A story about falling ill in ALS, the devil´s disease, with reflections and criticism you can have as a physician after onset of ALS.

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ALS is sometimes called the devil´s disease. It usually affects fully healthy often physically very active persons in late middle age. For me it took about 18 months from the first symptom that made me suspect the disease until I was bound to a wheelchair. I use to say "from off-piste skiing to a wheelchair in 18 months".

This is a personal story about falling ill in ALS. It deals with personal experiences of the disease but also with the view you as a patient and physician can get on the available treatment and research. It also includes a lot of criticism against the current research in neurology. The presentation does however not claim to be entirely scientific. Personal comments about the science are included and some hard data about the disease, which research colleagues of mine and I jointly have concluded. The last two years I have surely read at least two thousand articles and abstracts within the subject areas neurodegenerative or neuroinflammatory diseases and autoimmune diseases. I started with this first about one year after the first symptoms, as I initially believed what all said to me about the disease, that there is no alleviation or cure.

Initially in the presentation below there is a description about the disease and its etiology and what is claimed in the scientific literature about the disease whose background and treatment we are still groping in the dark after. After that follows my own medical or clinical history with personal reflections and arguments for a criticism directed towards a laid-back attitude found among many neurologists who do not seem to have heard of therapy ex juvantibus.

ALS is a relatively rare disease, about 200 persons fall ill every year in Sweden. The incidence has increased with about 50 percent during the last 20 years. About 70 percent of those affected are of male gender, but in Sweden ALS is mainly known through two well-known women who have given the disease a "face", May Fant and Ulla-Carin Lindqvist, but also through Håkan Sundin a famous bandy player. In USA the disease is called Lou Gehrig´s disease after a famous baseball player and baseball Hall of Fame member, who died in the disease 1941. ALS is twice as common in Sweden as in USA and 4 times as common in the Netherlands compared to Sweden. The majority of those fallen ill are in the age range of 40-70 years, but some, even younger than 25 years of age, are affected. The mortality, after the diagnosis is settled, is 50 percent within 2 years and 80 percent within 5 years. It is rare that the patients die as a consequence of other diseases. Both cortical and spinal motor neurons and glial cells die. The clinical picture is faceted with everything from peripheral paresis (progressive spinal muscle atrophy) to bulbar symptoms with speech and swallowing problems or combinations of these symptoms. Some patients can be totally quadriplegic but still able to talk, breathe and eat, while other patients can walk, drive a car but not swallow or speak without a PEG. The majority die from respiratory insufficiency. I know of one patient that died from respiratory insufficiency and he was able to work until an airway infection caused his death. Famous persons that have died due to the disease are among others Mao Zedong and David Niven. Steven Hawkins is the one that has lived longest time with the disease and he fell ill with the juvenile form before the age of 25. There are cases when the progression of the disease is halted or some kind of remission can be seen. Those affected are often fully healthy persons, often physically very active, and few are affected by common disease as cardiovascular disease or cancer. In the "Gothenburg-ALS-material"

there was only one of about 800 patients with myocardial infarction. Diseases with autoimmune origin are however overrepresented in those diagnosed with ALS, but this has until now not been a reason for consideration, and more about this will follow. The common view is that the disease has a genetic origin but also can be triggered by external factors and therefore the etiology is often described as multifactorial. Players of soccer (football) and of American football have been overrepresented in some studies. There are today about 12.800 ALS-related publications searchable in PubMed. The diagnosis ALS, a disease lacking effective help, is normally not set before it is fully assured. When you search for ALS and autoimmunity in PubMed you get about 70 hits and when you search for ALS and inflammation you get about 270 hits. A common view today is that inflammation, sometimes of autoinflammatory origin, is an important factor in the ALS disease progression.

