



EDITORIAL

Michael Morgan

Lunteren 1997 lived up to its expectations as a key meeting for EURO-ATAXIA. Many reports were made, and decisions taken, that will affect the future working of the organisation. But science first. For those dominant ataxic people who may be feeling a little left out with all the excitement generated over Friedreich's Ataxia in recent issues of *Euro-Ataxia*, we are pleased to print inside a lengthy article by our new president, Ewout Brunt, specifically examining recent progress in dominant ataxia research. But of course it is the pace of developments in Friedreich's Ataxia Research that continues to grab attention. Inside, both Michel Koenig and Massimo Pandolfo give updates on the current state of play.

Cardiomyopathy is a frequent complication arising from Friedreich's Ataxia. Inside Pieter A. Doevendans of University Hospital Maastricht gives an overview and analysis of *Cardiac Problems In Friedreich's Ataxia*.

It's reassuring to see how scientists and clinicians world-wide are concentrating and co-ordinating their efforts on Friedreich's Ataxia Research. Towards the end of last year a major meeting was held in Melbourne, Australia. Martin Delatycki presents his assessment of what transpired.

Communication and computerisation was the chosen theme for this year's 'living with ataxia' session at the Lunteren conference, from which is derived two papers: the first, *My Life With A Computer*, by Carolien Koopmans, outlines the tremendous boost using a computer can give to anybody with ataxia going through education and pursuing a writing career; whilst the second, by Marco Meinders, explains just what lies behind the acronym INTERNAF.

The business side of the conference was dominated by two events. EURO-ATAXIA has joined EAGS – the European Alliance of Genetic Support groups. We print a presentation by Ineke Roelofs of EAGS on European co-operation in Genetics.

Also EURO-ATAXIA faces difficult financial times ahead as our EU grant hasn't been renewed. Immediately this means that there won't be a board-meeting in Brussels next March. Instead we'll be concentrating all our efforts on the 1998 AGM to be held in Turku, Finland between 25-27 September. Fuller details on this, and all other EURO-ATAXIA business, may be found inside in *Business Report*, written by Dagmar Kroebel.

Finally as this editorial was completed on 31 December 1997 I'd like to wish everyone a happy and successful new year.

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MEDICAL-SCIENTIFIC DEVELOPMENTS IN THE RECESSIVE ATAXIAS

Michel Koenig, Strasbourg

1996 may have been a breakthrough-year for Friedreich's Ataxia (FRDA) research but ongoing developments in 1997 have proved to be even more exciting. With the discovery of the molecular defect in FRDA we now have the tools to understand why the disease develops and this gives some hope for finding therapies in the future.

In collaboration with the group of Massimo Pandolfo it took us 8 years to find the gene that is responsible for FRDA. Genes are made of DNA, the substrate of hereditary information. They code for proteins. But not all parts of a gene code for the protein; there are also non-coding sequences (introns) between the coding parts (exons). What we found a year ago was that the FRDA gene is a little gene made of five exons. There was some controversy whether the FRDA-gene is really this small gene or is larger. Some were of the opinion that the larger, neighboring gene, called STM7, was also part of the FRDA-gene. Now the controversy has been solved, by demonstration that the FRDA and STM7 genes are distinct.

The FRDA Major Mutation

What goes wrong in the gene of FRDA patients? Nearly all patients have an abnormally long sequence in the first intron of their two FRDA genes. This sequence is a repeat of three letters: GAA. Normal individuals have 7 to 30 repeats. Patients can have from 100 up to 1300 repeats!

Most dominant ataxias are also caused by abnormally long repeats in genes. But these repeats are smaller, always have the three letters sequence CAG and *always* occur in the coding part (the exon) of a gene. They cause the encoded protein to contain an expansion of glutamine (called polyglutamine expansion) which is toxic for some neuronal cells. In FRDA, the repeat expansion is in the non-coding part of the gene. The FRDA protein, which we baptized frataxin, will therefore not be enlarged but will be dramatically reduced in amount. There is a correlation between the number of repeats and the amount of residual frataxin and hence the severity of the disease. Patients who have only 100 to 400 GAA repeats will start the disease later in life and will be less affected.

With the identification of the major mutation, testing of potential carriers now becomes possible. However, the carrier frequency in the general European population is low (1/100), although not negligible. Relatives of patients and their spouses can now be tested, so they know exactly the risks for their children to come.

The Origin of the Mutation

In most cases, the parents carry the GAA expansion mutation on one chromosome. In rare cases, parents of

an affected child have a number of repeats that does not cause the disease. This is called a premutation: the sequence is too large to be normal and stable, but too small to cause the disease. Large expansions derive from these premutations, in most cases several generations earlier. In turn, premutations come from repeats that are at the upper edge of normal alleles (called the 'large' normal alleles) and this is an even slower process. We found out that all individuals who carry a 'large' normal allele are the descendant of a single ancestor who lived most likely several thousand years ago and who had a mutation from a 'small' normal allele to the first 'large' normal allele. This ancestor was a person of Caucasian (Indo-European) origin because FRDA and 'large' normal alleles are not found in Far-East Asia, for example.

