

## Duchenne Muscular Dystrophy.

### Research for a Duchenne Therapy: Questions and Answers.

Completed on **15 April 2007**

E-mails from all over the world reach me with many questions concerning my research reports, but I cannot answer them all individually. And because the same and similar questions are sent by different patients and families, it is better to write this questions-and-answers text which I am sending to all whose addresses are on my e-mailing lists. This text will be updated with new answers to additional questions. It exists also in German and will soon be available in Spanish, too.

You have probably read all my research reports, especially the two last ones about the meetings of the Duchenne Parent Projects in Cincinnati and London in July and October 2006. Those of you who have not received them yet, may read and download them as pdf files from the internet at [www.duchenne-research.com](http://www.duchenne-research.com) in English, German and Spanish. Some of the questions were already answered in these reports.

I am answering the many questions as well as I am able to. However, I am not a medical doctor but a biochemist, therefore, I should not give any medical advice. But for many years now, I have experience in describing the scientific results of the research for a therapy of muscular dystrophy. This and the participation at research meetings as well as the personal acquaintance with many researchers help me to write my reports and also these answers with no or very few mistakes. But no guarantee can be given and any legal liability is excluded. But I am asking everyone of you, and especially the researchers who are receiving this text also, to send me comments and suggestions for additions and changes, if necessary.

To understand my answers, it is often advisable for you to understand some of the scientific background of cell biology and of Duchenne muscular dystrophy. If you are not certain, please read again the explanations in my reports. In the following text, the questions, often rephrased by me, are printed in italics, my answers are in normal print.

#### Clinical trials with Duchenne boys.

*Please let us know how our son can participate in a clinical trial. We are prepared to do everything and to go everywhere, because then he obviously would have a chance for a cure.*

The clinical trials with Duchenne patients have just started in 2006 in Columbus/Ohio in the United States and in Leiden in the Netherlands. In London and in Newcastle in England, another one will begin in 2007. You find the details in my reports. Only very few children participate in these trials. They are coming from the neighborhood of the clinical centers because they have to be clinically checked repeatedly and they must have a precisely known mutation in their dystrophin gene.

It is important to understand that in these first trials, only one single muscle is being treated locally. Even if the results are positive – which we all hope – i.e., if sufficient new dystrophin appears without serious side effects, and if this single muscle is functioning better afterwards, then, in spite of this, the children will not obtain any therapeutic benefit. Their muscular dystrophy will neither be cured nor slowed down! With these first trials, one wishes only to prove that the new methods – above all exon skipping and mini-gene transfer – are really working. One looks only for a “proof of principle”.

Only when this has been proven, the next step, a systemic application will be tried very carefully. I.e., the potential drugs – antisense oligoribonucleotides, AONs, or adeno-associated viruses charged with mini genes – will be injected into the blood circulation so that they can reach and treat all muscles. These systemic trials will start not

earlier than at the end of 2007 and will be performed also with few children from the neighborhood of the clinical centers.

For these reasons, it does not make sense to travel with the sick child to the trial centers from far away or even from other countries and to live near them for many months. This would be much too expensive and would not bring any advantage. The best the families can do to get access to a therapy as soon as possible is to be a member of one of the active muscular dystrophy associations, to register the child in the data banks which are now being established, and to read up-to-date research reports. If I have your e-mail address in my mailing lists, you will get my research reports as soon as they are ready in English, German, or Spanish.

*Is it really always necessary to perform clinical trials?*

Yes, they have to be done, because nobody knows beforehand whether something new, that perhaps works somewhat positively in mice and dogs, will do the same in young and older Duchenne children.

A child is not a large mouse and there are also differences between a dog and a small child. If e.g. one gives, without much thought, an inhibitor of myostatin or billions of modified viruses with mini-dystrophin genes, to sick children and something happens – the child is worse off than before or even dies – then there will be merry hell and the entire gene therapy research will be interrupted worldwide, perhaps for many years. Research is already progressing too slowly. Therefore, nothing should be forced or risked. A new step towards a therapy should not be started before the preceding one has given good results.

In the Nature issue of 29 March on page 474, there is a comment on this subject, on the request of hopeless cancer patients to get a drug which only has been tried on rats. The scientists are of the opinion that these people too, who have even less time than Duchenne boys, should wait for the results of properly performed clinical trials.

