

2010 MDA Research Report 2010-10-29

It is once again a great pleasure to be able to write this year's Research Report for you.

Most of this report will be taken up with news from clinical/scientific research conferences that I have attended this year but there will also be some additional and more recent news. It is important to note that, in general, the research reported at these conferences has been based in overseas research institutes, although, much of it has been conducted through international collaboration and some has included Australian researchers. On this occasion, I am not reporting on relevant research from any specific Australian laboratories.

Towards a Brighter Future, 2010 Neuromuscular Disorders Conference, Sydney, Australia on Friday 26th and Saturday 27th February.

[Organisers: Deb Robbins (Duchenne Foundation Queensland) and Kathryn North (Institute for Neuroscience and Muscle Research, Children's Hospital at Westmead, University of Sydney)]

Several hundred delegates attended this conference ranging from patients and parents through clinicians and allied health professionals to research scientists. The conference included at least some coverage of most different kinds of neuromuscular disease (NMD), their diagnosis and characteristics, current approaches to their management, quality of life issues, ongoing clinical and scientific research (especially the establishment of research networks) and potential future therapies. Speakers discussed bone, respiratory and cardiac care in these diseases, as well as, the place of physiotherapy, occupational therapy and podiatry in the different conditions. Not least was the presentation putting forward the Danish model of Rehabilitation in NMD, by Dr Jes Rahbek with whom I recounted the visit to MDA SA almost 20 years ago by Klaus Bach, a young man with Duchenne muscular dystrophy (DMD) from Denmark. Klaus made a great impression on us, being some 30 years of age, driving an incredibly sophisticated electric wheelchair with built-in ventilator and accompanied by two devoted carers. Klaus not only visited us but also places in other Australian states, including Uluru. Because it was impossible to attend everything of importance or of interest, I am restricting this report on the conference to just a few aspects of clinical and scientific research.

Dr Katie Bushby (Acting Research Chair of Neuromuscular Genetics, University of Newcastle-upon-Tyne, UK) especially emphasised the organisation she helped to found, TREAT-NMD, which has now become a global network with research, industry and parent-patient organisation co-operation and input. One of the important outcomes of the conference was the establishment of an Australian network and its linkage with TREAT-NMD. South Australia's representative in the network is Dr Suzanna Thompson from Women's and Children's Hospital who is on our Medical Advisory Panel. It was interesting to note that in one of her lectures, Prof. Bushby provided figures indicating some of the individual disease frequencies among all NMDs as follow:

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|--------------------|---|
| Myotonic Dystrophy | 28% |
| DMD/BMD | 20% |
| FSHD | 10% - others suggest that FSHD may eventually turn out to be the most common because many patients are missed due to its very variable severity |
| SMA | 4% |

Dr Katie Bushby and Dr Kathy North and her students all discussed an unusual set of muscular dystrophies caused by "Dysferlin" deficiency: dysferlin, like dystrophin, being another essential muscle protein. Its absence causes either Limb Girdle MD type 2 (proximal muscles affected) or Miyoshi myopathy (distal muscles affected). How come, they ask! This is a much more profound difference than that between Becker and Duchenne MD. So, what does dysferlin normally do? Dystrophin, as most people involved with MD now know, strengthens muscle cell membranes and protects them against the damage that always occurs in muscle exercise, especially strenuous exercise. Dysferlin, on the other hand, is believed to be involved in the repair of muscle cell membrane damage. So in the one case, too much damage occurs and in the other, not enough repair. But, again,

how can its deficiency cause both Limb Girdle MD type 2 (with proximal muscles affected) and Miyoshi myopathy (with distal muscles affected)? Similar questions can be asked about why only particular muscles are initially affected in facioscapulohumeral MD, those of the face, upper arms and shoulders. Answers and treatments in these conditions could be transferrable to many, if not all, other MDs. *For example, since this conference (in late September), Nicolas Levy and colleagues from the University of the Mediterranean, Marseilles, France, have reported finding a naturally occurring short dysferlin gene (equivalent to the mini dystrophin gene) in a person with a very mild form of Limb Girdle MD type 2. When this gene was used in rAAV-mediated gene therapy of dysferlin deficient mice, their disease was alleviated. [I discuss the mini dystrophin gene and rAAV-mediated gene therapy later in respect to the ICNMD12. As well, at the recent ICNMD12 and in scientific journals there has been considerable interest in cell membrane repair mechanisms. Along with dysferlin, caveolin-3, mitsugumin 53 and several other proteins are now known to be involved in the repair process and their action might be able to be controlled to improve the efficiency of repair. Intriguing to me (because of my interest in muscle chloride ion channels), Limb Girdle MD type 2 and Miyoshi myopathy have also been found by researchers in Montreal, Canada and Durham, UK, to be associated with mutations in a newly discovered calcium-activated chloride channel protein called anoctamin5.]*

