Wetenschap voor Patiënten

(Science to patients)

Seminar 1: **Is ME and/or CFS a disease?**

Web Seminar of prof. dr. K. de Meirleir, broadcast on november 2nd, 2012

I'm Kenny de Meirleir, I live in Belgium. I am a doctor of Internal Medicine and I have been working with ME/CFS patients since 1989.

Initially everything was focused on the psychological approach, such as re-habilitation and such. We soon realized, however, that this was not the right course to take. Through international collaboration, we started very early with biomedical research that is still running today. During my career I have already seen about 15,000 ME patients and I am still seeing more.

Is ME and/or cfs a disease?

For the time being ME has been classified as a neurological disease, under number G 93.3, by the World Health Organization. What we are dealing with – all things considered - is postviral fatigue. It was characterized as such for the time being. Many have tried to place it under F, which is psychiatry. For the moment it is still accepted under G93.3, so we consider it to be a neurological disorder, but with an immunological and metabolic component.

In case you want to know something about the condition itself: ME was first defined by Dr. Ramsay in England. He made many clinical observations and wrote a lot about it. He also described the four syndromes.

The disease evolves over time, it is a chronic condition. There are quite a few common complaints that occur in the majority of patients. One of them is fatigue, but one of the most important things he noticed, is that after the least physical effort recovery takes a very long time. That is probably the most important symptom, not so much the fatigue. It is the slow recovery period that plays a part.

Besides this, a variety of complaints occur such as a chronic sore throat, muscle pains and all sorts of other phenomena, that don't have a direct link with neurological diseases, such as stomach- and intestinal complaints. But it is a condition with a range of at least fifty different complaints, of which twenty occur in at least 70% of all patients.

So for the time being it remains a syn-drome, as the exact cause is still unknown. A lot of research is still going on to find out what is actually wrong when one has this syndrome.

What is the definition of Chronic Fatigue Syndrome?

The definition Chronic Fatigue Syndrome is actually infelicitous. It was introduced in 1988, as the result of a meeting of people from the Center of Disease Control and was published afterwards in a magazine. A first definition of CFS emerged.
The people who were present then, today also agree that to use the name fatigue in the title was an unfortunate choice. Therefore nowadays we prefer the term ME. In full: Myalgic Encephalomyelitis. It is something we should look into more deeply, as now the term CFS is common usage.

1988 is a long time ago and that makes it very difficult to switch back to what Ramsay called ME, earlier in the 1950s.

But we are also working full power to evolve into that direction, because many other diseases also include fatigue.
For example 93% of cancer patients also suffer from fatigue. So that is not at all specific for ME and it is no good to keep the term in the name. A majority of researchers and clinicians has chosen to bring ME back to the foreground, instead of using the term CFS.

A number of people don't recognize this condition. They not only do not recognize it, but they also don't acknowledge it and they actually prefer to look at it as neurasthenia.

This is not only determined scientifically, but also related to cultural aspects. When in Japan one says one feels tired, it actually implies a severe negative connotation. It means that in fact one feels depressed. The Japanese prefer not to use the word fatigue. And even in the south of France one should not say "Je suis fatigué". It means one in fact has made his will and is going to die soon.
So there is also a cultural aspect to the concept of fatigue. That's why we want to see it disappear as soon as possible.

All kinds of discussions are going on, mainly between psychiatrists and those who deal with psychological models, and those who actually perceive a biological model in this disease. That discussion is shifting more and more to the biological. Today 75-80% of American doctors acknowledge that this condition has a biological background.

The balance is clearly shifting in favour of the biological side, but meanwhile we have lost more than twenty years in this struggle.

Recently, a new definition was drafted. The first loose definition was created in 2001 and published in 2003. This actually determines clinical criteria.

The criteria of 1988 were based just upon research criteria. People wanted to talk about the same thing, so they had to create criteria.
The Canadian Criteria, which today have become the international criteria, are based on the clinical aspect.
A doctor's perception, the patient's condition, the symptoms present, the possible treatments.
Even though only the symptoms are dealt with, treatment is based on biological abnormalities. This was the first step. It was taken in 2001, when a group of Canadians together with four doctors from other countries drafted a first definition which was clinically oriented.

Today, 26 international physicians and scientists have worked out the clinical criteria that we call international criteria. For which there is great support, a large basis since in making this definition thirteen countries are represented. But again, the mills of science and politics grind slowly and it will certainly take a few more years to see it spread all over the world.

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Seminar 2: **Is it possible to diagnose ME/cfs?**

Web Seminar of prof. dr. K. de Meirleir, broadcast on november 9th, 2012

Definitely. ME can be diagnosed as a disease, because now we have criteria, clinical criteria. But on the other hand we have to stop excluding other conditions. And to stop concluding that if you meet these excluding criteria, you really have ME. There's no gain in this. Not for the patient, nor for the physician.

We have to concentrate on positive issues. We should look for different underlying conditions, mechanisms and disease processes. And we find them in most patients, or in almost all patients.
We have to stop focusing on excluding diagnoses, or exclusion. There are a number of things that clearly don't correspond with ME , but ultimately we have to think positively and search for mechanisms that will explain the symptoms.

If we consider ME and approach it in a positive manner, we notice all kinds of changes in the immune system. The immune system is dysfunctional. All sorts of chronic infections occur, which hardly ever – or rarely – occur in normal people. There's a big problem concerning intestine disorders, there are underlying intestinal problems such as dysbiosis, or an increased intestinal permeability.

Then there are the effects of oxidative stress, which lead to DNA impairment, impaired proteins and structures, amongst other things.
And we have also discovered prions, for example, in this condition. The mito-chondria or 'oxygen pumps' in these patients function poorly too. Which leads to a shortage of oxygen and energy supply within the body.

Then there are cardiac abnormalities, heart defects. And we have seen that the heart is not being filled completely, that there is too little blood volume. Certain organs in the body, like the extremities, experience extremely poor blood circulation as a result of key changes.

And the exercise capacity is extremely important. In the early phase of the condition, little reduction in exercise capacity occurs, but as the years progress the exercise capacity decreases quickly. Much faster than in normal aging.
That's why we see that it is mainly the ventilation that is disturbed.
The diaphragm, a very white muscle between the abdomen and the thorax, will start to function less well. People even become short of breath when speaking because ultimately the diaphragm will almost stop moving, or move less well. The ventilation reduction is quite spectacular and clearly present.

The recuperation after minimal effort is at times badly affected as well. I'm seeing people who say: 'I walked a hundred yards or I rushed to catch the bus and it took me a week to recover'. That's not something you'll find in normal people.

We've also come across neurological abnormalities.
For example, various studies show that compared to normal people the grey substance or brain substance is reduced.

There are also other disorders such as the malfunctioning of the short-term memory. The recalling of words, as well as other things concerned with the memory, can be so severely disturbed that you sometimes actually start thinking: Do I have Alzheimer's?
Patients often tell me during a consultation: 'I'm just like my grandmother with Alzheimer's, I have the same symptoms'.

And then there's also an increased sensitivity to stress. We notice that there is a disturbance in the hypothalamic – pituitary – adrenal axis. Resulting in reduced cortisol. This is also the difference with a real depression. Patients with a genuine depression have elevated cortisol levels, while our patients usually have very low cortisol levels. But its origin does not lie in the adrenal gland, it lies in the higher brain, actually in the hypothalamus.

Various muscle abnormalities have been detected. We also know that there is a malfunction at the molecular level of the ionic channels. Research has been done in that field as well. The mechanisms behind this have also been identified.

So these are for me the most important physio-pathological abnormalities that we are able to determine in patients. And which actually distinguish an ME patient from patients with other diseases.

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Seminar 3: **Is ME/cfs a hereditary condition?**

Web Seminar of prof. dr. K. de Meirleir, broadcast on november 16th, 2012

As is the case with many other complex diseases, there is a hereditary component. And we can infer this from the study by Dedra Buchwald in which she examined twins, where one of the twins had ME and the other one was healthy. Different types of twins were observed, both identical and non-identical.
This is an interesting study, but the result was that there was a weak genetic component - in the end there appeared to be no strong genetic component.

Other studies, which didn't involve twins but compared ME patients to healthy people, show there are a lot of minor deviations in the genetic system. Several of these, say about fifty, can cause a predisposition to develop ME. But I don't think this is a bigger factor than with other diseases such as certain types of cancer, MS, and other disorders. I think that, ultimately, when we consider the bigger picture, it won't be that important.

