



EDITORIAL

Michael Morgan

Organising the 2001 AGM proved to be difficult. Edinburgh in Scotland, was supposed to be the location, but it was suddenly changed to Gatwick, south of London. However, it seemed that Gatwick was not a suitable location either. So, the venue changed again to Ataxia UK's office in London. Then, London turned out to be too expensive for most delegates. Ataxia UK saw no possibilities to organise the meeting within the financial limits of most delegates and had sadly to withdraw their offer to host the meeting.

As happened before in 1997, when the Flemish suddenly withdrew, the Dutch saved the AGM again. The Dutch FA group will host this year's AGM in Lunteren, where we met before in 1995 and 1997. The date changed to 2-4 November as no other weekends were available. For the latest details see our website at:

<http://home.wanadoo.nl/euro-ataxia/agm01.htm>.

We will post the details up there as soon as we get them.

The medical news in this edition is taken up primarily with the successful breeding of an FRDA mouse. Inside, Michel Koenig gives a more or less scientific evaluation of what they have done, while Michael Morgan gives a more layman's point of view.

Newcomers to the world of Ataxia are Philip Grammont and his SCD Euro group. This started independently, but as it follows precisely the same aims as Euro-Ataxia, it was decided to bring it in as part of the main group.

All good things come to pass. This will be the last issue under the present editor. Michael Morgan has decided to retire and his successor will be named at the forthcoming AGM. He will continue to sub-edit articles sent in, but will, alas, no longer attend AGM's or public conferences. Basically, it's time we brought some new talent into the picture, and making way for the new generation seems the best course.

Having ataxia and trying to operate voice software is not an easy thing. Essentially the problem is one of controlling the ataxic voice into a consistent run of intonation for data input into a computer. Carolien Koopmans has been struggling for years with successive voice software programmes, but has finally found a way to master it. Inside she gives her assessment of how to make the thing work – which is a lot more than your editor can do.

Voice problems in Friedreich's Ataxia are now the subject of a study being carried out at the University of Ulster, in Ireland. Inside, Bronagh Blaney gives an overview of what this research is about, and also focuses on the day-to-day problems many ataxic people face.

CONTENTS

Editorial	1
Mouse models for Friedreich Ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits	2
There was a mouse.....	4
SCD Euro: First steps	5
Mastering Dragon NaturallySpeaking English	6
Dysarthria in Friedreich's Ataxia: University of Ulster research	7
Members & contacts	8

Editor

Michael Morgan
2 Glenhill Park
Glen Road
Belfast BT11 8GB
Northern Ireland
Tel: +44 2890 302944
Fax: +44 2890 302973
E-mail: mmorgan@utvinternet.com

Co-editors

Carolien Koopmans
Hans Doré
Marco Meinders

Lay out

Hans Doré
Mina Krüseman-erf 131
NL-3315 GE Dordrecht
Netherlands
Tel: +31 78 6212110
Fax: +31 78 6215287
E-mail: dore@daz.eur.nl

MOUSE MODELS FOR FRIEDREICH ATAXIA EXHIBIT CARDIOMYOPATHY, SENSORY NERVE DEFECT AND FE-S ENZYME DEFICIENCY FOLLOWED BY INTRAMITOCHONDRIAL IRON DEPOSITS.

Hélène Puccio, Delphine Simon, Mireille Cossée, Paola Criqui-Filipe, Francesco Tiziano, Judith Melki, Colette Hindelang, Robert Matyas, Pierre Rustin and Michel Koenig

Friedreich ataxia (FRDA), the most common autosomal recessive ataxia, associates degeneration of the large sensory neurons and spinocerebellar tracts, cardiomyopathy and increased incidence in diabetes^{1,2}. FRDA is caused by severely reduced levels of frataxin, a mitochondrial protein³ of unknown function. Yeast knock-out models, histological and biochemical data from patients heart biopsies or autopsies have shown that frataxin defect causes a specific iron-sulfur protein deficiency and intramitochondrial iron accumulation⁴⁻⁷. We have recently shown that complete absence of frataxin in the mouse leads to early embryonic lethality⁸, demonstrating an important role for frataxin during mouse development. Through a conditional gene-targeting approach, we have generated in parallel a striated muscle frataxin-deficient line and neuron/cardiac muscle frataxin-deficient line, which together reproduce important progressive pathophysiological and biochemical features of the human disease, including cardiac hypertrophy without skeletal muscle involvement, large sensory neuron dysfunction without alteration of the small sensory and motor neurons, and deficient activities of complexes I-III of the respiratory chain and of the aconitases. Our models allow to demonstrate time-dependent intramitochondrial iron accumulation in a frataxin deficient mammal, which occurs after onset of the pathology and after inactivation of the Fe-S-dependent enzymes. These mutant mice represent the first mammalian models to evaluate treatment strategies for the human disease.