*I am already an older Duchenne patient. Will there be a therapy for me also?*

Obviously, a therapy will be the more successful the earlier it is started, as long as there are still many muscles present. In my opinion, it is not certain that muscles that have already disappeared and been replaced by fat and connective tissue, can still be restored.

On the other hand, there are indications from the team of Professor *Jacques Tremblay* in Québec City in Canada, that the old myoblast transfer – now called transfer of myogenic cells – will work also in older Duchenne patients. This has already been tried on a 27-year old patient. The Canadian scientists would like to try this technique on not quite so old patients, younger than 18 years, but their planned studies have not been approved for ethic reasons.

There are a number of non-genetic therapeutic possibilities, which I have described in my reports, e.g. the inhibition of myostatin, the upregulation of IGF-1, steroids combined with cyclosporin, Idebenone, and Protandim. All these methods, once they are really working, should also be applicable in older patients. But probably, some muscles should then still be present.

## Exon skipping.

*The mutation in the dystrophin gene of my son is precisely known. Would exon skipping help him? And if that is so, which exon or exons would have to be skipped?*

One can answer these questions if one looks carefully at the cDNA sequence of the dystrophin gene. The cDNA is called that way because one obtains it by back-copying the mRNA into the DNA structure with special enzymes.

Thus, the cDNA contains only the joined exons without the introns in between. You can see the entire cDNA sequence on the Leiden muscular dystrophy internet pages:

[www.dmd.nl/seqs/murefdmd](http://www.dmd.nl/seqs/murefdmd).

On the last page of my Cincinnati report, you will find a detailed example for the skipping of exon 46 when exon 45 is deleted, i.e. already missing. If you understand this example, you will be able to determine from this sequence which exon or exons should be skipped to restore the reading frame after any other deletion. A list with the direct answers – then you do not have to examine the sequence – can be found in the thesis of Dr. *Annemieke Aartsma-Rus* who works in the research team of Dr. *Judith van Deutekom*. If you wish, I can send you this list by e-mail.

I am writing here my answers to the various questions with the boy's first name added, if I know it. It is important to understand that these answers can only be theoretical. They are based on the data of experiments with muscle cell cultures and with dystrophic mice and dogs. Only clinical trials on patients can prove whether a particular skip-

ping treatment will give the same positive results in Duchenne boys. And the first clinical trials with exon skipping are just beginning.

**Julian** has a deletion of exon 45, that means, exon 46 has to be skipped. I have explained the skipping of exactly this exon 46 on the last page of my Cincinnati report. Please read it!

In **Simon's** dystrophin gene, all exons from 45 to 52 are missing. Exon 49 was not mentioned in the report on the gene analysis, but it would be unusual if two different stretches of exons are missing simultaneously. Only the following exon 53 should be skipped, and not several ones, to restore the synthesis of dystrophin.

**David** has a deletions of all six exons 45 to 50. Exon 51 should be skipped, and this is exactly the exon which one tries to skip in the first clinical trials in the Netherlands and England. This means that David will probably be one of the first to benefit from this technique.

The son of **Sridhar** in New Delhi has a deletion of exons 46 to 51, leading to a shift of the reading frame. Therefore, a Duchenne dystrophy should develop. Skipping of exon 45 would repair the reading frame.

**Randy** has a point mutation inside exon 17, but I was not told the exact nature of this mutation. One would have to skip both exons 17 and 18 to restore the reading frame. But if the point mutation created one of the three stop signs in the dystrophin gene, TGA, TAG or TAA, then possibly PTC124 would help if it really works effectively.

**Noel** has a point mutation in exon 40. Here, one should only skip this exon 40. The rest of the answer would be the same as for Randy.

**Nadim** has a point mutation in exon 74 which has produced the premature stop sign TAG. In this case, PTC124 would help or one could skip the entire exon 74, then the stop sign would be eliminated.

In **Larry's** gene, exon 3 is missing. This deletion does not shift the reading frame, because both borders of the sequence of this exon are between two entire amino acid codons. Larry should develop a Becker dystrophy. This mutation concerns one end of the dystrophin protein, and one does not know yet whether this would lead to a more severe disease than a normal Becker dystrophy. The data banks, which are now being established, will be able to predict later – when a sufficient number of patients are registered – the clinical consequences of a certain mutation. However, one should also realize that patients with identical mutations, e.g. of brothers with Duchenne, can have completely different clinical symptoms. Thus, the absence or the structural change of the dystrophin does not always seem to be the sole cause for the clinical course of the disease.