Site of Expression of the FRDA Gene

As said before, FRDA is caused by the absence, or dramatic reduction, of frataxin. In order to understand how its absence causes the disease, we have to understand what is its normal function. For this, we first analyzed where (in which tissues) the frataxin gene is expressed. In humans, the frataxin gene is expressed in heart, liver, muscle and pancreas, but not in brain. A more precise analysis was performed on mouse tissues, for tissue availability reasons, but knowing that some human-mouse differences may exist. In the nervous system, prominent expression is seen in the dorsal root ganglia of the spinal cord. This explains not only the massive neurodegeneration seen in the dorsal root ganglia themselves but also in the posterior columns of the spinal cord and the peripheral sensory nerves of FRDA patients, since these structures contain the axons (neuronal wires) of the neurons located in the dorsal root ganglia. Other neuronal structures known to be affected in FRDA, such as the pyramidal tracts and the spinocerebellar tracts of the spinal cord do not express the frataxin gene at a level detectable by our technique. This may indicate differences between human and mouse or the fact that degeneration of these structures are secondary events. We also found expression in neurons of the granular layer of the cerebellum, which might explain part of the cerebellar symptoms. High expression in the heart explains the hypertrophic cardiomyopathy. We also found expression in several tissues that are not known to be affected in FRDA, such as liver, muscle, thymus and brown fat (the latter in new borns). This indicates that frataxin has a more widespread function than what is suggested by the site of the disease. A possible explanation for this discrepancy is that only tissues containing cells that do not divide, such as neurons and cardiocytes (heart cells), will express the disease since cells will not be replaced when they die.

Frataxin Function

What is frataxin doing in all these cell types? First, frataxin is a small protein of 210 amino-acids (the

building blocks of proteins), that also exist in many living organisms such as the round worm, the baker's yeast and even in some bacteria, which indicates a very ancient function for this protein. Second, frataxin is present in subcellular structures called the mitochondria, which are the power plants of the cells. We developed antibodies against frataxin, as a tool to detect this protein. Using these antibodies, we found that frataxin is associated with the mitochondrial membranes (the envelopes of the mitochondria). A first clue on frataxin function was obtained by analyzing the baker's yeast counter part, or more exactly, the mutant of the frataxin homologue (work of the groups of J. Kaplan (Salt Lake City), F. Foury (Louvain la Neuve) and R. Wilson (Philadelphia)). The yeast mutant has a mitochondrial 'disease' caused by a dramatic accumulation of iron within the mitochondria. This was reminiscent of the previously known, but overlooked, granular iron deposits specific of heart tissue from FRDA patients.

Role of Iron in the Mitochondria

As said above, mitochondria are the power plants of cells, by generating the universal fuel of living cells, a molecule called ATP. Schematically, this is achieved by transporting electrons, provided by food such as sugar and lipids, down an electro-chemical gradient along the mitochondrial membrane up to oxygen to produce water. The protein complexes that perform the electron transport contain iron necessary for this function. However, an excess of iron is damageable to the mitochondria, since electrons will escape the protein complexes too early and oxidize oxygen in a toxic form (the so called free radicals, such as the superoxide ion : O_2^-). Also, excess iron will convert the superoxide ions into an even more toxic form called the hydroxyl radical (OH^\cdot), and this will cause irreversible damage. The group of A. Rötig and P. Rustin (at Hôpital-Necker, Paris) have also found that in heart biopsies of FRDA patients, iron containing enzymes, such as the one in the electron transport complexes, are partially or totally inactivated, presumably by an excess of superoxide ions to which they are exquisitely sensitive. All these data point to oxidative stress (production of free radicals) as the mechanism of disease in FRDA.

Similarity with Other Neurodegenerative Diseases

Another neurodegenerative disease, the familial form of ALS (amyotrophic lateral sclerosis) is caused by mutations in the superoxide dismutase, the enzyme responsible for inactivating the superoxide ions. This again suggests a neurodegenerative mechanism by oxidative stress. More akin to FRDA is the ataxia due to isolated vitamin E deficiency (AVED), which is often clinically mistaken with FRDA. The major known role of vitamin E is that of a membrane anti-oxidant, acting by inactivating free radicals. It is therefore striking that the clinically similar FRDA and AVED seem to be caused, respectively, by an excess of free radical

production and by a reduction of free radical inactivation. How the lack of frataxin causes iron accumulation in yeast – and presumably also in patients, though probably to a lesser extent – is not known, since little is known as yet about mitochondrial iron import and export. This in fact is the goal of our present work.

Prospects for Therapy

Could a therapy be developed to remove iron from the mitochondria? One possibility put forward by Drs. J. Kaplan and M. Pandolfo is to use iron chelators to displace iron out of the mitochondria. However both mutant yeast and patients heart biopsy studies suggest that the cytosol (in which the mitochondria are 'floating') is already depleted of iron. It remains to be seen whether iron chelators will have any beneficial effects on mitochondrial iron and will not aggravate cytosolic iron depletion or cause general iron deficiency. An alternative approach would be to act on detoxification of free radicals with anti-oxidant molecules, many of which exist. A combination of the two approaches could as well be envisaged. Given the diversity of possible therapeutic protocols, it would be extremely valuable to have an animal model of FRDA, in order to test rapidly which one, if any, is the most efficient with least secondary effects. Such a mouse model is presently being constructed in our laboratory.

FRDA RESEARCH UPDATE

Massimo Pandolfo

Where are we now with research into Friedreich's ataxia? The short answer is that investigations are continuing at all levels.

At the DNA level, analysis of the properties and effect on gene expression of the GAA expansion (remember that in FRDA there is a GAA triplet repeat expansion in the first intron of the frataxin gene) is going on. It is now clear that the expansion results in a low level of frataxin (from 3-4% to 20-25% of normal), and the mechanisms are actively investigated in a number of models.

At the cellular level, it has been established that frataxin is a mitochondrial protein, expressed at highest levels in the tissues affected by the disease. Hints about its function came from experiments in yeast, indicating that in this organism frataxin prevents iron accumulation in mitochondria. Yeast cells without frataxin become also very sensitive to oxidants, and this is because iron reacts with some oxygen-derived molecules (normally generated in cells as by-products of respiration) to produce highly reactive substances (free radicals) that damage cellular structures. The Fenton reaction, quoted in a message to INTERNAF, is the reaction of iron with hydrogen peroxide that generates

the highly toxic hydroxyl radical. Some evidence of disturbed iron metabolism in FRDA patient was already available (e.g. iron deposits in the heart), and additional evidence was found recently (deficiency of some iron-containing enzymes also in the heart). Current research is focusing on investigating if frataxin deficiency in human cells also results in mitochondrial iron accumulation and oxidative damage. Mouse models of FRDA (frataxin deficient mice) are being developed in at least two labs and will be available in several months. These mice will make no frataxin at all, different from the human FRDA patient who still make some protein, so they may be very severely affected or even not viable. We have to wait and see. In addition, blood studies and studies with magnetic resonance imaging and spectroscopy are planned or being done to detect possible anomalies of iron metabolism that can be monitored in patients, and possibly used not only to investigate the disease process, but also to follow up the effect of any experimental treatment.