Mice homozygous for a conditional allele of *Frda* (*Frda*^{L3/L3}) were crossed with mice heterozygous for the deletion of *Frda* exon 4 (*Frda*^{Δ+}) and carrying a tissue specific Cre transgene [under the control of the muscle creatine kinase (MCK)⁹ and the neuron-specific enolase (NSE)¹⁰ promoters] to induce striated muscle- and neuron- restricted exon 4 deletion, respectively. For both crosses, the expected ratio of *Frda*^{L3/Δ}; MCK-Cre⁺ or *F Frda*^{L3/Δ}; NSE39-Cre⁺ newborns (MCK and NSE mutants, respectively) was obtained, indicating no significant embryonic lethality. NSE mutants present a weight reduction at birth accompanied by progressive neurological phenotype including ataxia, hunched stance, and loss of proprioception. They have a short life expectancy (24 ± 9 days) with a 41% weight difference at death compared to littermates. MCK mutants loose weight at around 7 weeks, and progressively develop signs of fatigue to die at 76 ± 10 days, with a 29% weight difference at death.

We observed a restricted absence of full length transcript and protein in skeletal and cardiac muscles of

MCK mutants, indicating 100% excision in these tissues. In contrast, excision of the full length transcript in the NSE mutants occurred in neuronal as well as non-neuronal tissues, such as heart and liver, as previously described¹⁰. In these animals, frataxin protein is absent in heart and is present in a variable reduced amount in brain, liver, and kidney. The incomplete excision observed in neuronal tissues, particularly brain stem, does not exclude the possibility of high rate of specific excision in neurons “diluted” in the mass of the other cells such as glia.

Both mutant lines exhibit a cardiac hypertrophy as substantiated by the wet weight (normalized to body weight) of hearts. Histological analysis confirmed the presence of cardiac hypertrophy, as evidenced by a thickening of the walls of the left ventricle, and showed myocardial degeneration with cytoplasmic vacuolization in the myocytes, evidences of necrosis, as well as post-necrotic fibrosis in the MCK mutants, presumably related to the longer disease duration. In MCK mutants, the initial cardiac hypertrophy develops into a dilated cardiomyopathy, consistent with the natural history of the human disease. The earlier onset of cardiomyopathy in NSE mutants compared to MCK mutants, despite less extensive excision in the former is puzzling. However, the pathologic changes in the other tissues are likely to explain the more severe presentation of the NSE mutants, and may contribute to the earlier heart involvement.

By heart electron microscopy of both mutant lines, we observed myofibrils with abnormal alignment and disruption, as well as disintegrating mitochondria with centrally placed tubular cristae, highly suggestive of a mitochondrial dysfunction. In addition, in the myofibrils of NSE mutants, 50% of mitochondria appeared to be swollen), and there was an abnormal abundance of lipid droplets. These lipid droplets are suggestive of a defect in one of the many steps of lipid homeostasis, and are frequently observed in sample tissues from patients with respiratory chain defects¹¹. In the MCK mutants, we observed atrophied myofibrils pushed to the periphery of the fiber, and a proliferation of mitochondria (presumably compensatory for a functional defect) with only rare swollen mitochondria.

NSE mutants also develop a rapidly progressive movement disorder characterized by gait abnormality with the average onset of ataxia at 12 days accompanied by progressive loss of proprioception. By 16 days, most of the NSE mutants were moribund and rapidly stop gaining weight (some even rapidly lost weight). Histological analysis of the NSE mutants nervous system revealed areas of degeneration and necrosis shared

with FRDA pathology, such as the dentate nucleus of the cerebellum and the brain stem (consistently observed in the trigeminal nucleus and tracts, the vestibular system and the cochlear nuclei and nerve). However, NSE mutants also exhibit spongiform degeneration in areas preserved in FRDA patients, such as the brain cortex, particularly the frontal cortical regions. Vacuoles were observed mostly within neuronal cytoplasm, and occasionally in neuronal nuclei and other structures.

On electromyographic measurements, sensory nerve conduction on the caudal nerve (almost exclusively composed of small diameter sensory axons) and motor evoked potential measurements were normal. In contrast, the absence of H band response (sensorimotor reflexes) after sciatic nerve stimulation indicates that the large myelinated proprioceptive sensory neurons are functionally defective. The peripheral nerve deficiency is therefore restricted to the large myelinated sensory neurons, a distinctive pathological selectivity characteristic of FRDA.

The prevailing hypothesis supposes that frataxin is involved in the regulation of mitochondrial iron export¹², and that impaired intramitochondrial iron metabolism results in iron overload⁴ and defective Fe-S formation⁶. Whether frataxin directly binds iron is currently controversial¹³⁻¹⁵. Recent studies in yeast suggest that aconitase deficiency is not a mere consequence of iron accumulation¹⁶. We found, in the 10 weeks old MCK mutants, the presence of small intramitochondrial electron dense deposits consistent with iron accumulation. The ferric nature of these deposits was further suggested by the positive Perls staining on histological sections. Iron accumulation appears to be a time-dependent event as no positive Perls staining was seen in the hearts of 7 weeks old animals, and electron dense deposit were not consistently seen. Direct measurement of iron concentration by atomic absorption spectroscopy in heart mitochondrial-enriched fractions revealed that at 7 weeks mitochondrial iron appears normal or slightly increased in MCK mutant heart mitochondria (791 ±108 ng iron/mg protein versus 749 ±35 ng iron/mg protein (n=4)), while at 10 weeks, heart mitochondrial iron is significantly increased [1049 ±205 ng iron/mg protein versus 579 ±65 ng iron/mg protein (n=4, p=0.005)], in agreement with the appearance of positive Perls staining. No iron deposits nor Perls staining was seen in the NSE hearts. These results demonstrate that iron deposits are subsequent and not causative to heart pathology.