Dr Jeff Chamberlain, University of Washington, Seattle, USA was hopeful but cautious about potential therapies for NMDs.

As yet there are no examples of gene therapy or stem cell therapy that improve function in any of the NMDs in humans and even in animals with NMDs only one example of gene therapy in a mouse MD has increased its lifespan. Many difficulties remain to be overcome – a recent gene therapy trial in DMD failed due to an immune response against the newly introduced dystrophin, itself. There are also problems with immune responses to the virus coatings in virally delivered gene therapy. *[Again, please see later.]*

“IF IT SOUNDS TOO GOOD TO BE TRUE, THEN IT PROBABLY IS”

As an example, some months ago there was a report in the Advertiser of a family taking their young son to China to receive stem cell therapy for blindness caused by optic nerve hypoplasia (underdevelopment) - at a cost of \$50,000. There is no reputable scientific evidence that stem cell therapy, as it currently exists, could be successful for this type of blindness or for NMDs. In fact, there are only very few examples of drug therapies that are beneficial in NMDs, corticosteroids temporarily halt progression of DMD and Myozyme can allow improvement of muscle function in Pompe's disease.

But – there are already many possibilities for the future and some are, even now, in clinical trial. What is the “BEST” method? As yet, there is none. The best advice is - don't put all of your eggs in one basket. *[I'll come back to this, below, in respect to Ataluren (PTC124).]* Combination therapies: exon skipping, stem cells, anti-inflammatory agents, muscle building agents and other drugs might all be needed at once or in sequence.

Dr Nigel Laing, Australian Neuromuscular Research Institute, University of Western Australia
According to clinicians in Wales where early post natal screening for DMD has been conducted since at least 1990, the rest of the world is still in the “Dark Ages” about this. Even though it can be argued ethically that screening should not be performed until an early therapeutic intervention is possible, it can equally be argued that knowledge can allow for planning within the family, for appropriate social assistance in advance, and for early application of any therapy if and when it becomes available. This would avoid having to wait for a positive diagnosis due to symptoms which can still be misdiagnosed up to the age of five years or more. In a worst case in Western Australia, a family had four sons with DMD and a fifth without, but who later committed suicide. Early knowledge of DMD in the first of their sons might have allowed this family to reduce the extent of their terrible tragedy.

12th International Congress on Neuromuscular Diseases(ICNMD12) in Naples, Italy, from Saturday 17th to Thursday 22nd July with Professor Giovanni Nigro as its President.

Some 1,000 delegates attended this Congress in which lectures, symposia and posters were employed to present scientific research and clinical aspects on most of the several hundred known neuromuscular diseases. As well, preparations for, and the results from, several clinical trials were announced.

ICNMD12 was the first in this series of Congresses to devote a full session to neuromuscular diseases of animals.

Dystrophinopathies in animals: Dystrophic dogs (Golden Retrievers, German Short Haired Retrievers, Beagles, Cavalier King Charles Spaniels), dystrophic cats (thick but weak muscles – known as “Schwarzenegger syndrome”), mdx mice. But we must remember “Ringo” the Golden Retriever with no dystrophin yet only a mild clinical condition and practically normal muscle strength. Genetically, Ringo has the same mutation in the dystrophin gene on his X chromosome as occurs in the rest of his litter, parental relatives and offspring but only he and one of his pups “Sufclair” are mildly affected. All other male members of this dog colony in Sao Paulo, Brazil, that have this mutation on their X chromosome, have, or have had, severe MD. What factor/s might compensate for the absence of dystrophin in Ringo and Sufclair is therefore a matter of intense research interest.

Sarcoglycan deficiency: occurs in Boston Terriers, various mice (equivalent to Limb Girdle MDs).

