness in **case 9**. In **case 14**, the low effectiveness during an overall treatment duration of 3 months made a change from clindamycine to cotrimoxazole 2 x 960mg in the combination therapy necessary.

6.1 Relapses

5 cases of relapses were reported: in **case 5** 3 weeks after completing the therapy, in **case 17** after 6 weeks, in **case 23** after 9 months, in **case 25** after 2 weeks and in **case 27** after 16 months. All relapses could be treated effectively with a further combination therapy and a decrease in symptoms or complete recovery could be achieved after a few days in all cases.

The average time in which the patients were free from symptoms until the occurrence of a **relapse in group A (cases 5 and 17) was 4.4 +- 4.8 months** (until the end of 01/2017).

The average time in which the patients were free from symptoms until the occurrence of a **relapse in group B (cases 23, 25 and 27) was 4.2 +- 3.8 months** (until the end of 01/2017).

The disease duration across both groups for patients with relapses ranged from 7 months to 50 years, with an average of 18.7 +-17.7 years

See also p. 107, discussion of relapses, p 108 relapse - prevention, and “addendum” p 111

7 Discussion, Comparison of Collectives

The cases presented in this study show that an immunocompetent patient can exhibit a "toxoplasmosis load", which can be active (Pavesio et al. 1992, Watt et al. 2015) and trigger intense chronic symptoms in the sense of an active toxoplasmosis (Ho-Yen 1990, Sharpe et al. 1991, Flegr 2013). The **disease duration** varies from 7 months up to 50 years; the average duration for **group A was 10 years and 5.8 years for group B**. The symptoms mostly showed a progression over several years, resulting in a severe clinical picture. Examples for these findings can be seen in cases 1, 5, 8, 11, 14 and 16 as well as 21-25.

Only 6 of the 27 patients were male, even though a seropositivity seems to be more common in men than in women (Wilking et al. 2016). Possible explanations for this discrepancy might be that the related health problems are generally addressed less frequently by men and / or are seen as part of wear-related pains and are thus not talked about. It is known that the seroprevalence of toxoplasma IgG in the total population increases with age (Jean et al. 2011, Wilking et al 2016). Maybe the development of parasitaemia, which leads to a measurable rise in antibodies in the progression of the disease is only a matter of time and an eventual weakening of the host´s immune system. These parasitaemia will probably increase with higher age due to a longer disease duration and exhaustion of the immune system, as postulated by Badhra and Khan (2012). This is probably also the reason for the average age in the seropositive group A (56 years) being 13.2 years higher compared to the seronegative group B (42.8), who also exhibited a shorter disease duration.

The toxoplasma IgG in group A was increased to 74.9 +- 86 IU/ml on average. The exceedingly high standard deviation indicates that the result is not represented very well. The reason is that this result is strongly influenced by case 17 with its exceedingly high IgG above measuring range. Disregarding case 17 would result in an average count of 54.5 +- 28.9 IU/ml.

Only in 4 cases in group A insignificant increases of IgM were seen. The average disease duration of these patients was 7.1 years and therefore below the group´s average of 10 years. Since there are clear indications for a possible absence of IgM detection (see also p. 12), it is obvious to conclude that IgM detection can only be expected in shorter disease durations.

Even in case 17 with its IgG above the measuring range and a disease duration of only 7 months, the IgM was not increased significantly. **This clearly points out that even only 7 months after the beginning of an active toxoplasmosis the IgM is not a reliable parameter.**

Since a significant IgM increase could not be detected in any of the cases, an exclusion of active toxoplasmosis by tachyzoid - specific IgM detection is obviously impossible, which is in accordance with Bretagne (2003).

In Group A, the level of lab results showed very little correlation to the expression of the symptoms. A tendency towards a more intensive expression of clinical symptoms in patients with higher IgG levels can be observed – though there are also examples in which this is not the case.

Thus, symptoms are expressed most intensively in e.g. case 5 with a disease duration of 50 years. Even though the level of toxoplasmosis IgG antibodies remaines moderate at 32.5 IU/ml, the IgM is negative. The clinical picture in case 5 can be compared most likely with cases 14 or 16, although the IgG levels in these cases are more than three times higher: case 14 presents an IgG of 97.9 IU/ml with a IgM level of 3.06 AU/ml, case 16 presents an IgG of 106 IU/ml with a negative IgM. One could also refer to similar severe cases 21 and 26 of group B as comparison across groups; these were completely seronegative with regards to toxoplasmosis

All things considered, a great number of variables determine the level of toxoplasmosis IgG: the patient´s age (see above), disease duration, immune status, toxoplasmosis activating factors, additional serious illnesses as well as possible past parasitaemia. These are the reasons why I would not expect a correlation between the level of IgG and the disease´s expression.

No patient of group B showed significantly increased toxoplasmosis antibodies. In group B, the average age is 13.2 years lower and the disease duration is 4.2 years shorter than in group A. An active immune system can force toxoplasma to change into the intracellular form of bradyzoites quickly and resolutely (Ho Yen et al 1992), and it is plausible, that this is more often the case in young patients. So it is very likely, that in younger patients parasitaemia of tachyzoites is only of short duration, so that no sufficient tachyzoite – specific antibody production is triggered to deliver positive results.

However, this does not lead to being asymptomatic. The reason could be, that bradyzoite – activity is strongly underestimated (Watts et al. 2015), and that it could be able to trigger symptoms. As there are no parameters to monitor these activity this could cause seronegative courses of the disease.

7.1 The prevalence of active toxoplasmosis

The mentioned prevalence of 2.1% refers to the 21 women and 6 men in this study only, related to an average of about 1250 patients quarterly. Since additional cases of active toxoplasmosis have been diagnosed and treated while this study was being written, the effective prevalence in my patients is probably significantly higher. There are also possibly some patients with an active toxoplasmosis among my patients, who have not yet been recognised because of reasons described before (see p 14 and 95). Starting from this random sample, one could conservatively estimate that with about 15 cases of an active, seropositive toxoplasmosis per practitioner´s surgery (with approximately 32.600 general practitioners and a current population of about 81.300.000 in germany) **about 489,000 persons or 0.9% of the population would be affected by an active seropositive toxoplasmosis**. If one calculated about 8 **seronegative patients** with an active toxoplasmosis per practitioner´s surgery, a **further 260,000 cases or 0.36% of the population** would have to be added. With reference to 32.606 general practitioners with 1000 cases each and about 32.606.000 treated cases, the risk to develop an active seropositive toxoplasmosis in case of an endemic infestation of about 50% of the adult population (Wilking et al.) is approximately 1 infection 33 per patients in a practitioner´s surgery in Germany. The risk for the seronegative cases would be 1 infection per 62 patients. This is a significant risk and the case studies show clearly how severe the progression of this disease can be. The figures also show clearly that the determination of toxoplasmosis antibodies in asymptomatic patients is not reasonable, especially since a secure exclusion because of negative antibody counts cannot be made.