We ourselves researched what we call interleukin-17, a chemical substance produced by our own immune system. And we have found shifts there too, point mutations, in other words a change in one amino-acid, which occurs more often in ME patients. And many more will probably materialise, but as a clinician I don't consider it to be that important. In the sense that the same applies to a lot of diseases.

One important thing that should be highlighted is the vitamin D metabolism.
We know that there are big differences in the receptors for vitamin D. And that for example there are quite a few differences in vitamin D receptors between Africans and people who live in Norway. This also has to do with the amount of sunlight present, so over thousands of years a selection among humans has taken place. In the end we all need vitamin D, not just for our calcium balance but also for our immune system.

A pre-selection has taken place in a certain direction. We have also researched this and we see there are also differences with regard to healthy people.

Compared to the normal population, shifts have been observed, but again none of such significance to be able to say that this deviation occurs in 50% of ME patients.
So there are differences in susceptibility for certain matters, but in the end this is not dominant in ME in the way that this can be seen in, for example, other congenital disorders.

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(Science to patients)

Seminar 4: **ME and Sleep Disorders**

Web Seminar of prof. dr. K. de Meirleir, broadcast on november 23th, 2012

Most ME-patients suffer from sleep disorders and many of them remember that at the onset of the disease they slept too much. At least twelve hours a day, where they used to sleep eight hours a day. It's normal that these sleep disorders slowly evolve into a sleep disorder which is characterized by lack of deep sleep, where one often wakes up at night. And usually another problem is added to it. One has to get up to urinate in the night, so sleep really becomes fragmented.

This is caused by blood flow disorders of the brain, and also by the effect of cytokines. These are substances which are formed by our white blood cells.
But we suspect the so-called gas neurotransmitters CO, H2S en NO to play a part in it too. Because they function like a neurotransmitter, and in normal circum-stances we can't do without. Yet in too large quantities they're causing problems with the neurotransmitters. Moreover there's also a disruption of the normal balance of neurons in the brain.
All this can lie at the basis of sleep disorders. Unfortunately in this context not much research has been done.

Yet we know for example that one of those cytokines, interleukin-6, comes with too much sleep.

Interleukin-6 is an inflammatory cytokine, which occurs at the onset of the disease, because the onset of this disease is usually accompanied by an infection, an infection that does not go away.
In this way the presence of the interleukin-6 may account for the occurrence of hypersomnia.

Still another cytokine, interleukin-10, is associated with sleep disorders. Interleukin-10 probably originates from an inflammatory reaction, because a cytokine actually is an anti-inflammatory particle. In the USA the association of interleukin-10 with sleep disorders has been demonstrated. That's not the whole story: low blood flow occurs in the brain as well. In general with some patients the blood pressure is extremely low during the night. It can drop to about 85 over 60, and we also know that certain parts of the brain receive less blood. There is an explanation for these sleep disorders, but that isn't limited to one single phenomenon.

Most probably they depend on several factors. We know that the studies done are partly too contradictory to serve as an explanation. Just because no thorough studies have been done. There are no thorough studies, in which patients have also been compared to normal people or twins have been studied. Those would be the best studies to demonstrate the possible mechanism of these sleep disorders.

As for the treatment of these sleep disorders, we have noticed that an EEG can be abnormal with these patients. And that an abnormal delta wave occurs. That's something which may lead us towards a treatment. We also know that there is little stage 3 and 4 REM sleep. A delta wave is one of the waves seen on an EEG. Normally this is an individual wave, but with ME patients we observe an alfa-delta intrusion.

So we notice an amalgamation of waves and also very little power in this delta wave. In English this wave is called delta power, and it differs from normal people.
This is one of the few scientific, objective evidences. This research has been done in the Brugmann hospital in Brussels.

It is the first time that a clear relationship between sleep disorders and ME has been shown with patients. This is determined by highly specialized EEG research. And it more or less justifies the treatment we've been applying for more than twenty years. Formerly, it wasn't actually justified, however the last twenty years we apply treatments based on anti-epileptic drugs. Short acting anti-epileptic medication is being used, which is active for six hours at the most, and they ensure a better quality of sleep.

Anti-epileptic drugs are no longer appropriate for epilepsy, because in fact it's difficult to coerce people to take a medicine 4 to 5 times every 24 hours. That's difficult indeed. Yet already from the early nineties onward we've been noticing that a certain anti-epileptic drug is highly suitable to enhance the quality of sleep. There are still some other drugs in the repertory of sleep medication that might be helpful, but in general they don't improve the quality of sleep. We notice minor stage 3 and 4 sleep, minor REM sleep, so there is little recuperation.

The impact of many hormones which has to decrease intensively during the night, doesn't do so.
For example we note that with these patients in the morning less cortisol and less growth hormone are being formed, where actually it should be at its peak. Normally such hormones have a peak very early in the morning, but this is not reached. Studies, 24-hours hormone-measurements studies have been done, which show an abnormal rhythm. That again has to do with poor quality of sleep.

And these drugs, the names of which I won't mention, can provide an artificial sleep. But they won't very frequently correct the defect or lack of stage 3 and 4 sleep. One has been sleeping all right, but one is as tired in the morning as when one fell asleep. This is an important issue that I should mention: one can ensure the sleep- and daily rhythm will be more or less maintained.

Because ME patients feel better in the evening, they often go to sleep later and later. They eventually create a circadian rhythm where they end up having to take dinner at three a.m. Which is extremely problematic for the rest of their families and for leading a normal life.

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(Science to patients)

Seminar 5: **ME and Pain**

Web Seminar of prof. dr. K. de Meirleir, broadcast on november 30th, 2012

The pains change during the disorder. Most patients who recall how they felt before the disease or in the run-up of the disease, remember they were free of pain in the beginning. The fatigue and the lack of recovery often occur before the start of the pain.

The various possible causes of pain are of a central nature. That is, cytokines, which are particles produced by our own white blood cells, can affect certain receptors and induce pain. This concerns mainly the so-called inflammatory cytokines, with one specific pointer to interleukin 1. They also occur in other disorders and animal models, and are accompanied by pain of central origin.

Bacterial neurotoxins also play a part. When the immune system has been seriously disrupted, all kinds of bacteria no longer can be eliminated. Or intestinal bacteria pop up, because the intestines are less capable of holding them back. Bacterial toxins can also cause central pain. Moreover there are a lot of other substances, such as nitrogen oxide, which play a role. We know for example that if we reduce the effects of nitrogen oxide, pain is also reduced. The same applies to a number of antibiotics that inhibit certain bacteria and also reduce pain.

There is also a problem with the opiate receptors. Endogenous opiates play a part in the brain, and with those receptors there seems to be a problem too.

An English group is engaged in manipulating those opiate receptors, as to also reduce pain in patients.

Perhaps the most important cause of pain is metabolic pain, pain from the metabolism. It is caused by a poor delivery of oxygen to the organs and also by mitochondrial dysfunction.
The mitochondria are responsible for the release of ATP to let all our organs function.

This is the most difficult pain to combat and the biggest problem, because there is no medicine for it. We can try to ensure the peripheral parts of the body getting more oxygen. We can do that artificially. But the release of several substances causing the large blood vessels to expand, automatically causes a contraction of the small blood vessels. Which is the cause of the cold feeling in the peripheral organs like fingers and feet, because the blood vessels themselves contract.

This is a result of an altered sympathetic nervous system that is more active as compensation, but still can't prevent H2S, NO and other vasoactive substances to cause expansion of the large blood vessels. To such an extent that the small blood vessels are contracting. I think many organs suffer from a chronic oxygen shortage. And this will also cause a shortage of oxygen in the peripheral nerves – which contain blood vessels as well.

So we have a mixture of neuropathic and metabolic pain. In my experience metabolic pain is the biggest problem because you can't cure it. Simply because there's an imbalance in the blood circulation.

Then there are all kinds of other factors. With this condition the red blood cells aren't functioning normally, and there is also a problem with oxygen supply.

I could mention an entire list of different mechanisms which all come down to the same. We call them ischemic pains, due to a shortage of oxygen to form energy. The result, of course, is also the production of much lactic acid. We and others have found the concentration of lactic acid in the blood to be up to three times the normal value while resting. In normal blood 0.6 to 1 mmol lactic acid per litre is found. In a ME patient it is not uncommon to find 2 to 2.5 mmol per litre. And that's a normal value in the blood of someone who's running the marathon of Rotterdam at considerable speed. In ME patients this is a normal value when at rest. That lactic acid comes from tissues, which must convert all their glucose in lactic acid as a final product. With much less energy supply.

As we have shown in a publication on the other hand there are also intestinal bacteria which produce both left- as right-turning lactic acid. Often the disintergration of D-lactate (animal lactic acid) is more difficult with ME patients because they lack the enzymes to do so.

