



EDITORIAL

Daniela Iser

“One can manage an ataxic lifestyle with comparative ease, but when was the last time that anybody asked you how you felt about it?” – This sentence appears later in a personal discussion about accepting an ill condition and it hints at the two-faced character of the life into which ataxic people are pushed as their disease progresses. On the one side, there is the physical manifestation of scientific evidence, and on the other, we recognise emotions and both personal and societal attitudes. It is an enormous challenge to find what, in yet another essay, is implied in “to have peace with” the type of reality projected upon what – why should it not be called *ataxic health*?

Some most important contributions dealing with “it”, that is with medical implications of ataxia, are listed in this issue together with reflections on that other aspect, “lifestyle” or the “feeling about it”. The area around SCA1 will be investigated and reported on, and two variations of treatment of Friedreich’s Ataxia explained in detail. On the other end of the rainbow, a treasure is demystified and brought into light: sexuality in connection with ataxia may touch upon a differentiated emotional theme of utmost private relevance.

Moreover, several reports on the proceedings and constellations in Europe, on research into ataxias as well as on medication on its way through bureaucratic worlds, can be found inside. A social event must be mentioned: the Irish have arrived. FASI is presented, the Friedreich’s Ataxia Society Ireland. And, *euro-ATAXIA* continues what seems to become a little tradition: we travel over the ocean to participate in the AGM of the National Ataxia Foundation.

But there is another aspect to ataxic life. It emerges after the plain facts were displayed and after people were confronted with their deepest emotional turbulences. It is *reflection* – and it can have the power to fuse the first two dimensions and to put them into a concordant relation. A few months ago, the news of an ill-fated artificial fertilisation with little children now at risk of developing ADCA in their later life, went the ghostly round in the media. The trilogy presented inside deals with the story itself, with the feelings of one young couple who suddenly dived deeply in an emotional vortex, and with ethical argumentations on the subject. A debate on bioethical issues in a global context will be resumed at the end of this Newsletter. It might provide an opportunity to consider ataxia and its surrounding areas as component parts within a larger frame.

CONTENTS

Editorial	1
Autosomal Dominant Spinocerebellar Ataxia Type 1 (SCA1)..	2
Friedreich’s Ataxia, 5 Years Later: Better Understanding, New Hope	4
Therapies for Friedreich’s Ataxia .	8
Orphan Medicinal Product Designation in the European Union.....	11
The Status of Idebenone.....	12
How to Fight the Ataxias	13
The Friedreich’s Ataxia Society Ireland (FASI).....	13
AGM 2002 of the National Ataxia Foundation (NAF)	14
Rolling the Dice on the Slippery Slope.....	15
Sperm Donor has ADCA – A Parents’ Story	15
Ethical Reflections on the Dutch ADCA and IVF Case	16
On Acceptance	18
On Acceptance	19
Sexuality	20
An International Forum on Bioethics	23
Members & Contacts	16

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AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIA TYPE 1 (SCA1)

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Hereditary cerebellar ataxias form a group of neurodegenerative disorders characterised by motor difficulties including loss of balance and coordination (1). In these disorders, cerebellar ataxia mainly results from selective degeneration of the Purkinje cells in the cerebellum, a region of the brain dedicated to coordinate the accuracy and precision of movements. Traditionally, a high heterogeneity and overlapping clinical symptoms made the classification of inherited ataxias a difficult venture. However, the identification of the genes implicated in human hereditary ataxia has facilitated not only to classify this group of diseases, but also to understand the mechanisms by which the corresponding genetic abnormalities lead to cerebellar degeneration. To date, more than 20 genes implicated in ataxia with cerebellar degeneration have been identified and the corresponding genetic defects elucidated. By understanding the mechanisms implicated in neurodegeneration, we should be able to develop and design rational therapies to treat these diseases. During the last ten years, I have been working to provide insights into the processes of neurodegeneration in spinocerebellar ataxias with the ultimate goal of finding treatment.

In 1993, Drs Orr and Zoghbi identified the gene responsible for Spinocerebellar ataxia type 1 (SCA1), the first gene found to be associated with an spinocerebellar ataxia (2). Patients with SCA1 have ataxia and variable signs of dysarthria, dysmetria, nistagmus, muscle wasting, and neuropathy (3). The disease is characterised by progressive loss of Purkinje cells and deep cerebellar nuclei in the cerebellum together with degeneration of neurons in the inferior olivary nuclei and pontine neurons in the brain stem. SCA1 is caused by the inheritance of an expanded CAG repeat within the SCA1 gene. Thus, SCA1 patients inherit a copy of the SCA1 gene with a number of CAG repeats ranging between 6 and 39, and a second copy of the SCA1 gene containing more than 40 CAG repeats, which is the pathological threshold (4). We and others demonstrated that in SCA1, the severity of the disease and age of onset are directly associated and inversely correlated with the length of the expanded CAG repeat (2, 4, 5). Therefore, an SCA1 patient with 80 CAG repeats in the SCA1 gene will present a more severe form of the disease than an SCA1 patient with 45 CAG repeats. The SCA1 gene codes for ataxin-1, a protein of unknown function, and since the CAG trinucleotide codes for the amino acid glutamine, SCA1 patients have a harmless form of ataxin-1 containing between 6 and 39 glutamines, and a pathological form of ataxin-1 with more than 40 glutamines. Consequently, spinocerebellar ataxia type 1 (SCA1) is included within the group of neurodegenerative disorders caused by expansions of glutamines in the corresponding gene

products. To date, in addition to SCA1, the group of polyglutamine disorders consists of five more types of spinocerebellar ataxias, including SCA2, SCA3 or Machado-Joseph disease, SCA6, SCA7 and SCA17, spinal bulbar muscular atrophy (SBMA) or Kennedy's disease, Huntington's disease (HD), and Dentatorubropallidoluysian atrophy (DRPLA) (6).

To understand the molecular mechanisms of neurodegeneration in SCA1 pathogenesis, we generated transgenic mice expressing a mutant form of ataxin-1 with 82 glutamines, that in humans results in a juvenile form of SCA1 (7). The expression of the protein was driven to cerebellar Purkinje cells, the primary neuropathological target in SCA1. A detailed phenotypic characterization of SCA1 mice revealed that at 5 weeks of age, mutant mice display an impaired performance on the rotating rod, a device designed to evaluate cerebellar function in rodents, without deficits in balance and motor coordination and, importantly, without any apparent cellular dysfunction and morphological alterations of the cerebellum (8). At 6 weeks of age, ataxin-1 aggregates in the nuclei of Purkinje cells of transgenic mice, which show minor neuronal abnormalities such as a mild loss of the cellular dendrites. After 12 weeks, transgenic mice develop ataxia, which worsens over time and is accompanied by some neuronal cell loss. At later stages, cerebella of transgenic mice reveal severe Purkinje cell loss and cerebellar atrophy. These findings indicate that the disease process in SCA1 transgenic mice is very similar to that observed in humans, and demonstrate that generation of an animal model for SCA1 is very valuable for investigating the disease at the molecular level. The finding that polyglutamine expansions cause alterations in the expression of specific genes at the first stages of the disease is very important because they could be targeted for therapeutically treatment (9). As the disease progresses, misfolded mutant ataxin-1, the structure of which is modified by polyglutamine expansions, is not eliminated properly. It aggregates in the nucleus and recruits, through the polyglutamine tract, a variety of proteins, including transcription factors, chaperones (proteins involved in protein folding), and components of the degradatory proteasomal machinery. Eventually, essential cellular functions are disrupted, becoming selectively toxic to specific neurons.

An important question was generated from these studies. Since ataxin-1 with polyglutamine expansions is detected in most of the cells and tissues examined, how is possible that neurodegeneration occurs in SCA1 in a few subpopulations of neurons? We addressed this question by searching for ataxin-1 interacting proteins. We showed that ataxin-1 associates with a nuclear protein, called LANP for leucine-rich acidic nuclear

protein, the expression of which is confined to the cellular targets of pathology in SCA1 (10) (Matilla, unpublished data). The ataxin-1/LANP interaction is regulated by the polyglutamine tract in ataxin-1, and the association is stronger when ataxin-1 contains a high number of glutamines. Furthermore, LANP is mislocalised by ataxin-1 to subnuclear compartments. As a result of these observations, we hypothesized that the expanded glutamine tract in ataxin-1 annuls LANP function in Purkinje cells. Since LANP seems to mediate regulation of transcription of specific genes in Purkinje cells, abolishment of LANP function may mediate selective cell loss during neurodegeneration in SCA1.

To investigate ataxin-1 function and disease pathogenesis, we also generated SCA1 knock-out mice (11). Using genetic engineering techniques in the mouse, we removed part of the SCA1 gene in order to abolish expression of ataxin-1 by the SCA1 gene. These studies revealed that mice lacking ataxin-1 are viable, fertile, and do not show any evidence of ataxia or neurodegeneration. However, SCA1 knock-out mice demonstrate some neurological deficits, including decreased exploratory activity, and impaired spatial and motor learning. In addition, SCA1 knock-out mice display electrophysiological deficits in the hippocampus, a brain area implicated in learning and memory. While the molecular mechanisms by which lack of ataxin-1 leads to the neurobehavioral and physiological deficits observed in SCA1 knock-out mice remain unknown, these observations point to a role for ataxin-1 in essential tasks for motor learning, and also suggest that ataxin-1 may have a role in the balanced regulation of calcium. An important observation made during the course of these studies is that, similar to SCA1 transgenic mice, SCA1 knock-out mice display motor learning and other neurological deficits at 5 weeks of age, without any apparent morphological alterations in the cerebellum. This data indicates that the early neurological impairment observed in SCA1 may be caused by loss of the cellular function of ataxin-1 and raises the hypothesis that normal protein dysfunction may also contribute to SCA1 pathology. Based on these observations, the disease in SCA1 is most likely caused by toxic effects from the polyglutamine tract, and by loss of ataxin-1 function.

Several conclusions arise from these studies. First, ataxia and neurodegeneration in SCA1 is caused by the presence of polyglutamine expansions within ataxin-1. Second, neurological impairment is caused by neuronal dysfunction and not directly by the result of cell loss. Third, loss of function of the normal protein and transcriptional deregulation may underlie the early stages of the disease. Fourth, cell loss in SCA1 may be triggered by cell specific protein-protein interactions. Finally, essential cellular functions are compromised during disease progression.

Scientific research carried out in Huntington's disease (HD), a disorder clinically characterised by loss of mo-

tor coordination that is caused by polyglutamine expansions in a protein called huntingtin, has recently revealed that histone acetylation deregulation, which is a cellular process involved in the regulation of gene transcription, underlies neurodegeneration in HD (12). Importantly, administration of inhibitors of histone deacetylation, such as butyrate or suberoylanilide hydroxamic acid (SAHA), stops neuronal degeneration induced by polyglutamine repeat expansions *in vivo*. These findings suggest a role of histone acetylation, and, therefore, transcriptional deregulation in Huntington's disease. It seems possible that pharmacologic manipulation of the levels of acetylation may slow or prevent progressive neurodegeneration. In SCA1, LANP forms part of a multiprotein complex that regulates the levels of histone acetylation (13). These observations, along with the fact that LANP is mislocalised to subnuclear compartments by mutant ataxin-1 in SCA1 (10), support the hypothesis that histone acetylation impairment might also be implicated in SCA1 pathogenesis. If this is the case, substances that regulate the levels of histone acetylation could be applied in SCA1 at early stages of the disease.

Despite the enormous efforts spent to identify the genes that are responsible for inherited ataxias, to characterise the corresponding gene products, and to decipher the molecular basis of neurodegeneration in these diseases, the prognosis of patients has improved very little during the last decade. We know now that neurodegeneration in spinocerebellar ataxias and other polyglutamine disorders is triggered by toxic events caused by the expanded polyglutamine tract contained in mutant proteins that compromise essential cellular functions. We also know that the deregulation of transcription activity of specific genes plays an important role in the early steps of pathogenesis. Both the investigation of the complexity involved in these processes and the elucidation of the molecular mechanisms and cellular pathways underlying selective neurodegeneration, should provide an opportunity to identify and understand all the cellular components that act early in the disease with the ultimate goal of designing rational approaches to target-based drug discovery.