7.2 Factors that promote an active toxoplasmosis

In **cases 11 and 23**, the symptoms of an active toxoplasmosis worsened immediately following a pregnancy. **This points to the high risk of mistaking an active toxoplasmosis for a post-natal depression.** In **case 1**, multiple factors affected the patient´s health (see description of the case). In **case 6**, symptoms occurred after two surgeries. In **case 7**, a chronic pus secreting wound has probably promoted the active toxoplasmosis. In the case of one young patient (**case 19**), it is likely that a pre-existing mild toxoplasmosis was intensified considerably by a mononucleosis**. A Chronic Fatigue Syndrom (CFS) with abnormal fatigue, muscular pains and concentration disorders can occur after a mononucleosis (White 2007). Keeping the case mentioned before in mind, it is imaginable that a fraction of these CFS cases can be attributed to activated toxoplasma** – and thus an effective treatment of the CFS would be possible. It is possible that other significant health burdens can promote the transition towards an active toxoplasmosis as well, only this often cannot be determined because in most cases this took place some years ago.

7.3 Latency times, therapeutic objective

Latency times of 1 – 6 months could be observed in 5 cases, where an initially weakening incident (e.g. multiple infections or surgeries) preceded the occurrence or worsening of an active toxoplasmosis (compare cases 1, 7, 16, 17 and 19). In these cases, the activation of a toxoplasmosis in an immunocompetent patient had presumably been promoted by previous severe infections or other health-affecting incidents. I suspect that the parasites increase their replication rate, as soon as the host´s immune system is suppressed in its activity. Nevertheless, the effect on the immunocompetent host seems to set in only slowly, so that the symptoms only become conspicuous after some weeks or months.

This is a problem that´s constantly affecting the anamnesis: the disease mostly starts in a slow and creeping manner, so that it is difficult to determine a clear onset of the disease or to define clear symptoms right from the start. Because of this, symptoms that point towards an active toxoplasmosis can often be misinterpreted by the patient as well as by the practitioner as signs of an (increasing) indisposition.

The sometimes very long disease duration of up to 50 years (case 5) shows that for some patients' immune systems it seems to be very difficult to regain control of the toxoplasmosis, once it has changed to an active stage of the disease. The key factor for this type of development might be an **exhaustion of the CD-8-T-helper cells**, which has been substantiated for toxoplasmosis patients by Badhra and Khan (2012); see also page 8.

As far as we can tell, there is no therapy that can eradicate toxoplasma completely and it remains to be seen, if the human immune system can do so. This should not be a significant problem for an immunocompetent person. Bradyzoites usually stop or severely decrease their replication under control of the immune system, also re-transformations from tachyzoites to bradyzoites (see Ferguson et al. 1989) can lead to a reduction of the symptoms. However, there would be no more trigger for an increased production of antibodies then (see also 1.5, p.10). Unfortunately, severe symptoms of the disease can also be observed in these cases, as has been verified in the seronegative cases of group B.

Studies, which focus on the effectiveness of the medication mentioned in 3) point out, that an impact should be mostly expected on the tachyzoites (Blais et al. 1993). It is possible that under therapy an increased transformation from tachyzoites to bradyzoites takes place. Murata et al documented 2017 that the medication mostly is not lethal to the bradyzoites , but this obviously does not rule out, that the activity of bradyzoites is reduced during therapy.

I**t is therapeutically decisive to influence the balance between the parasite and the host´s immune system substantially in favour of the host.**

In case of an active toxoplasmosis that cannot be controlled sufficiently by the host´s immune system, the pressure on the toxoplasma is enhanced during the antibiotic therapy, and presumably the parasite reacts with a downregulation of its activity, so that the immune system can maintain control on the parasite by itself afterwards. The parasite´s activity is then reduced so vigorously, that symptoms cease to persist. Thus, the therapeutic goal is achieved. It would be most interesting in this context to find out if the CD-8-exhaustion which has been substantiated by Badhra and Khan (2012), can recuperate during therapy and cause a long-term healing success.

7.4 Validity of laboratory results

Multiple factors determine, if at least the IgG is increased in case of an active toxoplasmosis. Bradyzoite activity alone might possibly start a symptomatic disease and there probably is no need for a tachyzoite parasitaemia to cause symptoms. In contrast to earlier findings, bradyzoites do not rest, but can be active, can multiply and can cause cell ruptures (Ho-Yen 1992, Fergusson et al. 1994 and 1989, Gross et al. 1992, and Watts et al. 2015). Bradyzoites only induce a low immune response (Smith et al. 1996) and the exposition to antigens in case of rarely occurring cyst ruptures is probably so limited that only very few antibodies are being formed, which in addition cannot be registered by routine test, resulting in seronegative courses of the disease.

A further explanation for seronegativity especially in young patients, would be that a highly active immune system possibly forces toxoplasma, to revert to a bradyzoite form at an early stage of the infection, and that bradyzoites may have to stay in this form to evade the immune system. The phase of exposition to antigens then is only very short. The average age of seronegative patients in group B is about 13.2 years lower than that of group A with positive IgG-findings; also, the disease duration in group B is about 4.2 years shorter than in group A. The toxoplasma possibly did not have as much time to exhaust the immune system and then cause a parasitaemia.

The toxoplasma-test systems only react to antibodies that are directed against tachyzoites, which is also true for the test used in this study, which showed a sensitivity of 81.8% in an evaluation done by Prusa et al. (2012) with regard to congenital toxoplasmosis.

Unfortunately, no fully developed, non-invasive test to determine the toxoplasma load, or to measure its activity, has been made available. Because of the very long disease durations with at times sporadic progressions (cases 8, 11, 13, 16 and 23), I presume that some of my patients might have gone through several phases of toxoplasmosis reactivation. Still, the antibody level might increase only if these reactivations lead to a parasitaemia and the release of a sufficient number of tachyzoites to trigger a (renewed) immune response.

The level of toxoplasma IgG showed no clear correlation to the intensity of symptoms, as shown above and in summary, and a significant IgM elevation was not registered in any of the patients.

