DMD certainly has a remarkable position amongst all hereditary muscle disorders. Noteworthy is its relatively high incidence as a “rare disease”, its X-chromosomal mode of inheritance, the high frequency of new mutations, as well as its relatively rapid and fatal course. For a century the disorder was considered to be untreatable. Only 40 years ago the patients’ “natural” age at death was 15 years. In those days the physicians left most of their patients untreated in large sickrooms until they died, usually from a lung infection. Only a few researchers wanted to investigate the etiology of the disease or to develop a therapy for it, because such engagements seemed to be without promise of success. Today we know that the affected gene product constitutes such a small amount of protein in the muscle cells that it was unlikely to be detected by conventional biochemical techniques.

Since the cause of DMD was unknown the physicians tried on the off-chance a great number of drugs that had been effective with other diseases (1, p. 214): none of them worked out! When in 1986 Lou Kunkel (2) isolated the so-called Duchenne gene and one year later Eric Hoffman (3) described its product, dystrophin, not only did all researchers and physicians, but also all patients and their parents believe that this would quickly open the way to a causal therapy. Today, a quarter century later, the end of this journey may be – more or less distinctly – in sight: availability of the much anticipated gene therapy. But even today we cannot predict when we will have completed this journey. The kind of gene therapy that is currently believed to have the greatest chances of success, namely “exon skipping” (4), will be applicable to about 80% of patients. But at present it is being developed and clinically tested in a phase-III trial for only those 13.0% who need the skipping of their exon 51 of the extremely large gene. For all the others, many more so-called “personal therapies” and other more conventional forms of treatment will have to be developed (regularly updated status report [5]). Obviously there are still many obstacles on this route and nobody knows when they will be removed. The parents, who see the strength of their children’s muscles wane every day, are desperate. Some of them accuse the physicians of this failure; others try to find themselves sources to accelerate research into gene therapy.

But is the situation indeed so hopeless for the Duchenne families? Let us briefly look at their general situation: how has it changed in the time span since the discovery of the dystrophin gene? There are many positive factors in support of genetic counseling. At least in the developed countries the often quoted figure for the incidence of DMD of 1 in 3500 male births is not true anymore. An effective figure is not available, but there is no doubt that the incidence has decreased in conjunction with progress in prenatal diagnostics (6). At the same time the degree of awareness of the disease both in general public as well as amongst general doctors has much increased owing to, in particular, the activities of the media and the great efforts of the advocacies (Telethon), as well as the general valorization of all rare diseases (RD) by the politicians (7). Therefore the ordeals of new parents, formerly often described as “odysseys”, are now considerably shortened.

But also in the field of treatment of DMD patients the said period from the 1980s till now has witnessed enormous progress that is already at the disposal of all patients. We are talking of a whole group of symptomatic therapies which, when applied together, have resulted in a doubling of the life expectancy from 15 to 30 years – and with a formidable improvement in the patients’ quality of life! There are not many other diseases which can claim similar success in such a short time span. In order to bring this home to the patients, their parents and their doctors, the editors of Acta Myologica have decided to devote the main part of the current issue to the progress in symptomatic therapy of DMD.

Even some 12 years before the discovery of the DMD gene defect Dan Drachman and his co-workers (8) reported a positive effect of prednisone on the natural course of the disease. But it took several years for this finding to be accepted by other physicians, probably because therapy involving glucocorticoids is known to possibly have grave side effects on occasions. Today, after many studies have been carried out in various countries throughout the whole world, studies which have tested diverse corticosteroids, various regimes of administration and variable doses, this kind of treatment has become accepted as the only available efficacious drug therapy. We have asked the group of Janbernd Kirschner, Freiburg, Germany, to review the field for this issue. In addition, the groups of Corrado...
Angelini (Padova) and W. Douglas Biggar (Montreal) present their own experiences. The most important result of all these studies is that this treatment enables one to delay by several years the age at which the patients become wheelchair-bound. According to today’s awareness this delay is of eminent importance because if the patients lose their ability to stand before puberty they will soon develop a rapidly progressive scoliosis, increasingly compromising their lung function. If the necessity to use a wheelchair can be delayed towards the end of puberty, the danger of developing scoliosis is largely averted.