So there are a lot of factors which cause the aerobic metabolism to shift to a more anaerobic metabolism. And to me this is also an important element in the occurring pain.

That's why pain management must be performed with an overall vision on pain. Often one can't cure this with one particular medicine, but with a more integrated approach one can usually cause a serious relief from the pains.

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Seminar 6: ME and Hormones

Web Seminar of prof. dr. K. de Meirleir, broadcast on december 7th, 2012

In general, we can say that the hormonal changes in ME are probably fully secondary. In other words, the result of an underlying mechanism, rather than being primarily at the core of the disease.

I very much want to argue against those colleagues who only treat the hormonal abnormalities. Because that way you don't actually treat the core of the disease, and you can also cause a lot of damage.

Having said this, the problem of hormonal abnormalities is probably rooted in what we call the hypothalamus. Due to various reasons, such as blood flow, neurotoxins and inflammation, the hypothalamus is in a kind of hibernation state. Like a bear in winter. Who also reverses his hypothalamus. And we know that the function of the hypothalamus can be reduced in different ways. The question is whether this is a protective mechanism or just the result of a number of underlying mechanisms. But if the hypothalamus does not function normally, neither will the pituitary. This is the gland situated at the lower end of the brain and that produces hormones, which control a lot of the organs in the body.

So we are looking at three levels here. But I think the problem is mainly situated at the first level. Because when we look at other organs producing hormones, we don't always see intrinsic problems there.

The problem has mainly to do with the hypothalamus. To illustrate this I can say that there are two hormones that are produced directly in the hypothalamus, and nowhere else within the body. The most important one is ADH, the anti-diuretic hormone, the hormone that is needed to concentrate urine.

We observe the activity of ADH becoming very low at a certain point during the disease. That's why people have to get up four or five times a night to urinate. Because there is too little of this hormone to be able to concentrate the urine.
Consequently, patients' concentration of urine is very low. Normally, urine is four times more concentrated in the morning than during the day, which is when you drink a lot. This is then already an indirect indication that there is a problem at the level of the hypothalamus.

The other hormone that is produced by the hypothalamus, oxytocin, seems to be present in a reduced quantity too and seems partly responsible for a change in the behaviour of some patients. They are more introspective, which is sometimes described as being autistic. That may be linked to a reduced production of oxytocin. Quite a few doctors prescribe standard nasal sprays containing ADH and oxytocin.
These are extremely small molecules that can easily be administered as a medication; as a nasal spray to prevent having to get up at night to urinate. In other words, a substitute is administered.

Moreover, we know that ME patients suffer from many thyroid problems. These are also concerned with hypothalamic abnormalities; but also with the auto-immune phenomena that occur in ME patients. The adrenal gland produces too little cortisol, so we're not dealing here with Addison's disease – an autoimmune disease of the adrenal gland itself.

The adrenal gland is probably poorly stimulated by the pituitary gland, which in its turn is controlled by the hypothalamus. This has been demonstrated in a number of studies.

We also see significant changes in ME patients in terms of the male and female hormones. Often, with men there is a progressive decrease of testosterone that doesn't correspond with aging, but develops much faster. In women all sorts of cycle disorders arise, which has to do with changes of pulsation. The hormone in the brain that is responsible for regulating the menstrual cycle no longer has its normal pulsations. That's because it is not produced in a constant stream. It comes in pulses and if an abnormality occurs in those pulses, we also see changes in progesterone and oestrogen occurring during the menstrual cycle.

Additionally, inflammation plays a role here. Many of our patients suffer from a very intense PMS, premenstrual syndrome. This has to do with changes in the prostaglandin metabolism.

And then there's also the question of why more women than men suffer from ME. My experience is that gender makes no difference, and in my practice we have at least 400 children under the age of 12. Up to the age of approximately 12 or 13, the ratio is one to one. After that the difference progressively extends to about four to one. Four women appear for consultation for every man. This is probably caused by various factors.

The immune system plays an important part in this, because oestrogens weaken a certain part of the immune system. Which is precisely the part that is essential to control bacteria living within the cells, the so-called intracellular bacteria, and to control parasites and viruses, like herpes viruses, which are already present within our body.

That is what we call the Th1 immunity. Testosterone stimulates Th1 immunity. Oestrogens, however, weaken the Th1 immunity, so that the T-helpers – the type 2 cells – eventually become more prominently active. We know that there is a very clear effect on the immunity. This is also a known fact outside ME research.

We see this deviation quite clearly, in such a way that predominantly from the age of 12 to 13, we see more and more women with this condition. So the type of person that we see during the consultations is a woman of an average age of 37. Because the strongest oestrogen activity occurs in the ages between 12 and 50.

An additional argument for example is pregnancy. During pregnancy, HCG is released, which is a hormone that induces testosterone. Many women with ME feel somewhat better during pregnancy, but immediately after pregnancy we notice a strong relapse. And as with MS, we see that three to six months after pregnancy spells of the disease occur (and this has not yet been reported but it's an observation we have made). And that too is most probably multifactorial.
But hormones play a part in this too.

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Seminar 7: **ME, the Immune System and several Virusses**

Web Seminar of prof. dr. K. de Meirleir, broadcast on december 14th, 2012

Disturbance of the immune system is most probably due to infections. With half of the patients these are a clear starting point. An infectious, flu-like syndrome occurred which set a number of things in motion.

The body may or may not be able to cope with infections. Some infections never disappear and settle within the body. In this condition the interaction between the immune system and infections has also been disturbed.
We observe that the immune system cannot cope with a number of infections , nor keep them sufficiently under control.

It is our view that with this condition several multiple infections are active simultaneously and that the immune system isn't able to get control over them. We think they also play a role in the process of the condition becoming chronic. Because they are continuously stirring up part of the immune system.

With the condition becoming chronic, another part of the immune system gets weaker and can't function in a normal way. For instance there's a very obvious connection with enteroviruses.
An American has proved that over 80% of ME-patients have an enterovirus in their stomach and can't cope with it. Which he found with just 20% of the normal population.

This implies that the enteroviruses are not the cause of the condition, but that the immune system isn't able to control them. When with 20% of normal people entero-viruses are to be found as well, one can conclude that this most probably isn't the cause of the condition. Just that this is a phenomenon which has to do with an altered immune system.

Other viruses like, for instance, the Epstein-Barr virus, the Herpes-6 virus, the cytomegalovirus and the parvovirus B19 are present in elevated levels in ME-patients. This also has to do with the Th1-immunity which has become weaker with ME-patients and which can't cope with the infections. Herpes-6 has been empha-sized, as it can both cause a weaker immunity in itself as well as be chronically active because of that weakened immunity. And it can cause all kinds of conditions within the body, which range from epilepsy to cardiac disorder etc. This perfectly fits the picture of ME.
Here again no acute virus is involved, but a virus which stays latent with most people and is found in increased measures and quantities with these cases.

The defense mechanism against bacterial infections is disturbed in ME-patients as well. Chlamydial infections, Mycoplasma and quite a lot of other intracellular infections are chronically present. With thorough examination one is able to measure quite a few infections. And one suspects them to play a role in the entire context of this condition. But then this also has to do with cellular immunity, the Th1-immunity malfunctioning. And as a consequence similar viruses are kept in check with difficulty.

With such patients parasites, primarily intestinal ones like Giardia and plasto-cytes, also occur in much larger quantities. All this indicates an anomaly of the immune system.

Larger studies, mainly from outside Europe but some of them in Europe, show a shift within the immune system, within the cellular immunity. There's a mutation in the so-called CD8 positive T-cells, the number of which at times is much lower. It's a well known fact that the natural killer cells, i.e. cells which absorb and kill tumor cells as well as viruses, are functioning less and at times are extremely low in number.

We notice that in reaction to the presence of micro-organisms more inflammatory cytokines occur – substances of our white blood cells which are connected to the production of interleukins and so called chemokines. At times within the blood of one single patient we find larger numbers of up to ten different interleukins or cytokines. This also causes a gamut of consequences.

Presently our main focus is on an enzyme called nagalase. Compared to normal people 97% of our patients show a higher level of nagalase. Higher nagalase counts result in bad functioning of the macro-phages – white blood cells in our tissues which also absorb particles that have to be removed. Macrophages are immunogenic and stimulate the immune system to remove, for instance, bacteria and viruses.

And I'm definitely not complete with this list of immune deviations. There's a large range of immune deviations which can be clearly identified. But classic medicine doesn't want to hear of them yet. Because scientifically their existence has been shown, but their clinical application hasn't been proven yet.