I found only very few deviations in the self-initiated laboratory results, as well as in the consideration of the results that I received from inpatient treatments and I could find no systematic deviations at all. **Judging from the numerous reasons mentioned above, I have come to the conclusion that this disease cannot be diagnosed reliably with the currently available laboratory parameters.**

Patients of both groups can exhibit similar intensive courses of the disease. The clinical assessment of the symptoms, e.g. by using a checklist, is probably the most sensitive method currently available to detect the disease.

7.5 Specificity of the therapy

Since clindamycine is effective against a multitude of pathogens, the initial effect observed in this study could also be attributed to an effect on other pathogens. However, the main effect of the treatment in most cases occurred only during the combination therapy with pyrimethamine, which proved to be more effective than clindamycine alone, as was to be expected following the findings of Blais et al. (1993). Apart from being effective against toxoplasmosis, pyrimethamine (Daraprim) as the main active substance is effective against plasmodia (malaria), *Cystoisospora belli* (Weiss et al 1988) and pneumocystis carinii, but the clinical pictures described above cannot be brought in line with these pathogens.

In summary, I thus conclude that in the cases mentioned above, an effect of the prescribed medication on another disease than toxoplasmosis is improbable in both the seropositive and the seronegative groups.

7.6 Discussion of symptom intensities and their reduction under therapy

I am fully aware of the principal disadvantages that occur because of the use of an analog scale from 1-10 in the assessment of symptom intensities, e.g. a high dispersion of the values. In the absence of more reliable laboratory parameters, I think this is the only way to identify patients with a suspected toxoplasmosis and document their therapeutic progress at the moment. **No single symptom alone allows the diagnosis of a toxoplasmosis.** Fatigue is a very sensitive, but unspecific symptom and all other symptoms can be pronounced surprisingly weak or missing in individual cases. The “checklist toxoplasmosis” (see attachment p. 125) is the result of intensive talks with affected patients and a extended research of former case reports. Under 2. on page 13 and on page 124 it is explained how the criteria are weighed.

The symptom intensity prior to therapy is mostly more pronounced in group A than in group B. Exceptions here are the symptoms listlessness, vertigo, peripheral oedema, sleep disorders and anxieties, which showed higher initial intensities in group B. A possible explanation would be that because of the lower average age in group B, the symptoms were experienced stronger as “age-related atypical”, which led to higher assessment concerning the intensities.

The symptom reductions in group B were consistently slightly higher, the therapy accordingly more successful on average than in group A. I attribute this to the shorter disease durations and the lower age in group B.

About the individual symptoms:

Abnormal fatigue affected all patients and is probably the earliest, most sensitive and unfortunately also very unspecific symptom of an active toxoplasmosis. Patients often have a strong need for sleep, but sleep reduces their fatigue only temporarily. In 8 cases, sleep disorders were also diagnosed, which surely had a disadvantageous effect in these cases, but which could not entirely explain the fatigue, especially since 19 patients did not report any sleep disorders.

In connection with an unusual fatigue, patients mostly mentioned a **permanent, profound exhaustion**, which probably is of great importance here. **One can conclude from case 27 that fatigue does not necessarily have to be related to a CNS symptomatic**, since this patient suffered from a pronounced fatigue prior to therapy, but not from concentration disorders.

The symptom intensities in both groups achieve the highest values of all symptoms with 8.8 (A) and 8.6 (B) and are almost similar despite the significantly shorter disease duration in group B. This leads to the assumption that the symptom probably reaches its full intensity early on in the progression of the disease and is experienced as being very burdening, independent of age. At the same time, the high **symptom reductions of 85% (group A) and 89% (group B)** point towards a good treatability.

Muscular pains also affect all patients and are a symptom with a high initial intensity (group A 8.2 / group B 6.5) and they are also an early occurring symptom in a lot of cases. **The pains can occur all over the body and can imitate a fibromyalgia with musculature that becomes painful on palpitation** (see cases 11 and 14). The pains typically increase with only light physical exertion and it has been proven effective to enquire about **pains in the upper leg muscles from climbing steps**. **In some cases, also frequent cramps were noticeable**. The 1.7 lower symptom intensity in group B with a high standard deviation is noticeable. In single cases, here especially in case 25, muscular pains can also be very low, **so that little or no muscular pains should not be seen as a deselection criterion for toxoplasmosis. The symptom reduction was 90% in group A and 94% in group B.**

It has to be stressed that there is also a possible overlap with a polymyositis, **as documented in case 27 on pp. 78-81**; see also Behan et al. 1983, Cuturic et al. 1997 and Paspalaki et al. 2001.

Concentration disorders affected all cases except cases 10 and 27. Enquiries about word finding disorders and disorders of the short-term memory were helpful in the anamnesis – these disorders were comprehensible for the patients and also so disturbing that some of them voiced concerns about a possible dementia. The intensity of this symptom has a tendency to increase with disease duration. When considering only patients with an initial intensity of 8 and higher, an average disease duration of 16.6 +- 15 years in group A and an average of 11.6 +- 8.5 years for group B is seen. Both values are – with high standard deviations – significantly higher than the average disease durations within the respective group. It nevertheless has to be taken into account that in case 7, a concentration disorder of 9 ocurred with a disease duration of only one year. **The symptom reduction in group B with a lower initial intensity of 6.5 is significantly higher at 84% that of group B with an initial intensity of 7.8 and a 74% reduction.**

Frequent profuse sweating occurred in 14 patients (82%) of group A and in 7 patients (70%) of group B. The patients reported about unusual, severe sweating from light physical exertion and also frequent nocturnal sweating. In group B, higher intensities with 8.8 were reported than in group B with 7.5. It is possible that the sweating was more intensive in group B or that is was experienced as more disruptive by the patients, which were on average younger than those in group A. **The symptom reduction in group B is slightly higher at 88% than in group A at 84%**.

Exertional dyspnea was reported by 11 patients of group A (65%) and 7 patients (70%) of group B. The initial intensities were 8.4 (A) and 7.4 (B). **The disturbances were equivalent to a heart insufficiency NYHA I-III** and also went along with an inadequate increase of heart frequency if only light physical exertion was performed. In 9 patients of both groups altogether (cases 1, 2, 5, 6, 8 and 16, as well as 22, 24 and 26), a cardiological diagnostic had been made in the previous history. In addition to echo and stress-echo, coronary angiographies had been done in 4 cases, a right-heart catheter in one case and a cardio-CT in one case. Despite the partially severe exertional dyspnea, the cardiological findings were inconspicuous. 8 of these 18 patients exhibited peripheral oedema, which improved under therapy (cases 1, 5, 8, 12, 14, 16 as well as 21 and 26). **The symptom reductions of 80% (A) and 82% (B) point to a good treatability.**

Toxoplasma-myocarditis could have caused the exertional dyspnea (compare Montoya et al. 1997), but there are also scientific references about a pulmonary involvement in the case of an active toxoplasmosis (Carme et al. 2002), so that an exertional dyspnea within the context of toxoplasmosis can be caused by pulmonary as well as cardiac involvement.