In **Manuel's** dystrophin gene, a duplication of the exons 8 to 12 has been found. This has shifted the reading frame, and Manuel, now 9 years old, has already typical Duchenne symptoms. After a biopsy, a dystrophin determination was done, and no dystrophin could be found. The Dutch researchers have already tried to repair duplications by exon kipping in laboratory experiments. This is not easy, but seems to work in principle. In Manuel's case, one would have to take out one of the two exon series 8 to 12 by skipping, or it would suffice to skip only the second exon 8, but not the first one. Whether this will work in

children, I cannot say. However, the development of such complicated therapies will probably not start before the normal exon skipping of deletions is available as a finished therapy for the sick children.

*When the reading frame is shifted, then the child has Duchenne dystrophy because a premature stop signal has appeared and no dystrophin is made. And when it is not shifted, then a Becker dystrophy will develop because there will be no premature stop sign but the dystrophin will be shorter than normal. Is this rule always true or are there exceptions?*

For **Steffen** who was born in 1982 and who is now 25 years old, Duchenne was diagnosed after a biopsy in 1986, but at that time, the gene had just been discovered and dystrophin was not yet known. He could walk until he was 15, even now he does not need mechanical respiration, and he has only a slight scoliosis. He still considers himself "very fit". In 1989, Professor *Raimund Forst*, at that time still at the University of Aachen in Germany, performed successfully the Rideau operation for the release of Steffen's contractures. A gene analysis in 1994 found that the four exons 3 to 6 are missing in his dystrophin gene. This means that the reading frame is shifted after the deletion, and that Steffen should have Duchenne muscular dystrophy. But his disease seems to develop in a much milder way. Apparently, such exceptions seem to happen once in a while.

In December 2006, the internationally known clinical specialist Professor *Victor Dubowitz* in London described in "his" journal *Neuromuscular Disorders*, Vol. 16, pages 865-866, a four-and-a-half year old boy who develops clinically like a Becker patient although he has a duplication of exons 18 to 30 which shifted the reading frame and thus, he does not have any dystrophin in his muscles.

Professor Dubowitz closes with the words: "If his clinical course does turn out to be milder than expected for the molecular genetic and immunohistochemical results, the laboratory scientists will have a field day knocking their heads together to provide some feasible explanations."

*How often will it be necessary to inject an exon skipping drug, an AON?*

This question is also discussed in my reports. It depends on the time the AONs are stable inside the muscle tissue. The estimates go from once per month to once per year. This just has to be determined in the clinical studies. The advantage of the method developed by *Luis Garcia* in France would be that the AONs will be made continuously by the transferred genes, i.e., then, ideally, only one single treatment would be needed. Details can be found in my report on the London conference. .

*Will it be necessary for each AON to go through all phases of the clinical studies? Wouldn't this require again a lot of time and money?*

Obviously, one will try to avoid this. But who knows whether the authorities in the different countries will accept abbreviated trials. Although the different AONs have a similar chemical structure, they have different base se-

quences. And these could interfere with different genes. Thus, one will not be able to avoid clinical trials. However, the growing experience will make this easier and certainly limit the time and costs.

## **Stem cells.**

*Recently, so many stories about the miraculous power of stem cells have been published in all kinds of more or less serious newspapers that we do not know whether to believe them or not. What are the scientists themselves saying about their results? Do they really mean that stem cells will bring hope for our children?*

Professor *Terence Partridge*, who now works at the Children's National Medical Center in Washington, discussed the "Promise of Stem Cells" at the PPMD meeting in Cincinnati in July 2006, and you can find a summary of his presentation on page 7 of my report on this meeting. Dr. Partridge considered as the most promising stem cell approach for a possible Duchenne therapy the work with mesoangioblasts as performed by Professor *Giulio Cossu* and his research team at the Stem Cell Institute of the Hospital San Raffaele in Milan. All the most recent results of these Italian researchers, which were published until the end of 2006, are summarized on pages 10 and 11 of my report on the PPUK meeting in London. May I assume that you have read these parts of my report again so that you will be able to understand the following text?

The mesoangioblasts used in these experiments were isolated from the blood vessel walls of mice and dogs. But to perform the next step towards the development of a therapeutic method for Duchenne patients, such stem cells must be derived from a human source. Dr. Cossu and his colleagues have indeed done this during the last months and published their new results in February 2007. They could not be mentioned in my report.