Nagalase – what is it?

Nagalase is a protein, a substance which breaks down another protein we need to activate our macrophages. At a certain point our macrophages have to be stimulated to absorb alien particles. Nagalase prevents this.

Quite a few sources of nagalase are known. The HIV-virus and certain intestinal bacteria, for example, produce nagalase. This too is subject to study right now. Which nagalase actually is more frequent in ME-patients and where it originates.

Wetenschap voor Patiënten

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Seminar 8: **ME and the Blood Circulation**

Web Seminar of prof. dr. K. de Meirleir, broadcast on december 21st, 2012

When one sees an ME patient on his first consultation, one notices he has cold hands, cold feet, a cold tip of the nose and cold ears. It means that there is a poor peripheral blood flow. We also often see low blood pressure. Even patients with overweight have low blood pressure, which is highly abnormal. On the other hand, we also see that heart rate is increased in most patients who are in rest. It is ten to twelve beats higher than in normal individuals.

Mainly investigated concerning blood circulation has been the so-called postural hypotension or sudden drop of blood pressure when getting to one's feet. This means there is a delayed adjustment to the body's position in relation to the ground. We see that in the morning while getting up, blood pressure often decreases and heart rate suddenly rises with 30 beats and one reacts very badly to the tilt effect.
There are tilt tables on which people are laid with their head down when suddenly the position of the table is changed. We know that adjustment to this is often very bad. This does not only have to do with the blood flow as such, but also with the state of the nervous system.

And sometimes patients become what we call really vagal, they get a very low heart rate and lose consciousness.

That kind of research already dates back to the 90s and was performed at the John Hopkins University.

Why is blood pressure low?

We see that quite a few vaso-active substances are released. Such as hydrogen sulfide, nitrogen oxide and CO. As waste from the metabolism, but also as a result of inflammatory processes in the body. Those lead to a permanent dilatation of the large blood vessels, forcing the small blood vessels into vasoconstriction.

We know that there are also a number of cardial abnormalities, such as insufficient filling. As a result of dilatation of the large vessels there is too little fluid in circulation and the heart is filled insufficiently. We also often see a mitral valve prolapse: the mitral valve will not completely close, because the blood volume is too low.

As the blood pressure is way too low, the heart won't need to use much power to push out the blood. This leads to a kind of chronic condition with a very low blood pressure and very little filling. And that has implications for all sorts of other organ systems, such as pressure towards the lungs, where the blood must be charged again with oxygen. But also for the pressure towards the periphery, from where oxygen and nutrients must be distributed to the various organs. This leads to a condition which may cause a metabolic disorder.

In the cardiovascular field, other things have been identified in ME-patients. An American cardiologist has shown that there are quite a few infections with viruses and he refers to the cytomegalovirus and to herpes-6.
With antivirals he was able to show that those viruses had an impact on the cardiovascular system, on the heart.

And that the pump functioned less well in ME-patients, due to the presence of certain endogenous viruses. Those are viruses we have had since our youth, but which are present in larger quantities in such patients and which cause a reduction of the pump function of the heart. He has been able to present beautiful results of very aggressive treatments. That is also preliminary, because I don't think others until now have reproduced these studies.

With regard to circulation, I think there is also a low-grade inflammation, an inflammatory condition, or inflammatory state that has its effects. And that a lot of substances are released which cause the normal regulation of blood pressure and the normal regulation of the so-called perfusion of the tissues to be disturbed. Though it is never found in patients in the first phase, there is a hypersensitivity to adrenaline, and also changes in the receptors, or sensitivity for adrenaline has been described.

This is a condition with so many abnormalities , one person could live through twenty lives.
But one of those abnormalities is that a change of sensitivity develops in the receptors for adrenalin, which leads to changes in blood pressure.

There are also other hormonal changes related to blood pressure, which I consider more as compensation mechanisms. But you won’t see them in people in the first stage of the disease. They sleep too much, are awake briefly and don’t do much exercise. This usually concerns someone who has a flu-like condition, with low blood pressure and generally feeling unwell. With them we don’t find the peaks in blood pressure.

Wetenschap voor Patiënten

(Science to patients)

Seminar 9: **ME and gastro-intestinal problems**

Web Seminar of prof. dr. K. de Meirleir, broadcast on december 28th, 2012

There are quite a few deviations known of the gastrointestinal system. In my opinion, gastrointestinal specialists don't listen to their patients very well, as they probably could have been the first to identify the problem of ME and bring it to people's attention.

The gastrointestinal complaints that ME patients have range from nausea to bad digestion, abdominal pains, constipation, diarrhoea, and a spastic colon. It's quite a list of symptoms, with more than 90% of all ME patients having gastrointestinal problems.

The stomach starts to contract poorly. We are familiar with the mechanism, it's called gastroparesis. 88% of our patients suffer from a stomach paralysis or gastroparesis. Which of course leads to a situation where the whole digestion chain is disturbed. If the food stays in the stomach for too long, all other processes are no longer in sync. By then the pancreas will have had all its fluid secreted in the intestine, where there is still no food because the stomach is contracting too slowly. Therefore patients will often experience an immediate feeling of being full and not being able to eat anymore, because the stomach is filled directly and is not emptied.

The number of people with ME that take so called H2 blockers is higher than 90% I would say. H2 blockers inhibit gastric juice secretion, not only due to a disturbed gastric acid secretion, but also due to the fact that there is a backflow of stomach contents into the oesophagus. This causes the lower portion of the oesophagus to become irritated, which in turn is a source of chest pain, of waking up at night with pains, which also leads to digestion problems and not being able to eat properly.

There are intestinal absorption problems at the level of the intestine because many ME patients develop food intolerances – intolerances that they didn't have in the past. This again has to do with the immune system.
It would be going too far to explain this in detail here, but we do notice the occurrence of food intolerances.

We know that food tolerance builds up between the ages of 1 day and 15 months. During this period, we gradually learn to tolerate and digest all types of food. In fact, patients lose a part of the tolerance that they had built up in the past. This has to do with changes in the underlying immune system.

Diarrhoea and constipation are sometimes major problems. Changes occur in the peristalsis. We think this also has to do with a number of toxic substances. Such as NO, a gas that is known to be more often released in ME patients. NO paralyzes smooth muscle tissue, and the entire gastrointestinal system consists of smooth muscle tissue.
Also what we call the autonomic nervous system - the parasympathetic and the sympathetic nervous system - in ME patients is disrupted. We see that a clearance of substances takes place in the stomach, sometimes resulting in explosive diarrhoea alternated with constipation.

Then we also have the intestinal flora. With this condition, the pH of the intestine is altered considerably. We notice an overgrowth of certain categories of intestinal bacteria and that other intestinal bacteria do not quite die out but do decrease gradually in quantity. As a result, a dysbiosis occurs, an imbalance in the composition of the intestinal flora. This has implications for the release of toxins. Very recently we found that one specific type of bacteria – Lactonifactor – has multiplied tremendously in ME patients compared to control groups. We discovered this in both Belgian and Norwegian patients.

This type of bacteria is of the Clostridium family, with which we are familiar and which is responsible for the production of a certain toxin, which again changes the metabolism in another way. But we also see for example that E-coli, a beneficial type of intestinal bacteria, is often present to a much lesser degree.
E-coli is responsible for instance for the production of amino acids – the pre-cursors for serotonin and dopamine in the brain – the happy hormones. Dopamine is considered to be a happy hormone, while serotonin is associated with depression. So it is highly likely that a number of co-morbidities, such as depression, are partly caused by this dysbiosis, this abnormal composition of the intestinal bacteria.

This summary is by no means complete. Very many digestive problems exist and we generally focus a lot of attention on these, because the intake of food is essential. A small percentage of patients must even be fed in a different way, for example through tube feeding, because enormous problems regarding food tolerance and the regular movement of the gastrointestinal system have arisen.

Wetenschap voor Patiënten

(Science to patients)

Seminar 10: **ME, Co-morbidity and Exclusion Criteria**

Web Seminar by prof. dr. K. de Meirleir, broadcast on January 4th, 2013

With the patients we see, other conditions with similar symptoms have usually already been excluded. For instance, a malfunctioning thyroid (hypothyroidism) or a thyroid that works too hard (hyperthyroidism); the adrenal disorder Addison's disease; Cushing's syndrome, when too much cortisol is produced; Lyme disease caused by bacteria called Borrelia; rheumatoid arthritis, diabetes and other autoimmune disorders.