Listlessness, which was mentioned by 12 patients (70%) of group A and 5 patients (50%) of group B, was mostly experienced as being very disturbing, since the entire daily routine and the social life suffered permanently and significantly because of it. This was felt to be downright burdening by some patients, who had been very active before. As seen in the profuse sweating, higher intensities were reported by group B (8.8 vs. 8.1). **A higher symptom reduction in group B at 90% versus a 76% reduction in group A is most remarkable**; the lower age and the shorter disease durations may be positive factors here.

With regards to the symptoms “irritability”, “depressive moods”, “anxieties” and “oedema”, gender-related differences were observed. **The significance of this study with reference to gender specificity has to be evaluated with considerable caution, since men might be underrepresented in the study and the self-assessment of men and women with reference to their psyche could possible vary.**

There are numerous studies on the impact of toxoplasma on the psyche and behaviour (Coccaro et al. 2015, Yolken et al. 2001, Torrey et al. 2012, Flegr 2007 and 2013), up to more frequent suicide attempts (Townsend et al. 1975, Yagmur et al. 2010, Dalimi and Abdoli 2012). A detailed discussion of these symptoms and these studies can and should not be conducted here, since a related scientific paper would be a better place to do so.

Increased irritability with high intensities (A. 8.5 / B: 7.0) occurred in 9 patients **(53%) of group A** and 4 patients **(40%) of group B**. Cases 2, 3, 4, 7, 11, 12, 14, 16 and 17 as well as 19, 20, 21 and 25 were affected. **The symptom reductions were 67% (A) and 90% (B).**

On the one hand, most patients were quite self-critical with regards to this symptom in the anamnesis but still frequently dissociated from their irritability in an obvious manner. They mostly had the impression that their irritable and exuberant reactions often had no objectively plausible reason and thus felt uncomfortable with these reactions. Some patients had domestic problems and / or trouble at the workplace due to these behavioural problems. This symptom mostly improved surprisingly quickly under therapy.

Across both groups, 83% of all men and 38% of all women were affected, whereas the initial intensity for men was evaluated slightly higher at 8.2 than at 8 for women. The symptom reduction of 56% in men was significantly worse than that of 86% in women. The disease

duration of 8.4 (+- 8 years) in men was 1.4 years below that of 9.8 (+- 9.8 years) in women. The age of 51.4 +- 12.4 years in men is 7 years higher than the 44.4 +- 12.3 years in women. The one man, who was not affected (case 22, age 53), was the patient with the shortest disease duration in this study (3 months).

In summary one can say that an **increased irritability is frequent in men who show an active toxoplasmosis**. They are also affected after only a shorter disease duration and are affected more intensively than women, with a lower symptom reduction.

It cannot be ruled out that the slightly higher age of the affected men has influenced the results. Since the unaffected man is older than the subgroup´s average, I conclude that the low disease duration (in this case only 3 months) has a stronger influence on the symptom irritability than the patient´s age.

Depressive moods occurred in 7 patients of group A (41%) and 4 patients of group B (40%). The intensities were high at 8,0 (A) and 7,5 (B). Cases 5, 8, 9, 11, 12, 14, 16 as well as 21, 23, 24 and 25 were affected. The average disease duration of 20,4 years in group A was about 10.4 years above the overall average. The average disease duration for the 4 patients of group B was 10.8 years (+- 9.3 years) and was thus about 5 years higher than the group´s average of 5.8 years (+- 7.2 years). This leads to the assumption that depressive moods are typical symptoms for a long disease duration. One patient with a symptom intensity of "7" (case 21) had only suffered for about 3 ½ years from an active toxoplasmosis; these symptoms can thus occur significantly sooner. This is in concordance with a high standard deviation referring to this subgroup. The **symptom reductions of 65% (A) and 78% (B)** led to a significant increase in the patient´s quality of life.

Across the groups only 1 of 6 men (17% / case 25) mentioned depressive moods, whereas 10 of 21 women (48%) did the same. The male patient was case 25 with a disease duration of 24 years and an age of 57. In this case, the initial intensity was 10, which got reduced by half to 5. The female patients were cases 5, 8, 9, 11, 12, 14, 16, 21, 23 and 24 with an average disease duration of 16.2 years and an average age of 49.9 years. The average initial intensity in women was 7.6; this was reduced to 2.4 with an average symptom reduction of 72%.

Across the groups, 6 of the 11 patients with depressive moods also suffered from sleep disorders (54% / cases 9, 11, 14, 16 as well as 21 and 25), which could potentially intensify the depressive moods. In this case also, only one patient is male (case 25). Permanent fatigue and other symptoms of an active toxoplasmosis can of course also intensify depressive moods, so that

finally the emergence of these symptoms and their improvement under therapy has to be seen as being multifactorial.

Across the groups, 5 of the 11 patients with depressive moods also suffered from anxieties (45% / cases 5, 9, 11, 12 and 25). Only one patient is male (case 25), which is in concordance with the finding that anxieties occur more frequently in women (see next page).

Across the groups, the coincidence of depressive moods and increased irritability is less obvious; only 4 of the 11 (36%) patients with depressive moods also suffered from increased irritability (cases 12, 16 as well as 21 and 25) . An increased irritability occurs more frequent in men than in women. Patient 25 (male) is also the exception in this subgroup.

Anxieties in the sense of anxiety disorders occurred in 6 patients of **group A (35%)** as well as in 2 patients of **group B (20%)**. The affected cases were 5, 9, 11, 12, 14 and 16 as well as 25 and 26. **5 of these 8 patients (62%) also suffered from depressive moods (cases 5, 9, 11, 12 and 25).** The symptom reductions of **76% (A)** and **92% (B)** point towards a good treatability. The average disease duration of 21 +- 15 years in group A and 14 +- 10 years in group B suggests that this is a typical symptom of a long disease duration.

In the case of a 57-year old patient (case 9), the active toxoplasmosis had been persisting for only 6 years, so this symptom might also occur in earlier stages of the disease. In case 11 a 39-year old patient who was the youngest patient with this symptom had been suffering from an active toxoplasmosis for 9 years. The patients could dissociate from their anxieties in most cases, as they experienced them mostly as being not appropriate to the situation.