The Italian workers looked for similar stem cells in the walls of the small blood vessels of human muscle tissue obtained from diagnostic biopsies. They found such stem cells there, but their properties were somewhat different from those of the mesoangioblasts. Therefore, these cells were called "pericyte-derived cells" or "pericytes" for short. Their properties were exactly those which stem cells should have when they were to be used for a Duchenne therapy, namely: (1) They are easy to isolate from human biological material like muscle tissue; (2) they can be multiplied substantially in the laboratory to amounts necessary for a systemic treatment of children; (3) it is possible to transfer into them "healthy" dystrophin-gene sequences with viral vectors; (4) they are able to migrate from the blood circulation into the muscles; and (5) they develop to functional muscle cells inside the living muscle tissue.

The most decisive results were obtained in experiments with mdx mice which, in addition of not having any dystrophin, also had their immune system inactivated by genetic manipulation. One month after three systemic injections of normal, that is non-dystrophic, pericytes into the leg arteries of five of these mice, 200 to 450 new dystrophin-containing muscle fibers were found per standard cross sections investigated. When human pericytes from

Duchenne patients, which thus had mutated dystrophin genes, were first treated with virus vectors containing mini-dystrophin genes, were injected similarly into these mice, 190 to 320 new muscle fibers containing mini dystrophin were found in the investigated muscles. The function of the muscles in the treated mice were measured also and found to be significantly improved.

It is important that pericytes from dystrophic human muscle tissue could be multiplied in the laboratory as well as those from normal muscle. That means that – at least in young patients – these dystrophic stem cells had maintained their growth potential. Therefore, the pericyte-derived cells seem to be ideal adult stem cells for a future cell therapy. Dr. Cossu and his colleagues are now planning clinical studies with Duchenne patients probably to be started in about one or two years.

Obviously, these promising results of the experiments with muscle stem cells, first from mice and dogs, and now also from muscles of Duchenne boys have considerably raised the hopes of Duchenne families, and of the researchers as well, that a therapy with adult stem cells will be a real possibility in the not too distant future. Therefore, it is understandable that Dr. Cossu's international colleagues have looked critically at all the scientific details of his experiments, and some have asked, even in publications, whether all control tests had been done, especially those with the immune suppressive drugs alone, because it is known that at least one of them, cyclosporin, can lead to a temporary functional improvement of dystrophic muscles. These questions were raised after the earlier experiments with animals. However, the new experiments were done with mice which did not need any immune suppression, because their immune system was genetically knocked out.

*Does it make sense to keep cord blood of a relative frozen in a blood bank in order to have later stem cells for the sick child?*

I have passed this question on to Dr. Cossu and obtained the following answer: "As for the cord blood, mesoangioblasts are not derived from them, so cord blood is not useful for our method, but of course it may serve other strategies."

Those who need the most up-to-date information about what one should know when considering preserving cord blood, should download from the internet the statement "Cord Blood Banking for Potential Future Transplantation" of 8 January 2007 of the American Academy of Pediatrics: [www.pediatrics.org/cgi/content/full/119/1/165](http://www.pediatrics.org/cgi/content/full/119/1/165). An application for muscle diseases it not mentioned there.

Dr. *Mayana Zatz* in Sao Paulo, has published on this subject. I will ask her what she would recommend.

## Laboratories for gene analyses.

*Which laboratories perform gene analyses?*

I know the addresses of six laboratories: In the UK: DNA Laboratory, Genetics Centre, Guy's Hospital, **London** SE1 9RT, Dr. *Stephen Abbs*, Tel. 020-718-82582; in the USA: Eccles Institute of Human Genetics, 15 N. 2030 East

Street, **Salt Lake City**, UT 84112, Dr. *Kevin M. Flanigan*, Tel. 801-587-9540; in the Netherlands: Department of Medical Genetics, University of Groningen, Antonius Deusinglaan 4, 9713AW **Groningen**, Dr. *Annemarie van der Hout*; and in Germany: Institut für Humangenetik, Universität Würzburg, Biozentrum am Hubland, 97074 **Würzburg**, Professor *Clemens Müller-Reible*, Tel. 0931-8884063; Institut für Humangenetik und Anthropologie, Im Neuenheimer Feld 328, 69120 **Heidelberg**, Dr. *Marion Cremer*, Tel. 06221-562504; and MGZ Medizinisch Genetisches Zentrum, Bayerstrasse 53, 80335 **München**, PD Dr. *Elke Holinski-Feder*. There are certainly many more, but these six are those which I know relatively well.