Sometimes there's a discussion whether or not it could be MS, multiple sclerosis. Because for some ME patients, the difference between a diagnosis of MS and of ME is really small. Sometimes ME patients have minor brain lesions, identified through brain research or an MRI brain scan. But usually these are too small and their location doesn't correspond with MS. On the other hand, 25% of the ME patients also have an elevated protein level in the spinal cord fluid, which can lead to the discussion as to whether or not it is in fact MS. But really ambiguous cases of MS form an exclusion diagnosis.

In total we have listed about twenty conditions in the ICC which form exclusion criteria for ME. This is of course not exhaustive.

In future, it is likely that a number of those exclusion criteria will be included as a co-morbidity, as a condition that can be the result of, or which may occur simultaneously with this complex condition. At the moment, I can't give a definitive answer on this, but it concerns only those cases with similar symptoms. And those with a clearly different biological picture, specific to those conditions, which have nothing in common with ME will be definitely considered as exclusion criteria.

What things can best be tested for first?

I believe that neither a computer nor a general consultation can replace a physician. The clinical picture of the people we see varies tremendously. It depends on whether the disease is in an advanced stage, or if the condition is in its first six months. These are totally different clinical pictures. The approach, in addition to the classic clinical investigations and the asking of questions, the history – what happened in the years prior to the disease – is very important. And the family history. As well as what kind of toxic exposure there might have been.
A global anamnesis is of great importance here.

Next, very specific investigations into the possible mechanisms of the dysfunction of the different organs must be performed. A broad screening is desirable to establish what is playing an important role in the disease persisting. Actually we look at a number of vicious circles within the different mechanisms. We try to break through them with the existing resources, so that they are neutralised. That's the best we can do today, because it's a chronic disease.

I don't think that the aim is to cure every single ME patient, but our aim should be a good quality of life for every ME patient.

To get as many people as possible who want it, back into the labour process and back to work.
And to give a normal life back to all the young people who haven't yet suffered irreversible consequences from this disease, and to let them forget they ever had ME.

Is ME contagious?

I think we will be able to say more about this in 2013. Today we can only talk about published, not about unpublished research. But we do suspect that a subgroup of patients can be contagious, in certain circumstances. In general it's assumed that patients aren't contagious. Just a few governments have decreed that ME patients are not allowed to give blood. There are five I believe, including Belgium, the Netherlands, Canada and Australia. Most countries still haven't taken a stand on this.

In the coming months I expect that this subject will be discussed in more detail, because we are also looking for infections, infectious proteins. I expect more light to be shed on this in the coming months. But overall it's not true to say that every ME patient is definitely contagious.

Wetenschap voor Patiënten

(Science to patients)

Seminar 11: **Twelve answers to questions - ME Origin and Causes**

Web Seminar by prof. dr. K. de Meirleir, broadcast on January 18th, 2013

About the name ME: Have inflammations of brain and spinal cord been demonstrated or not?

They have certainly been demonstrated. Dr. Natelson showed that 25 % of ME patients have a higher than normal white blood cell count in their cerebrospinal fluid. At autopsies also evidence of the presence of corpora amylacea was found, a kind of inflammatory infiltrate, but again only in a small percentage of patients. Then there are a number of other issues. Radiographic studies show deviations of the dorsal horn of the spinal cord, and also reduced grey matter was found. This reduction of grey matter is visible on a brain MRI.

Does a healthy lifestyle prevent the onset of ME?

In my opinion it's not possible to prevent the onset of ME through a healthy life-style. A number of other factors beyond ones control determine the onset of ME.

Is it possible to objectively assess exercise intolerance?

Exercise intolerance occurs primarily after physical exertion. The best way to measure this is by doing two peak exercise capacity tests separated by 24 hours.

In healthy people work capacity will show no reduction after 24 hours. In ME patients on the other hand this capacity is reduced with an average of 22% after 24 hours.

Why does PEM (Post-Exertional Malaise) sometimes occur later on or delayed?

PEM stands for Post-Exertional Malaise, which means feeling unwell after a significant exertion or even - when you are seriously ill - after a minor physical strain. This is a result of a disruption of many body systems. The sympathetic nervous system, hormones controlled by the brain, the supply of all kind of substances needed for nutrition such as glucose - quite a few body systems are disrupted. It's explicable that stress, like an exertion, can have more consequences in such patients.

Is POTS (Postural Orthostatic Tachycardia Syndrome) typical for ME?

POTS and its relationship with ME was discovered a long time ago. This was described then by researchers from Hopkins. POTS is also a disease that has several causes. But in my opinion a number of substances responsible for the expansion of the large blood vessels, such as hydrogen sulphide and NO, play a big role. When the larger blood vessels expand, there's relatively less fluid present and this causes problems when standing upright. In reaction the smaller blood vessels contract and finally the blood flow to organs, such as muscles, diminishes. But it's actually a complex condition in which also the nervous system is involved. A number of abnormal reactions arise, caused by a hidden inflammatory process.

What's the relationship between POTS and cognitive impairment?

The relationship between this is a dis-rupted blood flow in the brain, caused by

the underlying mechanisms of this disease. And the cerebral blood flow is better when one lies down than when one sits or stands upright.

Are intestinal problems a cause or a result of ME?

There are pre-existing problems, but those are also present in the general population. So I don't think that those are the main cause of ME. But a lot of problems arise later on in this disease, as a result of a malfunctioning immune system. And the immune system determines what happens in the intestines.

Does blood-brain barrier impairment play a role in the aggravation of ME?

In itself a weakening of the blood-brain barrier hasn't been proven yet, but we very strongly suspect this is present. There are multiple factors in this disease that can provoke such a weakening.

What is the role of strain and (psychical) stress?

I don't consider this to be a cause but rather a consequence of ME. That's to say one becomes more stress prone. This is a result of all kinds of hormonal and neurological changes, which causes an ME patient to become more sensitive to stress. These changes have greater consequences than in normal people, so ones resistance decreases and one tries to avoid stressful situations.

Why are ME patients more susceptible to chronic infections?

ME patients are very susceptible to chronic infections, because there is a change in the immune system. Especially in a later stage of this disease, the TH-1 immunity diminishes, is less present, becomes less strong. There's also a reduced natural killer cell activity, and a dysfunction of B- and T-cells, that's to say they don't function properly.
So in fact one can say that it's rather normal that some infections, such as intracellular infections, fungal infections and latent viruses present in our body, are reactivated.

How do you explain to your near ones why too much noise, light or impressions make you ill?

Many ME patients feel bad when they're exposed to excessive sound or light, or when it's too busy around them. This is a result of a number of neurotoxic substances present in their body. You can explain to your relations, that because of these neurotoxic substances your body is poisoned and the brain is overloaded.

Why are ME patients' blood sugar levels often too low?

Low blood sugar levels often occur in ME patients. This is a consequence of the fact that ME patients absorb sugar more, absorb it faster, because there's a shift to the so-called anaerobic metabolism. On the other hand there's a problem with the mechanisms required for releasing sugar as soon as the blood sugar level drops. A number of hormonal systems, responsible for a stable blood sugar level, partially fail. And thirdly we know that in a subgroup of patients the production of insulin is too high, causing more sugar to be absorbed from the blood flow into the cells.

Wetenschap voor Patiënten

(Science to patients)

Seminar 12: **Misdiagnosis / Related Diagnosis and Tests**

Web seminar by Prof. dr. K. de Meirleir, broadcast on February 1st, 2013

Which other groups of patients run the risk to be misdiagnosed with CFS?

Actually a wrongful diagnosis of CFS is a complicated concept. Because CFS is defined on the basis of a number of symptoms and exclusion of other disorders. But if you don't look for these, the diagnosis ME/CFS is very easily made.

Many patients suffer from chronic infections or severe hormonal disorders, which may be regarded as secondary in this disease. For us it's very difficult to debar a diagnosis of ME/CFS. Suppose that in additional examinations one delves really deep, and a number of pathological issues are found, at what point does one stop to call it CFS and ME, while in fact a different condition is being described?

What other deviations do you diagnose by which people eventually are excluded from ME? Does this occur often?

This is rather common. We should exclude for example Lyme disease and other chronic infections with clinical pictures similar to ME. I think this isn't done often enough. Only a superficial examination by an internist is done, which subsequently leads to a diagnosis of ME. Thus, different diagnoses are hardly considered.

When do you diagnose that a patient has CFS and not ME?

People in whom we discover a chronic infection in an early stage, without the typical other pathologies seen with ME, are diagnosed with this infection. But when the clinical picture and complementary examinations point to the fact that there are a lot of effects which most likely are irreversible, a diagnosis of ME has to be held on to. It's all about effects and irreversibility.