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FRIEDREICH'S ATAXIA, 5 YEARS LATER: BETTER UNDERSTANDING, NEW HOPE

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It is probably the right time (and the right place) to update information for both Friedreich's ataxia patients and their clinicians on the recent progresses made in research dealing with this disease. For patients, mainly because a better understanding of the mechanisms inherent in the disease should result in new therapeutical hopes; for clinicians, because a very first therapy is now available and should be proposed as soon as possible to each patient.

The idea of this article is first to describe – with hopefully simple words and schemes – how we understand (or think to understand) Friedreich's ataxia. Next, it aims at summarising the actual data obtained by using idebenone in the various trials carried out in different countries. Then, the paper will end with the report on new tools now available for making further (let's hope also faster) progresses in our fight against the disease.

I. First, a little bit of genetics...

The discovery in 1996 of the gene that is responsible for Friedreich's ataxia, the so-called *frataxin gene*, was a real breakthrough in the research of this disease. But first, you have to remember what a gene is. There are thousands of genes (about 40,000) in the nucleus of every single cell that, all together, constitute the human body. Each gene is present in two copies per cell, one inherited from the mother and the other one from the father. At a closer examination, a gene consists of thousands of four basic components – the famous bases, A, T, G, C – the precise sequence of which contains a given message. These many messages are necessary for the cell to manufacture its various components.

The abnormality of the gene observed in most patients with this disease consists in of a long repetition of a three-letter sequence (GAA repeats), which hampers the normal reading of the message of this gene. This overlong sequence of repeats is present on one copy of the gene in about 1 in 90 people, but two abnormal copies are necessary to develop the disease. Such a condition is called a *recessive* disease (*dominant* diseases are those which happen even when only one copy of a gene is abnormal). In other words, if two persons, having each one copy of this long sequence in the frataxin gene, have a child, there is a 25% probability that the child will receive two copies of this abnormal gene and develop the disease. Notice that the probability is unchanged for each new baby, whatever the status of the other children may be. However, the possibility to examine the genes of the foetus now allows offering prenatal diagnosis of this condition to the family.

Enough of genetics, only one last observation: the message contained in the frataxin gene is necessary to manufacture frataxin, one of the cell proteins. There are several kinds of proteins in a cell, but some of them, including frataxin, could be compared to workers in a city: they build, transform, and fix the cell during its life. In the cells from Friedreich's ataxia patients there is not enough frataxin (because of the difficulty to read the message of the gene) and, as a result, the function of frataxin is poorly ensured, and some cell types, neurons and heart cells in particular, do not like that at all. But what is the function of the frataxin?

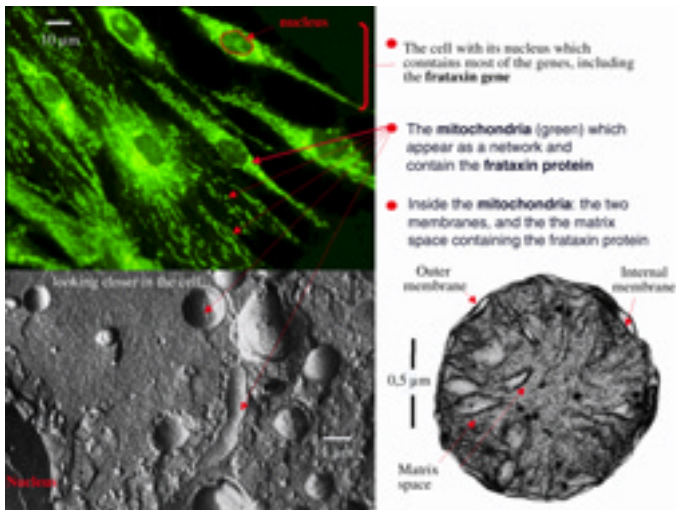


Figure 1. The mitochondria: a network responsible for energy production, handling of oxygen and manufacture of many cellular compounds, present in all the cells of the organism.

II. How does Frataxin work, according to our thoughts?

As soon as the frataxin gene was identified as responsible for the disease, a number of laboratories have tried to understand the function of the frataxin. The very first question was to know where frataxin was located in the cell. All studies carried out on this point conclude that this protein was essentially found in the *mitochondria* and that mitochondria do not function correctly when frataxin is low or absent in a cell. Therefore, Friedreich's ataxia is one of the numerous *mitochondrial diseases* known in humans. Again, we need to stop a while here to recall what mitochondria are (Figure 1) Basically, there are mitochondria in all human cells. They can be compared to power plants – including the network of high voltage wires – of a city. They are the place where food (sugar, lipids, etc), having been broken into small pieces before, is burned, so as to produce the energy that is necessary to build up and to maintain the cells. That is the major task of the mitochondria, and it is a quite dangerous task. Indeed, if any comparison should be made with power plants, it has to be with nuclear ones! Why so dangerous? Because mitochondria need oxygen (like a real fire) to burn food derivatives and, if the process becomes uncontrolled, parts of the energy will be diverted to produce very reactive components, the so-called *radical oxygen species* that can destroy a number of both mitochondrial and cellular components. Mitochondria are not only there for energy production. They are also a place where numerous components that are useful for the cells are manufactured, transformed and exported to other cell compartments. Therefore, when mitochondrial function is affected, there is a potential problem in either the energy production, or/and the overproduction of radical oxygen species, or/and the manufacture of different components necessary for the cell. With this in mind, you probably know enough about mitochondria, so let's do the next step.

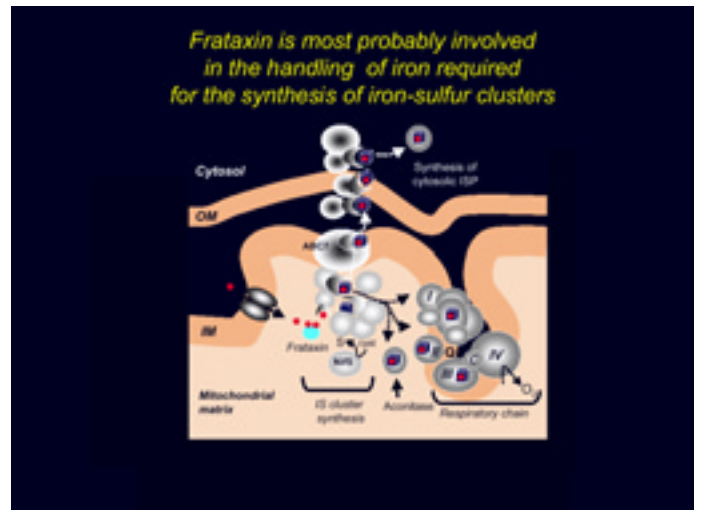


Figure 2. The most likely function of frataxin within the mitochondria.

After the frataxin gene had been discovered, scientists looked at cells that were artificially depleted of frataxin (as a matter of fact, the cells that were used were baker's yeast). They observed a quite important accumulation of iron in the mitochondria, at the expense of iron found elsewhere in the cell. Therefore, the most obvious hypothesis was put forward: the frataxin protein is, in one way or another, involved in the regulation of iron transportation in (or out of) the mitochondria.

At the same time, we discovered that a particular subtype of proteins was defective in heart cells of the patients. This type of defect had never before been observed in any other disease. It is, therefore, quite specific of Friedreich's ataxia. These iron-sulphur proteins are very important to both the mitochondria, since several of them are involved in the mitochondrial energy production system, and to the rest of the cell, because one of these proteins controls the intake of iron by the cell itself (Figure 2). As indicated by their name, iron-sulphur proteins also contain iron. So, iron appears to play a key role in the disease.

Iron gets rusty when oxygen is present (and remember that oxygen is present and used up in the mitochondria). In consequence, it can be quite dangerous if it is accumulated somewhere in the cell, for example in the mitochondria. Indeed, the rust reaction is accompanied by the formation of radical oxygen species, mentioned above as dangerous by-products of the mitochondrial functioning. This is why more iron could mean more radical oxygen species and a dangerous problem for the cell.

We go back to 1997, one year after the discovery of the gene. There were three hypothesis. The first supposed that frataxin might be required for the synthesis of the iron-sulphur proteins. This accounted best for the specific defect of these proteins observed in patients' heart cells. The second implied that frataxin could be involved in iron transport into (or out of) the mitochondria, which fitted well with the observation of iron accumulation in the mitochondria when no frataxin was

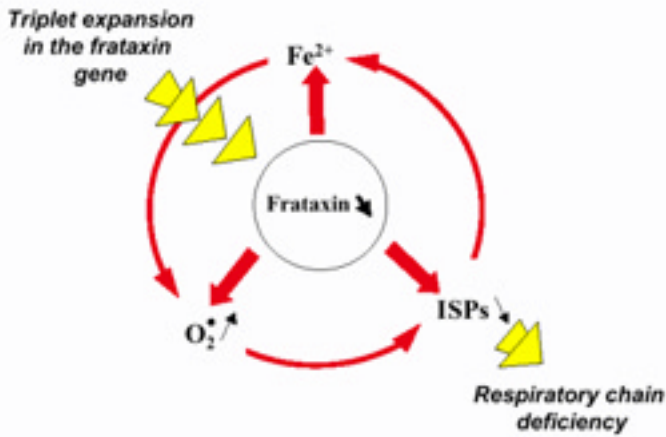


Figure 3. The vicious circle at work in Friedreich's ataxia

present. The third said that frataxin could be a factor controlling radical oxygen species (that are able to destroy the very sensitive iron-sulphur proteins) produced by the mitochondria. The released iron would be accumulated in the mitochondria. Indeed, these three hypothesis could be associated to form a kind of vicious circle as depicted in the scheme (Figure. 3).

It is not necessary to go into further detail, but at the moment, it seems that the first hypothesis is the right one. Frataxin may primarily be involved in iron-sulphur protein synthesis, and all the other abnormalities would be the consequence of that. As a result, the disease is a multi-step disease (Figure 4). It starts with a low activity of the iron-sulphur protein, and results in slowing down the energy production by the mitochondria. The progression of the disease will bring about the activation of the reaction circle depicted above, with more iron being slowly displaced from the cell to its mitochondria. These may then desperately attempt to manufacture the missing iron-sulphur proteins by pumping in more iron. The consequences of activating this vicious circle of reactions can be numerous and variable, because many factors (food, environment) may affect these reactions. In addition, we recently noticed that impaired iron-sulphur protein functioning also affects the ability of the cells to protect themselves against radical oxygen species. This tends to further enhance the consequences of the overproduction of radical oxygen species by the mitochondria.