Dystroglycan deficiency: occurs in Sphinx and Devon Red Cats.

Myotubular myopathy: occurs in Labrador dogs – a colony is being established.

Inflammatory myopathies: have been studied in Italian dogs – serotonin (a neurotransmitter also involved in mood) is implicated.

Polysaccharide storage disease: occurs in Quarter horse-type horses – can be treated by feeding a diet including long chain fats.

Myotonic myopathy: has been found in a Czech foal.

Latest News of Ataluren (PTC124)

- (a) Most of you will already know that the two clinical trials of Ataluren (PTC124) for DMD/BMD have been suspended earlier this year because the drug does not seem to have had any significant effect compared to placebo in the six minute walk test. Only some boys receiving a low dose of Ataluren seemed to have some positive response while boys receiving higher doses had no response – an outcome that was discussed at the Congress but is still not understood and could well be a placebo effect. This result, while very disappointing, has not been a surprise to members of our MDA Medical Advisory Panel and our Medical and Scientific Research Advisory Panel. You may remember that these panels cautioned that, in their opinion, inadequate basic research had been done in animals with MD to convince them that clinical trials in humans were warranted. The present outcome might sound like a case of “We told you so”, however, as was included in my 2009 report, just as it is the duty of our advisory panels to warn against alternative therapies that do not have the backing of accepted medical and scientific evidence, so too, it is their job to advise where hype is excessive and where hope is minimal. What was immensely discouraging to me, personally, was that, in this particular instance, enormous amounts of funding, amounting to millions of dollars, was provided by Parent Project and by MDA USA to support the trials of Ataluren. Public pressure for these trials was intense and this was, unfortunately, aided and abetted by several premature research publications, especially one in the prestigious scientific journal, Nature.
- (b) *In the last few weeks, I have been encouraged to discover that the National Human Genome Research Institute of the National Institutes of Health, USA, have initiated an investigation into perceived coercion to participate (described more moderately in the details of the investigation as “learning about motivations for being involved”) in the clinical trial of Ataluren (PTC124).*

Encouraging News on Steroid Therapy

In contrast to the news of Ataluren, Dr Eric Hoffman, Children’s National Medical Center, Research Center for Genetic Medicine, Washington DC, USA, gave a lecture on the development of novel steroidal drugs to improve muscle regeneration, and improve muscle function in MD.

Still the only drugs proven to have a beneficial effect on DMD are the steroids (also known as corticosteroids or glucocorticoids), prednisone and deflazacort.

How do they work? It is still not certain but they do NOT work in the way that the testosterone-like anabolic steroids work, that is, the drugs used illegally by sporting “wannabees”.

Dr Hoffman and colleagues have been studying the chemical structure of the corticosteroids to determine which areas of the structure (four joined carbon rings with several spike-like hydrogen atoms and other chemical groups sticking out from them) have the beneficial effects and which cause the side effects. It seems that modifying the structure of these substances, and removing those groups at positions 9 and 11, can make them 40 times more effective at reducing inflammatory activity and fibrosis when tested in animals, without the usual side effects of chronic steroid administration. These new agents have been named VBP drugs.

With respect to understanding just what these drugs do, it seems that their beneficial effects are mainly on synchronising events in muscle that are associated with inflammation and fibrosis. In DMD, for example, it is the muscle itself that is driving the inflammatory process. Some muscle cells are continually and randomly being damaged associated with random inflammation, fibrosis and repair. When synchronised waves of inflammation, fibrosis and repair occur, the repair is more successful. Interestingly, both inflammation and fibrosis are also associated with asthma and these same drugs are effective there too. Normally, in the lungs and gastrointestinal tract, synchronised waves of repair take place each night associated with circadian peaks and troughs of secretion of the natural steroid, cortisone, from the adrenal gland.