In this respect, we find a similarity to the symptom “increased irritability”. Despite this dissociation, the patients were intellectually unable to suppress the anxieties, which resulted in a severe impairment of life quality in some cases. Indirect positive effects of other symptom reductions, e.g. decreasing muscular pains and an improvement of exertional dyspnea, might have played a role in the symptom reduction of anxieties, but the improvements under therapy were so pronounced and quick (most patients already reported about an initial improvement within the first 10 days of treatment) that I would rather assume a direct effect on the symptom.

Only 1 patient (case 25) is male. Or put in another way: **across the groups 7 of 21 women (29%) and 1 of 6 men (17%) exhibit this symptom.** If one examines only the women across the groups with regards to this symptom, an average age of 51 +- 9.9 years and a disease duration of 18.9 +- 15 years with an initial intensity of 8.1 and a reduction down to 1.9 (reduction 78%) can be recorded. The 57-year old male patient showed a disease duration of 24 years, an initial intensity of 10 and a symptom reduction of 100%. Even though this is just an individual case, one can presume that anxiety disorders can affect also male patients severely, given a sufficiently long disease duration.

The **gender-specific differences** can be summarized to the extent that women are affected significantly more often by depressive moods and anxieties. Many patients pointed out depressive moods as well as anxieties, so there is a definite overlap of symptoms. The symptom “irritability” is found more frequently and slightly earlier in men, combined with a higher intensity and a lower symptom reduction.

The impression arises that in some cases the relatively more frequent irritability in men can be seen as replacing the relatively more frequent depressive moods and increased anxieties in women. In this context I would like to point out again the works of Flegr (2007 and 2013), in which the author discusses the influence of a latent toxoplasmosis on the human personality and changes of physiology. A further gender-specific difference is also observed with regards to peripheral oedema, as will be discussed on page 105.

Visual disturbance occurred in 9 patients of group A (53%) and 3 patients of group B (30%). The patients unanimously reported only intermittently occurring visual disturbances, which caused a “blurry” sight, in parts triggered by longer reading or exhaustion. The average intensities were not very high at 6.6 (A) and 4.0 (B), but were still experienced as being very disturbing at times. Almost all patients had received an ophthalmological consultation, without the cause for the disturbances being found.

The visual disturbances improved in only 4 of 9 patients of group A, i.e. in 44% of all affected patients (cases 8, 9, 12 and 17), but in all patients of group B (cases 20, 21 and 25). The average improvements were 42% in group A and 80% in group B.

The average disease duration in the 5 patients without improvement was 12.8 years, i.e. 2.8 years higher than the average of group A; the average symptom intensity in these cases was 7.6 (+- 2.3), i.e. higher than the average intensity of the overall group (6.6 +- 2.6). The two patients with the most severe visual disturbances of “10”, who did not experience any improvement during therapy (cases 14 and 16), had disease durations of 18 and 30 years.

However, among the patients with improvement of their visual disturbances were also 2 cases with a disease duration of 15 years (cases 8 and 12) and one patient (case 19) with an active toxoplasmosis that had only been persisting for 2 years – thus there is no clear correlation between disease duration, the occurrence and the improvement of visual disturbances**.**

In the 44% patients of group A, who experienced an improvement, the initial intensity was 5.25 (+- 5.7) with a reduction to 0.25 (+- 0.2), corresponding to a decrease of 96%. So an improvement of the visual disturbances has only been recorded for 44% of the seropositive cases, but in these cases the results were very good.

A possible explanation for the visual disturbances could be a cortical processing disorder of the visual signal with regards to a CNS involvement. Such a visual disturbance is called **"cortical visual impairment"**; it is typically followed by "blurry" sight. Infections of the so-called TORCH group that also includes toxoplasmosis are seen as possible causes. Despite intensive research, it was impossible to find precise information about this type of visual disturbance in connection with toxoplasmosis.

Unsystematic dizziness occurred in 7 patients (41%) of group A and 3 patients (30%) of group B. These are the cases 6, 7, 8, 11, 12, 14, 16 as well as 19, 25, 26. Patients typically reported that the dizziness only occurred intermittently; the descriptions point towards a similarity to the intermittent occurrence of visual disturbances. Of the 10 patients with unsystematic dizziness and 12 patients with visual disturbances, 5 patients showed both symptoms, thus there only seems to be a slight overlap. The **improvements of 70% (A) and 100% (B)** point out that this symptom can be treated well. In which way dizziness develops within the scope of an active toxoplasmosis cannot be evaluated here.

Peripheral oedema were seen in 6 patients (35%) of group A and 3 patients (30%) of group B. These were the cases 1, 5, 8, 12, 14, 16 as well as 21, 25, 26. Swelling occurred predominantly in the hands and feet; in the area of the hands, this sometimes interfered with fist closure. **All patients, who showed peripheral oedema also suffered from exertional dyspnea** (see also p. 102). This also points to the fact that the oedema might be partially caused by cardiac involvement. Nevertheless, feelings of tension and swelling in the area of the hands are by no means typical symptoms of a heart insufficiency and the exertional dyspnea might as well be caused by a pulmonary involvement, as observed by Carme et al 2002 and discussed on p. 103.

I am inclined to the opinion that these are partially swellings of the connective tissue. Noteworthy in this context are especially cases 5 and 12. In both patients, lipoedema of the legs had been diagnosed, which improved under therapy from 7 to 0 (case 5) and from 10 to 0 (case 12). In summary, the **improvements of 65% (A) and 100% (B)** point out that the peripheral oedema can be treated well.

This symptom is also seen **more frequently in female patients**. Apart from patient 25, all other affected patients were female. This means that with 8 patients, **38% of all women were affected in contrast to one affected man (17% of all men)**.

The initial intensity for women was 7.25 (+- 2) with a reduction to 1.5 (+- 1.2), corresponding to a 74% symptom reduction. The disease duration was high at 17.6 +- 14.8 years, but with a high standard deviation. The shortest disease duration occurred in case 21 (3.5 years), the longest in case 5 with 50 years.

The affected man had been suffering from the disease for 24 years, the change of intensity from “5” to “0” resulted in a symptom reduction of 100%. A possible explanation for this difference could be the connective tissue of women, which tends to be softer than male connective tissue and is therefore more prone to oedema formation.