III. Urgent: Protection against radical oxygen species by using idebenone

The best therapy in the disease would obviously be to produce more frataxin in the cells of the patients. To achieve such a goal, there are different possibilities. First, the ideal solution would be to replace one of the two copies of the frataxin gene and reintroduce a good copy of it, an approach better known as gene therapy. Numerous labs work on this approach for many diseases. But there are still numerous problems to be solved. One of the most important difficulties is to find a way to send the gene into all the cells; a second one

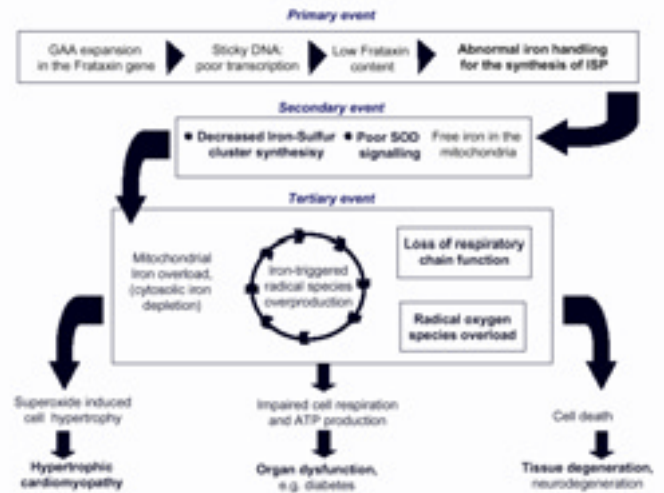


Figure 4. More details on the mechanism of Friedreich's ataxia: What possibly happens in the cells of the heart and in the neurons. The disease has several steps. Some of them might be reversed by using an antioxidant that protects from radical oxygen species.

is that of ensuring the stability of the gene after sending it. Unfortunately, a long list of problems could be listed. We carefully watch over every progress made with these problems, but we honestly have to admit that progress is quite slow. Moreover, it is difficult to predict when, and also if, this kind of approach will be successful in a type of disease where many remote cells have to be treated before an effect can be seen. I told you at the beginning that in most cases of Friedreich's ataxia a long repetition of a GAA sequence in the gene causes difficulties to read the gene properly, as if it was folded up and made sticky due to the improper interactions of the abnormally long sequences. Therefore, scientists in different laboratories try to see if there could be a way for the cells to better read this abnormal gene. If, by chance, a solution could be found to enable partial unfolding of the abnormal gene, even if not totally efficient, it might solve a part of the problem. However, even if such a solution does exist in a test tube, nobody knows how to make it work in the cells of the organism. Hopefully, there are other means to fight the disease.

Reports from several research groups working on Friedreich's ataxia have shown that *radical oxygen species* undoubtedly play a central role in this disease. Four years ago, we suggested to use a compound, idebenone, which is able to counteract the effect of radical oxygen species. Compounds that neutralised radical oxygen species are called *antioxidants*. Several antioxidants have been identified and some of them are available on the market as drugs or even vitamins. They have slightly different properties that change their efficiency: they neutralise different oxygen species; they target different organs, and go into different compartments in the cells. Idebenone was selected on the basis of its particular properties, which seem to be the best in the context of Friedreich's ataxia. Different trials have been performed with this compound and all but one (a very short assay of 6 weeks) concluded that idebenone (5 m/kg/d) tends to reduce the thickness of

<u>1998</u>	3 patients / 6 m treat. / decreased cardiac hypertrophy / no improvement of ataxia (Hôpital Necker, Paris, France; <i>The Lancet</i>)
<u>2001</u>	8 patients / 1 y treat. / scores of ARS scale improved in all patients (Hospital Sant Joan de Déu, Barcelona, Spain; Arthur et al. <i>Euromit 5</i>)
<u>2001</u>	9 patients (5 treated) / 6 weeks treat. / neither improvement of cardiac hypertrophy nor of neurological condition (St Josef Hospital, Bochum, Germany; Schöls et al. <i>Neurosc. Lett</i>)
<u>2001</u>	11 patients / 1 y treat. / decreased heart hypertrophy in all patients / no improvement of ataxia (Hôpital Sainte-Justine, Montréal, Canada; Emond et al, <i>WebSite</i>)
<u>2001</u>	29 patients (15 treated) / 6 m treat. / reduced heart hypertrophy / no improvement of the ARS scale (Besta National Neurological Institute, Milano, Italy; for ataxia (Mariotti et al. <i>J Neurol.</i>)
<u>2002</u>	38 patients / 6 m treat. / decreased cardiac hypertrophy (50% of the patients) / no improvement of ataxia (Hôpital Necker, Paris, France; <i>Heart; Free Rad. Res.</i>)
<u>2002</u>	50 patients / 1 y treat. / decreased cardiac hypertrophy / no improvement of ataxia (The french official trial; Hôpital de la Salpêtrière et Hôpital Necker, Paris, France)
<u>2002</u>	122 patients / 0.5 to 3 y treat. / decreased heart hypertrophy / no improvement of ataxia; quite variable improvement of the voice and/or delicate movement (Hôpital Necker, Paris)

Table 1. Trials of idebenone in FRDA (2002: 6 trials, open or placebo-controlled)

the heart walls and the cardiac hypertrophy. This is summarised in the table 1. In several patients, increasing the dosage from 5 to 10 or even 15 mg/kg/d was found to be beneficial. Unfortunately, idebenone is not a very stable compound in the organism and we are even not sure that the amount of the drug is sufficient to obtain a maximum effect. As far as we can conclude, the drug does not have a significant effect on the ataxia. It may still have some beneficial effect on the progression of the ataxia, but as this is different in each affected individual, it is quite difficult to reach a firm conclusion. The “quantification” of the ataxia (the ataxia scale) is far from being a simple task, which adds to the difficulty of drawing conclusions. Therefore, any effect of the drug on the neurological aspect is not so simple to determine. However, the fact that the drug had some spectacular effects on the voice and on the delicate movements for several patients, indicates that the drug probably also reaches the nervous system. Absence of obvious effects of idebenone on the ataxia might also result from the facts that its concentration may not be sufficient, and that the potential replacement of destroyed neuronal cells is quite difficult, as it requires a very long time. Also, the efficiency of idebenone to counteract radical oxygen species in neurons may be modest.

Conclusion for idebenone (provisional conclusion.): it is now quite clear that idebenone represents the very first drug that can interact with the course of the disease, especially by counteracting a potentially life-threatening cardiomyopathy. It is therefore highly recommendable to make this drug available for all patients even if it has no effect on the ataxia, as it is a fact that this drug has no significant side effect in humans.

IV. New tools, new hopes

If we want to have a chance to win the race against the disease, it is mandatory to have a convenient system to identify drugs and a representative model to test them. During these two last years, both have been made available, even though they are not absolutely perfect yet. First, a human cell system was devised that may allow identification of active drugs against

artificially induced oxidative stress. Indeed, culture conditions were found with skin fibroblasts from patients which did not resist oxidative stress, whereas control cells did. This should allow identification of new antioxidant compounds that have to be further tested in a model system. This model system has been devised by using mice in which the frataxin gene can be inactivated after birth, either specifically in the heart alone or both in the heart and the nervous system. Results of this inactivation are strong reduction of levels of frataxin in these tissues, the iron-sulphur proteins progressively losing their activity, the heart becoming hypertrophic and the mice displaying serious neurological deterioration, iron accumulation being observed at the end stage. This mouse model, therefore, reproduces the main features of the disease and can now be used to test drugs *in vivo*. With these tools being made available, we can now hope to discover and test new compounds more or less rapidly.

To make things go faster, one could also think (and we do!) to slightly modify idebenone and try to increase its stability in the human organism. We hope to increase its efficiency at a lower dosage. However, modifying the molecule (as well as only changing its presentation and dosage) will require tedious and expensive studies. Only later can we have the new material and make it available to patients. Even before we start, we have to extract from scientific literature all data describing compounds that are neuroprotective antioxidants. Such compounds do exist, and if they are already available as drugs, they should urgently be tried in patients, and both efficiency and potential side effects should be observed. If these chemicals have only been studied in cell models, they should now be tested in FRDA mouse models. It is crucial to focus on already identified and available antioxidants if we consider the delay that may occur occurring after the identification of a new molecule in a laboratory until it is availability on the market.

Provisional conclusion

I hope that this text was an understandable presentation of what we believe is the mechanism of a decreased frataxin level resulting in decreased iron-

sulphur protein content, oxidative stress and final dysfunction the cell, leading to Friedreich's ataxia. I hope to have convinced the readers that idebenone absolutely has to be used, even if only to protect the heart. Treatment must not be discontinued until a more efficient drug is available. Time is not on our side. However, considering the major progresses in the understanding of this disease, new tools now available to rapidly identify and test drugs, and the number of groups focusing their activity on this disease as well as and the quite good relation among each other, I am reasonably confident that new drugs will soon be tested and made available to fight the disease.

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THERAPIES FOR FRIEDREICH'S ATAXIA

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The background to the genetics and disease mechanisms involved with Friedreich's Ataxia (FRDA), have been covered in the article by Dr Rustin and we do not need to revisit these here. We would like to briefly outline the scope for potential treatments in patients with FRDA and describe the results to date of combined vitamin E / coenzyme Q10 therapy trials.

Possible Therapies For Patients with Friedreich's Ataxia

Therapeutic intervention in patients with Friedreich's ataxia can be used at a number of different levels. First of all there are the therapies associated with treating the symptoms of the disease. FRDA is associated with a diverse group of symptoms involving the heart, diabetes, skeletal problems, swallowing, speech, mobility and coordination. It is important that these symptoms are monitored and where appropriate treated with drug intervention, surgery, physiotherapy etc. It is particularly important for patients to have periodic cardiological assessments.

Secondly as we begin to understand what goes wrong in FRDA at the molecular level, we can begin to treat the disease more effectively. Since the discovery of the genetic defect in FRDA we have come a long way in our understanding of the effect of this genetic abnormality. We know that the normal FRDA gene is responsible for producing a protein known as 'frataxin'

which is found in all cells of the body, and that the genetic abnormality in patients with FRDA results in decreased levels of this protein. Consequently, we need to understand what this protein normally does (its primary function) and what happens when this function is lost and whether this leads to additional problems (secondary effects). If you can replace the primary function of frataxin then this will target the root cause of the disease. However, secondary effects associated with the loss of frataxin may also contribute to the disease progression and may be more amenable to therapy.

What do we currently think is going wrong in FRDA?

Since frataxin was shown to be located in the mitochondrion, the so called 'battery of the cell', a lot of work has focussed on what happens to the mitochondrion in patients with FRDA. The mitochondrion produces most of the energy required by the cell to function normally and those cells that need the most energy -i.e. muscle, heart and brain cells- have a lot of mitochondria. In the cells from FRDA patients it is clear that there is a problem with energy production. In addition there is evidence that damage by free radicals is increased and iron accumulates in the mitochondria. All these changes are believed to be secondary effects of the loss of the frataxin protein. It is currently believed that frataxin is either involved with

making iron available for specific reactions in the mitochondrion, i.e making proteins that require iron for their normal function (so called iron sulphur proteins), or as an antioxidant protecting the mitochondrion from the damage induced by 'free radicals' generated as a by-product of its normal function.

Therapies: Evaluation of Benefits

FRDA is a slowly progressive disease which can affect a number of different parts of the body including nerves, spinal cord, heart, muscles, eyes and speech. To understand if a new therapy has any influence upon any of these symptoms it is important to know how these symptoms progress over time, how they vary between patients and what factors may influence this progression. This type of information is starting to be collected and studied and our understanding of these processes is now improving.

In addition to the assessment of the clinical symptoms, it is possible to make a number of medical and scientific measurements (bio-markers) in patients to give a better understanding of how the therapies may be working. To date bio-markers of FRDA have been used to assess the degree of thickening of the heart wall (cardiac hypertrophy – echocardiography), the amount of energy generated by the heart or skeletal muscle (31 phosphorous magnetic resonance spectroscopy – 31 P MRS), or markers of free radical damage.

In addition to using these measurements, we believe that it is also important to identify how FRDA affects the every day lives of individual patients and to obtain the patients' own perception of their disability. To do this we require a questionnaire which has been tailor made for patients with FRDA and we are in the process of designing and testing one. We propose to use the finished questionnaire on a regular basis to identify how the disease progresses in a wide range of patients and then use it to help determine how therapy influences disease progression.

Therapies: How do we replace the Primary Function of Frataxin?

FRDA is caused by a decrease in frataxin protein. Consequently the ideal therapy would involve restoring the frataxin levels in all the cells. The genetic mutation in patients with FRDA results in the molecules sticking together and blocking the production of the frataxin protein. This raises the possibility of finding drugs, which may interfere with these 'sticky' structures allowing for improved production of the frataxin protein in affected patients.

An alternative strategy uses gene therapy to add a new functional copy of the frataxin gene. Because most of the cells in the body need frataxin it will require the new copy to reach a wide range of cells. Before this can become a possibility for FRDA a number of general problems relating to gene therapy (also applicable to other diseases) need to be overcome.