Animal studies suggest that the future for steroid treatment is very bright with VBP drugs promising all the benefits of prednisone or deflazacort without the serious side effects of short stature, weight gain, bone fragility and mood alterations. *[Other researchers have reported that unrelated anti-inflammatory agents, such as Etanercept, have beneficial effects in mouse muscular dystrophies.]*

Uncertain News on Stem Cell Therapy

There is continued interest in mesoangioblast (stem cell) therapy. Dr Jordi Diaz-Manera from Barcelona, Spain, in a brief “late breaking news” report described successful mesoangioblast therapy in mice with dysferlinopathy. No conclusive evidence was provided and this work has not, so far, been published in a scientific journal. Dr Diaz-Manera has worked with Dr Giulio Cossu from Milan, Italy, who published a heavily criticised paper in the journal Nature, several years ago on the claimed successful treatment of dystrophic dogs with mesoangioblasts. A major problem with Dr Cossu’s dog study was whether or not his mesoangioblast-treated dogs had more dystrophin positive muscle fibres than his control untreated dogs. There is still little information on whether, or how well, mesoangioblasts multiply after injection into muscle and how well they interact with or repair dystrophic muscle. Nevertheless, according to a poster shown at the ICNMD12, Dr Cossu is, on the basis of his inadequately controlled dog study, preparing for a clinical trial of mesoangioblasts in boys with DMD.

By contrast, a team of researchers led by Drs Huck-Hui Ng and Frederic Bard from Singapore has just reported on their attempts to determine why adult stem cells have a limited ability to reproduce themselves. They have investigated the 21,000 genes in the entire human genome to find which regulate the two important properties of embryonic stem cells, their ability to turn into any type of cell in the human body (pluripotency) and their ability to retain that ability through indefinite numbers of cell divisions (relative immortality) until triggered to develop into a specific cell type (differentiation). One of several important genes they discovered is PRDM14 which makes it easier to turn a mature adult human cell into a pluripotent cell equivalent to a human embryonic stem cell. This could provide a real advance in the preparation of muscle stem cells for the therapy of muscular dystrophies. In addition, ethical problems associated with the use of human embryonic stem cells would be avoided.

The State of the Art in Gene Therapy

There are both cautions and cautious optimism regarding gene therapy for NMDs.

I don’t intend writing much on exon skipping gene therapy using antisense oligonucleotides (AON) because this has been covered in my previous annual research reports and because most people know that some successes have been achieved. It will, nevertheless, be quite a long time before this

technique is generally available, it is likely to be very expensive and it might or might not be applicable to individual patients for various reasons including the extent of their existing muscle loss. It is not anticipated that it would be able to facilitate muscle restoration where the muscle cells had already been lost and replaced by fibrous and fatty tissue.

Among those undertaking the most advanced research and clinical trials of gene replacement therapy is Dr Jerry Mendell from the Nationwide Children's Hospital, Columbus, Ohio, USA. He and his colleagues have found dystrophin immunity due to blood T cells both before and after dystrophin transgene administration by viral vector. Obviously if there was a strong immune reaction to newly expressed dystrophin during treatment, this would prevent successful incorporation of dystrophin into muscle cells.

In their other work, recombinant adeno-associated virus type 1 (rAAV1) – (1) has been used in one completed clinical trial of alpha-sarcoglycan gene therapy for Limb Girdle MD type 2D (injected into extensor digitorum brevis muscles, double blind randomised trial with placebo control, safety assessment and then strength testing on follow up). There was sustained alpha-sarcoglycan expression for at least three months in three subjects and for six months in 2 of three other subjects. The third of this group had pre-existing immunity to the AAV, itself, resulting in markedly lower gene expression in this subject, – (2) is to be used in clinical trial of mini-dystrophin gene therapy for Duchenne MD (injected into both biceps muscles, with placebo control, safety assessment and then strength testing on follow up). The mini-dystrophin gene is a dystrophin gene with a large internal deletion of the kind that can cause Becker rather than Duchenne MD.

Dr Olivier Benveniste, Institute of Myology, Paris, France, also used an rAAV1 vector, this time in a clinical trial of gamma-sarcoglycan gene therapy for Limb Girdle MD type 2C. Evidence of gamma-sarcoglycan presence was found in the three patients who had received the highest dose out of the nine patients in the trial. No adverse effects were found.

Dr Jeffry Chamberlain and colleagues from the University of Washington, Seattle, USA, used rAAV6 in mice to show that they were able to deliver genes to muscles throughout the body after injection directly into the bloodstream.

New methods of improving gene/viral delivery to limb muscles are being investigated. For example, Dr William J. Powers, University of North Carolina, Chapel Hill, USA, is undertaking a safety assessment of "transvenous limb perfusion" in which fluid at high pressure is injected into limb blood vessels.