In the literature I experience that there is a groping in the dark for the disease etiology where scientists are occupied with theories related to their own research field. Rituximab, a breakthrough within Multiple Sclerosis (MS) therapy about 10 years ago, has not inspired those involved in ALS research to use this monoclonal antibody that destroys antibody producing B-lymphocytes. Knowledge integrated research involving different specialty areas is rarely observed and this is also the case regarding the cooperation between specialists in preclinical or clinical research. A complete picture of the clinical symptoms, not only focusing on the paresis, is something still not found in the literature. Many realize that the disease background most likely is complex and multifactorial but still they search for one or only a few main causes for the disease. The etiology mentioned in the literature involves e.g. mitochondrial dysfunction, aggregation of incorrectly folded proteins, oxidative stress or glutamate excitotoxicity i.e. accumulation of glutamate in the synaptic space and inflammation; everything giving rise to apoptosis of motor neurons and glial cells. Glutamate is in CNS the transmitter substance for about 40 percent of all neurons. There are reports of significantly reduced growth hormone (GH) serum levels in about 50 percent of the ALS patients and also reports of reduced testosterone serum levels in men. These findings are probably caused by those glutamate activated hypothalamic neurons regulating the gonadotropin and GH release.

Still missing is research that involves in-depth interviews of patients with descriptions of clinical symptoms other than paresis and extrapyramidal symptoms. About 50 percent of the patients report pain but this is extraordinarily poorly mapped and detailed reflections over this clinical fact are still missing. Pain is a symptom related to all inflammation and during the last few years inflammation, as an obligate element of the pathophysiology picture, has been emphasized by many scientists. At my discussions with patients, information about adverse bodily sensibility sensations, I have found are not uncommon. I myself have this in part of my face.

A Swedish research group has mapped the genetic background of ALS. My view is however that this research will not lead to a breakthrough in the therapy as genetic factors only, cannot explain the 50 percent incidence increase of ALS during the last 20 years. There have to be external factors too. Recently a well-known English research institute (Nuffield Institute) stated that neuroinflammation is an established factor related to many neurodegenerative diseases including ALS. Additionally they have demonstrated that this inflammation in the CNS is affected by the peripheral immune system. This means that pharmaceuticals used do not need to penetrate the blood-brain (BB) barrier to have an effect in the CNS. Rituximab used in MS is an example of this. At ALS an increase of peripherally activated T- and B-lymphocytes and of NK-cells are found. Despite the fact that inflammation and pain is reported and that a possible autoimmune genesis of ALS has been suggested, this has not been enough to motive the neurologists to initiate pilot studies with anti-inflammatory substances as

monoclonal antibodies and this I find remarkable in the perspective that 100 percent of the patients die from the disease.

Human endogenous retrovirus (HERV) has been linked to ALS due to the fact that about 50 percent of the ALS patients have increased levels of reverse transcriptase. About 8 percent of our human DNA is incorporated retrovirus sequences and it has been speculated if these, during special circumstances, can be activated and start a possible autoinflammatory process. The HIV-virus is also a retrovirus and it has been found that patients with HIV/AIDS can develop an ALS-resembling condition that regresses on treatment with HIV specific treatment when using reverse transcriptase inhibitors (HAART). The probability that these inhibitors would be effective also in ALS, if the disease is caused by retrovirus or sequences of this, is however not that high. It is however somewhat strange that there are no results published from pilot studies which have focused on this approach, especially when considering the rather mild adverse events reported with these pharmaceuticals. Regarding the etiology there are an increasing number of research reports suggesting an autoimmune genesis that may be related to a completed virus infection or a neurotrauma. These reports have however not led to any innovations affecting the therapy. I have got a report about a mother and her son, which both at the same time caught a severe upper respiratory infection. After one month the mother falls ill in progressive spinal muscular atrophy, a form of ALS, and her son in MS. The onset of an autoimmune disease closely in time after an infection is not anything quite unique, but these findings were not published by the concerned neurologist. More about a possible connection between ALS and MS is presented below.

Of value to notice is also that damages on self-antigens can occur through different mechanisms e.g. due to infection, trauma (e.g. traumatic orchitis) and through other environmental factors. It has actually been suggested that even a spinal disc herniation could trigger autoimmune reactions. TNF alpha blockers have also been used in orthopaedic pilot studies related to spinal disc herniation.