We observed a dramatic decrease in the intensity of succinate dehydrogenase (SDH) staining in the mutant cardiac tissues (NSE mutants at 2-3 weeks and MCK mutants at 7 and 10 weeks, with no significant difference in cytochrome c oxidase (Cox). Biochemical analysis of MCK (7 and 10 weeks) and NSE (at death) mutants cardiac tissues revealed that complexes I, II, III of the respiratory chain and aconitases were specifically deficient, consistent with the specific loss of Fe-S

proteins activities in patients heart⁶. We observed a 4 to 8 fold complex II deficiency and a 2 to 4 fold aconitase deficiency. No significant difference was observed in the heart of 2 weeks old MCK mutants, suggesting that despite absence of frataxin, the biochemical phenotype occurs with delay. In addition, preliminary results in neuronal tissues of NSE mutants suggest similar biochemical dysfunction. Therefore, it appears that multiple Fe-S enzymes deficiencies occur in parallel to pathology in the heart and central nervous system of the frataxin deficient conditional mutants.

Our results demonstrate that hearts from 7 weeks old MCK mutants have a marked deficit in respiratory chain complexes I-III and aconitase activities with no or limited intramitochondrial iron deposits and no measurable mitochondrial iron accumulation, which becomes overt at later stages (10 weeks). Moreover, the NSE mutant animals do not present any iron deposit at death, while a deficit in Fe-S enzymes is present. Both models therefore indicate that the Fe-S deficiency and cardiomyopathy are independent of mitochondrial iron accumulation, which is time dependent. Some of the tissue specificity characteristics of FRDA are reproduced in both models, independently of the Cre promoter specificity. As in patients^{2,6}, the skeletal muscles of both models show no histological, ultrastructure, or biochemical defect, despite extensive Cre recombination in this tissue in the MCK model. This indicates that skeletal muscles which normally expresses high levels of frataxin are not as sensitive as heart to frataxin deficiency. Similarly, despite large neuronal expression of the NSE39-Cre transgene, and particularly in the motor neurons of the spinal cord¹⁰, the latter do not show obvious signs of pathology in our frataxin conditional knock-out, both at the histological and electrophysiological level. The absence of motor nerve defect is a hallmark of FRDA², used for differential diagnosis with related conditions, such as Charcot-Marie-Tooth disease. Here again, part of the natural history of the disease is reproduced in the peripheral nervous system of the NSE mutants, even if degeneration in the brain structures is much more dramatic than in the human disease. Possible explanations for the cellular specificity of the pathology may relate to frataxin level of expression¹⁷⁻¹⁹, absence of regeneration capability, and higher sensitivity to mitochondrial dysfunction.

In conclusion, we have generated conditional mouse models for FRDA which exhibit important pathophysiological and biochemical features of the human disease. Our MCK model allows for the first time to demonstrate intramitochondrial iron accumulation in a frataxin deficient mammal but also that it does not represent the causative pathological mechanism. These models will allow for the detailed study of the mechanism of frataxin involvement in iron metabolism and Fe-S cluster biogenesis, and will be useful in the evaluation of treatment modalities, including antioxidant and iron chelators strategies.