Morning stiffness ranging from some minutes up to approximately an hour occurred in 5 patients **(29%) of group A** and 3 patients **(30%) of group B**. These were cases 5, 8, 9, 11, 14 as well as 19, 21 and 25. In cases 19 and 25, morning stiffness exceeded the respective patient´s muscular pains, which was most visible in case 25, since here a morning stiffness of 10 was countered by muscular pains of 1. This leads to the assumption that the symptom morning stiffness is not strictly related to muscular pains. In cases 5, 8, 14 and 27, different rheumatic disorders had been diagnosed in the history (seronegative rheumatoid arthritis, rheumatic monoarthritis, fibromyalgia), but the corresponding therapy had always met with little success. A certain clinical resemblance of an active toxoplasmosis to an active rheumatic disorder with regards to symptoms has to be noted. **The symptom reduction in group A was 95%, in group B 100%.**

Sleep disorders were reported by 5 patients **(29%) of group A** and 3 Patients **(30%) of group B**. The affected cases were 6, 9, 11, 14, 16 as well as 19, 21, 25. The patients predominantly mentioned a sleep maintenance insomnia with frequent and lengthy nocturnal alertness and difficulties in falling asleep again. Only in 3 cases (16, 19, 25) an increased irritability was noted at the same time, which shows that these symptoms do not show any close connection. Nevertheless, there seems to be a certain coincidence with depressive moods (see also p. 102).

7.7 Discussion of relapses

Since toxoplasma can still be persisting after a successful therapy, relapses are possible and the risk of relapsing seems to increase due to health-impairing factors such as severe viral infections (case 23), unusually high IgG counts (case 17), long disease duration (case 5) or insufficient duration of therapy (case 25). **All patients have to be informed about the possibility of relapses**, so that they can consult their practitioner again if needed. Five of my patients (18%) had suffered from a relapse until the end of January 2017. All of these patients had been treated with a combination therapy before. All asymptomatic intervals assessed next have been recorded until the end of 2017. The average asymptomatic interval until relapse in group A was 4.4 +- 4.8 months (cases 5 and 17). The average asymptomatic interval until relapse in group B was 4.2 +- 3.8 months (cases 23, 25 and 27**)**. The high standard deviation indicates that the asymptomatic interval can vary considerably. The duration of the asymptomatic interval until the occurrence of a relapse varied from 2 weeks (case 25) to 16 months (case 27). The average disease duration in the relapse cases across both groups was high at an average of 23.2 +- 17 years; the high standard deviation indicates that the disease duration is not the decisive factor for the occurrence of a relapse.

Case 5 is the patient with the longest disease duration (50 years) and a high disease intensity, who suffered from a relapse after only 3 weeks. The follow-up combination therapy was very effective; the patient is currently (March 2017) treated with a combination therapy once a week to prevent a further relapse.

In **case 17**, the disease had only been persisting for 7 months, but the high toxoplasma IgG (over 400 IU/ml, above measuring range) indicates a high tachyzoite activity. A relapse occurred as soon as 6 weeks post-treatment; this type of combination seems to carry a high risk for relapse.

In **case 23,** a relapse occurred after 9 months after a severe viral infection. The disease duration in this case is 15 years.

In **case 25** with 24 years disease duration, a relapse after 2 weeks had been promoted by the fact that the first treatment interval had to be stopped after only 12 days due to severe side-effects.

In **case 27** with a relapse after about 16 months, an interaction with myositis might have been decisive. This issue is being discussed in greater detail in the case studies. All patients have unanimously described the therapy of relapses as being faster and more effective than the first combination therapy. In all cases, the last effective combination therapy had been prescribed again.

The prevalence of relapses cannot be finally evaluated here, since the number of cases will probably increase in a longer period of observation. An appropriate follow-up observation over several years will be made with the patients of this study. Until today, only one patient (case 23) has developed a second relapse.

7.8 Relapse prevention

I n **case 5,** with the longest disease duration of 50 years, I prescribed a follow-up relapse prevention of once-a-week combination therapy; the patient was still being free from relapses 3 months post-treatment in 6/2017.

The risk of a relapse possibly increases, when a high disease duration (18 years) coincides with a high IgG (97.9 IU/ml), as in **case 14**. In this case, a very long therapy interval of 3 months altogether was needed. I also prescribed a follow-up relapse prevention of once-a-week combination therapy immediately post-treatment. In 03/2017, the patient had been free from relapse for 4 months.

The coincidence of a long disease duration (30 years) and a high IgG (106 IU/ml) also occurs in **case 16**; in this case also a follow-up relapse prevention of once-a-week combination therapy was prescribed. Since 12/2016, the patient had been free from relapse for 3 months.

8. Therapy of active toxoplasmosis in immunocompetent patients in the practitioner´s surgery

The effectiveness of a clindamycine monotherapy has been verified by Blais et al. (1993). An initial 5 - 10 day therapy with clindamycine offers the advantage of a low risk for side-effects due to the short period of prescription. The compliance is also better because of the lower number of pills; significantly more medication has to be taken during combination therapy. The improvements under clindamycine generally cover a decrease in muscular pains and fatigue, and potentially existing impatience and aggression frequently decrease as well. The patients usually describe a roughly 20 - 30% reduction of several symptoms within one week, so it is quite noticable to the patient as well as to the practitioner. Concentration disorders generally decrease only slightly in the beginning, profuse sweating seems to be reduced only after longer therapeutic intervals.

In cases with a very pronounced or very long persisting symptomatic it is advisable to prescribe not more than 3 x 300 mg clindamycine initially, because in some of the severe cases a slight increase of the toxoplasma related symptoms took place within the first two or three days. In all other cases a prescription of 2 x 600 mg has proved effective.

In some cases with a shorter disease duration and a moderate pronouncement of the symptoms, a monotherapy with clindamycine 2 x 600 mg alone for 1 - 4 weeks can yield good or very good results. A combination therapy can be skipped in these cases. Along with clindamycine, I prescribe a saccharomyces boulardii preparation as a prophylaxis to lower the risk of an enteritis caused by antibiotics.

In case the clindamycine does not yield positive results, it is likely that a further combination therapy will also be ineffective, but this does not necessarily rule out an active toxoplasmosis altogether. **In the cases recorded here, an effective clindamycine therapy guaranteed a very good effectivity of a combination therapy** (see methods and case studies).

It is essential to stay in frequent contact with the patient during therapy and to constantly monitor a possible loss of effectiveness or occurring side-effects. In these cases, the therapy can then be adjusted or changed accordingly. This was necessary in 10 cases (37%) of my study.