Already some 40 years ago it was noticed at postmortem examinations of ALS patients that there were intercalated antibodies around apoptotic motor neurons. Later on signs of complement activation, presence of circulating immune complexes, intercalation of complements, immunoglobulins, IGM-activation and immune complexes, have been seen in CNS at ALS. Additionally signs of activation of cytokines and chemokines have been seen. These findings suggest an activation of the immune system with overactivity similar to that seen at autoimmune diseases. Still there have been no systematic attempts with immunosuppressive treatments using available pharmaceuticals. Some neurologists claim that there is no idea of testing pharmaceuticals not penetrating the BB barrier at ALS and other neurodegenerative diseases. This conclusion is incorrect and can be understood by the fact that a change in the immune system activity and functionality can have a CNS effect as many of these inflammatory cells relatively easy pass into the CNS, e.g. monocytes and microglial cells. After allogeneic stem cell transplantation at ALS genetic material from the giver has been located in the CNS. This is proof that these immune cells pass the BB barrier. Due to the BB barrier the nervous system should be less exposed to the immune system. In the literature it has been speculated, if at damage to the nervous system, an autoimmune reaction would develop as self-antigens in the CNS are less recognizable by the immune system. The T-lymphocytes are programmed in the thymus to recognize the self-antigens and possibly the thymus ability to program T-lymphocytes correctly can be reduced in ALS.

There are also a great number of etiology explanatory models of more spectacular character which I choose not to mention here.

My strong belief is that the adaptive immune system is involved in the development of ALS and if an immune privileged site in CNS, due to any reason, becomes damaged and due to that becomes exposed to the immune system, this leads to clonal lymphocyte expansion both of T- and B-lymphocytes. I will return to this later on.

I have had a relation to ALS for many years. Good friends to our family, their youngest boy, who taught me to sail, was affected at the age of 35. It started with a foot drop and he consulted me, at that time a student of medicine, and I sent him to a neurologist. When he was diagnosed with ALS he had had acne vulgaris since a few years. Later on two older fellow medicine students have fallen ill in ALS. One died very quickly while the other lived at least 25 years. All three of us had during some period worked at the Institution of pathology, Sahlgren´s Hospital Gothenburg. Strange?!

Below I present my own medical history as a background. As high physical activity often has been mentioned as a background factor relevant for many who develop ALS, it might be of interest to know which physical activities that I have practiced. I have since early age dealt with some kind of sports and have been training regularly, during some periods 5 to 7 days a week. During my teenage period up to about 25 years of age I practiced football (soccer), hockey, handball, athletics, skiing (cross country and downhill), cross-country running, tennis, badminton, sailing, yes almost all sports. Later I played soccer, at just below elite level, up to over 30 years of age. 1965 I had an oxygen uptake of 74 ml per kg body weight and minute, similar to that of a famous Swedish elite cross country skier. I had five radial fractures during childhood and at least three concussions that led to hospital care. Another severe concussion in connection with soccer playing occurred at the age of 25 when the zygomatic nerve was kicked off. This has led to strange sensibility sensations when touched around the left eye and in the skin area where the nerve comes out from the temporal bone, combined with increased lacrimation from left eye. Five arthroscopies due to knee problems caused by soccer playing and possibly also due to athletics activities and dinghy sailing at an elite level. In addition to this I practiced downhill skiing up to the day I became ill. I have had one right-sided Baker´s cyst that ruptured at the age of 60, causing an arterial bleeding from the gastrocnemius muscle, in turn causing a compartment syndrome in the right lower leg with cessation of arterial flow in the foot. There are 5 or 6 similar cases presented in PubMed. I passed this without a fasciotomy. Ten years earlier I had a spinal disc herniation, which I have mentioned above. Another point of possible interest is that I during about 40 years had athlete's foot (tinea pedis). When this, in the area of the left foot arch, some 10 years ago, got very inconvenient, I treated it with terbinafine in the recommended oral dosage. The treatment was continued for 2 years instead of 3 months, the stated maximal duration of treatment. The treatment was completed in 2006 when I had felt the first symptoms of ALS. Otherwise I have been completely healthy, no medicinal treatments, normal blood pressure and a heart rate at rest of about 55 beats per minute today. I had a heart rate at rest of 32 when I was most fit.