These strategies are still a long way from being a re-

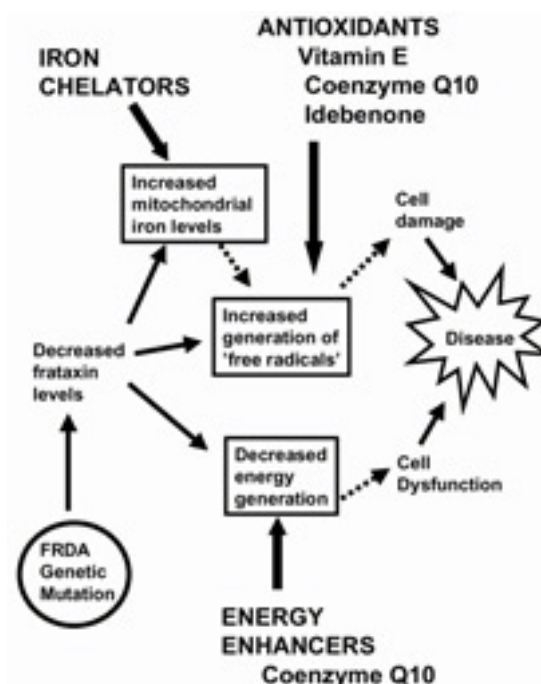


Figure 1. Potential disease mechanisms leading to Friedreich's ataxia and where therapeutic intervention is targeted.

ality but could offer significant benefits in the longer term.

Therapies: Targeting Secondary Effects

Which Therapies and Why?

There is a large body of evidence pointing to an increase in free radical damage (oxidative damage), a decrease in energy generation and an increase in mitochondrial iron accumulation in patients with FRDA. While these appear to be secondary consequences to the loss of frataxin they will undoubtedly contribute to tissue damage and disease progression. It may be possible to combat these effects using antioxidant, mitochondrial energy enhancement and iron chelation therapies which may improve the function of many cells stabilising the clinical progression of the disease and possibly resulting in minor clinical improvements (see Figure 1).

Antioxidant Therapy

FRDA patients have been treated with a variety of antioxidants including, Idebenone, coenzyme Q10 and vitamin E. Anecdotal reports of the use of N acetyl cysteine also suggest benefits

[<http://internaf.org/ataxia/nacupd.html>].

Idebenone is a modified version of coenzyme Q10, is well tolerated by humans, crosses the blood brain barrier, has been reported to be a relatively good antioxidant, and has been used in a variety of diseases with some benefits. The effect of idebenone upon cardiac hypertrophy in FRDA patients was assessed using echocardiography, and has been described in the article by Dr Rustin.

Combined Vitamin E and Coenzyme Q10 Therapy

Vitamin E is a naturally occurring antioxidant found

throughout the body in all cellular membranes but predominantly in mitochondrial membranes where it protects them from damage by free radicals. It is obtained in the diet and vegetable oils and nuts provide a particularly rich source. The potential benefits of vitamin E to patients with FRDA is strengthened by the observation that a disease with very similar clinical symptoms to FRDA is caused by a deficiency of vitamin E and responds to vitamin E therapy. Vitamin E has been taken in quite large doses by adults, (up to 1500-2100IU per day) with few side effects [reference 1] and has been shown to increase vitamin E levels in a variety of tissues including brain, muscle and heart. It has been used to treat cardiovascular disease, Parkinson's disease and cancers with varying degrees of success.

Coenzyme Q10 (CoQ10) is naturally found in cells where it acts both as an antioxidant and also plays a part in the energy generating system in the mitochondrion. Consequently it can act by not only protecting the cell against free radical damage but also by increasing the ability of the mitochondria to synthesise energy for the cell. Up to 5mg/day may be consumed in an average diet (very rich in soybean oil, meat and fish), but much larger doses for prolonged periods of time do not give rise to significant side effects [reference 2]. CoQ10 is readily taken up into the blood, the brain and liver and may interact with vitamin E in a positive way suggesting it may be more beneficial when the two are combined in a therapy. Consequently CoQ10 may not only protect the cells from free radical damage but also improve energy supply in FRDA patients.

Using a technique known as ³¹phosphorous magnetic resonance spectroscopy (³¹P MRS), in collaboration with the MRS Unit at John Radcliffe Hospital in Oxford, we have clearly shown that the energy produced by both the heart and skeletal muscle is decreased in patients with FRDA. This is in agreement with the suggestion that the loss of frataxin protein in the energy producing part of the cell (the mitochondrion) affects the ability of the cell to produce energy and therefore compromises the normal function of these organs contributing to the clinical symptoms.

We have been using a combined antioxidant and energy enhancing therapy involving a high dose of combined vitamin E (adult dose 2100IU/day) / CoQ10 (adult dose 400mg/day) therapy for over 3 years to determine whether it had any impact upon the clinical symptoms, heart problems and energy produced by heart and skeletal muscle in 10 FRDA patients.

After just 6 months of therapy the energy produced by the heart and skeletal muscle was significantly improved [reference 3] and these improvements were maintained throughout the 3 years of therapy. Provisional 3 year follow up data from this study showed the clinical parameters were stabilised or improved in 8 out of 10 patients and heart function had improved. This data is extremely encouraging, however, the ab-

sence of a placebo group made the interpretation of the clinical data difficult because it is not known how the patients would have progressed in the absence of therapy. Consequently, we have started a larger 2 year placebo controlled double blind trial to assess this therapy under more stringent scientific criteria.

Iron Chelation Therapy

Iron has been shown to accumulate in the mitochondria in FRDA patients where it may promote the generation of potentially damaging 'free radical molecules'. Consequently removing or sequestering this iron by iron chelation therapy may have clinical benefits. This approach has been successful in a yeast model of the disease. However, standard iron chelation therapies have not been shown to be capable of decreasing iron levels in mitochondria. An additional problem relates to the fact that FRDA patients have normal blood iron levels, and iron is required by the body for many important roles. If iron chelation decreases iron levels in general then this will give rise to additional clinical problems. To date there have been no published accounts of iron chelation therapy in FRDA. The development of new iron chelators that can specifically target mitochondrial iron may prove to be a better approach.

Mitochondrial Targeted Therapy

The primary problem in FRDA is localised to the mitochondrion and therefore a therapy specifically targeting the mitochondrion would be expected to be most beneficial. By chemically modifying therapeutic agents in such a way as to specifically target them to the mitochondrion may improve their effectiveness. This approach has been used in the laboratory for vitamin E and found to result in an 80 fold increase in mitochondrial vitamin E content. Such compounds have not yet been used in patients but may prove to be of particular benefit in FRDA.

Conclusion

Many of the symptoms associated with FRDA can be managed with conventional treatments and it is imperative patients are followed up on a regular basis by the appropriate clinicians. Advances in our understanding of the disease mechanisms underlying FRDA are enabling the use of established drugs as potential therapies in particular antioxidant treatments. Improvements in our understanding of how the disease progresses in different individuals and what factors influence the progression in conjunction with improved methods for assessing the various disabilities associated with FRDA also enable a better evaluation of therapy trials. When assessing disease modifying therapies the relatively slow nature of the disease progression requires relatively long periods of treatment (greater than 2 years) for any changes to be observed and shown to be consistent.

The findings of our combined vitamin E and CoQ10

trial are very encouraging. They clearly showed that there was a rapid and sustained increase in the energy generated in the heart nearly back to normal levels. The improvements in skeletal muscle energy generation parallel those of the heart but were less dramatic. Clinically we were able to demonstrate an increase in heart function after 3 years of therapy, although there were no consistent improvements in the thickness of the heart wall. The overall clinical symptoms were assessed and over the 3 years of the trial the clinical scores were better than predicted in 8 out of the 10 patients suggesting the therapy was modifying the clinical course of the disease. A more detailed evaluation of the influence of the therapy upon the clinical progression awaits the results of a larger double blind placebo controlled trial with 50 patients over 2 years.

ORPHAN MEDICINAL PRODUCT DESIGNATION IN THE EUROPEAN UNION

European Agency for the Evaluation of Medicinal Products

What does the EMEA do?

The European Agency for the Evaluation of Medicinal Products (EMEA), through the Committee for Orphan Medicinal Products (COMP), is responsible for reviewing designation applications from persons or companies who intend to develop medicines for rare diseases, so-called 'orphans'. The Agency also provides advice on the development of orphan medicinal products (protocol assistance).

What are Orphan Products?

'Orphan' medicinal products are for diagnosing, preventing or treating life-threatening or very serious conditions that are rare and affect no more than 5 in 10,000 persons in the European Union. Pharmaceutical companies are unwilling to develop such medicinal products under normal market conditions, as the costs of bringing them to the market would not be recovered by the expected sales of the medicinal product without incentives.

How is Orphan Development Stimulated?

In the European Union, the legislative framework to provide incentives for sponsors/pharmaceutical industry to develop orphan medicinal products was laid down in 2000.

Products eligible for the incentives listed in the next paragraph are identified through a new Community procedure for orphan designation.

What are the Incentives?

Exclusivity

For 10 years after the grant for a marketing authorisation orphan products benefit from market exclusivity. During that period directly competitive similar products cannot usually be placed on the market.

Acknowledgements

This research was funded by the National Lottery, UK and Ataxia UK and supported by Pharma Nord.

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Protocol Assistance

The EMEA can provide scientific advice to optimise development and guidance on preparing a dossier that will meet regulatory requirements. In this way the applicant of a marketing authorisation for an orphan product will maximise their chances of success.

Fee Exemptions

A special fund from the European Commission, agreed annually by the European Parliament, will be used by the EMEA to grant fee exemptions. Reduction of fees will be considered for all types of centralised activities including fees for the application for marketing authorisation and protocol assistance.

EU-Funded Research

Organisations developing orphan products may be eligible for grants from Community and Member State programmes and initiatives supporting research and development, including the Community framework programmes.

What is Orphan Designation?

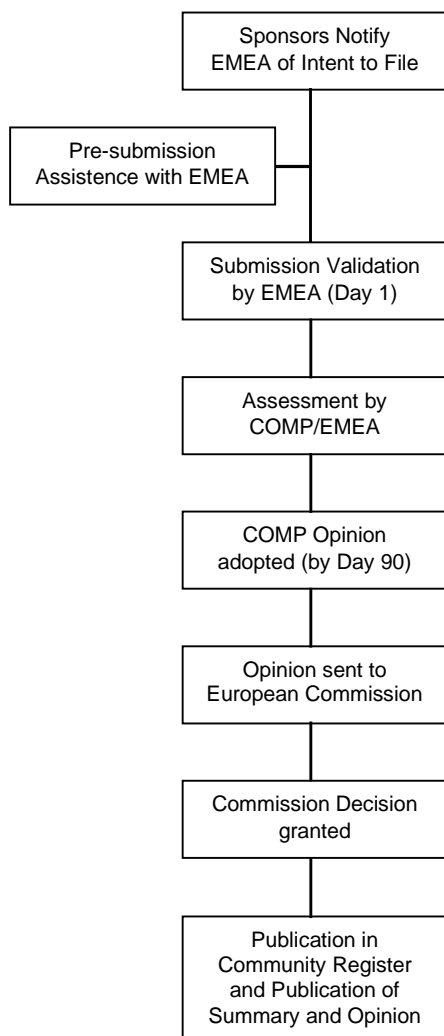
Orphan medicinal product designation assigns orphan status based on the criteria laid down in the Regulation (EC) No 141/2000 and permits access to the incentives.

Designation of orphan status is not an endorsement for the use of the product in the designated condition as it does not indicate that the product will satisfy the criteria for the grant of a marketing authorisation which is a separate step. The quality, safety and efficiency of the medicinal product in the proposed therapeutic indication can only be evaluated, as for any medicinal product, once the application for marketing authorisation has been submitted.