Latest Developments in Myotonic Dystrophy types 1 (DM) and 2 (PROMM)

Dr Charles Thornton from the University of Rochester, New York, USA, and others have reported that long stretches of repeat coding in DNA and RNA cause RNA-binding proteins to stick to them resulting in abnormal aggregates (called "foci") inside muscle cell nuclei. Foci are probably composed largely of "muscle blind-like" protein type 1 (MBNL1). Somehow they lower the levels of certain types of mRNA and cell protein production resulting in such symptoms as myotonia. Also, DM muscle contains more satellite cells (myoblasts) but these have a reduced ability to reproduce themselves (even less than in DMD) – a marker of this reduced replicating ability is that their chromosomes have reduced telomere length. Antisense oligonucleotides have great potential for reducing nuclear aggregates and for restoring normal mRNA transport and protein production in DM muscle cells.

Clinical trials of some agents are not too far off:

Morpholino AONs have already been shown to work against the myotonia of DM in animals but not against the muscle wasting, etc.

Pentamidine – is a small molecule with potential to treat DM but too toxic.

PROMM – no congenital onset, some CNS involvement, sometimes affects only one muscle on one side of the body.

An Outstanding Advance in Mitochondrial Disease Prevention

Unlike typical hereditary diseases, many mitochondrial diseases are passed from a mother to any or all of her children in an often complex way. At the Congress, Dr Billy Di Mauro from the Columbia University Medical Center, New York, USA, described a procedure involving *in vitro* fertilisation using an egg cell and sperm from the natural parents followed by removing the nucleus of the

fertilised egg cell at the appropriate stage. The practically pure nuclear chromosomal material obtained in this way is then transferred to a de-nucleated donor egg cell. Therefore, the resultant embryonic cells should contain only DNA from the natural parents but little to no maternal mitochondria and should develop free of maternally transmitted mitochondrial disease. This works successfully in experimental animals, including monkeys, and is being tested in humans.

Latest News in Ion Channel Diseases of Muscles (Channelopathies)

Dr Frank Lehmann-Horn of the University of Ulm, Germany discussed both the mechanisms of some of these unusual and uncommon diseases and new hope for their therapy. In the periodic paralyses, carbonic anhydrase inhibitors such as acetazolamide are often effective, as is the aldosterone antagonist, eplerenone. The carbonic anhydrase inhibitor, dichlorphenamide, is very effective but it is off the market. A new big trial is to be undertaken to be certain of its effectiveness, to gain new manufacture and government approval. This is very expensive.

The action of these agents seems to be to decrease the entry of sodium and water into muscle fibres, thereby increasing their excitability and strength back to normal and reducing muscle fibre oedema and damage.

Limb Girdle Muscular Dystrophies

Dr Kevin Campbell of the University of Iowa, USA, explained that patients with Limb Girdle MD, mdx mice and alpha-sarcoglycan deficient mice all show exercise-induced fatigue. Even a period of very mild exercise before a standardised 6 minute walk test has a significant effect on the walk test. It has been found that this is most likely due to a deficiency in a nitric oxide synthesising enzyme, known as nNOS. This reduces blood flow through the exercising muscle but, interestingly in the animals, the blood flow can be compensated and fatigue reduced by drugs of the Viagra type.

Altogether, 40 to 50 genes are now known to be involved with the MDs and of course many more if we consider all of the NMDs. For the MDs, 60 to 70% of the protein products of these genes are associated with the muscle cell membrane and are implicated in DMD, Becker MD and most of the Limb Girdle MDs, among others. This reinforces the importance of the cell membrane and also highlights its fragility, if not properly supported by surrounding proteins. Dr Campbell described a new assay for membrane fragility in which dye entry into muscle cells is watched following absolute minimum damage caused by a two photon laser light pulse.