Analysis of mutations is also continuing, including the rare frataxin point mutations, that is DNA abnormalities in the coding sequence for frataxin which cause a deficiency in a different way than the GAA expansion. Concerning FRDA cases without any mutation in the frataxin gene, in my experience (and also reported in published papers) there are rare individuals with a FRDA-like clinical picture whose disease is due to abnormalities in a different, yet unidentified gene on a different chromosome. If there are also cases with different, yet undetected frataxin mutations remains to be established.

Concerning perspectives for treatment trials in the not-so-distant future, discussion is going on among the participants to the network created at the Montreal meeting (29 May - 1 June, 1997). In addition, on October 29 some of us had a very interesting meeting in Baltimore in which many issues concerning possible drug trials in FRDA were discussed. Participant, in addition to myself, included Drs. T. Ashizawa (Baylor Coll. of Med., Houston), D. Geschwind (UCLA), H. Paulson (Philadelphia), B. Keats (New Orleans), S. Forrest (representing the Melbourne group), M. Scavina (Dupont Institute, Wilmington), and two hematologists, one from the Dupont Institute and one from U. of Utah. There was a general consensus that any trial with patients should be postponed until more basic research has been carried out. The key points are:

- a. Determine to what extent the yeast knock-out data can be replicated in human FRDA cells, including evidence of mitochondrial iron accumulation and of increased sensitivity to oxidants;
- b. Collect evidence of iron accumulation and oxidative damage in patients' pathological samples;
- c. Evaluate if iron chelators are effective in cell culture to remove excess iron from mitochondria and to correct any observed defect in FRDA cells.

Inclusion and exclusion criteria for a trial, possible drug choices, dosage, and route of administration, evaluation and testing of patients in trials were also discussed. In summary, if research results will confirm that this is a promising avenue, chelator trials may possibly be planned within the next year. I have also to say that some groups would like to go ahead in a shorter time with trials involving only antioxidant drugs, considered much safer than chelators. Antioxidants would not remove any excess iron, but would contrast its effects.

RECENT PROGRESS IN DOMINANT ATAXIA RESEARCH

Ewout Brunt

In this presentation, I will summarize existing data on dominant ataxia: I will highlight last years contribution in spinocerebellar ataxia (SCA) research before mentioning our own studies in the University of Groningen.

Dominant ataxia differs from Friedreich's ataxia in that, whereas in FA too little frataxin causes a loss of function, the dominant inherited ataxias or SCA's are supposed to be caused by a gain of function. Of every gene, two copies are present. In dominant ataxia only one gene is changed, has a mutation, while the other gene is normal. Therefore, in SCA, two different products of the same gene are expressed in the body. Until now, all dominant ataxias share the same type of mutation; an abnormal expansion of a CAG-trinucleotide repeat in the coding region of the gene. The letters CAG stand for 'cytosine', 'adenine' and 'guanine', indicating the nucleic acid elements that make up the DNA strand. One copy of CAG in the DNA produces one building stone, i.e. one glutamine amino-acid, of a protein. So expanded CAG repeats in the gene result in expanded polyglutamine stretches in the gene product protein, and the abnormal gene is translated into an abnormal protein.

Now, how do specific abnormal proteins cause cell death of certain cells in the brain? With one single exception, the function of the SCA proteins, called ataxins, is unknown. Possibly, the abnormal proteins, derange cellular metabolism, either by interfering with their normal function, or by interfering with another cellular function, and this may well cause a chain of events. Smaller or larger clinical and pathological differences between the SCA's, suggests that their respective ataxin proteins differ in their normal and abnormal function. However, it is well conceivable that in different SCA's, mechanisms of cell death share common principles.

In broad lines, the approach to untangle the mechanism of selective neurodegeneration in SCA has been: localization and identification of the responsible gene,

next, analyzing the gene product, and then, finding out its normal and abnormal function. Of course the aim of all this research is the possibility to treat people with this type of ataxia, and to slow down or stop the dying of nerve cells in their brains.

An estimated 50-60% of all dominantly inherited ataxia's have now been genetically localized or identified. At present, we know 7 types of SCA and one additional type of autosomal dominant ataxia called DRPLA (Dentato-Rubro-Palido-Luysian Atrophy). In 6 of these 8 types of dominant ataxia the genes have been identified (SCA1,2,3,6,7 and DRPLA), and individual diagnostic or presymptomatic testing for these types is possible. For the other 2 types, the genes have been localized (SCA4 and 5). For these types, diagnosis is only possible by linkage in relatively large families.

This year has seen important progress in SCA research. Transgenic mouse models have now been developed for two types of SCA; SCA1 and SCA3/MJD. In these animal models the function of the ataxin proteins and neurodegeneration in SCA can be studied in detail. At least three research centers work now with a SCA3/MJD mouse.

In 1997, the genes have been identified of 2 additional SCA types, SCA6 and SCA7. SCA6 is an entirely new type. It was assigned a number that had been reserved earlier, but that had never been used. Of SCA7, the genetical locus was already known. Similar to earlier identified SCA types (SCA1, 2, 3 and DRPLA), SCA6 and SCA7 also are caused by a CAG trinucleotide repeat expansion.