Useful Sources of Information

- Guidance documents, COMP Press Releases and Public Summary of Opinion for each Product: <http://www.emea.eu.int>
- Community Register of Orphan Medical Products and the Inventory of Community and National Incentives for Orphan Medicinal Products: <http://pharmacos.eudra.org/F2>
- Fifth-Framework Programme: <http://www.cordis.lu/en/home.html>
- Community Action Programme on Rare Diseases (1999-2003): http://europa.eu.int/comm/health/ph/programmes/rare/index_en.htm

The orphan designation procedure at a glance



EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS

Committee for Orphan Medicinal Products

Chairperson: Prof. J. Torrent-Farnell

Vice-Chairperson: Mr. Y. Le Cam

The committee is composed of one member nominated by each Member State, three members representing patients' organisations and three members nominated on a recommendation from EMEA

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THE STATUS OF IDEBENONE

Daniela Iser, Switzerland

In a press release from 22 November 2001 informing on the 18th meeting of the Committee for Orphan Medicinal Products, *Idebenone* (sponsor: laboratoires Takeda) was listed as having been granted Orphan designation by the European Commission. The cumulative criteria for such designation are deemed to have been met: first, the seriousness of the condition; second, the absence of alternative methods of prevention or treatment and a possible benefit versus available products; third, the rarity of the condition and a presumably insufficient return of development investments. EMEA explains that "designated orphan medicinal products are still investigational products which have only been considered for designation on the basis of potential activity. As a consequence, demonstration of the quality, safety and efficacy will be necessary before the product's activity can be confirmed and a marketing authorisation granted."

Idebenone is on the market in Italy and Portugal, but for a different condition (Alzheimer's disease), not Friedreich's ataxia. It is, for this disorder, still under investigation. When sufficient data is gathered to give evidence of a satisfactory benefit of *Idebenone* for persons with Friedreich's ataxia, Takeda will file the application for marketing authorisation (or product licence) either centrally to the EMEA or, on a national level, to the competent regulatory authority in a Member State of the EU. After revision of this data, and if *Idebenone* is held to be favourably affirmative for this rare condition, it may be placed on the market. The declaration of the price is a national matter.

No time table can be given concerning these procedures; official registration of *Idebenone* as well as price setting are handled differently in each country. Member associations of *euro-ATAXIA* are encouraged to find suitable and special agreements within a national

frame, so that afflicted individuals can have the drug. In some European countries (France, Switzerland), specific cooperation of Takeda, the local authorities and the medical body has been established. Idebenone is available to all ataxic people whose health may

profit from it.

Well then. A situation in which neurologists are free to give Idebenone to their FA patients is still a long way off. On the other hand, it is not Utopia any longer.

HOW TO FIGHT THE ATAXIAS

Marco Meinders, The Netherlands

During the last years, various programmes of the European Union to combat rare diseases have been initiated. Simultaneously, patients' organisations formed alliances to further influence European policies on rare diseases. One of these alliances is Eurordis, the European organisation for rare disorders. Founded in 1997 by four French patients' organisations, Eurordis now has more than 200 member organisations all over Europe. Amongst them are several organisations of people with ataxia.

On 14 and 15 June 2002, a European rare diseases awareness conference was held in Barcelona, Spain. It was organised by the European and the Spanish organisations for rare disorders (Eurordis and FEDER), the Spanish and Catalan governments, and the Autonomous University of Barcelona. Two member organisations of *euro-ATAXIA*, both of which are members of Eurordis as well, were present: Dr. Balthasar Schaap and myself represented the ADCA-Association of The Netherlands, and Isabel and Elisa Campos acted on behalf of FEDAES, the Spanish Ataxia Federation. They used the opportunity of the event to talk about possible means to boost scientific research so that treatment of ataxias would be found. The conference was also attended by Dr. Josep Torrent, director of the committee for Orphan Medicinal Products (COMP, a subdivision of EMEA, the European Agency for the Evaluation of Medicinal Products), and José Félix Olalla, subdirector of the Spanish agency for medicinal products. They helped Elisa and Isabel to be admitted to the Spanish Ministry of Health.

One possibility to promote scientific research is to set up a European network of scientists with an interest

in ataxia research. The idea was followed quickly by first steps towards its realisation: the network is being coordinated by Dr. Antoni Matilla from University College London. Any medical person and any researcher who is interested in ataxia research is kindly requested to contact him.

In September 2002, a conference is planned to take place in Spain. There, scientists will work out the details of the network. It can then be presented to the European Union. If it meets all requirements, including sufficient representation from the member states of the European Union, it will be most likely be adopted. The project will certainly have a positive effect on the development of therapies.

If you like to join the network for coordination and efficiency in ataxia research, please contact:

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Links:

ADCA-Association of The Netherlands: www.ataxie.nl
 Spanish Ataxia Federation: www.hispataxia.org
 Eurordis: www.eurordis.org
 EMEA: www.emea.eu.int

THE FRIEDREICH'S ATAXIA SOCIETY IRELAND (FASI)

Michael Morgan, Ireland

The Friedreich's Ataxia Society Ireland was founded in 1980 to cater for the needs of FA sufferers and their families. Initially, the Society concentrated mainly on supplying information to its members in relation to the disorder, on statutory and non-statutory services available to them, and on developing a liaison with similar groups throughout the world, especially in relation to research. It also arranged meetings and socials so that an interchange of ideas and experiences could be developed.

Very soon however, it was necessary to expand the

services of the Society over a wide spectrum of needs. It now caters for the following: specific and general information, meetings, socials, annual holidays; help and guidance in providing ground floor accommodation, assistance with fixtures, fittings and other aids; advice, support and guidance for families, especially after the shock of the initial diagnosis; general counseling; visitations; responding to the specific needs of those in the lower socio-economic brackets; and a commitment to research. The Society has published information booklets for medical persons and lay people, and it also

produces a newsletter.

Because FA affects more than only a child in a family, the Society is very conscious of the additional social and economic burdens placed on every member of that family – the disabled persons, the parents or guardians, and the non-disabled children – and it endeavors, as far as possible and practical, to respond to each of their needs.

FASI provides a wide spectrum of services covering the areas of health, social and welfare and it endeavors at all times to respond to the needs of its members, from the initial traumatic time when the disabled person has been diagnosed, through the difficult years of progressive deterioration, to the stage of coping with ‘independent living’. We are consciously aware of the fact that meetings, socials, holidays, and other interpersonal activities are wonderful platforms for developing a positive, hopeful and happy climate which can create strong bonds of friendship and a relaxed approach to life. Therefore, our quarterly socials and other activities together with our Annual Holiday and other respite breaks are essential safety valves and morale boosters for our disabled members and their families and carers. The annual holiday is held in a suitable and comfortable activity centre for a week

during the summer. It caters for about 30 disabled (from mild to severely disabled) holiday makers and involves the help of over 30 volunteers – some of whom are nurses. The week consists of seven days packed with fun and activity including swimming, boating, canoeing, bowls, archery, quizzes, karaoke, concerts and pub nights...The event is very carefully planned and organised with an organiser appointed to supervise, coordinate and control the event. The result is an exciting and enduring tonic for the disabled participants and a well merited break for their parents and carers at home.

In recent years, the vastly improved and developing relationship between the Health Boards and the Voluntary Bodies is leading to an upgrading of services for the disabled persons in this country, and though this is putting further burdens and responsibilities on the administration of the voluntary bodies, it is clear that better quality and more efficient services will improve and enhance the lives of the disabled and their families. This, no doubt, will copper-fasten the role of The Friedreich’s Ataxia Society in its efforts to respond to the needs of its members and to help them to achieve a dignified equality with the able-bodied members of society.

AGM 2002 OF THE NATIONAL ATAXIA FOUNDATION (NAF)

Peter Reussner and Conny Karg, Germany

Translation: Daniela Iser, Switzerland

Our American sister federation, the National Ataxia Foundation, had her 45th annual meeting 2002 in St. Louis, Missouri, early in March. We were there! The symbol of the city – an arch eighty meters high – inspired the motto of the assembly: “Gateway to Hope”.

Of course, the Americans do things a bit differently than we do in DHAG (Deutsche Heredo-Ataxie Gesellschaft): First, everything is much bigger (NAF has 8000 members, ten times as much as DHAG). This year, 350 members, guests and carers were present. Second, the meeting took place in a very good and expensive hotel, the Hilton. In comparison with our earlier experiences, however, the rooms were not really suitable for the needs of disabled people. There were but a few adapted rooms, and these were taken quickly. Therefore, we had to stay in a “normal” room, and we had some difficulties there. Moreover, the costs were very high again (\$ 400), but we had known this.

The meeting itself was spectacular, it was well organised, and its talks and topics were highly useful and interesting. It opened with a discussion on Coping (that is “life strategy” and responding to the question of “how can I live up to the best with my disease?”). Similar to our own experiences in DHAG, a positive attitude toward one’s self and one’s own activities was of central importance.

Further issues were alternative therapies, where the inner attitude is important, and the management of

annoyance and stress, that have to be avoided. News from the field of medical research announced that the number of dominantly inherited ataxias, or SCAs, has climbed to 22. Furthermore, a new type of recessive ataxia has been identified and given the name of SAX1. It is something like a mixture of Friedreich’s Ataxia and Ataxia Telangiectasia. And: our American colleagues were not too shy to talk about problems of sexuality.

There are several different animal models – worms, mice, fish and fruit fly – to help research and development of therapies. Test tubes allow experiments in a lab.

The intended clinical study of the drug Idebenone suggests taking increased doses in different phases. The trial was widely discussed. Detailed information can be had at NAF’s homepage, www.ataxia.org, and links.

We thought that Dr. Susan Perlman’s presentation (University of California, Los Angeles) on various different possibilities of treatment for ataxias was exceptionally good. Many symptoms – stress was on the

Question	Answer in 1977	Answer in 2002
What disease do I have?	10% of the diseases known	more than 50% known
Is there a cure?	No	No
Is there any treatment?	No drug evaluations	18 drug evaluations
Is there research?	223 publications	902 publications (2001)
Are my children at risk?	No gene tests available	16 gene tests available, more on the way

neurological and on the mental areas – of the disease can be treated after all. The disorder itself, however, can not. Dr. Perlman showed us an impressive slide that listed instances of medical progress. (See figure.) Treatment with stem cells allows much hope for devel-

oping cures of diseases like ataxia in the future. However, a lot of research needs to be done. March 2003 will see the next assembly of members of NAF in Atlanta/Georgia. It will certainly be worth while attending again.

ROLLING THE DICE ON THE SLIPPERY SLOPE

Marco Meinders, The Netherlands

On the morning of Tuesday, 26 February 2002, the silence in our office was abruptly disturbed by the violent ringing of a telephone. A reporter. Would we like to react to the news that a sperm donor is found to have the hereditary disease ADCA? His sperm fathered eighteen children for thirteen couples of parents. In those years, nobody could suspect that the donor had Autosomal Dominant Cerebellar Ataxia, he knew nothing yet himself and there was no specific gene test available at the time.

That week, we did not have a single quiet moment. More than one hundred reporters called. For days, we could not switch on the television without being confronted with this broadcast. The newspapers paid a lot of attention to the dispatch, too. Thus, we received about 40 requests for information in three days, whereas we usually consider one a day a lot. Furthermore, within three days, about 2000 people visited our website – which is 45 times as much as the normal number of visitors.

As a result to all the media attention, virtually every-

one in our country heard about ADCA. That's nice. However, there are now thirteen families here whose happiness has been disrupted. That is not so nice...At first, there were years of unwanted childlessness. These were followed by that unspeakable happiness that a baby is born. And now, this child might have a hereditary disease. What is to be done? Is the donor really the father? When will there be certainty whether or not the disease will develop? And what to tell your son or daughter? And what to tell your family and friends?

There are some bright spots. Information on the disease is available, there are others who also have it, and the future seems promising because of the advancements in scientific research. Small bright spots in much darkness.

[Translation of: Publiciteit door drama / by Marco Meinders. – Maarssen (NL): ADCA-Vereniging Nederland / ADCA-krant (ISSN 1569-9234), year 9, nr. 2, April 2002.]