These last couple of years you have been testing ME/cfs patients for Lyme with improved tests.
What's your experience with these? What's the risk of being wrongly diagnosed with Lyme's disease?

The last few years a lot of new tests did pop up, which give us a better understanding of intracellular infections. We have already found - for instance - quite a few patients with Brucella, chronic brucellosis; or Lyme disease, chronic borreliosis, or a chronic Bartonella infection. At present the count is approximately 50% of all ME patients. So the diagnosis ME is now seriously being questioned.

There's an increasing number of ME patients who're also afflicted with Bartonella (cat scratch disease). Yet in the second web seminar on November 10th you say we shouldn't start from exclusions. So what's the effect of co-morbidity in ME?

On this question, which actually implies Bartonella is found in patients, I would like to give some comments.

The Bartonella infection found in many ME patients is not cat scratch disease. Cat scratch disease is Bartonella Henselae, but in the meantime 32 other (sub)species of Bartonella have been discovered.

We suspect very strongly that several other Bartonella infections are at stake and not Bartonella Henselae, as only in 3% of the patients antibodies against Bartonella Henselae are found.

We don't know what the actual role of this infection is. It's only been a year that people are being treated for this infection. Some people recover completely and others recover partially. In my opinion the diagnosis ME mustn't be abandoned, but I think the impact of Bartonella is different in every patient.

What's the relationship between IBS (PDS) and ME/cfs?

There's a relationship between ME/cfs and IBS, Irritable Bowel Syndrome. A lot of people suffer from it, yet there are also many people who don't have ME but do have IBS.

IBS has to do with abnormal intestinal bacteria, with an abnormal digestion, with an abnormal acidity in the intestines. This is something also found with a lot of ME patients. I personally think this has to do with changes stemming from the immune system, which caused different intestinal bacteria. Also a chronic low-grade inflammation causes changes in the peristaltic movement and an altered degree of acidity in different spots in the intestines.

What does a low number of natural killer cells imply?

in the blood of ME patients often a low number of natural killer cells is found. I have my personal opinion on this.
In my opinion the total number of natural killer cells within the body isn't reduced, but they have actually moved to the tissues to help fight infections. As in Lyme disease, in which the number of CD57 positive lymphocytes is reduced, I suspect this to be an identical mechanism, which lowers the number of NK-cells in the blood, but makes us find a higher number of them in the tissues.

What does activation of the complement system imply?

Activation of the complement system is also to be found in ME patients. This activation occurs during an inflammation. In most ME patients a low-grade inflammation, a non-specific immunity is triggered. Complement is an aspect of the non-specific immunity. It's a part of the recuperation process, but since the recuperation process is not complete, changes in the complement will remain present.

What's the use of an MRI-scan, a Spect-scan or an EEG in ME/cfs?
Neurologists perform numerous tests on ME patients, among others an MRI of the brain. This MRI may demonstrate changes in the structures of the brain. For example, when the volume of grey matter is diminished, there will also be deeper grooves in white matter. Sometimes small areas of demyelination are present, where the myelin disappears. In English we call those UBO's (Unidentified Bright Objects). Similar to MS these are small areas of 2 to 3 mm, but their location doesn't correspond with MS and they are much smaller.

With a Spect scan, which is sometimes requested, one can detect the difference from depression. The blood flow disorders in ME patients are different from those in depression.

Another examination ordered by neurologists is an EEG. An EEG provides little information, unless it's a quantitative EEG. Then often a form of micro epilepsy is seen. Waves are different from those in normal people, there's an increased sensitivity of the brain.

What exactly is the problem with the mitochondria?

A number of people in the world are investigating the mitochondria in ME patients. They have determined a number of things, like the mitochondria producing less ATP. Mitochondria serve to generate basic energy, in the form of ATP. The actual cause for this malfunctioning disturbance, hasn't been demonstrated yet. But in fact a number of neurotoxins like hydrogen sulphide that is released, are interfering with the mitochondria. Thus they cause the mitochondria to function less well. Also the release of abnormal proteins may interfere with the mitochondria and reduce their function. So there are a number of mechanisms known to be connected with a poor function of the mitochondria and with ME.

Is there a genetic connection between autism, MS and ME?

In this area only a few studies have been done. When one speaks about genetics and ME, we know there's a number of issues concerning immunity. And also in the other body systems that cause a genetic predisposition for ME.

But this actually applies to any disease. There's also a clear link between ME patients and families in which autism occurs. This connection becomes clearer and clearer. Autism is a disorder which is determined genetically as well as by environmental factors, and probably is also provoked by bacterial causes. It's a *wide*-spectrum *disorder,* very diverse. A lot of research is needed to determine the actual relationship.

MS, Multiple Sclerosis and ME are also interlinked. There are families of which some members suffer from ME and others from MS. So there's a clear genetic connection. More research on this is needed.

Wetenschap voor Patiënten

(Science to patients)

Seminar 13: **Sleep, Pain and Nightmares**

Web Seminar by prof. dr. K. de Meirleir, broadcast on February 15th, 2013

What's the scientific explanation for patients feeling better in the evening than in the morning?

In my opinion, which is based on scientific research on ME patients feeling better in the evening and feeling worse in the morning, this has to do with the fact that their sleep isn't invigorating. It's actually of poor quality, because several hormones that should work and raise in level at night, don't.

Cortisol levels, for instance, are relatively low, while normally in men the highest level of cortisol occurs at about 7 a.m. So ME patients have a different around the clock rhythm. Moreover there's a serious problem with the release of melatonin. Melatonin makes you sleepy and apparently it isn't produced at all or much later which causes a phase shift to occur.

These are just a few examples, In my opinion it's much more complicated. But there's clear scientific evidence for an abnormal circadian rhythm to occur in ME patients.

In web seminar 4, "ME and Sleep Disorders", you say: "Patients go to sleep later and later".

Is this caused by the poor quality of sleep, or by lack of melatonin...?

Patients go to sleep later and later because the on/off switch within the brain doesn't function well. They produce insufficient melatonin, resulting in going to sleep later and later and waking up much later during the day, which causes a total disturbance of their circadian rhythm. Unlike healthy people they aren't adjusted to normal daylight anymore, and therefore their system gets disturbed and they go to sleep later and later.

What's the cause of ME patients having so many nightmares? Is it neurochemical or psychological?

Many patients get nightmares and they can be entirely explained neurochemically. There are changes in the serotonin metabolism. Serotonin plays an important role in the brain. We know that especially in ME patients who have a co-morbidity, like a Bartonella or a Lyme-infection, many nightmares occur. Meanwhile we know the mechanism that causes less tryptophan to be converted into serotonin, causing a serotonin shortage in the brain. Personally I think this to play a role in causing those nightmares.

What's the probable cause of pain?

Many ME patients suffer from diffuse pains, both headaches and muscle pains. In my view central pains also have to do with neurochemical activities, which are the result of neurotoxins and changes in neurotransmitters.

Peripheral pains, the pains in the extremities, to my opinion have to do with a deficient blood supply, which implies a more anaerobic metabolism, and more lactic acid to be produced, causing a shortage of energy and a toxic waste product called lactic acid.

Is it possible to objectify pain? Can you influence the pain by thinking differently?

As for pain traditional medications exist it can be treated with, once you understand the possible causes. There are of course other ways in which you can influence your brain too. But in my opinion these are not really helpful solutions when you suffer very severe pains. I think it's possible to mentally influence a mild, dull, chronic pain. But if you really suffer pain which has organic roots, it will be very difficult to treat it without medication.

What's the cause of the epileptic-like shocks within the bodies of ME patients?

Many ME-patients suffer from epileptic-like shocks or experience muscle fasciculations. These also have a neuro-chemical basis. It probably has to do with disturbances in the ion channels too, through loss of calcium, potassium etc. from the cell, causing an imbalance. This creates a mild form of epilepsy, sometimes perceptible and often not.

Wetenschap voor Patiënten

(Science to patients)

Seminar 14: **ME and Treatment**

Web Seminar of prof. dr. K. de Meirleir, broadcast on March 1st, 2013

Oxygen treatment/therapy: what are the pro's and cons?

Administration of oxygen has its advantages and disadvantages. Oxygen increases the release of free radicals, which can be harmful. On the other hand it can be very useful to help people with severe pain and with strong acidification.

The oxygen used at home, isn't administered through oxygen cylinders anymore, like inhospital. It comes from a device that transforms air into almost 100% pure oxygen. So this doesn't depend on the supply of oxygen cylinders.

Is the oxygen one gets in hospital akin to your oxygen treatment?