How did the disease start for me? During a week with off-piste skiing in March 2010 I discovered a weakness in right lower leg and gradually, something resembling a drop-foot, developed. I visited a neurologist and an orthopaedic in May. The orthopaedic suspected a spinal disc herniation with paresis and the neurologist supported that diagnosis in combination with Charcot-Marie Tooth´s disease (CMT) due to my high-arched feet. Gradually a positive Trendelenburg's sign on the right side

was added. About 10 years earlier I had had a right-sided spinal disc herniation at the L4-L5 level that healed spontaneously. During several years that followed, I had pain now and then from the right side gluteal region and a MR performed showed a lateral foraminal stenosis which was surgically treated during the autumn of 2010. The drop-foot disappeared but I did not become quite well. A new neurology examination was performed later 2010 but nothing new came up. Additionally I had some weakness in the back when standing up together with a squeezing sensation around right lower leg. Due to recurrence of symptoms with pronounced pain, a reoperation was performed in April 2011.

It is not correct that ALS only affects motor neuron as 50 percent of the patients have pain and adverse sensibility sensations. First during the summer of 2011 ALS was diagnosed after lumbar puncture showing slightly increased levels of neurofilament protein in the cerebrospinal fluid. I myself diagnosed the disease during autumn 2010, when I did not become well after the operation, but a suspicion of ALS I had already after the first clear symptoms during the spring. The only abnormal serum test results I had was a positive RA-factor and an increased myoglobin (SR was 1 mm). Results from clinical neurophysiology tests were thus indicating ALS. I had fasciculations, first mainly in the leg muscles but later also in the pectoral muscles. No swallowing problems or problems with arms or respiration.

Now afterwards I can relate my disease onset to other factors that actually puzzled me during some years. During the 00-decade, I often had nightly symptoms of cramping from the right calf. 2005-2006 I had pustules and furuncles on strange bodily locations. They were painful and occurred behind the ears, on the earlobes, the forehead, the scalp down to the neck, over the sternal bone and on the back. Problems like these I had never had before, with the exception of minor problems as a teenager. I also noticed something resembling a butterfly exanthema in the face. In addition to this I had some strange sensations of pain in the feet. Eventually I got problems when I went down on right knee, problems to bend down to tie the shoelaces. A few years before the disease onset I started to have problems when abducting right leg to enter the driver´s seat in my car. I also experienced some weakening of my hands; the champagne was not as easy to open as before. From having been extremely agile I had a stiff back, and in some sense, a whole stiff body and I had general pains and felt an increasing tiredness that seemed to come from within. I became increasingly immobile. The aging seemed to be rapidly approaching. This was not what I had expected as all relatives on my mother´s and my father´s side had died in a relatively high age, between 85 and 99. Previously I was able to bend down with straight legs to touch the floor with my hands, and now I was at least 30 cm from the floor when I tried. I did not understand what was happening. I used to have a very good body control and also a very good ball-sense. I could take a football and make tricks with it almost as good as when I was an active team player. This ability of mine had now disappeared and my thought was, “OK, this is what happens when getting old”.

As I quite early suspected ALS, I read quite a lot about the disease from the web and I knew that, with the exception of Riluzol, there was no other therapy able to extend life expectancy more than two months. Later studies have shown that early therapy can extend life expectancy up to 1 year, but these results have been questioned. The published literature also very clearly showed that the cause to disease is not known, with the exception of when the disease has a familiar or genetic origin, which relates to about 10 percent of the cases.

How did I react when I was faced with the set diagnosis, which I myself had suspected for a longer period? Did I start crying? No I mainly become very angry and I thought that I was prepared to fight and that it should take long time for the disease to break and beat me. The colleague, who set the diagnosis, said that there were much ongoing in the research, why I should have faith and hope for the future. After having taken part of the literature more in detail I was able to confirm that he was right, but unfortunately not very much in the therapy area, which actually has been the case for MS. At the same time, when I had been presented the diagnosis, my conviction was that the ALS research should be well established, progressive and very much "on top" why there should not be very much to do, at least not for me. A try to pick up and familiarize oneself with problems would probably be pointless. To start treatment with Riluzol, giving an increased life expectancy of two months, I thought was meaningless and not an alternative for me. My wife Bibbi was more chocked by the information of the disease than I was as she was less prepared, but I remember that we both pointed out that we together now were prepared to do the best of the situation. Without all support and help from her this far, my present life would not have been possible. It was more difficult for our children and their families and they were deeply chocked. I myself felt more of anger as I had made plans for the coming years, which now were demolished. I was to retire the summer of 2011 and planned to buy a sailing boat. We have a country house just by the sea and a pier of our own perfect for a sailing boat. I have all my life made plans for the future and now I thought that the reality made all my planning useless and this I thought was damn unfair. On the other hand I have for many years considered what Astrid Lindgren so wisely has stated, that "life is a preparation for the death", but to die before the age of 70, was nothing, that I had calculated with.