SPERM DONOR HAS ADCA – A PARENTS' STORY

Arlette Buchrnhornen, ADCA-Association of The Netherlands.

February 2002. The news are omnipresent: *Sperm donor has ADCA*. At least eighteen children may carry the faulty gene, may develop the disease.

Many truths and untruths appear in lots of newspapers and magazines. It keeps a lot of people occupied, especially people with Autosomal Dominant Cerebellar Ataxia (ADCA is a symptomatic classification. Genetic screening has revealed quite a few possible locations of genes on different chromosomes that can be responsible for the disorder. However, only a smaller number of genes are actually known – the one that is the cause for the spermdonor's type of ataxia is not).

But how do you cope with something like this as one of the parents or as the donor himself? I think that I am not the only one to ask this question. For this reason, I sent a letter to the hospital in Den Bosch. I wanted to interview the donor. My request was to forward my letter to him, so that he could decide himself. After all, he is "just" another person with ADCA and with a story to tell.

Later, I received a letter implying that the hospital refused any cooperation. So did the parents who were involved. To them, obviously, it is most difficult to tell

their story, because many more issues are involved.

I called at the guest book at www.ataxie.nl, and found one couple who was willing to tell their story. Because they want to remain anonymous, we communicated by e-mail. I think it is very brave of them to talk about this personal experience!

I wish all donor children and their parents a lot of strength for the future.

Here are the answers to my questions:

How long before it came into the news, did you get the message that the sperm donor has ADCA?

Well, that was very short, only four days in between. We were told on Thursday, and next Tuesday it was on the news.

I have read that the parents were informed by the family doctor, how did this happen?

Our family doctor called us in the afternoon and asked if we had a moment for him that evening. There was something that we, as parents, had to know about our daughter, but we did not have to worry immediately. Well, you will understand that this is exactly what we did!

That evening, he showed up around eight o'clock. The

children were upstairs and were not allowed to come downstairs before being called by us. We have two children. Our daughter is the donor's, and our son is my husband's. For us, this was a reason for happiness: according to the doctors, my husband could not father any child (a little mistake!).

He had heard the story only two days before at the hospital, where he had been invited for a consultation. There, they asked him to inform the parents, because he knows his patients better than the medical staff in Den Bosch.

What was your first reaction?

Well then, you hear that story and you think "why our child?" Why is a grave being upturned after thirteen years (our daughter is turning 12 this year)? We buried the donor and everything associated with it a long time ago. We are happy, the four of us, and then this! And you do not understand anything from the papers he left. What is going to happen now? Then you're together again, you talk and cry. How must we go on? And then there is the question: is she his? After all, we have another child.

The hospital did give us the chance to have this checked. To us, this was very important. With an excuse, we had a blood sample taken from our daughter for a DNA-test. We had to wait for the result for three weeks, and with lead in our shoes, we went to hear the result. And then we got another blow in the face, as the donor was the father.

We always said to each other that we would not tell her about the donor. My husband is her father, and that stays that way. But now, we are torn between telling her and not telling her. We think that she is entitled to know if she is going to be ill or not. But how to tell that she might get ill? But that may not be so difficult. How to tell her that her daddy is not her daddy, and then also that she might get ill. We do not know. This was our secret. We feel like we are going through hell, and on top of that the hell that is to come!

Are you glad that the hospital informed you, of would you have preferred not knowing it?

That is a bit double. You do not know what is yet to come. On the one hand yes, after all, it is about the future of your child. On the other hand, no, what you do not know does not hurt.

Do you intend to have her tested if that becomes an option?

We have had her blood sample kept in Amsterdam in case a test becomes available. We hope that everything will turn out all right, and that we do not have to tell

her anything. If the result is not good, then we will wait till she is older and able to understand. She has the right to know.

Have there been talks with you at the hospital?

Through our family doctor, we received a letter from the hospital, in which they expressed their sympathy. And in case anything comes up, they have their medical staff at our disposal. They did offer us help from a social worker and a neurologist to talk this over with us. But we are not ready for this yet. We do talk about it with our family doctor, because he knows us, and we know him.

How do you cope with something like this, when you cannot share your feelings with anyone?

That was not easy. That is why we decided to tell my husband's brother and his wife. They kind of knew what happened back then. We had told them that we had a semen mixture with a donor, because we wanted to have a child. When the story about the donor hit the media, they hoped that this did not involve us. But, alas, after three months, I could not keep my mouth shut any longer, it had to come out. After having it told, my sister-in-law and me cried quite a bit. That was some relieve. A burden falls from your shoulders when you can talk about it with someone else. Not that we talk about it all the time, but it is nice to be able to talk about it, when something happens. My husband also told his boss and a colleague. They had noticed something too. So, if we have to, we can turn to them as well.

How did you find out about the ADCA-Association, and do you find support there?

Our family doctor told us about the ADCA-Association (we have become a member). I often look at the guest book on the internet to see if other parents are looking for contact by e-mail. I think it would be nice to talk with others. But so far, I have not seen anything.

Do you know how old the donor was when he first had symptoms?

I understand that he was halfway his thirties. His father died, and it turned out he had ADCA. We do not blame him for anything. We feel sympathetic with him, because he could not have foreseen this. And I am certain that he has a lot of problems with this too. We are talking about eighteen children with thirteen couples he helped to get a child. A child we are very happy with. One last thing: we will not have our lives dictated by ADCA. We go on exactly as we did before ADCA entered our lives.

ETHICAL REFLECTIONS ON THE DUTCH ADCA AND IVF CASE

Susanne Boshammer, Institute for Ethics, University of Zürich
Translation: Norbert Anwander

Earlier this year, it was disclosed that a Dutch sperm donor who had fathered 18 children suffers from ADCA. Those who take a negative view of modern re-

production technologies may see this case as confirming their scepticism. In the face of such unfortunate events people look for somebody to blame, and in this

particular case many think they know whose fault it all is: Parents who refuse to accept the natural fact of their childlessness and resort to artificial means such as IVF (In Vitro Fertilisation) to get children need not be surprised when these technologies get out of control and make them wish they had never used such methods. Neither should these people complain.

Yet the times when human reproduction could not be controlled, but was purely nature's work, are long over. They were history even long before methods were found to provide childless parents with a baby by using a donor's sperm. Most people welcome the fact that women and men are to a large extent able to determine for themselves whether and when to have children. We have good reason to consider this as a considerable step forward which nobody may seriously want to see undone.

However, as parenthood is no longer a matter of fate but the result of individuals' decisions, human reproduction raises issues of moral responsibility. These problems engage ethics. Ethics is the discipline which, taking our freedom of will and action as its starting point, inquires into what to do and how to evaluate our actions from a moral point of view.

From this moral point of view the case at hand raises two major issues of particular ethical relevance: First, bearing in mind the incalculable risks involved, is it legitimate for a couple to use donated sperm and IVF in order to satisfy their desire to have a child? Second, what should parents and doctors do when they know that the children are potential carriers of a severe hereditary disease and may pass it on to their offspring? Do parents have a right to conceal such knowledge from their children? Were doctors under a duty not to reveal such information, or should they, on the contrary, have passed it on much earlier?

In order to answer these questions, it may help to remind ourselves of the facts. What happened?

Thirteen couples, who unfortunately cannot have children the natural way, make use of IVF to become parents. 18 children are born whose father is a sperm donor who, when he gave his sperm, did not have a clue that he carried a dominant hereditary disease. Neither could the clinic know this, since to this day there is no gene test available for this disease. Years later, the sperm donor developed symptoms. He alerted the clinic, where doctors waited for three years before they informed the families involved. Parents were told by their family doctors about the likelihood of 50% of their children being the carrier of a dominant gene which is known to cause a disease that starts to affect people in their thirties or forties. This life-threatening disease may seriously impair the quality of life of those affected.

Do these distressing circumstances support the views of those who think that sperm donations and IVF should be banned? The fact is that as far as the probability of passing on the gene for ADCA is concerned there is no difference between test-tube and uterus.

For any individual, the risk of being the carrier of a defective gene, is completely independent of whether they were conceived under natural or artificial circumstances. Which means that those who decide to use IVF impose no higher risk on their future child than those who are lucky to have children the natural way.

Neither does the fact that this was a case of heterologous IVF, i.e. the sperm was donated by a stranger, make much of a difference in terms of risk. Since there is no test for ADCA available, nobody can know whether they carry the gene until the disease has actually broken out. The only evidence can be gained from looking at one's family history. The gene responsible for ADCA is a dominant one, which means that at least one of the parents will also be affected. On its own, this fact provides no argument against heterologous insemination, i.e. fertilizing an egg cell with the sperm of a man whose family history is not known to the prospective mother. It points, however, to the clinic's duty to test sperm donors carefully and to get all information available about their hereditary disposition. We cannot know whether this was done in this case, since those in charge at the clinic involved apparently maintain their silence.

It might be suggested that at least the size of this predicament was due to the sperm donation. True, it is rather unlikely nowadays for a single man to father 18 children the natural way. From an ethical point of view, however, such "arguments by numbers" cannot be decisive. Each individual counts as much as any other. It is not the number of people affected that makes this such a depressing case but the situation and fate of each individual on their own.

To sum up: Since the suffering of the parents and their children has nothing to do with the methods of sperm donation or IVF, neither those who make it available nor those who take it up are to be blamed. It is simply due to the fact that, as long as there are hereditary diseases, human reproduction involves risks that we can neither precisely calculate nor eliminate altogether. Understandable as it may be that we feel the need to find somebody to blame for it, when such misfortunes happen, and to call both those who make the modern reproduction technologies available and those who take it up to account for it, I think we have no right to do so.

With regard to the second issue, i.e. the question of how to deal with the knowledge about a potential disease, it seems to me that no general answer can be given. A few brief comments will have to do. While it seems obvious that doctors are obliged to pass their information on to the parents concerned, with regard to their duty to tell their own children the situation is rather complicated. As long as no gene tests are available, nobody can tell for sure whether the children have actually inherited their unknown biological father's disease and carry the defective gene. In each case, the probability is 50 percent, it is thus as likely as it is unlikely. And even if one day we could be cer-

tain about this, we would still not know if and when the disease will break out.

When questions such as these arise, a so called “right to ignorance” is often appealed to. This right means that everybody should be able to determine for themselves what sort of information they want to have, for instance, about their genetic make-up, about their origin as well as about their future and what they would rather not know. It is up to each person whether to exercise their right or not. In the case under consideration, it seems to me that we have good reason not only to assume that these children have such a right but also to think that they would exercise it if they were in a position to decide for themselves. The knowledge others have gained about them is of no use to these children, nor has it any information value for them. Not only is knowledge that there is a certain probability that one carries a disease of which nobody can tell if and when it will break out, of no use, it will even positively cause serious harm.

Things are different, however, when the children have reached an age, when they develop their own life-plans and start thinking, for instance, about starting a fam-

ily. At this stage, information about one’s disposition for a disease becomes much more important. The right to ignorance now comes into collision with the duty not to impose intentionally the risk of harm on one’s own future children. It seems to me that there are good reasons to assume that in this case the duty not to harm overrides the right to ignorance. Which means that at this stage there is good reason to tell the children about their potential disease.

If there is still no gene test available at that time, based on the statistical probability of the gene’s being passed on, nine people will wrongly assume that it would be irresponsible for them to have children and to impose on them the risk of a severe hereditary disease. Not only will these people have to live in the constant fear of a severe disease that affects themselves, but they will have to refrain from starting their own family. Even worse, years later, when such tests may have become available, they will have to realise that they need not have abstained. Unlike their parents they will not be allowed to make their arguably deep desire to have children come true. It is at this point that the tragedy reveals itself in its entirety.