He and his colleagues have shown how an enzyme, known as LARGE, adds sugar groups to the muscle cell membrane protein, alpha-dystroglycan. This effectively provides the glue to attach extracellular connective tissue proteins (lamins) to alpha-dystroglycan and so, through dystrophin, to the intracellular cytoskeleton, thereby stabilising and strengthening the muscle cell membrane. Defective sugar addition (glycolysation) can cause MD and other, even more severe, diseases because cells other than muscle cells can be affected, as well. Importantly, mutations in lamins, themselves, can also cause MDs, cardiomyopathies, nerve axon neuropathies and even premature aging. Gene therapy with LARGE is effective in normalising muscle in some mice with MD. *[Please refer to accounts of clinical trials of gene therapy for human Limb Girdle MD, in "State of the Art", above]*

Some Questions and Comments Raised Regarding Clinical Trials

Are they always necessary? What are the ethical considerations of running them?

Does the cost of a new, extremely expensive drug always justify the improvement in the quality of life of the patient? What if that improvement is very small?

Do you treat a baby with a disease, and at what cost, if grandma (who has presumably lived quite a long life) has the same defect?

If a very rich patient with an unknown NMD has a full genome sequencing screen and comes to a clinician with all of the genetic data on a computer disk, what does the clinician do?

It is often argued that it is always better to treat before rather than after disease onset. This looks good to researchers, clinicians, administrators and governments, but what if the disease wasn't going to occur in that person, or was only going to be very mild, anyway?

It must be taken into account that the pipeline of future drugs is almost empty (research is too expensive).

Willingness of patients to participate in clinical trials is rapidly diminishing. People are jaded by lack of success, e.g., in MND and DMD.

Reliable and reproducible measures of the outcome of therapeutic intervention are absolutely essential.

The Increasingly Recognised Importance of Having Better Biomarkers of Disease

Generally used chemical biomarkers such as creatine kinase (CK) are not always reliable indicators. They are also present in the blood at high levels after exercise in some people and are present at reducing levels as muscle mass decreases. Therefore lower levels after a trial therapy do not necessarily indicate decreased dystrophy or improvement. Some newly recognised chemical biomarkers such as “osteopontin” might be better indicators – increased levels correlating with the dystrophic process in mdx mice, also found in DMD muscle biopsies, they are associated with inflammation and fibrosis in mdx mice, at least.

Physical biomarkers, some of which are quite new, include: Ultrasound (imaging), MRI (magnetic resonance imaging), fMRI (imaging while functioning, for example while the brain is performing a specific activity), Magnetic Resonance Spectroscopy (MRS, measuring chemical components of tissues), Near Infrared Spectroscopy (NIRS, various kinds of imaging), cathepsin-based NIRS (for example, imaging of the pathology in dystrophic muscle), fNIRS (imaging of the flow of oxygen rich blood through tissue).

Spinal Muscular Atrophy (SMA) and Motor Neuron Disease (MND/ALS)

The disease mechanisms resulting in SMA are now well understood and several clinical trials are under way or proposed. An additional role of survival motor neurone (SMN) protein in transport inside nerve axons has been found. It then, presumably, has a function at the nerve terminal/ neuromuscular junction or even at the muscle as has previously been hypothesised. The major/original role of SMN is known to be in mRNA splicing.

Many preclinical trials have already produced positive results in mouse models of SMA. Dr Arthur Burghes and his colleagues from the Ohio State University in Columbus, USA, has made an extensive study of the SMA mouse. They have found that by raising levels of the survival motor neurone (SMN) protein to just 25% of normal, disease is prevented. Therapeutic agents for SMA must be able to pass through the walls of nervous system blood vessels (known as the Blood Brain Barrier) which often impede the free passage of otherwise useful drugs, etc. Promising treatments include AONs that can increase expression of functional SMN from the undamaged SMN2 gene that is present in most patients (a mutated SMN1 gene being the usual cause of the disease). Gene therapy using rAAV9 as the viral vector to carry SMN transgenes into motor neurons also has potential.

Considerable advances in the understanding and in the early diagnosis of MND/ALS are also being made and although Riluzole is still the only treatment that has been proven to prolong life in humans, many new clinical trials are producing interesting results. Currently, Vascular Endothelial Growth Factor (VEGF) is in a clinical trial being conducted by Dr Wim Robberecht and colleagues at the University Hospital, Leuven, Belgium.

Sporadic MND/ALS has recently been found to be associated with paraoxonase gene (PON1, 2 and 3) mutations but that there is also some form of gene – environment interaction that leads to increased susceptibility.