These laboratories will be able to solve also the difficult cases. Thus if a gene analysis has not given a precise result in a "normal" laboratory, please contact one of these specialized laboratories. But one should not forget that the suspected disease is perhaps not Duchenne but another dystrophy, and then one would look at the wrong gene.

*Will a drug against muscular dystrophy also help my son? But we do not know which dystrophy he has.*

Then one cannot answer this question. I am always repeating in my answers how important it is to have a precise diagnosis. In my reports, you will find the details of the modern genetic diagnostic methods. In many countries, there are experienced laboratories where one can have these analysis performed. I have listed some addresses for the previous answer. For these tests, one generally does not need to travel with the sick child to the laboratory, about 5 to 10 ml of full blood with an anticoagulant added is sufficient in most cases. It can be taken by the family doctor, and he can send it to the laboratory.

## Research for other muscular dystrophies.

*Will the results of Duchenne research be applicable to other muscular dystrophies?*

This will probably be so but only indirectly. When a Duchenne therapy is finally ready, then it will be easier to treat other muscular dystrophies with similar methods, e.g. the many limb girdle muscular dystrophies whose genes are also known. This will probably take many years, because even for the first Duchenne therapies, between 5 and 10 years are still necessary. Also for these patients, it will be important to know the exact mutation in the gene for their disease.

And obviously, the pharmacological methods, which do not demand a genetic manipulation, should be applicable for other muscular dystrophies, too. But they have to be ready for Duchenne patients first, before they will be studied in clinical trials on patients with other muscular dystrophies. I have described these pharmacological methods in my reports.

## PTC and other companies.

*Our son has a premature stop codon, therefore, PTC124 might be a useful drug for us. How can we get in contact*

with the company that makes PTC124?

As before, I will keep track of the newest developments, not only of the substance PTC124, and then mention them in my future research reports as soon as possible. Those who would like to get information directly from the company, which now performs trials with PTC124, can find it on the internet: PTC Therapeutics, South Plainfield, NJ, USA, [www.ptcbio.com](http://www.ptcbio.com).

There are a number of other companies working on the development of Duchenne therapies and which I have mentioned in my reports. You will find their internet addresses with Google or another search program.

**Asklepios** Biopharmaceuticals Chapel Hill, North Carolina, mini dystrophin gene transfer; **AVI** Biopharma, Portland, Oregon, morpholinos for exon skipping; **Ceptor** Corporation, Hunt Valley near Baltimore, Maryland, calpain inhibition with Myodur; **LifeVantage**, Denver, Colorado, Protandim; **Mirus** Bio Corporation, Madison, Wisconsin, gene transfer with plasmids under pressure; **Pro-sensa** B.V. Leiden, Holland, exon skipping with 2O-methyls. **Santhera** Pharmaceuticals, Liestal near Basel, Idebenone; **Transgène**, Strasbourg, gene transfer with plasmids; **VASTox** plc, Abington near Oxford, upregulation of utrophin; **Wyeth** Research, Collegeville, Pennsylvania, inhibition of myostatin with MYO-029.

### Protandim and other things.

*Should we give our son now Protandim? Or Idebenone or HCT 1026?*

You will find detailed information on Protandim in my London report. I mention there, too, that this extract from five plants has been clinically studied with healthy adults and that a significant increase of the activities of catalase and superoxide dismutase was found, the two enzymes which destroy the damaging free radicals in the body much more efficiently than the vitamins C and E can do it. The details of the trial with adults have been published now, you may ask me to send you this publication by e-mail.

No studies with Duchenne boys have been performed yet. But one is working on this. Professor *Joe McCord* wrote to me that the first experiments with mdx mice have been done and that there are first results, but much more results are needed for arriving at a final conclusion.

Concerning the question whether one should give the sick children already now the Swiss drug Idebenone or the American Protandim, Ms. *Sally Hofmeister*, mother of a teenage Duchenne boy, has written the following: "Everyone has to decide for himself whether he will give his child these things without the scientific proof, or whether he believes that this is the right thing to do at any rate. I myself would be very cautious. An Idebenone trial is going on in Belgium, but whether it will give the desired results, we will see. I would wait for the final results in order to know exactly what I will give my son. The same is true for Protandim."