When I the summer of 2011 was diagnosed with ALS I had to use crutches to walk. I had pronounced problems when trying to get out of my car that was too low. Early 2011 I hardly managed to walk the steps up to the upper floor at our country house and in November 2011 I was permanently wheelchair bound. We stayed in the country house until the end of November until a wheelchair lift had been installed in the staircase of the house where we live permanently. In September 2011 we managed to fly to Malaga Spain where we had rented a flat adjusted to people using a wheelchair. Around Christmas 2011 we installed a wheelchair lift also at our country house.

As I at the Karolinska Institute had been involved in immunology research of an immunostimulating substance with possible effects on infections, we decided in September 2011 to make a full blood immunology screen involving all available testing at the laboratory. One reason for this was that I experienced an increased immune system activity, as I was extremely tired and had pronounced problems with pustules and furuncles, as presented earlier. We found that the number of B-lymphocytes expressing a specific chemokine was very much increased (about 300%) compared to what is normally found in healthy persons, and this was quite unexpected and had never been reported for ALS patients. Analysis of this blood component from other ALS patients supported the finding in my blood. We did then analyse samples from MS patients and these also showed increased levels although not that high. We searched for a blocker of this chemokine and found one but the company that had developed that substance had finished the research related to the substance. After some further activities I found that an angiotensin II blocker on the market, irbesartan, had those effects we searched for why we decided to start treatment with that drug. Within one day my ability to walk improved from 10 to 50 meters but during the coming few weeks this immediate improvement unfortunately returned to the pre-treatment situation. This was probably due to the fact that at ALS multiple chemokines are expressed and activated in the cerebrospinal fluid, why the

outcome on my ability to walk, was not surprising. The inflammation thus utilized other ways. Early 2012 my neurologist and I decided to start treatment with MabThera (rituximab) a monoclonal antibody that destroys all B-lymphocytes but not the antibody producing plasma cells. Rituximab was by around 2005 considered as a breakthrough in the medical treatment of MS both at primary progressive and at progressive relapsing MS.

We started in March 2012 treatment with MabThera in the dosage used at MS. Despite the fact that information was available confirming that antibodies and different immune complexes were involved in the ALS disease development, there was no report published that rituximab treatment had been tried at ALS. Additionally it had for some years been suggested that ALS could be an autoimmune or an autoinflammatory disease. The possible value of anti-inflammatory or immunosuppressing treatments was however something that no one seemed to have realized. This is remarkable when considering a disease with 100 percent mortality. Testing of substances like Enbrel, Remicade, Humira, Tysabri, Lemtrada and Orencia thus could be of interest, but that does not seem to have occurred as there are no published results available. Recently the substance tocilizumab was reported to have a positive effect on ALSFRS-score at ALS. Any objective criteria for a treatment effect were however not presented. Tysabri (natalizumab) and rituximab are also interesting candidates for testing. Natalizumab is a substance that prevents the invasion of inflammatory cells over the BB barrier. Pilot studies should have been easy to perform but no neurologist seems to have taken the initiative. I have got to know many patients with ALS and one of these had been a medical director at an international pharmaceutical company and based on his competency he suggested to the physician responsible for his medical care that Orcina should be tested. This suggestion was however immediately turned down as meaningless. This is really remarkable to me, when considering the disease mortality. What did this physician risk to lose? Every physician has the right to treat any disease based on the free prescription right, only that the patient consents after being fully informed about possible risks associated. What had this patient to lose? Maybe it was the physician who risked losing something?