Clinically, SCA6 is characterized by a relatively late onset, on average about 50 yrs, and a relatively 'pure' cerebellar ataxia with little spasticity. This type of dominant ataxia has clinically been known for almost a century as 'Holmes type of dominant ataxia'.

The SCA6 gene is particularly interesting for two reasons. The first reason is, that this gene also is responsible for two other neurologic disorders, both of which have episodic manifestations; familial hemiplegic migraine, and familial episodic ataxia type 2. The three diseases caused by mutations in the same SCA6 gene, are called allelic diseases. In familial hemiplegic migraine, attacks of migraine are followed by hemiplegia lasting several days. In familial episodic ataxia type 2, periods of hours to several days of ataxia occur, but between the attacks, patients move normally. In fact, episodic manifestations not only occur in familial hemiplegic migraine and episodic ataxia type 2, but also in SCA6. As we could confirm in the 4 Groningen SCA6 families, two notable aspects of SCA6 are the occurrence of episodes of ataxia, and attacks of headache in about half of the patients. The episodes of ataxia last up to several days, and sometimes occur many years before the actual progressive ataxia starts. The mutations of these three allelic diseases differ. Familial hemiplegic migraine is caused by a single nucleic acid 'missense mutation', which leads to the sub-

stitution of an aminoacid in the protein. Episodic ataxia type 2 is caused by a 'point mutation', which leads to a truncation of the protein.

The second reason why the SCA6 gene is particularly interesting, is because this gene, also known as the CACNL1A4 gene, is the only SCA gene of which the function is presently known. It codes for a protein that is part of a voltage operated calcium channel, which happens to be prevalent in the central nervous system, notably in cerebellar tissue. This calcium channel belongs to a large group of ion-channels, which open (are 'activated') either by message molecules ('receptor operated'), or by a shift in voltage over the cellular membrane ('voltage operated'). Each of these ion-channels regulate the entrance into the cell or the egress from the cell, of a single type of molecule like sodium, potassium or chlorine. Following opening of the channel, these ions usually run 'downstream' along with a concentration gradient.

The SCA6 or CACNL1A4 gene protein is the '1 alpha 4 subunit' of a calcium channel, which plays an important role in nerve cell excitation. It regulates the entrance of calcium into these cells, which serves to normalize the membrane potential following depolarization. Calcium not only plays an important role in membrane excitation, but also in cell metabolism, and here a possible link to neurodegeneration may be found. If calcium accumulates in the cell, it becomes toxic and may cause derangement of cell metabolism. An excess of calcium impairs the energy metabolism and may cause cells to die. This is for instance what happens after a stroke.

Summer 1997, three simultaneously appearing papers described the SCA7 gene on chromosome 3p. The mutation causing SCA7 is another CAG expansion, which is translated into a polyglutamine stretch in the gene product protein. Like in SCA1, 2 and 3, the function of the SCA7 protein is not known. Clinically, SCA7 differs from all other SCA's by the occurrence of progressive loss of sight in addition to ataxia in some of the affected family members. This loss is due to retina degeneration.

August of 1997, another important advancement in SCA research was published, together with comparable findings in Huntington's disease. Huntington's disease is another autosomal dominantly inherited neurological disease, which like the SCA's, is also caused by an expansion of a CAG trinucleotide repeat. In both SCA3/MJD and Huntington's disease, abnormal tangles have been found in the nuclei of brain cells. These tangles consist in part of the abnormal SCA and Huntington proteins (ataxin and huntingtin). The finding that the abnormal proteins in SCA and Huntington's disease accumulate in the nuclei of certain cells, is considered an important step forward in the understanding of the degenerative process in these diseases. The fact that comparable diseases share this

phenomenon, suggests that a more general principle may be at stake.

Finally, let me mention a few research topics that we have focused on in Groningen. With a fine genetics department and some large SCA3/MJD families, we have a good opportunity for clinical neurological research.

In one large SCA3/MJD family, we have confirmed that anticipation (the earlier onset of symptoms in next generations), and instability of the CAG repeat expansion are more pronounced in paternal than in maternal transmission. Recently, we have looked at a relation between the age at onset and the progression of functional impairment, and at a relation between the CAG repeat expansion and the various clinical manifestations like spasticity, and dystonia (abnormal, writhing, involuntary movements). For the study of brains from deceased SCA3 patients, for the donation of which we are very grateful, we take part in international collaboration.

To summarize, 1997 has been another very good year for dominant ataxia research, with two new SCA's identified, and exciting progress going on, in the unraveling of the actual degenerative process. And of course thanks to the many people with ataxia who support this research, and whose benefit is its aim.

CARDIAC PROBLEMS IN FRIEDREICH'S ATAXIA

Pieter A. Doevendans, University Hospital Maastricht, Netherlands

Approximately 90% of the patients suffering from Friedreich's Ataxia will develop symptoms of cardiac disease. In general, the ataxia precedes the onset of cardiac symptoms. Most patients will develop a cardiac disease that is called 'left ventricular hypertrophy'. This presents itself as an increased thickness of the left ventricular wall and septum. A minority of FRDA patients however, do not develop hypertrophy; rather left ventricular dilation occurs. There is an ongoing debate whether FRDA patients have coronary artery disease and which arteries are involved. As well an important problem in Friedreich's patients are arrhythmias, which can be life threatening.

In 1987 Dr. James published a paper in the *British Heart Journal*, where he showed the interaction of the different components of the heart, contributing to the development of cardiomyopathy. The molecular deficit, caused by Frataxin deficiency, could very well lead to cardiac neuropathy, indicating impaired nerve supply to the heart, coronary artery disease and changes in the myocardium, and resulting in cardiomyopathy. The diseased nervous system and coronary artery system can also contribute to the development of the cardiomyopathy. In discussing the cardiac problems, we

will focus on the symptoms of the various cardiac diseases, the diagnosis and, in addition, the therapeutic interventions.