Professor *Rudolf Korinthenberg* of the children's hospital in Freiburg wrote to me: "As long as these substances are not even tested in a pilot study on Duchenne patients,

they should not be recommended. In my opinion, the biochemical explanation alone is not sufficient. If the parents discover them on the internet and wish to try them on their own initiative, that is their problem. We should avoid to raise unjustified hopes which then are being destroyed over and over again."

For the HCT 1026, the situation is the same. On page 11 of my London report, I say that this drug liberates the gaseous hormone NO and inhibits inflammation, and that it increases the effect of the mesoangioblasts in mdx mice significantly. Dr. Cossu commented: "Do not try anything that has not been tested in clinical trials. A small open trial will start soon, and if positive, we will ask TREAT-NMD to organize a large blind trial. Only then shall we know whether this molecule is efficacious in humans as it is in mice."

### When will there be a therapy:

*How long will it take until a therapy will be available for our boys?*

I have asked this question in an interview with the Dutch researchers *Gertjan van Ommen*, *Judith van Deutekom* and *Gerard Platenburg* 2004 in Monaco. Please read the entire interview on the pages 10 and 11 of my report Monaco 2004/1 on the internet: [www.duchenne-research.com](http://www.duchenne-research.com).

The most important sentence in this interview was: "We think, 10 years would be a reasonable estimate for seeing the first promising application of the antisense work for Duchenne. Of course, we hope it will take less, and there is a chance that it will take less." Of the ten years, seven still remain. In my interview in Cincinnati, Professor *Steve Wilton* said that the Dutch estimates are rather realistic. But it could also take only five to six years until a successful treatment of the first Duchenne boys will be there. And Gerard Platenburg in Cincinnati and Judith van Deutekom in London said something similar.

But please understand that one should never take these estimates literally. The uncertainties are substantial, the original 10 years can also mean 5 or 15 years. These estimates were criticized by some parents representatives. They were of the opinion, one should not give the families this information. The numbers are too uncertain and they would discourage them. Would you, the parents of the sick children, prefer that one does not speak about this? I would be interested in your opinion.

*Do the scientists talk to each other or do they keep their results secret? Are they perhaps farther ahead than we think?*

Yes, they talk to each other. They meet often at the frequent international conferences, and what they had not yet published or presented at the meeting, they discuss during the dinner or over a beer at the bar.

But it takes several months until their results are published in one of the prestigious journals like Science, Nature, Neuromuscular Disorders, Cell, and others. It takes that long because these journals insist that the manuscripts are being checked and commented on before publication

by scientists working in the same field, who, however remain anonymous. This is called "peer review". And before something has not appeared in print, it is not allowed to speak or write about it. I am respecting these embargoes also in my reports.

Obviously, the researchers do not stop working while their manuscripts are in print, and, therefore, they are already somewhat farther ahead than we are able to know. A quite new example of the talking-to-each-other is the ENMC workshop in Naarden in the Netherlands from 23 to 25 February 2007 about the cooperation of the British and Dutch exon skipping teams. And the European Consortium for Stem Cell Research met in Bellagio in Italy on 3 and 4 April 2007 under the direction of Dr. Cossu to talk mainly about the mesoangioblasts.

### **Please no questions about the medical and social management.**

*Please tell us, which medical measures should be applied, physical therapy, ergo therapy, pain treatment, Rideau operations? And how about problems with the father, when to use a wheelchair, who can help, etc.?*

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If you send me your e-mail address, you will receive all my future research reports as soon as they are ready in English. They are also available in German, Spanish, and in some other languages.

These and similar questions I just cannot answer. I know quite a bit about the medical treatment of our Duchenne children, but I am not a medical doctor and, therefore, should not give any medical advice. In many countries, there are centers, mainly at the children's hospitals of the universities, where there are specialists for muscle diseases who can answer all these medical and social questions. The addresses can be found on the internet pages of the muscular dystrophy associations in the different countries.

As you have seen in my reports, I discuss only the results of the scientific research for a therapy of Duchenne muscular dystrophy. At the large international conferences as those in Cincinnati and London last year, the newest research results on the medical and social management of the patients are also reported and discussed. I have often been asked to also write about them in my reports. But I am not that young anymore and there are just some physical limits even when writing the research reports. But I will continue to write the reports for you, as long as I can, because your e-mails, which reach me from everywhere, tell me how important this information is for you.