The oxygen administered through a so-called oxygenator, is almost equal to the pure oxygen administered in hospital through cylinders.

What do you expect from Rituximab?

For those who have never heard of Rituximab: Rituximab is an antibody against B-cells, used to treat cancer patients with B-cell lymphoma.
Researchers from Norway found that people with ME temporarily improved while given this treatment. I consider this to be an excellent diagnostic study. It entirely confirms our hypothesis on ME.

But I don't consider this to be a long-term solution, because practically all patients relapse. So a new injection will be necessary after six or twelve months, which is extremely expensive, to replace these B-cells, which don't function in a normal way, by young and healthy B-cells. Those young, healthy B-cells will function properly for some time, but will again become involved in the disease process. Therefore it isn't a definitive solution. Due to the fact that we have few other drugs, this is at present a legitimate experiment.

Ampligen. Is it effective? For whom and for whom not? How does it work?

My experience with Ampligen dates from 1992 until 2001. We gave Ampligen to approximately 150 people then. So I can only speak from my own experience.
Ampligen partially works like Interferon and mainly combats the viral aspect of the disease. So those ME patients in whom the viral aspect of the disease is dominant, will profit most from it. I think it's possible it will become available on the market. That doesn't depend on me and I don't really have any insight into this, as it all happens in the USA.

Are you familiar with feces donation? Is this a useful approach?

We hear of some patients who choose to have a stool transplant. This means stool from the intestines is removed and replaced by stool from a healthier individual. I believe this also can give a temporary improvement as fewer toxins are released in the body, but again it's no definitive solution. Because the problem isn't so much the intestines, but the immunity of the intestines. This abnormal flora will grow again. And after all such a stool transplant isn't an enjoyable treatment and must be repeated regularly.

The only indication for this concerns ME patients who have a very strong overgrowth of Clostridium. Clostridium is an extremely dangerous and toxic microbe. But the same applies to people with an overgrowth of Clostridium who don't have ME. I think that the academic hospitals who are doing this at this moment, both in the Netherlands and in other countries, do focus on patients with a dangerous overgrowth of Clostridium.

Heart-rate monitoring and pacing. Can you briefly explain what it implies? What do you expect from it?

Several researchers have established that ME patients have rather irregular heart rhythms, with major variations. This has to do with changes of the sympathetic nervous system, causing a less adequate control of the heart rhythm.
I do think all this can more or less help if one is in control of this. But again this isn't a treatment of the cause.

Pacing is applied in order to use less energy. That's to say to use the energy for things one absolutely wishes to do, to make it through the day in an acceptable and human way. Therefore I believe pacing is an alternative for people who are chronically ill and for whom few treatment options are left. They must learn to deal with the amount of energy they have left. That seems a possibility to me, but one that should be addressed only when the patient has tried all normal treatments.

Doesn’t long-term administering of antibiotics kill the colonic flora?

When one administers broad spectrum antibiotics for a very long time, then one destroys the colonic flora. But when one is very careful and uses narrow spectrum antibiotics to treat a specific infection, this will not happen. There are numerous examples, as for instance in tuberculosis, in which one administers antibiotics for eighteen months.

But that's a very narrow spectrum antibiotic, therefore the colonic flora isn't seriously disturbed. If one uses antibiotics, in cases of very acute infection one chooses broad-spectrum antibiotics, like with any other individual. But when one is going to use long-term antibiotics to combat a very specific intracellular infection, one chooses a narrow spectrum antibiotic that has little effect on the colonic flora.

Wetenschap voor Patiënten

(Science to patients)

Seminar 15: **ME, Remedy and Hope**

Web Seminar of prof. dr. K. de Meirleir, broadcast on March 15th , 2013

Is it possible for patients to recover just through their own powers?
And in that case should they be above a certain limit with regard to the severity of ME?

The only serious study that has been conducted in this area in the past is one by Dedra Buchwald, in which she questioned a large number of ME patients on the course of their disease. The conclusion was that after three years of illness only 3% of the people spontaneously recuperated. The only reservation that should be made here is that it was a study conducted via the telephone and not one which people registered for in a hospital or polyclinic.

What kind of research do you think will have the best chance of producing a biomarker for ME, following a successful replication study?

We suspect a number of biomarkers will be detected in 2013 or 2014, because a lot of research is being done in this field right now, based on tissue research and on deep sequencing.

“Deep sequencing” is a new technique used for DNA analysis. It will ultimately identify a number of things we previously weren’t able to identify.

This research is in progress. This research is in full progress.

Could you describe a few recent discoveries?

A number of discoveries have been made recently. The first results of "deep sequencing" show that ME patients suffer from multiple infections, so they carry many chronic infections, many more than healthy people. I believe this will be the evidence that the immune system, the defence system, isn’t functioning normally. I think that this will soon be published.

Do you notice a changing attitude among physicians?

A very gradual and slow shift in attitude is taking place, because publications continue to appear on the subject of the psychological model of this disease, continuing to create confusion. There’s a lot of criticism of these studies and about the way they’re performed, of their statistics, withholding of data, etc. But these publications are written by persons with influence and they continue to cause a stir in the medical world.

It's really difficult for people who focus on the biological basis of this disease to obtain and maintain credibility, when there are people who continue to make statements based on bad and unreliable studies.

There are patients who recover overnight. Does this mean that they didn't have ME?

Occasionally there are people who recover overnight from ME. The question is: what is the biological basis of ME? Until this is described, you can’t say that there was an overnight recovery.

There is probably some kind of disease process or mechanism present, which disappeared by chance, or as a result of treatment actually intended for something else. And all of a sudden all the symptoms just disappear. As long as there are no better evaluations of patients, based on biological research, it's not possible to say that you can be cured of ME overnight.

Is there consensus among scientists, who, for example, are specialized in Lyme and ME-comorbidities, on the existence and criteria of ME?

At the moment I have a lot of contact with people who study Lyme disease and other chronic intracellular infections, such as chlamydia, Bartonella and so on. So a form of cooperation in the scientific field is developing.

The criteria overlap each other to a great extent, but I don't think that anyone has started to study this entire overlap yet. Currently we are working on a publication which compares ME patients with Bartonella to those without Bartonella and which looks at the differences in their symptoms. I expect these kinds of studies to take place more and more in the coming three to four years.

Wetenschap voor Patiënten

(Science to patients)

Seminar 16: **ME and Low-Dose Naltrexone (LDN)**

Web Seminar of prof. dr. K. de Meirleir, broadcast on March 29th , 2013

What is LDN, how does it work and is it applicable?

The question is whether LDN is useful in the treatment of ME/cfs. In recent years, a significant amount of research has been conducted into the use of LDN for the treatment of fibromyalgia and ME/cfs, including studies carried out at Stanford. Some studies have also been done with MS patients.

LDN stands for Low-Dose Naltrexone, in other words a low dose of Naltrexone is used, which is an opiate receptor blocker. Our brain contains multiple opiates with receptors, and Naltrexone will compete with these opiates for those receptors.

There is an intravenous form, called Naloxone, and an oral form, called Naltrexone. Although the commercial form of Naltrexone consists of 50 mg tablets, very low doses are used to treat ME, between 0.5 and 4.5 mg, which will partially block the receptors. The hypothesis is that this will induce the body to produce more opiates. So the drug acts as a stimulus for more opiate production, because we suspect that these are suppressed during the whole disease process.

This has a number of benefits. Although it has hardly any effect on fatigue, it does have a number of other positive effects, such as on sleep and on the pain the patients suffer, because there are also peripheral effects. We don't just have opiate receptors in the brain, but thanks to the blood flow we also have peripheral opiate receptors.

Opiate receptors play an important role in the adaptation of the blood flow, of the skin. That's a real problem with ME/cvs. Because the thermo-regulation system doesn't function properly, is not well adapted. And also because substances often circulate that cause the large blood vessels to expand, but also cause the smaller blood vessels to constrict, in other words to be reduced in diameter.

There are still numerous other effects on the microglia in the brain, and this is being researched.
The advantage of this treatment is that it is very cheap. And it's a symptomatic treatment for a number of symptoms that are very bothersome for ME patients.
In my view, LDN is well on its way to becoming a standard treatment for certain symptoms that occur in ME/cfs.

Wetenschap voor Patiënten

(Science to patients)

Seminar 17: **ME and the Brain**

Web Seminar of prof. dr. K. de Meirleir, broadcast on April 12th , 2013

What are the most important disturbances within the brain regarding ME?