First of all, the correct diagnosis for Friedreich's Ataxia involves molecular genetics to show the Frataxin mutations. Electrocardiography is used to evaluate the cardiac rhythm and conduction. Echocardiography can be used to visualise the cardiac compartments and the cardiac tissue. A similar more advanced technique is provided by magnetic resonance imaging, which reveals even more details. In some instances it may be necessary to obtain a tissue sample. This can be done by biopsy, where small tissue fragments up to 1 mg can be obtained from the right ventricular tissue or septum.

Arrhythmias can be diagnosed by electrocardiography and divided into:

1. bradycardia, indicating a slow heart rate, mostly based on disease in the sinus node, which is the cardiac pacemaker;
2. high heart rates (tachycardias) which can be further divided into supraventricular arrhythmias, which in general are not life threatening, and ventricular tachycardia, which can be life threatening due to the loss of pump function during high rates.

The symptoms of bradycardia are palpitations, dizziness and syncope. The appropriate therapy would involve a pacemaker to correct the slow heart rate. Tachycardias can be recognised through the increased heart rate. The change from a normal to a fast rate can give rise to syncope and in some cases sudden death can occur. The supraventricular tachycardias in general can be treated with drugs that control the heart rate, such as digitalis, beta-adrenergic receptor blockade or amiodarone and sotalol. The effects of these drugs on ventricular tachycardias is less clear and in some cases it may be necessary to implant a device capable of recognising the ventricular arrhythmia and applying the appropriate electrical therapy.

Most FRDA patients will develop hypertrophic cardiomyopathy. The possibilities for the heart to adapt to alterations in the hemodynamic system are limited. Cardiomyocytes (cardiac muscle cells) that are damaged cannot be replaced and the myocytes can only adapt by increasing in size. There is no increase in the number of cardiomyocytes. The adaptation of the heart as a whole depends on the response of the individual myocytes, but hypertrophy can either be symmetrical, involving all parts of the heart, or asymmetrical, when mostly the septum becomes hypertrophic without a clear increase in wall thickness of the rest of the heart. In sporadic cases left ventricular dilatation is the first sign of cardiac disease. The treatment is dependent on the symptoms. The most important symptoms the patient can develop due to hypertrophy is dyspnea, chest pain, dizziness and syncope. To reduce symptoms beta-adrenergic receptor blockers can be used. Angiotensin

converting enzyme inhibition might be beneficial and in some patients treatment

with diuretics is necessary to reduce the blood volume. Relief of symptoms has been described for patients treated with calcium-blockers like verapamil. The syncope can be related to the development of arrhythmias and, therefore, anti-arrhythmic drugs may be indicated in some cases. None of these therapies has been shown to stop the progression of cardiac disease or result in a clear improvement of cardiac function. However, for a relief of symptoms these drugs can be very helpful.

Not much is known about coronary artery disease, which can develop in Friedreich's Ataxia, but it has been shown that an obstructive process can occur, which is different from atherosclerosis and which mainly involves the smaller vasculature of the heart. The symptoms are chest pain, initially during exercise, but in a few cases also in rest. Therapy is symptomatic again and mostly focuses on vasodilating drugs: nitrates and calcium-channel blockers. There have been some cases described in the literature, that first present with cardiac symptoms *before* the onset of ataxia. For instance, in some younger patients chest pain has been the first presenting symptom. In the literature there is also some evidence for a relation between the size of the GAA repeat and the amount of myocardial wall thickening. This has been reported by Isnard in a circulation paper early in 1997. There is no absolute relation, and so it's not possible to predict the phenotypic changes knowing the genotype. But still we know that the GAA repeat size has a definite effect on cardiac disease. To get more information on cardiac disease it will be essential to develop the correct animal model. A specially-bred 'knock-out' mouse could give us a model where Frataxin is only deficient in the heart and not in any other tissue. This would allow us to assess the direct impact of Frataxin deficiency on cardiomyocytes. The gene-targeting techniques are available and we hope that we can perform these experiments in the near future. This will also allow us to study the effect of treatment on cardiac function in general and on cardiomyocytes specifically.

FRIEDREICH'S ATAXIA IN AUSTRALIA: Report on the meeting in Melbourne

Martin Delatycki

The Murdoch Institute, Melbourne, provided the setting for a major meeting on Monday, 24th November 1997 to discuss research being done in Friedreich's ataxia in Eastern Australia. The aim of the meeting was to bring together parties from Melbourne and Sydney who are actively involved in Friedreich's ataxia research, as well as allowing members of the Friedreich's Ataxia Support Groups from Victoria,

NSW and Queensland the opportunity to meet those involved in research as well as each other.

Members of the Friedreich's ataxia research team at the Murdoch Institute, as well as the Gene Therapy research team talked about the research they were doing currently.

Kathy Williamson spoke on behalf of herself and Sherry Cook about the work they are doing on defining the promoter region of the Friedreich's ataxia gene. All genes have control elements which tell that gene when to produce its protein and how much. It is important when one is thinking of doing gene therapy that this region is defined and understood as it needs to be introduced with the gene.

Lachlan McDonald and Kate Elliott spoke about the mouse model for Friedreich's ataxia that they are currently developing. The uncertainty of how long this would take was spoken of because of the uncertainty about, firstly, how long it would take to introduce the faulty gene into the mouse, and secondly, whether a mouse with the faulty gene will display features of Friedreich's ataxia or not. This work is very important because when a mouse model becomes available different therapies can be tried and a better understanding of the process which leads to the damage in the nervous system can hopefully be obtained.

Tracy Evans-Whipp described her work with the herpes virus and its possible role in gene therapy for Friedreich's ataxia. The herpes virus has a natural ability to deliver genes to the central nervous system. In its native form it is of course very dangerous to the central nervous system, and so Tracy is working on ways to use the useful elements of this virus without the dangerous ones in an attempt to deliver genes to the nervous system.