Familial MND/ALS makes up 5% of all MNDs and many of these cases are associated with mutations in the SOD1 gene. It has recently been found that the SOD1 protein is secreted into the fluid that surrounds brain cells and that the mutated form of SOD1 triggers harmful inflammatory reactions and neuronal death. This leaves the way open to use immunogenic methods to destroy the mutant SOD1. Specific synthetic antibody fragments might be able to bind mutant SOD1 and eliminate it. Synthetic antibody fragments are now under consideration for use as a complement or alternative to monoclonal antibody drugs (those whose names commonly end in “mab”) in many other branches of medicine.

Advances in Peripheral Nerve Diseases

Two genes that had previously not been suspected to be involved in Charcot-Marie-Tooth disease were implicated by the discovery of mutations that in one case caused loss of an essential enzyme function and in the other caused a toxic gain of function. [*Please see FSHD, below*]

To date, positive benefits of exercise training, dietary supplements and drug interventions have not been definitely proven in CMT. There are current trials of long-term aerobic conditioning in CMT and in the less severe muscular dystrophies where there is reasonable evidence that this form of exercise therapy can be helpful in improving strength, fitness and endurance without damaging muscle. Experimental therapy with the turmeric extract, curcumin, has been successful in several animal models of peripheral nerve disease, including CMT1B mice. Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease of peripheral nerves that, in about three-quarters of all cases, can be treated relatively effectively. Several treatments are available, each being about as effective as the other, but of these corticosteroid therapy is the least expensive.

Diseases Involving the Neuromuscular Junction

Dr Angela Vincent from the University of Oxford, UK, gave a thorough review of the scientific understanding and up-to-date therapeutic approaches to the treatment of myasthenia gravis (MG). Although it has long been known that MG is an autoimmune disease, with the immune system usually attacking acetylcholine receptors at the neuromuscular junction, exactly what is being attacked in up to 10% of cases is uncertain. Presently used therapies include anticholinesterases, thymectomy, immunosuppression and plasma exchange. Good responses are being obtained with the experimental use of monoclonal antibody drugs that inactivate specific components of the immune system. Some of these may be especially useful in myasthenic emergencies.

6th International Assembly of the World Alliance of Neuromuscular Disorder Associations on Wednesday 21st and Thursday 22nd July in association with the ICNMD12.

The WANDA Assembly was organised by Allan Bretag (Australia, President of WANDA), Ysbrand Poortman (The Netherlands, Vice President of WANDA), Anna Ambrosini (Italy Telethon) and Cira Solimene (UILDM – the MDA of Italy). These Assemblies are held every four years in conjunction with the clinical and scientific ICNMDs and attended by WANDA Board Members and delegates of national NMD organisations. This was the first time that NMD Associations from all continents were represented. Reports from Board Members covered developments in NMD organisations in each continental region:

Southern Africa – Lee Leith (presented by Allan Bretag)

North Africa – Ekram Abdel-Salam

South America – Mayana Zatz

North America – Alex MacKenzie

Europe – Boris Sustarsic

East Asia – Ikuya Nonaka (presented by Ichizo Nishino)

Australia/Oceania – Kathryn North

As well, videos, invited speakers and poster presenters illustrated topics as diverse as orthopaedic procedures in DMD, fund-raising by telethon, palliative procedures for a person with an NMD as well as for all involved in their care and the structure and administration of the large NMD organisations, AFM and TREAT-NMD.

The major focus at this meeting, however, was on co-operation between NMD organisations in European, North African and Middle Eastern countries bordering the Mediterranean. In this regard, a forum was set up and chaired by Anna Ambrosini and Maryze Schoneveld van der Linde. Speakers discussed opportunities for, and barriers to, their closer interaction. The final resolution was for the relevant delegates and their organisations to pursue co-operation and strengthen alliances among Mediterranean NMD associations. National and international neuromuscular clinical centres as models were discussed, especially the Rehabilitation Centre for NMDs in Denmark and the Neuromuscular Omnicentre (NEMO) in Milan.

Specific national NMD organisations were represented by Cira Solimene (Italy), Serge Braun (France), Coskun Ozdemir and Yakup Sayin (Turkey), Valerie Cwik (USA), Eduardo Tizzano (Spain) and Henrik Ib Jorgensen (Denmark). Boris Sustarsic also represented the European Alliance of Neuromuscular Disorder Associations (EAMDA).