I have been in contact with many ALS patients who can report similar skin lesions as mine i.e. with pustules and furuncles, but what I have experienced there is no ALS expert who sees these as disease related. Listening to the experiences and the observations of the patients does not seem to be an important part of the physician´s clinical practise any more. The intensive tiredness and pains, that about 50 percent of the patients experience, indicates that inflammation can be a crucial element in some patients. Tiredness is a significant feature of the clinical picture of many autoimmune diseases, especially in connection with relapses. To systemize the clinical symptoms, which not are part of the normal image of the disease, does not seem to have occurred. Symptoms that are not related to effects on motor neurons seem easy to disregard. One can ask if the distance between clinicians and pre-clinicians today is too far. It is also of interest to notice that skin and nerve tissue both develop from the ectoderm. It is therefore not strange that some patients with neurological symptoms also present different skin lesions, if the origin to the disease is autoimmune or autoinflammatory.

In March 2012, when the serum myoglobin had increased to a level three times above the upper normal level, I started therapy with rituximab and within a month my myoglobin value was more than halved. This is a proof that the denervation ceased, at least partly, but still the myoglobin value was about 30 percent above the upper normal level. At the time when rituximab was started I could not write by hand and hardly on the computer keyboard and these problems were almost instantly resolved. The extrapyramidal symptoms and the dystonia and dyskinesia in my hands and fingers

disappeared. The disease progression stopped, at least in the legs, while the condition in the arms and hands improved to an almost normal level as the pain in the arms disappeared and the strength improved. The face and neck fasciculations disappeared almost instantly and within 6 months about 90 percent of the skin symptoms had disappeared. My sensibility sensations in the face also disappeared. The disappearance of fasciculations I interpreted as a proof of some reinnervation or a restoration to functioning motor neurons, i.e. that the inflammation was slowed down due to a significantly reduced antibody production. The ALFRS scoring was almost stable for one and a half year and this was actually the first time a slow up of the ALS disease activity was verified with objective criteria after therapy in an individual patient. This was quite sensational and the case report is now compiled as a manuscript to be submitted to a recognized scientific journal. The data we have collected both for ALS and MS will also be published and here there is information supporting that these two diseases are relatively similar although the level of inflammation and expression of B-lymphocyte chemokines is significantly higher at ALS than at MS. This supports that ALS is an autoimmune disease like MS and that the so called hygiene hypothesis probably could be relevant also for the ALS development. This is also supported by the fact that the incidence of the disease, in analogy with most autoimmune diseases, in recent years has increased. A number of studies have also shown that the serum levels of NKT-cells and cytotoxic CD 8-T lymphocytes are increased at ALS which supports ongoing inflammation and maybe also autoimmunity. Based on this it is very hard to understand why Lemtrada, used at MS, has not been tried at ALS. My extreme tiredness improved during treatment. Earlier, when healthy, I seldom slept for more than 6 hours a night but after fallen ill my need for sleep was dramatically changed. Another very painful symptom was the feeling of ice cold feet although they objectively were not cold. This made me sit with my feet on a heating pad not to be too troubled. It is also very troublesome not to be able to turn around in the bed due to the disabled legs. Not to be able stand up is also very disturbing. Every visit to the toilet, when having to lift oneself with the arms over to the toilet, is a very exhausting exercise. To take a shower in a shower chair is also done in similar way. It normally takes two or three hours in the morning before I am dressed and have had breakfast. Bibbi, my wife, helps me with the dressing as I cannot do this myself. Recently my arms and hands started to sag in the way they did about 1.5 year ago. Today I am unable to lift a packet of milk and can hardly squeeze the toothpaste from the tube. Ceiling hoists are installed in the sleeping rooms and bathrooms.

Based on the positive response seen during treatment with rituximab, which I today believe has significantly extended my life, it is not impossible that an autologous stem cell transplantation (AHSCT) can help in ALS, like the one applied for patients with MS. Preparations for such an intervention are ongoing as a resetting of the adaptive autoimmune system seems to be needed. This treatment intervention has today a relatively low mortality although varying due to the condition treated. The intervention is today also used at non-life-threatening diseases as therapy resistant RA and SLE with good results similar to what is seen at MS where the mortality is only a few percent. At conditioning with subsequent AHSCT the majority of the autoreactive B- and T-cell clones causing ALS should be possible to eliminate. The new lymphoid precursors will then undergo a new positive and negative selection in the bone marrow (for B-lymphocytes) and in the thymus (for T-lymphocytes) and the random recombination will probably not cause the same autoreactive B- and T-cell receptors on the lymphocytes. My ALS, and probably many other´s ALS, have probably an autoimmune origin and thereby should be controlled by the adaptive immune system. That is why AHSCT could be a reasonable way forward at ALS. Autologous mesenchymal stem cell transplantation maybe is an even better intervention. Based on the information earlier presented, it is very strange