Louise Wangerek spoke of her work with liposomes, which are fatty particles, in delivering genes to the central nervous system, whilst Kumaran Narayanan told of his attempts to deliver mRNA to cells. mRNA is derived from the DNA and subsequently makes protein.

I spoke of my work in attempting to define whether or not the findings of Professor Kaplan and his group regarding iron build up in mitochondria in yeast can be confirmed to underlie Friedreich's ataxia in cells from patients. At this time there are no definite answers to this question.

Bob Williamson spoke of the general difficulties with delivering genes to cells and that other therapies may become available before gene therapy. These therapies include iron chelators such as desferrioxamine and antioxidants such as Coenzyme Q.

Garth Nicholson from Sydney spoke of his patients who have features consistent with Friedreich's ataxia but do not have the typical gene fault. This may lead to the finding of genes which have faults in it leading to a picture very similar to Friedreich's ataxia. He also spoke of the importance of studying patients who have point mutations in the Friedreich's ataxia gene as a way of learning about how the gene causes the disease.

Ian Alexander presented information about gene therapy using adeno associated virus being used in his laboratory at the Children's Medical Research Institute at the New Children's Hospital in Westmead. He told how this virus can very successfully get into cells and he demonstrated a very elegant system of looking at dorsal root ganglia cells which are cells primarily affected in Friedreich's ataxia.

A session was spent discussing possible therapies for Friedreich's ataxia, including iron chelator therapy and antioxidant therapy. A recent meeting was held in Baltimore at the American Society for Human Genetics Meeting which was attended by Sue Forrest from the Murdoch Institute. It was agreed by the main players in Friedreich's ataxia research from around the world that the trial of iron chelator therapy should not commence for at least 6 months until further work is done, looking at whether there is iron accumulation in mitochondria in patients with Friedreich's ataxia. The other problem discussed was that it is difficult to define whether therapy is having a beneficial effect in a disease which progresses as relatively slowly as Friedreich's ataxia does, thus it is highly desirable that other ways of finding success can be found, such as laboratory tests or the availability of a mouse model.

A committee was set up consisting of Garth Nicholson, Professor Ed Byrne and myself to discuss possible treatment trials and the best way to go about these. It was agreed that any trial should be undertaken on an Australia-wide basis so that people will be given an equal opportunity to participate and that the largest possible patient numbers are available to participate.

This was an extremely worthwhile meeting in that those of us working on Friedreich's ataxia were able to benefit from the experience of others in the field and to discuss further work that needs to be done. It also allowed for a database of patients known to various participants to be set up so that as developments happen and any trials are started, as many people as possible will know.

MY LIFE WITH A COMPUTER

Carolien Koopmans

The Personal Computer appeared on the market at a moment that was perfectly timed for me. My physical condition was so bad that I already had to give up a lot of things that I liked to do, because I wasn't able anymore. Boredom was just around the corner. Let me tell you about my life without and with computer. And see for yourself what a great invention that device is in my case.

I have never been a star in writing. I will always remember the lessons in writing I had in grammar school. Especially those lessons on hot summer afternoons when the pencil almost fell out of your hands because of the sweat. During the writing lessons the pupils had to write down the same sentences ten times or more to train to write in a regular and beautiful way. Somehow I never mastered the art of beautiful writing. Looking back, that was the first sign of my FA.

I was also a slow writer. That never bothered me when I was in grammar school. The teacher always waited till I was ready before she dictated a new sentence. What a shock it was when I went to secondary school. During the first weeks I stuck up my hand at the beginning of every hour, asking the same question over and over again: "Can you slow down a bit?" The first moments after my question the teacher really slowed down, but after a few minutes he fell back in his own speed again. Looking back I realise that the teachers were only doing their job and had to complete an educational program in a fixed period. By copying the notes of my fellow pupils, sometimes taking their notebooks home with me, and training to remember what was taught, letting my mother type my papers, I managed to graduate.

I went on to University to study history. By now my FA was getting worse – my first day was also my first day in a wheelchair. For writing I got an electric typewriter with a very useful correction tape. I still couldn't type without mistakes and it took me quite a while before I finished a page, but it was sufficient. We had to write a few papers, but in most cases I could work together with fellow students and of course they did the typing.

Another problem during my study were the libraries. The card-trays I needed were always the ones at the top that I couldn't reach, so I always had to ask somebody to look up the title and the library-number of the book. Usually I needed the help of another student to pick the book from the shelves. As a matter of fact, I developed quite a good intuition to pick out friendly and helpful persons.

After my graduation I started a job as a scientific researcher at the faculty of history at Erasmus University in Rotterdam. (I was able to get that job thanks to a law caring for the employment of disabled.) I then

started to work for a Ph.D., which meant a dissertation. A historical dissertation is somewhat different from a medical dissertation; to get a Ph.D. in history you have to write a thick book (mine was more than 300 pages) on the basis of an intensive literature study and a time-consuming archives research.

My dissertation was on the development of the economy and population of my home-town Dordrecht in the 19th century. I started with the literature and the research at the archives. I thought I would manage by leaving the future typework over to the secretary. Or to be honest, I didn't care if I would ever finish my book, as long as I kept my job and my income. When Hans and I bought our first PC, we soon realised that I would never have managed without a computer.

At the time I started my work at the archives, another one of the adventurous journeys in my life began: Hans and I got steady and married. That wondrous agreeable adventure is still going on.

The first computer we bought was planned to be chiefly used as a word processor by me. It was a miracle right from the start. I could just begin writing a text, save it at the end of the day and work further on it the next day or even week. A paragraph that was forgotten could be inserted afterwards. Sentences that didn't seem to be right could be altered and formulated in a better way. I could now change a text as long as I liked and just print it when I was completely satisfied. Imagine, what a luxury it was for me to be able to write texts that were more than one or two pages long. And perfect texts, without mistakes.