References

1. Durr, A. *et al.* Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N. Engl. J. Med.* **335**, 1169-1175 (1996).
2. Harding, A.E. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* **104**, 589-620 (1981).
3. Campuzano, V. *et al.* Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum. Mol. Genet.* **6**, 1771-1780 (1997).
4. Babcock, M. *et al.* Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. *Science* **276**, 1709-1712 (1997).
5. Foury, F. & Cazzalini, O. Deletion of the yeast homologue of the human gene associated with Friedreich's ataxia elicits iron accumulation in mitochondria. *FEBS Lett.* **411**, 373-377 (1997).
6. Rotig, A. *et al.* Aconitase and mitochondrial iron-sulphur protein deficiency in Friedreich ataxia. *Nature Genet.* **17**, 215-217 (1997).
7. Lamarche, J.B., Shapcott, D., Cote, M. & Lemieux, B. Cardiac Iron Deposits in Friedreich's Ataxia. in *Handbook of Cerebellar Diseases* (ed. Lechtenberg, R.) 453-458 (Marcel Dekker, New York, NY, 1993).
8. Cossee, M. *et al.* Inactivation of the Friedreich ataxia mouse gene leads to early embryonic lethality without iron accumulation. *Hum. Mol. Genet.* **9**, 1219-1226 (2000).
9. Wang, J. *et al.* Dilated cardiomyopathy and atrioventricular conduction blocks induced by heart-specific inactivation of mitochondrial DNA gene expression. *Nature Genet.* **21**, 133-137 (1999).
10. Frugier, T. *et al.* Nuclear targeting defect of SMN lacking the C-terminus in a mouse model of spinal muscular atrophy. *Hum. Mol. Genet.* **9**, 849-858 (2000).
11. Watmough, N.J. *et al.* Impaired mitochondrial beta-oxidation in a patient with an abnormality of the respiratory chain. Studies in skeletal muscle mitochondria. *J. Clin. Invest.* **85**, 177-184 (1990).
12. Radisky, D.C., Babcock, M.C. & Kaplan, J. The yeast frataxin homologue mediates mitochondrial iron efflux. Evidence for a mitochondrial iron cycle. *J. Biol. Chem.* **274**, 4497-4499 (1999).
13. Adamec, J. *et al.* Iron-dependent self-assembly of recombinant yeast frataxin: implications for friedreich ataxia. *Am. J. Hum. Genet.* **67**, 549-562 (2000).
14. Musco, G. *et al.* Towards a structural understanding of Friedreich's ataxia: the solution structure of frataxin. *Structure Fold Des.* **8**, 695-707 (2000).
15. Dhe-Paganon, S., Shigeta, R., Chi, Y.I., Ristow, M. & Shoelson, S.E. Crystal structure of human frataxin. *J. Biol. Chem.* **275**, 30753-30756 (2000).
16. Foury, F. Low iron concentration and aconitase deficiency in a yeast frataxin homologue deficient strain. *FEBS Lett.* **456**, 281-284 (1999).
17. Campuzano, V. *et al.* Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* **271**, 1423-1427 (1996).
18. Koutnikova, H. *et al.* Studies of human, mouse and yeast homologues indicate a mitochondrial function for frataxin. *Nat. Genet.* **16**, 345-351 (1997).
19. Jiralerspong, S., Liu, Y., Montermini, L., Stifani, S. & Pandolfo, M. Frataxin shows developmentally regulated tissue-specific expression in the mouse embryo. *Neurobiol. Dis.* **4**, 103-113 (1997).
20. Dierich, A. & Dollé, P. in *Methods in Developmental Toxicology and Biology* (ed. Klug, S.a.T., R.) 111-123 (Blackwekk Science, Oxford, UK, 1997).
21. Sambrook, J., Fritsch, E.F. & Maniatis, T. *Molecular Cloning: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).
22. Rustin, P. *et al.* Biochemical and molecular investigations in respiratory chain deficiencies. *Clin. Chim. Acta* **228**, 35-51 (1994).
23. Dupe, V. *et al.* In vivo functional analysis of the Hoxa-1 3' retinoic acid response element (3'RARE). *Development* **124**, 399-410 (1997).
24. Doevendans, P.A., Daemen, M.J., de Muinck, E.D. & Smits, J.F. Cardiovascular phenotyping in mice. *Cardiovasc. Res.* **39**, 34-49 (1998).
25. Burck, U., Goebel, H.H., Kuhlendahl, H.D., Meier, C. & Goebel, K.M. Neuromyopathy and vitamin E deficiency in man. *Neuropediatrics* **12**, 267-278 (1981).
26. Koenig, M. Friedreich Ataxia and AVED. in *The Metabolic and Molecular Basis of Inherited Disease* (ed. Scriver, B., Sly, Valle) Chapter 232 (MacGraw-Hill, New York, 2001).

THERE WAS A MOUSE...

Michael Morgan

The news last February that two French FRDA research teams had succeeded in breeding 'knock-out' mice went largely unreported. But this in fact represents another major stage in the development of effective therapeutic interventions and drug treatments against FRDA, because now we have an invaluable research tool that will allow us to open up the study of disease pathology, and carry out large-scale testing. In short we're a step closer to our ultimate goal of stopping FRDA in its tracks.

But, first, we need to ask why is it so important to develop a mouse – or indeed any animal - model, and, second, why was this so difficult to achieve in practice?

Some may still be surprised that the original research on FRDA took place using yeast. In fact the humble yeast model has proved its worth as a tool for scientific research many times over. But there's just so much you can do with yeast, that's the trouble. No process of neurodegeneration or cardiomyopathy can be analysed using yeast – both of which are vital to FRDA research – and this effectively rules out yeast as a contender. It must be done on an animal which shares a similar, mammalian structure to man, and the best candidate for this is the mouse. Life isn't so bad for the lab mice either. It may be short but there's no risk of a grue-

some end by poison, or by being ripped apart by the neighbour's cat. Whatever the animal welfare issues involved, experiments using mice is vitally important. To analyse drugs with any efficacy you *must* use a mammal structure, and this means the mouse. Now with the 'knock-out' mouse model in place it becomes possible to experiment on a serious level with drugs such as Ibedonone.

Of course the same researchers have attempted to breed 'knock-out' mice before this. Unfortunately, the creatures died within very short periods of foetal life. The reason behind this was actually quite simple: without any Frataxin at all, life is unsustainable. Those of us with FRDA have depleted levels of Frataxin in our bodies, not none at all. The problem thus facing researchers was how to limit the amount of Frataxin present in the mouse – a sort of 'fine-tuning' approach which would allow enough Frataxin going in to ensure survival, but yet which would allow for sufficient, serious loss in the specific areas that the scientists wished to study. The solution was hypothesised to generate conditional mouse models for FRDA whereby 100% knock-outs (where the amount of Frataxin drops at around birth from normal to zero) could be achieved but only in selected tissues – in the heart and muscle in the MCK mouse, or in the heart, neurons and liver in the NSE mouse. The research is attempting to fine-tune this even further by breeding mice who have their Frataxin knocked-out in neurons only.