The duration of the combination therapy is 3 - 10 weeks, depending on the therapeutic response. The combination therapy comprises: **pyrimethamine 25 mg (Daraprim) 2 x 1, calcium folinate 15 mg 1 x 1 and sulfadiazine 500 mg 4 x 1.**

In case of a sulfadiazine-intolerance or decreasing effectiveness, clindamycine 4 x 300 mg (here mostly 2 x 600 mg) or azithromycine 500 mg 1 x 1 can be administered as alternative combinations with pyrimethamine (Hannemann et al. 1992, Hökelek 2015).

Cotrimoxazole 960 mg 2 x 1 in combination with pyrimethamine and calciumfolinate is further alternative, as is Spiramycine (Rovamycin) 1,5 mio 3 x 2, which can be prescribed as monotherapy as well. Further therapeutic options are being discussed in detail in Helieh (2013) and Hökelek (2015).

It has to be pointed out clearly that during a pyrimethamine-based therapy, an adjuvant prescription of folinic acid is vital for the prevention of side-effects. The prescription of (cheaper) folic acid would be ineffective and thus the risk for side-effects would be increased, since pyrimethamine inhibits the conversion of folic acid into folinic acid (Luft, 2000).

It must also be noted that in patients with immune deficiencies or conditions post-transplantation, or in patients taking a immune suppressing or immunmodulating medication because of other reasons (for example rheumatic diseases) an active toxoplasmosis and the corresponding therapy can cause a higher risk, and therefore should be treated in hospital.

All patients should be informed that relapses might occur since a complete eradication of the parasite is currently impossible. With reference to previous findings, relapses can be treated effectively.

Addendum 5.11.2017: The probability of a relapse can be minimized by the following procedure:

1) after a clindamycine run in of one week prescription of a combination therapy until the Patient is free from symptoms, but at least for 3 weeks, followed by a
2) relapse prophylaxis with two treatment days (for example Wednesday and Sunday) a week with the last successful combination therapy for at least four weeks and then switching to a
3) relapse prophylaxis with one treatment day a week with the last successful combination therapy for at least four weeks.

9. Conclusions

An active toxoplasmosis that requires treatment in immunocompetent patients is a lot more frequent than it has hitherto been assumed. The prevalence of an active toxoplasmosis that requires treatment in this study was 2.1%, which seemed a surprisingly high rate. While this study was being assembled, another 10 cases came to the fore. The therapy in these cases had not been finished by the end of 1/2016 (acceptance deadline for this study), thus they were not included in this paper. I assume that the prevalence in the general practitioner´s surgery is about 3% or even higher. This could mean that about 1% of the overall population in Germany are affected (see 7.1 p 94).

There is an overlap with symptoms of a chronic active toxoplasmosis with *chronic fatigue,* and it could be possible, that some of the patients who have been diagnosed with a chronic fatigue, are suffering from an active toxoplasmosis and thus might have a therapeutic option.

The antigene surface structure of bradyzoites differs significantly from the tachyzoites´, and the IgM and IgG response against bradyzoite cysts can be very weak (see 1.5 and 1.6 pages 10 - 11). There are strong indications that activity within the bradyzoite cysts can also trigger severe disease symptoms, but this cannot be detected with the tachyzoite - specific tests that are currently used.

The deselection criterion for an active toxoplasmosis that has been used so far, i.e. a missing tachyzoidspecific IgM and IgG assay, is no longer acceptable. A deselection by means of IgG assay is highly doubtful and a secure deselection by means of IgM assay or even PCR is not possible (see pages 11 and 12). Some cases of an active toxoplasmosis that require treatment even exhibit a complete seronegativity with missing IgM and IgG assay.

This leads to the conclusion that in these patients, the disease has been triggered predominantly by toxoplasma activity within the bradyzoit cysts. Laboratory parameters that can identify such activity will have to be developed urgently. Until these parameters become available, a screening by means of a questionnaire, as presented in this study, is the only option to identify these cases.

Such a screening can yield valuable insights in patients with symptom combinations of undefined myopathy, exhaustion, concentration disorders, chronic fatigue, undefined heart insufficiency and weakness, undefined depressive episodes, aggressive behavioural changes and anxieties or patients with diagnoses as seronegative PcP, fibromyalgia and somatoform pain disorders.

If this leads to the reasonable suspicion of an active toxoplasmosis, a probatory treatment with clindamycine for 5-10 days seems appropriate to identify those cases, in which a combination therapy for 4 - 6 weeks can be reasonable and promising. This method nevertheless does not claim to definitely exclude an active toxoplasmosis.

The well-known combination therapies are highly effective, but have to be adjusted or changed often in the course of the treatment due to loss of effectiveness or occurring side-effects. Thus, a close monitoring of the patient is a vital part of the therapy. The high symptom reductions of up to 100%, even after some very long disease durations and the increase in life quality documented in the case studies, indicates that a toxoplasma therapy can be a valuable addition in the practitioner´s surgery. Relapses can occur but can also be treated without problems. A long-term observation of the patients mentioned here is scheduled, to allow for more precise findings.

The risks of toxoplasmosis have to be rated fundamentally higher. Necessary consequences would be the elimination of toxoplasma from the food cycle as completely as possible and categorical full-cooking of risky food items, and thorough washing of vegetables prior to consumption. The diversity of toxoplasma (see 1.7, p.12) and the fact that atypical toxoplasma with high virulency potential have already been documented in Germany also strongly support that there is a real need for action. The patients suffering from an active toxoplasmosis have to be identified and to be treated accordingly.

Furthermore we should aim at a significantly lowered epidemic level, as it is documented especially in northern Europe. This would lead to a lower risk for infection and an active toxoplasmosis in the long run and would thus reduce the burden for the patients and the health care system.

I am convinced that the findings presented here would be confirmed and specified in more extensive studies – this would of course involve a concerted effort of many collegues. I hope that I could offer some motivation to do so.

Dr Uwe Auf der Straße MD, april 2017

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11 Appendices

How to work with the survey of average results

How to work with the checklist toxoplasmosis

Checklist Toxoplasmosis; symptoms arranged according to frequency of occurrence

survey of average results **group A**

survey of average results **group B**

How to work with the survey of average results (p 126 / 127)

Example: 100% of the patients in group A suffered from fatigue with an Intensitiy of approximately 9, which was reduced to approximately 1,5 after therapy, the average reduction of this symptom is 85%. Please note, that the average reduction in % of the symptoms has been calculated by summing up the individual symptom reductions in % of all patients of this group, and the relation between average initial intensitiy (“9”) and the average intensitiy after therapy (“1.5”) does, for mathematical reasons, not result in the average reduction in % of the whole group.

How to work with the Checklist Toxoplasmosis

The Checklist Toxoplasmosis is based on the visual analog scale, with points from 0 to 10.