Another set of important measures has accompanied this drug therapy using corticosteroids, all of them aimed at prolonging the period of walking and standing. These include orthopaedic appliances like light-weight orthoses and prop-up wheelchairs. More important than these appliances are the surgical operations on the patient’s ankle, knee and hip joints. The earlier in life these operations are performed, the longer the Duchenne boys are able to continue walking and standing. The instrumentations, in many countries linked with the name of Yves Rideau, Poitiers, will be described in this issue by Raimund Forst and Jürgen Forst, Erlangen, two collaborating brothers who are amongst the most prominent experts in this field.

Even if the cases of scoliosis do not reach Cobb angles to the degree formerly seen in untreated boys, the functionality of the lungs nevertheless decreases with increasing age because of the progressive weakness of the respiratory muscles. Therefore assisted ventilation has been a big boon for the patients, with great strides forward since the 1980s. A reduction of size and energy requirement of respirators as well as access of air through a mask in front of the nostrils as an alternative to the established tracheostomy have been the biggest steps forward in this area. Yves Rideau, Poitiers, one of the pioneers of assisted ventilation, who has always strived at improving the respiratory conditions of DMD patients, reports his new concept of a “tracheal nostril”, i.e. a new intratracheal approach to supplying air to the patients’ lungs in his special contribution at the end of our series.

Together with the enormous prolongation of the lifespan of DMD patients, we have become aware of a completely new aspect of the disease, i.e. the discovery that not only the skeletal muscles, but also the cardiac muscle is affected by defective dystrophin. The problems evolving from this defect and their prophylactic as well as acute symptomatic treatment was first recognized and studied by Giovanni Nigro's team at Naples. Obviously the corresponding contribution by the two major editors of AM is a matter of course.

I am happy to say that also the Ulm Muscle Centre is represented in the cycle of contributions to this issue. The approach to drug therapy reported by Frank Lehmann-Horn and his co-workers concerns the early muscular oedema which is intracellular, has an osmotic origin and is cytotoxic. It is hoped that the specific aldosterone antagonist eplerenone can inhibit the fibrosis of both skeletal and cardiac muscle, and thus slow the dystrophic process.

Finally we present a review of a field that has also developed since the 1980s and will certainly gain impact in the years to come. This is the testing of drugs that hold promise for useful therapy on the mdx mouse, the most common animal model of DMD. The review has been written by Annamaria de Luca from Bari.

It is our pleasure that the greatest living champion of the fight for treatment of Duchenne muscular dystrophy patients, Prof. Yves Rideau, could be persuaded to recount his own experiences with the early attempts of symptomatic therapy. He, who after retiring from his chair at Poitiers is now closely associated with the muscle centre at Naples, has named his contribution “Requiem”…

Reinhardt Rüdel
Division of Neurophysiology, Ulm University, Ulm Germany

Acknowledgments

The Author gratefully acknowledges support by Luisa Politano, Jane Miller, Günter Scheuerbrandt and Frank Lehmann-Horn.

References

1. Emery AEH, Emery MLH. Duchenne muscular dystrophy or Meron’s disease. 2nd ed. Oxford: Oxford University Press 2011.
2. Kunkel LM. Analysis of deletions in DNA from patients with Becker and Duchenne muscular dystrophy. Nature 1986;322:73-7.
3. Hoffman EP, Brown RH, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987;51:919-28.
4. Wilton SD, Fall AM, Harding PL, et al. Antisense nucleotide-induced exon skipping across the human dystrophin gene transcript. Mol Ther 2007;15:1288-96.
5. Scheuerbrandt G. www.duchenne-information.eu.
6. Mendell JR, Shilling C, Leslie ND, et al. Screening for Duchenne muscular dystrophy. Ann Neurol 2012;71:304-13.
7. Council Recommendation of 8 June 2009 on an action in the field of rare diseases. Official Journal of the European Union 2009:C:151/02.
8. Drachman DB, Toyka KV, Myer E. Prednisone in Duchenne muscular dystrophy. Lancet 1974;14:1409-12.