As said above, the successful development of a mouse model is a crucially important step in that it now clears the way for drug experimentation on mammals, which hopefully should be the last stage before testing them on humans. The mouse model will also make it possible to derive cellular models and cell cultures, which in turn, will make possible new procedures for drug identification. Large-scale blind screening for new drugs will be more efficiently performed on mammalian cell cultures (drugs don't penetrate so readily in yeast cells, due to their thick protective wall). And so, the development of the FRDA mouse model takes us that bit closer to our overall goal: that of turning Friedreich's Ataxia around from being an untreatable disorder into a treatable one.

SCD EURO: FIRST STEPS

*Philippe Grammont, SCD Euro Chairman
(translated by Gillian Dupuis, SCD Euro Secretary)*

Familial Spastic Paraplegia is a neuro-degenerative condition characterized by spasticity and progressive weakness in the lower limbs. The age at onset seems to decrease with successive generations. And, FSP is very rare.

Studies concerning the frequency of spastic paraplegia in France show that about three people are affected in every 100,000. In Norway, it is estimated at 14 in 100,000, whereas in Germany some studies estimate it at only 1 in 100,000.

We can therefore estimate the total number of sufferers in the European Union (15 countries) as between 20,000 and 50,000.

SCD Euro emerged as an attempt to bring together all sufferers of Familial Spastic Paraplegia in Europe within a common organizational framework. This will aim at two goals: First, the creation of a transnational network throughout Europe will help build community, strength and confidence among FSP sufferers. Second, setting up an organizational presence at European level will help gain EU recognition, hopefully leading to more substantial support.

While SCD Euro aims to work at European level there are a number of national organizations in existence already. The Familial Spastic Paraplegia Group is a British group, having about 200 members. It is contactable on the internet at:

<http://www.fspgroup.org>.

The BSSP stands for Bundesarbeitsgemeinschaft-Sebsthilfegruppe für Spastische Spinalparalyse Erkrankte. This German group also has about 200 members. The Tom Wahlig Stiftung is a foundation named after a sufferer of this extremely rare condition. His family created the foundation with the aim of making this condition recognized and furthering research. They can be contacted at:

<http://www.fsp-info.de>.

In Sweden, there is a Swedish Discussion Forum, which can be contacted via email at:

HSP-sweden-owner@egroups.com.

The Association Strümpell-Lorrain is a very active association that is regularly called upon by people world wide (South America, Asia) and by patients in neighbouring countries. It has 450 members at the present time.

There are as well groups being set up in Portugal, Switzerland, and Finland.

As well many FSP sufferers have joined larger existing organizations for neuromuscular diseases. Interestingly though Familial Spastic Paraplegia is not universally considered as being neuromuscular.

Nevertheless the Finnish MS Society, to cite one example, does, and is ready to join a European federation if it were to be created.

There are other more isolated individual European sufferers, who have joined the American forum, at their site: <http://hspinfo.org>. This discussion group via Internet is made up of about 300 members who mainly live in the USA, as well as Canada, Australia, and New Zealand.

In May 2000 the first international HSP (Hereditary Spastic Paraplegia) meeting was organized - bringing together both sufferers and researchers. The Strümpell-Lorrain Association and Tom Wahlig Stiftung both gave presentations in the view of promoting international community and participation so that we may stay as close as possible to the particular interests of the European Community of sufferers of familial spastic paraplegia.

In January 2001, the Strümpell-Lorrain Association created a European federative association, known as SCD Euro (Spino-Cerebellar Degeneration in Europe), with the aim of grouping together existing national groups and helping other countries to create their own organizations. FSP Group (Great Britain) and TWS (Germany) have already joined the federation.

However, it was then discovered that there was already in existence an organization operating on a European level for people with Spino-Cerebellar Degeneration. SCD Euro now wants to be part of this, and intends becoming a sub-group of Euro-Ataxia – the European Federation of Hereditary Ataxias. This long established and well-connected group brings together national organizations of sufferers of Spino-Cerebellar Ataxia (a similar condition).

It seems particularly important that SCD-Euro collaborates with the European medical network SPATAX (created in France). SPATAX is primarily a scientific research network, focusing specifically on spastic paraplegia and ataxia.

Alongside this SCD Euro hopes to organize regular symposia and events in different European countries and collect money for research. These projects can only come to be if they are accepted by well-placed authori-

ties – particularly in the European Union. SCD-Euro is also planning to develop a website of its own. Up to now they have been operating on the Strümpell-Lorrain Association's web site: <http://assoc.wanadoo.fr/asl.spastic/scdeuro.htm>.

For the immediate future the objectives of SCD Euro are to obtain its own site: scdeuro.eu, to publish and disseminate information about the condition, and also to offer help and support to sufferers of the disease. We are also keen to develop contacts with the medical world and research (including collaboration with the SPATAX network).

Research wise, there are at present 19 teams (neurologists and geneticists) from 4 member states of the European Union. We hope to include representation from all at the first meeting of SPATAX, to be held in Paris, on September 28th and 29th, 2001.