that attempts to treat ALS with immunosuppressive substances like MabThera, Tysabri and Lemtrada (alemtuzumab), where the last substance destroys both B- and T-lymphocytes, have not been tried. Some neurologists claim that they are reluctant to testing new therapies in pilot studies by applying the freedom of prescribing right, with the argument "you never know what happens". If you do nothing you know what will happen even if that is definitely not what the physician or the patient want to happen. That the disease at least partly may be autoimmune is a piece of information that obviously has been neglected by recognized scholars within neurology. It is an accepted fact that an infection can serve as a triggering factor in connection with autoimmune diseases. There is also a connection between high physical activity and athlete´s foot (tinea pedis). Can this infection trigger ALS or is it the reverse? Can tinea pedis protect against ALS in predisposed individuals when this low activity infection occupies the immune system? Recently it was shown that hookworm infestations protect against MS. In Denmark and Germany there are now pharmaceutical projects ongoing that are aligned with this fact. The idea that an immunoactive substance not passing the BB barrier cannot affect inflammation within the CNS must be a misconception. The barrier is not closed but partly open for immune cells. Rituximab does not pass the BB barrier but still the substance has been shown to be effective at Chronic Fatigue Syndrome (CFS) and at MS and now also at ALS. Now is the time for re-evaluation. CFS was claimed to be an untreatable psychiatric diagnosis similar to NMDA receptor encephalitis and now these two conditions are cured with anti-inflammatory substances like rituximab (MabThera). Maybe autoimmune diseases that are part of the hygiene hypothesis can be prevented if we from an early age introduced a low activity and harmless infection in one organ, e.g. the intestine, and by that prevented the development of autoimmune diseases in those individuals particularly predisposed to this.

Finally I can point out that damage to the nervous system can occur by trauma, infections, through effects of environmental factors or by combinations of these and thereby trigger an autoimmune reaction. For this to happen, a genetic predisposition for autoimmune diseases and of course also genetic background factors giving a predisposition specifically for ALS, are needed for ALS to develop. Now it looks like rituximab can be a kind of breakthrough in the treatment of ALS, similar to its breakthrough at MS. AHSCT, an even bigger breakthrough at MS especially at early instituted therapy, is also very promising. The probability that AHSCT could work also at ALS is therefore obvious. One study of rituximab for the treatment of ALS was recently approved by the Ethics committee at the Sahlgrenska University Hospital Gothenburg.

This article will probably be rejected by established researchers within the field and I will probably be described as an idiot when scrutinizing ideas about possible connections regarding etiology and possible therapies. Unfortunately I have not coped with the task to present all relevant references I have read, as most of the time nowadays is needed for the basal activities related to survival.

The fact that the neurologists have not been very offensive in the evaluation of different therapeutic pilot projects at ALS, I interpret as a sign that the general idea among physicians today is that new therapeutic alternatives preferably should be developed by the performance of randomized double-blind studies. I myself took part in one study which was prematurely terminated as the substance did not have any therapeutic effects. I had been given active drug but my tiredness was not at all affected. My message to the neurologists therefore is to listen to the patients. I myself was lucky to meet a prestigeless action-oriented, curious, research experienced, retired neurologist, who really listened to the patient. After having talked to colleagues who are patients I can conclude that the

personal properties of my neurologist are not met very often nowadays and to be a colleague in many cases is undesirable for the physician that also is a patient.

To those colleagues who express their view about euthanasia claiming that this is nothing we should introduce in Sweden, I only want to say that they have no right to speak before they have been affected by ALS. We have too many “smart-ass” among the physicians that by virtue of their title present opinions about things where their expertise is no better than that from ordinary people. The frequency of suicide is about six times higher among patients with ALS. Why should I, as a physician, have the possibility for own euthanasia? I look forward to a life with total paresis of both arms and legs and maybe with the possibility to talk and swallow by myself. Or, do I really do that?