Writing my dissertation really was something I enjoyed very much. And that was nice for Hans too. He can go off to work in the morning and come home in the evening, knowing I won't miss him. Not at all or not too much, I am a loner too. And Hans was fascinated by the computer right from the start. He is a real wizkid now. Without his help I would never have finished my dissertation. He didn't interfere with the contents – that was my full responsibility – but Hans cared for the graphics, tables and lay-out.

At the same time we got our first PC Hans and I got word of the existence of a Dutch FA-group. We were quite curious because – with the exception of my eldest brother – we didn't know anybody with FA. Hans and I went to a meeting and I was immediately asked to become secretary. Because of my PC I was able to write minutes and other necessary texts and letters, so we said "yes". It was very interesting, both the social and the medical side. And in 1989 Euro-Ataxia was founded. At the moment that organisation is even more worthwhile than our national group.

Apart from solving my writing problems, the computer is of great help in my communication with other people. Talking always has cost me a lot of concentration I have never been an easy talker, but that didn't bother me too much. In social situations I experienced few problems till a couple of years ago, but to communicate about serious or official matters, I prefer to write a let-

ter instead of using the phone. Not only because I can express myself so much better on paper, but a clearly formulated letter makes a much better impression than such a childish-sounding and weak voice over the phone.

After I got my doctor's degree, I began writing another book, this time with even more pleasure because the subject really had my heart. But then suddenly, from one day to the other, my hands felt terribly numb and stiff. According to my neurologist, it probably is what they call a neuropathy. Anyway, I couldn't type anymore. What a disaster! But I tried not to panic. Hans and I tried to find a solution. The only solution we could think off was a computer that could be commanded by voice. But was my voice good enough for that?

We soon found out there was a program on the market, called VoiceType, that might just be what I needed. You have to say a letter to the microphone (alpha for a, bravo for b, charlie for c, delta for d, and so on) and the letter appears on the screen. You can also train the program to put complete words on the screen; you only have to say the word and spell it once; the next time you say that word, the computer will recognise the sound and knows what symbols to put on the screen. It is a self-learning program. That means the following. By saving a sound-file of all the commands you say into the microphone each time you use the program, the computer will recognise your voice easier every time you use VoiceType.

As you will understand easily, VoiceType does require a voice that is – at least a bit – regular. The salesman honestly told us that he doubted if I would ever manage to control it. Hans had his doubts too. But after a few weeks of stubborn trial and error, the program recognised my voice well enough. Commanding my computer by voice really is at the top of my capabilities. Whenever I'm tired or have a bit of a cold, the computer doesn't respond to my voice. And it keeps having trouble with some of my commands. But what a relaxed way of working! Much more relaxed than using a keyboard and typing in texts with those unco-operative fingers of mine.

The last years brought us the fax and electronic mail, the latter being one of possibilities provided by the Internet, so I hardly use the telephone anymore. The fax and e-mail are attached to Hans' computer. We agreed that if I want to send somebody a message, I just have to write a text and Hans will fax or e-mail it. To give you an example of the practical advantages of those two devices: with Michael Morgan I have a quite good contact in this way. That's because we can't communicate by speaking, as we just don't understand each other, due to both our bad ears, my troubled speech and his Irish accent. Even Hans thinks it's difficult communicating with some FA'ers on the phone, so he prefers communicating with them by fax or by e-mail. The Internet is a real solution for us disabled too. Looking up book-titles or other information from behind the computer-screen. Or buying books, ordering a

computer or a pizza, just sitting at your desk. Or chatting the night away. But Hans and Marco will tell you about the mighty Internet.

I want to end my story with a few philosophical words. As your body has deteriorated as far as mine, no wonder the question “Why do I still go on living?” now and then pops up. But there’s no answer to that question. Both life and death are matters over which we, human beings, don’t decide. I have learned from Buddha that clinging desperately to life is bad for your mental sanity, but that it is also not wise to cling to death too heavily. If you wait for death too eagerly, it sure seems a long time before it will come. Instead, I will do my best to make the best of the time I’m still alive, enjoying the good times and trying not to make too much fuss over my bad luck. That’s my way to thank Hans and my parents for their good care.

Note

The VoiceType I use is a DOS-based program. Nowadays there are more and better (Windows-based) voice-recognition programs available. The best known is DragonDictate by DragonSystems.

INTERNAF, the International Network of Ataxia Friends on the Internet

Marco Meinders

Within a relatively short period of time, an international network of ataxia-friends has emerged whose members keep in touch through electronic mail (e-mail). The basis of INTERNAF is to send individual electronic mail messages to a central electronic mailbox. E-mail sent to the mailbox is then automatically distributed to all the people who have subscribed to that service, forming a ‘mailinglist’ (as they say in techno-speak). Thus a single message sent by me from the Netherlands to INTERNAF is automatically – and virtually instantaneously – delivered to every other INTERNAF participant around the globe. Just imagine: 1 message will reach a world-wide audience of 400 within seconds, each one of whom can reply to it again within seconds, or just as fast as they can type on a keyboard.

The Internaf-mailinglist was started by several volunteers in the United States, Canada, and the United Kingdom. At present, over 400 people have subscribed to this mailinglist (which is free). Most of the members are ataxic themselves, but there are also members who are active in a patients’ organisation, like myself, or who know an ataxic person. Most members are from the United States and Canada, but there are members from around the globe. The commonly used language is English, but sometimes someone posts a message in another language. A volunteer then makes sure that this message gets translated.

From the Internaf-mailinglist, we now also have a mailinglist for professionals: Internaf-pro. This is primarily for scientists, clinicians and other ataxia researchers, and, unlike the Internaf-mailinglist, this mailinglist is for invited people only.