ON ACCEPTANCE

Michael Morgan, Ireland

Acceptance of disability is complex. When I say “I accept my disability”, what do I really mean? There are a number of senses in which the term is being used. Moreover there are different levels of experience in life which produce often contradictory behaviour: the intellectual and rational versus the emotional and irrational. As well it’s entirely possible to be schizoid: both a rational acceptance and an emotional rejection. Christians have a prayer which might be pertinent here:

God, grant me the Serenity to accept what I cannot change, the courage to change what I can, and the wisdom to know the difference.

In an immediate sense, I find I can readily accept my disability as a fact of my life, no more, no less. Yes, that’s me sitting in a wheelchair, so what, let’s get on with it, seems a fine, assertive attitude to take. What I won’t for a moment accept, however, is the bullshit that goes with it, of which, god knows, there’s plenty. I refuse to accept the treatment doled out to disabled people by society, and by this I refer to the social exclusion, marginalization, discrimination and disempowerment of disabled people in many walks of life. I could reel off any amount of statistics to back this up. Disabled people lose out on employment and on education and other less formal but nonetheless crucial areas of social interaction. On an everyday level too, to say so and so has not accepted her/his disability can be a social put-down, a means of dismissing somebody

within an inter-personal setting. There’s a social expectation almost of passivity, even inferiority, of disabled people within normal, group interactions, and if you doubt it, try bucking the disabled role. That’s what Daniela Iser was referring to (cf. *On Acceptance* in Newsletter no. 21) when she said she was accused of not accepting her disability when she simply held contrary views. It’s a way of shutting her up, of disempowering her. But social expectations are social phenomena. Being part of the social make-up of life these things are changeable and should never be meekly accepted as one’s lot. Remember the second line of the prayer, the admonition to change what you can. It’s a call for action, not submission. Ataxia, alas, is not a social phenomenon but a physical reality. It is a progressive, relentlessly disabling disease with no social input whatsoever. Although medical research may yet develop effective interventions, its physical status marks it as inherently unchangeable, and it’s within this context that we can legitimately speak of acceptance as recognition of external reality.

The Media invariably uses military metaphors when describing life with disease or disability. We are often said to be battling against disability, as if locked into a heroic yet doomed struggle against insuperable odds – I too am Spartacus! The idea comes from ancient stoic philosophy as developed by the Greeks (Diogenes) and Romans (Seneca the younger, Marcus Aurelius). Seneca for instance said battles could be fought in bed as much as on the battlefield. Moreover, if you look at the obituary pages of contemporary newspapers, you’ll find

precisely the same idea expressed. So what is stoicism, at least as we apply it here? Stoicism remains first and foremost a defence mechanism for the self. The self is rooted in consciousness and mind, not only separate from but superior to the physical body. Disability and disease are merely physical phenomena, external to the self and its workings. Stoicism allows us to face the vicissitudes of life head-on. Disabled and ill people are thought highly of if they behave with stoical fortitude – a stiff upper lip as our British friends would say. The drawback in this is that it leads to a denial of the emotional impact of disability. Disabled people are flung into a fight (in a metaphorical sense), and this leads to a denial or refusal to acknowledge the impact of what is happening on an emotional level.

Ataxia is a progressive disability and is best thought of as happening in stages. Young ataxic people are encouraged always to fight – to do as much as they can for as long as they can. But fighting disability cannot go on forever. At some point a renegotiation with external reality is bound to happen. The problem is that the young person may be psyched up always to fight and struggle with disability, but then what happens when the disability progresses to a newer level? Does the fight continue at a lower level or does the person simply shrivel and retreat from reality? The main psychological disturbance comes, as far as FA is concerned, at the point at which the individual FA person uses a wheelchair. Sometimes this can be traumatic after being brought up to fight his or her disease. The shift seems more like a surrender of what has gone before rather than a simple adjustment to new circum-

stances. To cry out in such a circumstance is natural, yet it is this very protest that is stifled and dismissed by saying that he or she has not accepted their disability. It's not just that someone cannot adjust to the physical reality – this is easy enough – it's that at a deeper emotional level one is being asked to capitulate. Overall I think of acceptance as a life-long process of continual negotiation in which the disease operates like a ratchet slipping us down into a lower level as years go by. For myself I have now slipped into severe disability as opposed to, say, 20 years ago when I was merely disabled. The point is that my sense of self has remained the same even though the disease has progressed. One has to accept physically progressive disablement and weakness, but the crucial point is that the self retains its own identity no matter what the changes in the body may be. Adopting a stoical approach to physical degeneration while retaining psychological resolve to maintain equilibrium however is never going to be easy. The stoical approach to life may well be effective, but it comes at quite a high price of emotional withdrawal. One can manage an ataxic lifestyle with comparative ease, but when was the last time that anybody asked you how you felt about it? I think myself that the worst of living with ataxia is this sort of emotional withdrawal or disaffection. This comes across as an inability to respond emotionally in many circumstances, like a willed repression. And yet we carry on. Life with ataxia is never easy, no matter how well adapted you seem to be. Acceptance is always going to be problematic.

ON ACCEPTANCE

Carolien Koopmans, The Netherlands

The article 'On Acceptance' in Newsletter no. 21 came to me as a nice surprise. In a way, I consider it as a follow up to my own article 'Accepting Help' in Newsletter no. 19. Therefore, I'd like to react to it on my turn.

I have indeed thought a lot about the subject and think it is very important. I will gladly philosophise a bit further on the question. When you are going to reflect on a subject, you often start with looking it up in the dictionary. It's a pity that the dictionary in question doesn't mention the meaning I had in mind when I wrote my article: *to have peace with, to feel no urge to fight*. I could comment on all the meanings that were found so far, but I would like to give a more general view on the subject.

Ataxia is a rotten disease, there is no question about that. But there is no choice in having the disease, or not having it. If you have the disease, there is nothing that will change that fact. Some 'patients' develop a more serious form than other 'patients'. You can only hope that the disease won't develop too severely in your case. But I think that you do have a choice in the

way you look at your disease. The choice you have is psychological, not physical. Of course, the way in which you can look at your ataxia depends on your upbringing, your social status, your financial position and so on. I realise that the circumstances differ from country to country. But that doesn't mean you can't make any general statements.

As to the physical side, we depend upon our doctors, and as to the future, on our scientific researchers. Although I doubt that ataxia can be cured completely or wiped from the earth, I welcome the scientific research into ataxias. I believe that a lot can be improved concerning progression and symptoms of the diseases. But scientific research takes its time to result in practical therapies. So the physical aspect can only improve in the future. But we live today, and so we have to enjoy our lives as best as we can, here and now.

If you have to choose a way of thinking about your own disease, you'd better choose a way that gives you the best feeling and the best results (which means a good mood and mental stability). The division into psychological and physical aspects is – like all divisions we

make in our minds – artificial. The two aspects interchange constantly. When you are in a good mood, you can stand a lot of physical problems. But when you don't feel good, you tend to get grouchy quickly. In my experience one can change one's psychological attitude, however time-consuming this may be. You have to be critical about the thoughts you have, and you need to think about the consequences your thoughts may have. The attitude towards yourself is inspired by the attitude that other people have towards you. Alas, people nowadays are very materialistic, they are obsessed with temporal things, and with self-interest. In many people's view, someone who isn't rich, beautiful and 100% healthy, is of no importance. A lot of people are so narrow-minded; they seem to be able to judge you from the outside. When they see a person in a wheelchair, they immediately draw the conclusion that this person is not interesting, and from your slurred speech they will quickly conclude that you are not well in your head either. Don't let yourself be disturbed by the unfriendly attitude of such people.

Fortunately, not all people are narrow-minded. Please remember that some people present to the world only the mask they are wearing. Please remember that everybody is a victim of the spirit of our time. Don't judge people too quickly; you don't want them to judge yourself too quickly either. A lot of people are much nicer when you get to know them better. To fight the dumb and narrow-minded people is a waste of time, and you scare off people that might otherwise be good friends (to know more about overcoming the overwhelmingly negative way of thinking in most people, read the paper "The adventure of a hero", *euro-ATAXIA* Newsletter 8 (1995) which I wrote for the AGM 1995).

Temporality and self-interest are two key concepts in

the predominant way of thinking. It is a way of thinking that leads to no good results, that won't give you a better feeling about yourself. You have to realise that you are only one of the living human beings since the human race evolved or – in Christian terms – since God created Adam and Eve. How many people have lived since the existence of man? What is the importance of having ataxia, or not having ataxia, if you look at life in this way? The disease will have less, even minor, importance. When you look at the millions of people on earth, what does one individual mean? The earth will go on turning if you are not alive. To quote George Harrison from the album "Sgt. Pepper": "Life flows on, within you and without you." What does it matter if you have ataxia or not?

No one lives or can live without other people. But a person's thoughts are his or her own. You can try to share your thoughts with other people, but the life you live stays your own life. Each person has his or her own unique history. That sounds a bit lonesome, but it is a truth you can't change. Its extent varies from person to person, but a human being has – apart from his or her individual side – a social side. He or she enjoys life most if he or she has good relations with other people. To get good relations, it is sometimes necessary to push your self-interest aside and let the interest of someone else prevail.

This way of thinking can solve a lot of problems. It is much easier to have peace with your ataxia, if you see things in perspective. Life is much more agreeable if you don't constantly fight a fight you can never win. And this way of thinking paves the way for your good humour. It is so relaxing to laugh away the sad side of life.

SEXUALITY

Larry Schut, MD, Maple Lake, Minnesota

Remember when an off coloured joke was the only way in which sex was brought up in a conversation? Remember when a love scene in a movie faded out as the kiss was about to become passionate? Remember when a condom was called a safe or a rubber and hidden behind the drugstore counter under the cash register? Now, what do you see? It is sex on TV; its sex in the movies; it is sex in the music videos and the picture doesn't fade out. Nothing in life is left to the imagination anymore. Sexual issues are also on the public agendas, prevention of sexually transmitted disease, for example, consequences of unprotected sex, Aids programs in school, abortion rights, pornography on the Internet-you could go on and on naming areas where sex is an issue. Our standards for sexual behaviour have liberalized. We don't rely on transfer of sexual information through jokes or bathroom humour anymore. We discuss sexual behaviour much more openly than ever before. Sexually deviant behaviour

also receives more media attention. However, this may reflect an actual increase in such things as violent sex crimes, sexual abuse, and pornography. But I see an area where things have not changed, an area where we avoid meaningful discussion, when we tiptoe around issues and where problems lie hidden and no attempt is made to meet them head on.

I am referring to sexuality in the person with neurological damage. When we really analyse the liberalization brought forth by the sexual revolution, we realize that it is mainly to sexual activity and the sexuality of the able-bodied, and if you will, the sexiness of the "Pepsi generation."

With some exceptions, persons with disabilities are not shown having sex or being desirous of having sex or even being desirable for sex. For some reason it doesn't seem to fit the image. If my leg were cut off would that mean that I no longer cared for sex? If I were to lose motor control of my legs and arms would I suddenly

lose the basic urge and need for intimacy and closeness? When these changes occur, I might feel a great loss, and it might change my self image a great deal, but I am still the same “me”. I can still care and feel. I can still desire closeness and intimacy. The January and February 1992 issue of *Headlines*, which is published by the New Medico Rehabilitation System addressed sexuality and neurological damage. It reviewed issues regarding sexuality in patients with disabilities. There are myths about sexuality and people with disabilities according to Sigmund Howe, Ph.D. He was a clinical psychologist and clinical director of New Media Rehabilitation Center in Boston. He said, “One myth is that disabled persons are asexual or hypersexual and if a person has a relationship with a disabled individual it must be because the person cannot find anyone else.” Another myth is that penile and/or vaginal orgasm is the only satisfying form of a sexual experience and when one is incapable of this performance there is no point to becoming a sexual person. A third myth is that intimacy is a low priority for persons with disability. On the contrary, our thinking is that if a person is able bodied, then it is a high priority, and he or she does not have any problem with sexuality. This gets at the heart of the matter.