We also want the network to work effectively by representing sufferers, with hopes that the medical network will extend to all of Europe.

Finally, both Gillian and myself hope to be able to come to this year's Euro-Ataxia AGM. Hope to see you there.

MASTERING DRAGON NATURALLYSPEAKING ENGLISH

Carolien Koopmans

After using NaturallySpeaking Dutch for a while I tried to master NaturallySpeaking English also. That proved to be very difficult. My pronunciation turned out to be too different from what the program expected. Especially commands as 'Correct That', which you need if the program understands something wrong, were constantly misinterpreted. It took a lot of practice and patience, but finally I succeeded. Michael Morgan asked me to write down how I did it, as it could be of help to other people.

First you should know that apart from being unable to use my hands on a keyboard or a mouse, my eyesight is very bad. It is impossible for me to see all the pull-down and pop-up menus from Windows. So I needed the help of Hans. Hans knows how to work with Windows, so he knows all the menus.

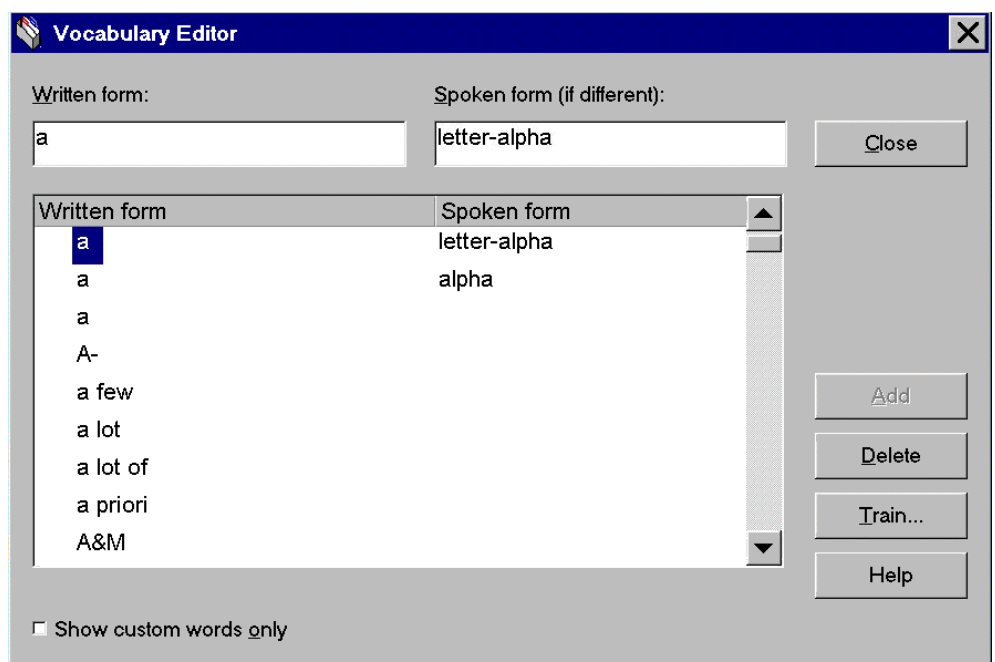
The first thing you'll have to do is a general training: you have to read out aloud one of the stories that are on the NaturallySpeaking CD. I am a slow talker so I spoke three or four words at a time. Hans clicked away or skipped the words

the program didn't accept of me. (When after some months I reinstalled the program I even read the story word for word.) After the reading of the story my speech files could be saved and I could install some options like the pause between words. For most people this general training is enough to get the program started. But for me with FA and dysarthria it was only the beginning. The real training now had to begin.

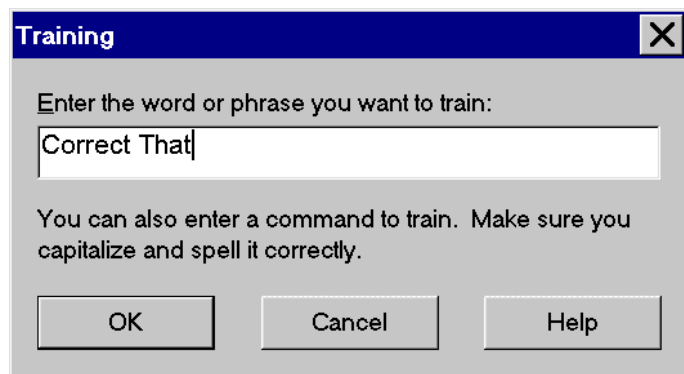
NaturallySpeaking has two menu options for training. First there is the 'Vocabulary Editor'. This is a long list of words the program knows. You can edit the list but you can also select a word and train it. The program will record the way you pronounce that word and save it to its speech files. And there is a menu 'Train Words'. This menu can also be used to train commands. Commands are certain phrases the program recognises as such and not as dictated text. In the 'Train Words' menu you have to type the word, phrase or command you want to train and then record the way you pronounce it.