That's yet another chapter in the entire ME story. Numerous neurologists have studied this in the past 20 years. First of all, blood circulation disorders have been observed. Very early on, in the early 1990's, it was proven that there was a reduced blood flow within the brain stem. Later on, SPECT scans showed that several parts of the brain receive less blood than normal, causing disturbances.

Additionally, autopsies on very ill patients led to certain findings. For example, Corpora amylacea, small foci of abnormal tissue, were found, as well as neuro-inflammation, inflammation of the brain itself. In 25 to 30% of all patients excessive levels of white blood cells were found in the cerebrospinal fluid. So this is the case with a minority of the patients.

Then there are other issues that were discovered indirectly. The HPA axis, which actually starts in the brain and is regulated by serotonin among other things, is disturbed. And this is the opposite of what we observe in a depression for example. Here we see a suppression of the HPA axis, possibly due to a shortage of serotonin in the brain.

What impact do these disturbances have?
What are the practical consequences, considered clinically?

Memory defects, especially in the short-term memory. There are concentration disorders: it takes more time to answer a question. This is probably caused by delayed interactions between neurons. Brain cells are called neurons. The transmission of information between these cells is probably slower. This has been demonstrated by Natelson's group in the USA, who showed in a very specialized study that for a specific task a much larger area in the brain is activated than usual. Compared with healthy people, that is.

ME patients also suffer from failures of other functions, but these are of a very diverse nature, ranging from very limited to very extensive.

What are the psychological characteristics of these disturbances?

With regard to the psyche: the third part of the question. There are often signs of depression, but this isn't a typical depression. Because, as mentioned earlier, we usually observe a depression with low cortisol.

In a real depression, as observed by psychiatrists, we notice high cortisol levels. And a sharp increase in the excretion of cortisol in the urine in a 24-hour period. So it's a different type of depression, which may have to do with low levels of serotonin in the brain.
The fact that classic SSRIs used to treat a depression do not work, or even worsen the condition, is proof of this too.

Other psychological symptoms are probably related to infections and inflammations. All kinds of changes in behaviour for example.

There's a small subpopulation that has fits of temper accompanied by occasional loss of control of their own behaviour, probably related to inflammatory conditions.

So the psychological and neurological symptoms in ME are quite varied, quite comprehensive and are similar to symptoms often seen in other diseases. Which is why confusion so often occurs. In the new international guidelines, the International Criteria (ICC), in addition to the neurological and secondary symptoms, attention has also been given to the psychological symptoms.

Wetenschap voor Patiënten

(Science to patients)

Seminar 18: **ME, Th1, Th2 and Th17**

Web Seminar of prof. dr. K. de Meirleir, broadcast on April 26th , 2013

Effect and function

First of all I maybe should explain what Th1 and Th2 are. T-helper cells have become well-known thanks to HIV. These are the cells which are hit by the AIDS virus. That's how these T-helper cells caught general attention. The concept of Th1 and Th2 continues, because the T-helper cells type 1 play a part in viral, fungal, intracellular bacterial and parasitic infections.

Th2-immunity plays a much larger role in bacterial infections and also in the development of allergies. Th1- and Th2-cells, which are lymphocytes, are also involved in checking B-cells. B-cells provide humoral immunity, ensuring antibodies are being produced when needed at a given moment. So when there is an imbalance in Th1 and Th2-immunity, this also often leads to changes in humoral immunity.

Now what do we see with ME/cfs? We see that a large majority of patients show a shift to a Th2- immunity. In our study 85% of ME-patients had an immunity with a ratio shift towards Th2 with a decreased Th1-activity. This of course paves the way for viral infections, fungal infections, parasites etc., because of diminished resistance from our immunity.

What we also notice and which hasn't been discussed yet, is that Th17-immunity - which actually should have been called Th3 but was called Th17, interleukin 17 at the onset being described as related to these type of T-helper cells - is more prominent in ME/cfs-patients. So we notice more Th2 and Th17 and a decrease of Th1.

I think this is an important observation, but not of vital importance to the cause of this disease. It might be an element important to scientific research. To study the entire pathophysiology , the whole course of the disease. It's an element which we measure and determine, because it has to be taken into account while starting a certain symptomatic treatment.

Wetenschap voor Patiënten

(Science to patients)

Seminar 19: **Subgroeps of patients**

Web Seminar of prof. dr. K. de Meirleir, broadcast on May 10th , 2013

Is it possible to classify ME-patients into different groups?

Based on symptoms you can clinically subdivide ME/cfs. There are people who are just tired and have few other complaints. There are also patients who mostly suffer pains and whose fatigue isn't that bad. There is a whole clinical gamut, and it's possible to classify patients that way if needed.

Ramsay did it based on a timeframe. Ramsay is the first one to have described the evolution of patients over time. From people who slept too much at the onset of their illness - which is called hypersomnia - gradually changing into people who were no longer able to sleep, to sleep deeply. With long-term observation he saw these people having an altered circadian rhythm. It didn't remain stable. That way you can also classify patients.

The second way to create subgroups is to use biological markers, such as inflammation etc. This is called a pathophysiological classification. You can use Th1- and Th2-ratios as a model to classify patients. For example with MS an acute relapse is typical to a Th1-disease. Whereas ME/cfs more often is a Th2-dominant disease.

Within the whole gamut of ME/cfs there are also patients who are more Th1-like and in whom the interleukin2-ratio compared to the interleukin4-ratio, which is Th1 over Th2, is in-creased.
With whom you can say that Th1 prevails. This applies to a small group of patients. That's another way to classify them.

The third way is through scientific research, based on molecular changes. Right now there is quite a lot of molecular and genetic research going on. In that way you can also classify patients. But I think that's quite premature and not yet standardized. I think the International Criteria, as published recently, describe the whole gamut of patients. And that it is up to the individual caregiver to search for what's fundamentally wrong, rather than saying someone belongs to this or that group.

I think it is more important for the patient to choose a correct scientific approach, so that one knows what's going on with him. And that currently available means in medicine are applied to improve the condition of patients.

Wetenschap voor Patiënten

(Science to patients)

Seminar 20: **Sense and nonsense of tests**

Webseminar by prof.dr. K. De Meirleir
broadcast on May 24th, 2013

Is the determination of the ATP-profile a useful test?

ATP is the sole chemical form of energy supply we have to – for instance - make our muscles contract so that we can move. And also to keep our metabolism functioning.
So we constantly have to produce ATP. This we do from phosphocreatine and by using it up, which means the conversion of sugars and lipids.

We produce ATP continuously. A cell will never have low ATP. In that context the use of ATP is somewhat debatable, because the ATP level is very difficult to determine. That is something that changes continuously. In Western Europe those tests aren't used, only in Great-Britain. And its practical use to me seems limited, unless it is combined with an intervention to try and make people to produce more energy.

In my opinion this isn't the main problem. An ATP-reading as it is done in Great Britain, and not by us in Europe, may confirm that the metabolism is disturbed. And that there is a lower production of ATP. But this is the case in many chronic illnesses.
So it is actually not specific for ME/cfs, but might be a reason to make decisions concerning a symptomatic treatment. To help patients in their overall condition.

Is H2S a reliable marker and what does it show?

The H2S test indicates metabolites of the H2S gas, as they are secreted in urine. The test will be positive when there's a change of colour after the urine has been in contact with the liquid of the testkit for three minutes.

What does this test measure? It shows the presence of more H2S-metabolites, but also a shift in the Th1/Th2-ratio. The more positive the test, the greater the dominance of Th2.
This test is interesting for screening: given the fact that 85% of ME-patients show a dominance of Th2, it's interesting for gp's to determine if there's a Th1/Th2-shift, without having to talk about ME.

What are NK-cells and what is their function?

The question is which role is played by NK-cells and how this is being evaluated in ME/cfs.

NK-cells are circulating immunity cells, natural killer cells. It's in the name: they will kill tumor cells and viruses. So they're playing an important part in our immunity.

Quite a long time ago in the ME-story it was discovered that in many patients there's a low quantity of NK-cells as well as a diminished functionality of the same. That's an important fact. But again not very specific.

Recently we saw that for instance with chronic Lyme disease and Bartonella infections there's a low NK-activity and a low quantity of NK-cells too. That's a concrete fact and one of the many factors in the immune system of ME-patients.

Is testing for NADH useful?

Again NADH is a test which some physicians request. I think its main goal is

not diagnosis, but to trace if a possible addition might be useful.

The ratio NAD-NADH is being looked at, substances that play a role in one's metabolism. When there's an abnormal ratio, it explains why muscles acidify sooner.
And also the intolerance for alcohol, present in nearly 100% of the patients, can be explained by a disturbance in the balance between these substances.