Myths arrive at lack of understanding and discomfort of issues with sex and sexuality. Let’s look at a typical situation. We have a patient and a health care provider. The patient may be afflicted with an obvious physical condition, or physiologic dysfunction such as ataxia. The conversation comes around to discussing the physical aspects of ataxia, and the strategies to best live with it. We talk about coping mechanisms, means by which we will work and live in our society. But what about the hidden disability? The one that no one admits to or talks about because it is so personal. Yet, it creates a great feeling of anxiety, that is anxiety for the patient, anxiety for the spouse, and anxiety for the health team member. That hidden area is in the area of sexuality. I am not talking simply about sexual performance, or the ability to experience orgasmic sex. I am talking about sexuality in the broader sense. I’d like to paraphrase Nancy Holland of the MS Society, and her definition of sexuality, “It is the integration of one’s feelings about his or her sexual identity that is one’s masculinity or femininity as well as one’s self image, in relation to and interaction with others.”

You see, “self” is my very essence, this is something that is uniquely me. As we grow and mature we form the concept of self. I am not someone else. I am an entity, separate and distinct. This concept is influenced by a host of forces, among them being genetics which plays a very important role, perhaps more than we know. Environmental influences, parents, siblings, peers, personal experience all have input into the formulation of self. Then this amalgamation of genetics and environmental influences forms the basis for our development of self concept.

When you look in the mirror in the morning, what do

you see? You see an image, certainly, but it isn’t much more than just a moving picture. It doesn’t tell you about what you think of yourself or your understanding of how others see you. You might see yourself as nice looking, even attractive or you might not like what you see. More importantly, what do you think about the image that you portray to others? Are you pleasant? Are you acceptable? Are you sought after for friendships? And, more personally, are you confident that another person is willing to develop a close relationship with you? This is the basis for our sexuality. Sexuality means a lot more than the sex act or sexual performance itself. Darlene Scheffel, registered nurse from Loma Linda University, is also quoted in the *Headlines* article mentioned earlier. “Let’s not forget that intimacy isn’t just sexuality. It is communication and comfort and caring as well.”

So, now you say, sexuality is more than just the sex act. My feelings about myself play a big role in my interaction with others. I still have a need to communicate and a desire to give and receive full expression to my sexuality. How do I get over the hurdle of my disability and my sense of loss, my anger, my grief and fear of rejection?

First of all, let me give you some suggestions. One has to face certain facts that the disability exists and that the feelings exist. And then you have to work on the reality that the condition, namely ataxia in this case, just doesn’t go away. And then, don’t try to carry this load by yourself. Begin the process of communication with others, so that the hurt and anger aren’t borne alone, isolated from the support and care of others.

Actually, I am not talking only to the person with ataxia itself, but I am also talking to the spouse, or the close, personal friend, to the relatives, to the care givers and to the health team member. Each one of us has to examine his or understanding of one’s sexuality, feelings about oneself and individual ability and willingness to relate to others. For example, our ability to talk about death with others is dependent on our having dealt with our own mortality. So, it is that we cannot become comfortable with and sensitive to the sexual and intimacy needs of disabled persons until we know where we ourselves are at with respect to self esteem, intimacy, and sexuality.

I’d like to suggest the following key words to embrace in the process of forming friendships, developing the intimacy and experiencing the sexuality you desire, even without the performance of the sex act. These key words are awareness, honesty, communication, flexibility, and creativity.

Let me begin with the first key word, awareness. Ignorance is not bliss. Ignorance causes discomfort, discomfort causes anxiety, anxiety creates tension. Tension destroys relationships with others, let alone inhibits building relationships. So, whether you are the person with ataxia or a spouse, a partner, a friend, or a health care provider, you should always be aware that there is a potential for a problem with sexuality. Understand

that most people are afraid to uncover and look at this problem. Recognize the physical changes and try to uncover and look at this problem. Recognize the physical changes and try to understand the emotional reaction of the individual and be prepared to deal with the behavioural symptoms.

The next word is honesty. Don't deny the feelings that you have about the issues of sexuality whether you are the patient, or the spouse, the friend, or the care giver. If you feel that your disability has diminished your sexuality and that you might as well forget about it, you are not likely allowing yourself to be in touch with your true feelings. If you are a partner of someone with ataxia, you may have to admit that you have a negative response to the disability. It has happened to this very important person in your life and you don't really know what to do about it. You may have to share your concerns with someone outside your relationship. It is important to find an experienced professional who can give you counsel in this area. Some professionals can be tongue tied when it comes to talking about these matters.

The next word is communication. This is an out growth of honesty. Once a person has faced the reality of a situation, recognized the possible consequences, and admitted the feelings, then one can begin to peel away the layers of embarrassment, even the shame and guilt and lay the concerns on the table. This is critical to a positive relationship. This professional should give feedback uninhibited by his or her hang-ups or value judgements.

After communication, the word is flexibility. I want to tell you a story about one of my patients. About 20 years ago, she was admitted to the hospital with an attack of Multiple Sclerosis. Her husband had been away for a couple of months for basic training in the Army Reserves. His unit arrived home late one evening so he did not arrive at the hospital until 10:30 that night. The hospital personnel relaxed their visiting hours rules which was greatly appreciated by the patient and her husband. A little later, a nurse noted that the door was closed, so she looked in the room. The curtain was drawn but she saw a reflection in the mirror that the husband, fully clothed, was lying beside his wife. She almost tripped over her feet as she ran out, hurried down the hallway and summoned the evening supervisor. Security was called. The husband was sent home red faced, the patient was scolded for inappropriate behaviour and subsequently, several meetings were called to develop plans for exercising vigilance and to avoid such unseen behaviour by patients in the future. This happened 20 years ago so it might be handled differently today. This incident points out that the expression of sexuality on the part of patients are not always sensitively dealt with by health professionals. We need to be sensitive to the fact that sexual behaviour frequently needs to be adapted to the desires and particular needs of both the disabled person and the partner.

The last key word is creativity. We are so task orientated in our jobs and day to day living activities that we often limit our imagination. When this happens our creativity is stifled and we tend to plod through each day failing to dream dreams or just plain have fun. When burdened by a chronic neurological disease, a person feels even more limited. Indeed, dreams are sometimes shattered and fun is just an elusive concept. Ataxia truly can be burdensome. But, having it does not have to mean despair. In fact, my job as a neurologist is sometimes a joy because of the positive attitude and bright outlook many ataxia patients bring with them into my office. One of my ataxia patients beamed as she showed me a newspaper picture of her carrying the Special Olympics torch a short distance across Minnesota. Create memories such as this. Try to do something different every day. Surprise a friend with an unexpected phone call. Plan an outing or a short trip, maybe even a long one. You will feel better about yourself. That is what this sexuality business is all about. It doesn't mean that you must have a sex partner to feel loved and special.

Education and research on issues of sexuality have not kept pace with other areas of psycho-social research. Nothing has been written about ataxia and sexuality, but recent studies on sexuality and Parkinson's disease, stroke, epilepsy and head injury have been conducted and reported. This is encouraging. Information about sexuality and Multiple Sclerosis is found in Dr. Randall Schapiro's book, "Symptom Management in Multiple Sclerosis." The book can be obtained from Demos Medical Publishing Inc.; 386 Park Avenue South; New York, NY 10016. There are similar sexuality concerns in ataxia and multiple sclerosis. Editors note: Dr. Schapiro's book is also available on the Internet, www.amazon.com is one site where it sells for \$13.97.

Deane Daves, Ph.D., a neuropsychologist in Texas, has seen a deficiency in sex education in health care settings such as rehabilitation facilities. She makes the case for specialized sex education and sexual awareness for the staff. She advocates non-judgmental retraining for all patients and guidance, support and education for partners and family members. In rehabilitation facilities she would like to see privacy rooms. A new book just off the press is called, "Making Love Again" written by Virginia and Keith Laken from Winona, MN, deals candidly and sensitively with his impotence after prostate cancer surgery. This book may be appropriate for some of you. It costs \$24.95 and is available on line or can be ordered at bookstores.

Finally, in his book Dr. Schapiro writes, "Perhaps the single most helpful approach to managing sexual difficulties is to focus on becoming comfortable with your body, which is a goal that requires time and commitment. It is important to identify your positive personal qualities and to put effort into feeling good about yourself by taking care of your body through exercise, diet, dress, and so forth. Feeling good about yourself will

help to defeat the myth that you must have a 'perfect' body to be sexually attractive."

AN INTERNATIONAL FORUM ON BIOETHICS

Daniela Iser, Switzerland

Early in June 2002, the Federal Foreign Office of Germany and the French Ministry of Foreign Affairs, in conjunction with the National Ethics Council of the Federal Republic of Germany and the National Consultative Ethics Committee for Health and Life Sciences of the French Republic, organised a forum with the title *Towards a global bioethic? An intercultural policy dialogue* in Berlin, Germany.

The introductory text with intentions and goals and the final statement include essential questions and findings to the presently active international debate on the issue of how medical progress in its manifold aspects could or should be handled. They demonstrate that critical views from different societal backgrounds need to find a global consensus for these difficulties. For example: the Catholic Church claims that human life begins with the fusion of egg cell and sperm cell, but in Hindu opinion, an embryo is not a human being. India, therefore, does not have problems to do research on embryos that are not older than 13 days. Or: rabbis in Israel do not mind reproductive cloning, as it can serve to improve God's creation (1). The Forum was supposed to provide an opportunity not only for policy-makers and prominent scientists but also leaders of civil society and representatives of the private sector from Africa, Asia, America and Europe to meet and discuss such complex issues in depth and see whether collective opinions can be assumed and a general chorus is possible at all.

The content of the descriptive matter of invitation and programme ran as follows:

"At the latest since the production of the first working draft of the human genome sequence, gene technology as well as in particular stem-cell and embryonic research have been at the centre of public debate.

The ongoing debate highlights not only the extraordinary scientific and medical potential of these advances but also their momentous ethical, legal, social and commercial implications. New developments and research in the field of gene technology raise issues central to our understanding of human life and existence.

How can we keep up with the pace of developments? What should be our response to the new ethical issues, potential medical advances, commercial opportunities and political challenges?

Clearly, scientific progress also means new issues are placed on the international agenda. A number of international organizations have already begun to address various questions arising from the gene technology revolution (patent protection, biomedical applications, bioethics, ban on cloning). As far as the international debate on such issues is concerned, there has been little

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effort so far to involve the developing countries. Some emerging economies, however, are manifestly keen to contribute to these advances. What are the expectations fuelling genetic research and what is the role of philosophical, cultural and religious values in this area? (2) The text of the final declaration sketches the fact that some questions in the bioethical field must not be answered within the borders of a region or a country, not even a larger part of this globe. These parts, on the other hand, need to be involved in intense dialogues, however difficult they may prove to be. They are indispensable.

"There is a growing consensus that bioethical and related biopolicy issues need to be reflected in an international context taking into account the philosophical, cultural and religious values of different societies. The participants were invited to discuss if there is a minimum consensus on a global bioethics acceptable to all. After two days of intense and free discussions they found that there is emerging consensus in the following areas:

- *Necessity to ban effectively reproductive cloning of human beings by any appropriate means, such as an international convention.*
- *Social justice, equitable access to scientific progress, accessible health care systems.*
- *International cooperation; joint research in biotechnology, stem cells and genomics as well as in their ethical, legal and cultural background is essential. International cooperation should respect the diversity of cultures. It must not lead to exploitation.*
- *Recognition of the potential of stem cell research as well as its controversiality due to ethical concerns.*
- *Prohibition of commercialisation of the human body, especially a ban on international trade of embryos. Attention should be given to avoid the exploitation of women.*
- *Necessity to further address the question of germ line interventions.*
- *Commercial aspects of biotechnology should not compromise the inalienable primacy of respect for human dignity and human rights. (2)*

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1. Güntner, Joachim. *Kulturelle Differenzen – Ein internationales Forum zur Bioethik*. Neue Zürcher Zeitung, 7. June 2002.
2. Reprinted with permission by the Federal Foreign Office of Germany

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