The first thing I had to train was the alphabet. With two or three mouse-clicks from the Vocabulary Editor Hans selected the letters from the alphabet one by one, I read them aloud and Hans saved them to my speech files. You can choose between a few ways in which you can train the alphabet. I chose the NATO-alphabet because I am used to it. But you can mix when you spell out a word. So when the computer doesn't accept my 'golf' for g I switch to 'gee'. After I trained the alphabet I trained some words. Hans typed in the word and I spoke it, just as we did when we trained the alphabet – every word or letter three times.

Next we had to train some commands with the 'Train Words' menu. If you type a command in the 'Train Words' menu you have to spell and capitalise it correctly; all commands are capitalised. This proved the hardest part. As I said above the program didn't accept the command 'Correct That'; I trained it 10, maybe 20 times, but it just didn't work. I didn't know if the



problem was caused by the two r's or by the th following the t. I tried to train the program to accept the command as 'Oops' (which was the correct command in VoiceType, the speech recognition program I used before) but that was too different a word. You can manipulate NaturallySpeaking a bit but not too much. Anyhow after much trial and error the program accepted the command if I pronounced it as 'Correc Ted'.



After each session during which my voice is clear and the program listens to me well, I save my speech files. If my throat is unclear and hoarse I do not save the changes to my speech files. If I saved them but afterwards realised I didn't want to, Hans knows how to install the backup. Hans also knows how to use the Vocabulary Editor. If a wrongly spelled words gets in my speech files he knows how to delete it.

It is a bit difficult to get the program started but once it is used to your voice NaturallySpeaking is fantastic.

DYSARTHRIA IN FRIEDREICH'S ATAXIA: UNIVERSITY OF ULSTER RESEARCH

Bronagh E. Blaney

Dysarthria sounds pretentious but is simply the Latin name for speech changes – a common feature of a wide range of neurological disorders. Dysarthria of varying degrees is well-nigh universal among FRDA people. The exact nature of the changes vary from individual to individual but will involve symptoms such as slurring of speech, difficulty controlling volume or a voice that sounds hoarse. Many if not most in the FRDA community will also be aware of those painfully embarrassing social situations wherein accusations of drunkenness are readily made. Now researchers at the University of Ulster, outside Belfast in Northern Ireland, have become the first to study the precise nature of dysarthria in FRDA – in itself a fairly unique and novel form of the disorder. At the University of Ulster work is being carried out examining speech in FRDA in three domains: perceptual (how speech sounds to the listener), acoustic (the physical speech waveform) and physiological (the physical speech production system). The study is currently examining the speech of men presenting with FRDA in Northern Ireland. Basically information on

the following areas is being sought:

- What are the first speech symptoms?
- When do the first speech symptoms usually occur?
- Is there a pattern to the onset of these speech symptoms?
- At what rate do speech changes occur?

The study involves visiting participants in their own homes, four times over a twelve-month period. During each visit speech samples are recorded, in order to document the onset of speech problems, the pattern and the rate of change.

As could well be expected, one of the things reported by FRDA participants so far has been that most have their own particular horror story to relate on how they were accused of being drunk. While this is often laughed-off or otherwise treated light-heartedly, in fact it makes for great embarrassment and difficulty in everyday social interaction for many. In recognition of the problem Ataxia UK are currently conducting a consultation with FRDA members on what they would like to see, perhaps an identity card with the wording, "I'm not drunk, I have Ataxia" or some such warning, printed in different European languages. Think: if you thought it was difficult to convince a policeman in your own country that you are not, in fact, completely blotto, think about how much more difficult it would be to convince a foreign policeman when you don't even share the same language.

If you'd like to hear more details on the University of Ulster research, or maybe participate, please contact:

Bronagh E. Blaney
Lecturer in Communication Disorders
University of Ulster
Shore Road
Newtownabbey
Northern Ireland
BT37 0QB
Tel: +44 28 90366573
Email: be.blaney@ulst.ac.uk

EURO-ATAXIA BOARD

Ewout Brunt, President
Hooiweg 72
NL-9761 GT Eelde
NETHERLANDS
Tel/Fax: +31 50 3091109
E-mail: e.r.p.brunt@med.rug.nl

Michel Koenig, Vice-President
IGBMC
1 rue Laurent Fries, BP 163
F-67404 Illkirch Cedex-C.U. de Strasbourg
FRANCE
Tel: +33 3 88653399
Fax: +33 3 88653416
E-mail: mkoenig@igbmc.u-strasbg.fr

Dagmar Kroebel, Secretary-General
Haagwindelaan 19
B-3090 Overijse
BELGIUM
Tel: +32 2 6571510
Fax: +32 2 6576176
E-mail: dk.euro-ataxia@skynet.be

Theo Schimmel, Treasurer
Dorsvlegel 83
NL-3763 ZN Soest
NETHERLANDS
Tel: +31 35 6019382
E-mail: schimmel@casema.net

Evelyne Delion
3, allée Xavier Bichat
F-77420 Champs/Marne
FRANCE
Tel/Fax: +33 1 64687036
E-mail: cscevelyne@compuserve.com

Peter Reussner
Hinrich-Thiess-Strasse 52f
D-22844 Norderstedt
GERMANY
Tel/Fax: +49 40 55446898
E-mail: peter.reussner@t-online.de