In an evening session, Ysbrand Poortman explained one function of WANDA as facilitating a “Roadmap to Treatment. Kate Bushby dealt with TREAT-NMD as an organisation providing tools for the entire neuromuscular community from patients through research laboratories to big pharma *[It is particularly important to mention, here, the publication by TREAT-NMD of a DMD Family Guide on the Diagnosis and Management of boys with DMD. This can be found on the internet at:*

www.treat-nmd/patients/DMD/familyguide/]

In the same session, Anna Ambrosini described the European Neuromuscular Centre (ENMC) as a “platform of patient empowered organisations” and Woon-Chee Yee discussed the Asian and Oceanian Myology Center (AOMC) as an organisation with a major involvement in educating and training young neurologists and allied health professionals in clinical, scientific and research aspects of neuromuscular diseases in East Asian developing countries.

Dr Francesco Muntoni from University College London, UK, gave a summary of the newsworthy items that had been presented during the concurrent ICNMD12 meeting. I have included most of his points in my account of the ICNMD12 meeting, above. However, Dr Muntoni also especially emphasised new diagnostic techniques including chips (something like those used in computers) capable of detecting thousands of NMD mutations in a small DNA sample, all at once. As well, he noted the rapid advances being made towards treatments. At the ICNMD11 in Istanbul, just four years ago, AON exon skipping was reported as a possible therapy for DMD but there have now been several clinical trials proving its safety and potential.

Among many items under discussion during the Assembly was the important consideration of holding future meetings at a “virtual site” using the latest internet technology with real-time video streaming. This would allow the participation of patients, parents, carers and NMD organisation representatives from anywhere in the world. It would overcome real obstacles such as the affordability and difficulty of travel and accommodation for patients and their carers and especially for those from developing countries.

Miscellaneous News from Recent Research Publications

Heart Muscle Cell Membrane Repair

A report published earlier in the year by Dr DeWayne Townsend and colleagues from the University of Minnesota USA, suggests that an unusual material called poloxamer can be injected into the blood stream of dystrophic dogs from where it passes to the heart to repair damaged membranes of heart muscle cells. If this proves to be reproducible and non-toxic and is feasible for use in humans, it might benefit not only people whose hearts are being damaged by muscle diseases but also people whose heart muscle is being damaged for other reasons. Its present disadvantage is that it requires chronic long-term intravenous infusion.

Selenoprotein N deficiency

At the October meeting of the World Muscle Society in Kumamoto, Japan, Dr Pascale Guicheney and her colleagues have shown the possible reason for the muscular atrophy that occurs in selenoprotein N deficiency. In this disease, there is some basic defect in the satellite cell population that does not prevent muscle development or even regeneration after initial muscle cell damage. During the repair and replacement of these damaged muscle cells, however, a large portion of the existing satellite cells is used up so that few, if any, are available to participate when future episodes of regeneration are required. So there is progressive muscle loss.

Facioscapulohumeral Muscular Dystrophy (FSHD)

FSHD is one of the most common hereditary neuromuscular disorders in Western populations. In most patients, it is associated with contraction of a DNA coding repeat region on chromosome 4, but this contraction can also occur in the absence of disease, so the underlying genetic mechanisms have remained elusive. Dr Richard Lemmers and his colleagues from the University of Leiden Medical Centre, The Netherlands have recently shown that FSHD patients carry additional DNA sequence variants that act to stabilise RNA transcripts from the normal gene, DUX4. Accumulation of these

excessively stable RNAs possibly has a toxic effect, known as a toxic gain-of-function, which is likely to be a contributing factor in this disease.

Oculopharyngeal Muscular Dystrophy (OPMD)

In mid-year there was unexpected good news from Dr Janet Davies and colleagues of the University of Cambridge, UK, for people with this rare disease which affects the muscles that move the eyes and those associated with swallowing. The simple chemical compound, cystamine, suppresses the toxicity of the expanded repeat region of the gene involved in OPMD in human cells and in a mouse model of the disease. Cystamine appears to act by inhibiting the enzyme, transglutaminase 2, and it is suggested that other such inhibitors might prove to be effective therapeutic agents.

As you can see, much is being achieved but much more needs to be done, so, please give generously to support NMD research.

Professor Allan Bretag
Director of Research