Recently, Internaf has opened its own web-site at <http://internaf.merseyside.org>. Here, a lot of information can be found on the Internaf-mailinglist, the Internaf-pro mailinglist, as well as an awful lot of medical information on the Ataxias and organisations of ataxia-patients world-wide. The Internaf web-site also offers links to web-sites of Internaf-members!

EUROPEAN CO-OPERATION A presentation by Ineke Roelofs

Report by Marco Meinders

Mrs Ineke Roelofs was asked to give a presentation on co-operation within Europe at EURO-ATAXIA’s annual general meeting. As vice-director of the VSOP and secretary-general of the EAGS, she was very pleased to have this opportunity. The VSOP is the Dutch Alliance of 50 national supportgroups concerned with genetic and non-genetic congenital disorders, and the EAGS, the European Alliance of Genetic Supportgroups, its European umbrella organisation.

Mrs. Roelofs divided her presentation in two parts. In the first part, she spoke about the VSOP, leading her up to the second part, in which she gave an outline of the work of the EAGS. The following is a summary of her presentation.

Co-operation in The Netherlands: The VSOP

Founded in 1975, the VSOP now has 50 member organisations, representing over 250.000 families involved with genetic or non-genetic congenital disorders. The VSOP aims at increasing public awareness of, commitment and co-responsibility for heredity and congenital disorders in general, and in particular with respect to the people affected.

Common interests are:

- Reliable and well-balanced information,
- Facilities for early detection, accurate diagnoses, genetic services and psycho-social guidance,
- Reflection on social, ethical and legal issues and
- Research (The VSOP has several endowed chairs and participates in research projects).

As an example of the work of the VSOP, she showed some sheets with pamphlets and brochures from information campaigns produced by the VSOP, and she briefly talked about the VSOP’s telephone hotline which receives thousands of calls per year from people with problems on hereditary of congenital disorders.

European Co-operation: The EAGS

The European Alliance of Genetic Supportgroups is concerned with the interests of people concerned with hereditary disorders on a European level. Some fields of interest are genetic testing and screening, discrimination and stigmatisation, exploitation of human genome data, genetic progress and research, patenting biotechnological inventions (the Patent Directive), UNESCO's "Universal declaration on the human genome and human rights" and the European Union's "Action program on rare diseases and orphan products".

Some principles of the EAGS are that the interests of people involved are paramount, that research efforts must be maximized, that care services and treatment must be improved and made available on the basis of equity and equality, that abuse of genetic information must be resisted and rejected, and that we should have an involved and well-informed society.

EURO-ATAXIA is a member of the European Alliance of Genetic Supportgroups. The EAGS's next annual general meeting will take place in Lisbon (Portugal) from May 12-13. Further information is available per February 1998.

BUSINESS REPORT

Dagmar Kroebel

As indicated in a previous edition of *Euro-Ataxia* the 9th Annual General Meeting provided the opportunity for some serious discussion on policy and structure within EURO-ATAXIA, as well as a changeover in personnel and the addition of new members. Most of this business took place at the Sunday morning meeting, traditionally the session set aside for official business and reports, on 26 October 1997.

Election of New President

This year EURO-ATAXIA has had three presidents. Manfred Van den Kerchove, unfortunately, had to resign in March and Hans Doré stepped in as interim-President, but only until a new President was elected at Lunteren. Ewout Brunt was voted to the position unanimously. He said, "Most of you know me by now and know that I have an interest in Ataxia. I am available on request, but I must say I do not have much time."

New Members

The new members who joined EURO-ATAXIA this year were the ataxia group within the Swedish Neurologiskt Handikappades Riksförbund, and Daniela Iser, Switzerland. She will in a way represent the Schweizerische Gesellschaft für Muskelkrankheiten.

The Financial Situation

For this year we applied for a grant from the EC DGV,3. As all other European groups we were not granted. This year's meeting was possible thanks to grants from the VSN (ECU 1500.-), the ADCA-association (ECU 1000.-), and other sponsors (ECU 3500.-).

Theo Schimmel distributed the budget we presented to the EC this year. The financial situation for 1998 therefore is very unclear. Next year we will apply again for a grant from the EC.

Organisation of the AGM in 1998

Next year's AGM will take place in Turku, Finland, from 25 to 27 September. Eila Niemi adds: "Since we have no idea of the financial situation of EURO-ATAXIA in 1998 we prepared a draft budget which has to be discussed. (The draft was distributed by Eila during the meeting.) The overall costs are in Finland two times as much than in Holland. The Finnish MS-Society will contribute to the EURO-ATAXIA meeting with a substantial grant of FIM 41000. In 1998. EURO-ATAXIA has to contribute with about ECU 4500.

Every participant will have to pay his own travel expenses and about ECU 40. Are the participants willing to have next year's AGM in Finland and pay some by themselves?" The answer was yes.

Next Year's Board Meeting

To save money there will be no official separate board meeting in March 1998. If necessary we can have an unofficial board meeting in 1998 with the members who live in Belgium and the Netherlands. We can communicate by telephone, FAX or e-mail.

Network of Communication

During the board meeting in March we agreed that we like to stimulate the contacts between medical professionals and we ask every group if they could find a person who is willing to serve as a contact for this more or less informal group. I would like to ask all members about the situation in their country. Please communicate all contacts to Hans Doré, who will prepare a list. The list will be sent to the members and to all national Ataxia Groups.

It will be an informal group, so we do not have to organize meetings. If it doesn't work, we have to reconsider its organisation.

Inside the World Federation of Neurology is an informal ataxia research group. Its former secretary was Jorge Sequeiros from Portugal, but we received a message from him that now Subramony will be secretary of this group. They are in close contact with Pandolfo. They publish a Newsletter which is distributed by e-mail and by fax. We are on the mailinglist and via *Euro-Ataxia* Newsletter we will keep you informed.

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