Marco Meinders
Antilopespoor 482
NL-3607 VP Maarssen
NETHERLANDS
Tel/Fax: +31 346 580417
E-mail: ataxia@wxs.nl

Eila Niemi
Box 15, Seppäläntie 90
FIN-21250 Masku
FINLAND
Tel: +358 2 4392130
Fax: +358 2 4392133
E-mail: eila.niemi@ms-liitto.fi

Manuela Bruscia
Via delle Badie 39
I-50047 Prato
ITALY
Tel: +39 0574 631393
E-mail: many.titta@iol.it

Michael Morgan, Editor *Euro-Ataxia*
2 Glenhill Park
Glen Road
Belfast BT11 8GB
NORTHERN IRELAND
Tel: +44 2890 302944
Fax: +44 2890 302973
E-mail: mmorgan@utvinternet.com

EURO-ATAXIA MEMBERS

Association Belge de l'Ataxie de Friedreich
Rue Longue 68
B-6260 Bouffloulx
BELGIUM
Tel: +32 71 504248

Deutsche Heredo-Ataxie Gesellschaft e.V.
Haussmannstrasse 6
D-70188 Stuttgart
GERMANY
Tel: +49 711 2155114
Fax: +49 711 2155119
E-mail: dhag@ataxie.de

Associazione Italiana per la lotta alle
Sindromi Atassiche
Viale S.Lorenzo-Residence 'Azalea' 12/E 2
I-00040 Tor S.Lorenzo-Ardea (Roma)
ITALY
Tel: +39 6 91014662
E-mail: nazionale@AISAonline.cjb.net

Friedreich's Ataxia Group
10 Winchester House
Kennington Park
Cranmer Road
London SW9 6EJ
UNITED KINGDOM
Tel: +44 20 7582 1444
Fax: +44 20 7582 9444
E-mail: office@ataxia.org.uk

Asociacion Madrilenana de Ataxias
Hereditarias
C/. Galileo 69, 1º
E-28015 Madrid
SPAIN
Tel: +34 1 4482169

VSN – Werkgroep Ataxie van Friedreich
Haagweg 306
NL-2324 NC Leiden
NETHERLANDS
Tel: +31 71 5320660
E-mail: jon@bunnig.nl

ADCA-Vereniging Nederland
Fazantenkamp 839
NL-3607 EC Maarssen
NETHERLANDS
Tel: +31 346 563913
E-mail: ataxia@wxs.nl

Suomen MS-Liitto – Finlands MS-Förbund
Rare Neurological Disabilities Group
Box 15, Seppäläntie 90
FIN-21250 Masku
FINLAND
Tel: +358 2 4392111
Fax: +358 2 4392133
E-mail: ms-liitto@ms-liitto.fi

Connaître les Syndromes Cérébelleux
3, allée Xavier Bichat
F-77420 Champs/Marne
FRANCE
Tel/Fax: +33 1 64687036
E-mail: cscevelyne@compuserve.com

Ataxia Group – Neurologiskt Handikappades
Riksförbundet
Box 3284
S-10365 Stockholm
SWEDEN
Tel: +46 8 6777010
Fax: +46 8 241315
E-mail: nhr@nhr.se

Schweizerische Gesellschaft für
Muskelkranke
c/o Daniela Iser
Rüthhofstrasse 51
CH-8049 Zürich
SWITZERLAND
Tel: +41 1 3402323
Fax: +41 1 3402324
E-mail: daniela@iser.ch

Association suisse de l'Ataxie de Friedreich
La Chenaletta
CH-1566 St.-Aubin
SWITZERLAND
Tel: +41 26 6772256
Fax: +41 26 6773356
E-mail: sabine@achaf.org

CONTACTS IN EUROPE

Ataxia Telangiectasia Society
33 Tuffnells Way
Harpندن
Herts AL5 3HA
UNITED KINGDOM
Tel: +44 1582 761437
Fax: +44 1582 765014

Friedreich's Ataxia Society of Ireland
San Martino
11 Mart Lane
Foxrock
IRL-Dublin 18
IRELAND.
Tel/Fax: +353 1 2894788
E-mail: fasi@tinnet.ie

CONTACTS OUTSIDE EUROPE

National Ataxia Foundation
2600 Fernbrook Ln
Suite 119
Minneapolis, MN 55447
USA
Tel: +1 763 5530020
Fax: +1 763 5530167
E-mail: naf@ataxia.org

Association Canadienne de L'Ataxie de
Friedreich
3800, Rue Radisson, Suite 11
Montréal, Québec H1M 1X6
CANADA
Tel: +1 514 8991586

Friedreich's Ataxia Association of New South
Wales
31a Chisholm Street
Turramurra, 2074
Australia
Tel: +61 2 94408233
E-mail: jenniec@ihug.com.au



Euro-Ataxia is registered as a charity in Belgium: VZW 9240/92

Secretary-General: Dagmar Kroebel, Haagwindelaan 19, B-3090 Overijse, Belgium

Tel: +32 2 657 1510; Fax: +32 2 657 6176; E-mail: dk.euro-ataxia@skynet.be; WWW: <http://home.wanadoo.nl/euro-ataxia>

Bank: Dexia, Pachecolaan 44, B-1000 Brussels; acc. no. 068-2063656-08