“0” is introduced to the patients as “free from symptom”, or without any complaint concerning the named symptom. “10” is introduced as “the worst expression of this symptom you can think of”.

It is advisable, to work through this checklist consequently in all assessments during therapy, because the clinical picture of an active toxoplasmosis is complex and many patients are overchallenged with a general question concerning their symptoms.

Provided a thorough differential diagnosis has been performed, it has been proven useful to weigh the symptoms as follows:

The risk of an active toxoplasmosis is high, if at least

The symptom fatigue and 3 of the next 5 symptoms (including listlessness), are positive with a score of at least „5“,

or

The symptom fatigue and 2 of the next 5 symptoms (including listlessness) and two of the remaining symptoms are positive with a score of at least „5“,

or

The symptom fatigue and 2 of the next 5 symptoms (including listlessness) and the symptom „visual disturbance“ are positive with a Score of at least „5“.

note: The symptom „visual disturbance“ in the sense of intermittend „blurred“ vision has, provided that ophtalmologic diseases have been excluded, a high predictive value. The symptoms listed as „additions“ were seen to seldom or showed to much variations to use them as criteria, but still they are probably linked to active toxoplasmosis as they improved remarkably under treatment.

Checklist

Toxoplasmosis

Mrs / Mr.....

Age: ….....years **duration of symptoms**.....

	toxoplasma IgG ….....IU/ml	**toxoplasma IgM .**..... AU/ml
	date: ….....	date:….....
therapy:	.....	.....
fatigue	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
muscular pain	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
concentration disorder	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
profuse sweating	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
exertional dyspnoea	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
listlessness	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
irritability	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
visual disturbance	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
dizziness	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
depressive moods	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
anxieties	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
morning stiffness	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
oedema hands feet	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10
sleep(maintenance) disorder	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10

additions: feeling of abdominal pressure and nausea

cephalgia

joint pains

swelling of lymph nodes

survey of average results group A, 17 patients

Age: 56 years **duration of symptoms** 10 years

toxoplasma IgG 75 IU/ml **toxoplasma IgM** <3 AU/ml

	initially	after 4 weeks therapy
symptom	**frequency %**	**symptomreduction %**
fatigue	**100%** 0 1 2 3 4 5 6 7 8 **X** 10	0 1**X** 2 3 4 5 6 **85%**
muscular pain	**100%** 0 1 2 3 4 5 6 7 **X** 9 10	0 **X** 2 3 4 5 6 **90%**
concentration disorder	**94%** 0 1 2 3 4 5 6 7 **X** 9 10	0 1 **X** 3 4 5 6 **75%**
profuse sweating	**82%** 0 1 2 3 4 5 6 7**X**8 9 10	0 1 **X** 3 4 5 6 **84%**
exertional dyspnea	**65%** 0 1 2 3 4 5 6 7 8**X**9 10	0 1 **X** 3 4 5 6 **80%**
listlessness	**70%** 0 1 2 3 4 5 6 7 **X** 9 10	0 1 **X** 3 4 5 6 **76%**
irritability	**70%** 0 1 2 3 4 5 6 7 8**X**9 10	0 1 2 **X** 4 5 6 **70%**
visual disturbance	**53%** 0 1 2 3 4 5 6**X**7 8 9 10	0 1 2 3 **X** 5 6 **42%**
dizziness	**41%** 0 1 2 3 4 5 6**X**7 8 9 10	0 1**X**2 3 4 5 6 **74%**
depressive moods	**41%** 0 1 2 3 4 5 6 7 **X** 9 10	0 1 2 **X** 4 5 6 **65%**
anxieties	**35%** 0 1 2 3 4 5 6 7 8**X**9 10	0 1 **X** 3 4 5 6 **76%**
morning stiffness	**29%** 0 1 2 3 4 5 6 7 **X** 9 10	0**X**1 2 3 4 5 6 **95%**
oedema hands feet	**35%** 0 1 2 3 4 5 6**X**7 8 9 10	0 1 **X** 3 4 5 6 **65%**
sleep(maintenance) disorders	**29%** 0 1 2 3 4 5 6 7 **X** 9 10	0 1 **X** 3 4 5 6 **72%**

additions: feeling of abdominal pressure and nausea: 3 patients;
reduction from “9” to “1.7”

survey of average results group B, 10 patients

Age: 43 years **duration of symptoms** 6 years

toxoplasma IgG < 3 U/ml **toxoplasma IgM** < 3 AU/ml

initially after 4 weeks therapy

symptomfrequency %			**symptomreduction %**
fatigue	**100%**	0 1 2 3 4 5 6 7 8**X**9 10	0 **X** 2 3 4 5 6 **89%**
musclar pain	**100%**	0 1 2 3 4 5 6**X**7 8 9 10	0 **X**1 2 3 4 5 6 **94%**
concentration disorder	**90%**	0 1 2 3 4 5 6**X**7 8 9 10	0 1**X**2 3 4 5 6 **84%**
profuse sweating	**70%**	0 1 2 3 4 5 6 7 8 **X** 10	0 **X** 2 3 4 5 6 **88%**
exertional dyspnea	**70%**	0 1 2 3 4 5 6 7**X**8 9 10	0 1**X**2 3 4 5 6 **82%**
listlessness	**50%**	0 1 2 3 4 5 6 7 8 **X** 10	0 **X** 2 3 4 5 6 **90%**
irritability	**40%**	0 1 2 3 4 5 6 7**X**8 9 10	0**X** 1 2 3 4 5 6 **60%**
visual disturbance	**30%**	0 1 2 3 **X** 5 6 7 8 9 10	0 **X**1 2 3 4 5 6 **80%**
dizziness	**30%**	0 1 2 3 4 5 6 **X** 8 9 10	**X** 1 2 3 4 5 6 **100%**
depressive moods	**40%**	0 1 2 3 4 5 6 7**X**8 9 10	0 1 **X** 3 4 5 6 **78%**
anxieties	**20%**	0 1 2 3 4 5 6 7 8**X** 9 10	0**X**1 2 3 4 5 6 **92%**
morning stiffness	**30%**	0 1 2 3 4 5 6 7 **X** 9 10	**X** 1 2 3 4 5 6 **100%**
oedema hands feet	**30%**	0 1 2 3 4 5 6 7**X**8 9 10	**X** 1 2 3 4 5 6 **100%**
sleep (maintenance) disorder	**30%**	0 1 2 3 4 5 6 7 **X** 9 10	**X** 1 2 3 4 5 6 **100%**

additions: feeling abdominal pressure and nausea: 2 Patients, reduction from 9 to 5