CONFERENCE REPORT

Reports on the 16th and 17th Annual Scientific Meetings of the Asian and Oceanian Myology Center

As detailed in the accompanying article, *Neuromuscular Disorders in Asia and Oceania: a History of the Asian and Oceanian Myology Center (AOMC)* [1], the AOMC was established to provide the latest updates in research and to give overviews of clinical aspects of diagnosis and treatment (where possible) of Neuromuscular Diseases (NMDs) especially for the benefit of young neurologists, scientists and allied health workers from developing countries in the region.

16th Meeting, Singapore, 2017

The 16th Annual Scientific Meeting of AOMC was held in Singapore, on 6th to 8th August, 2017 with the venue for the meeting being the 4th Floor Grand Ballroom and neighbouring meeting rooms at the Grand Copthorne Waterfront Hotel.

Drs Umapathi Thirugnanam and Josiah Chai (AOMC Executive Board Members), acted as Co-Chairmen who organised the meeting assisted by a Local Committee comprising Drs Ang Kexin, Kalpana Prasad and Kamal K. Verna all from the National Neuroscience Institute with support from the Japan Foundation for Neuroscience and Mental Health. Delegate registrations totalled 240 with 158 international participants from 21 Countries and Autonomous Regions, some, such as, Laos, Sri Lanka and Vietnam being represented for the first time. Altogether, for the AOMC's clinico-scientific presentations and symposia, there were 41 Faculty presenters from Australia, France, Mainland China, Hong Kong, India, Israel, Japan, Laos, Malaysia, Myanmar, Pakistan, Philippines, Singapore, Sri Lanka, South Korea, Taiwan, Thailand, the United Kingdom and the United States. As well, representatives from neuromuscular clinics, patient care organisations and charitable trusts and foundations participated in two service-oriented sessions entitled: "Enabled Living – Challenges and Opportunities in AOMC Countries" and "Myology in Asia". Travel grants were given to 24 young doctors and medical technologists from under-resourced regions of Myanmar, Thailand, Pakistan, Laos, Vietnam, Sri Lanka, Philippines, India and Iran.

On the first day of the conference, proceedings were mainly devoted to information sessions and educational workshops for patients, carers, allied health workers and trainee clinicians. Updates on various neuromuscular diseases were presented by respective experts and there were extensive panel discussions around brief presentations from patient support groups. Of particular interest were, the Singapore experience of a Multi-Disciplinary Clinic for Neuromuscular Disorder patients compared with the scarcity of resources in some other countries in the region. A Lunch Seminar from Dr. Zohar Argov discussed Clinical Clues in the Evaluation of Myopathies. The afternoon comprised workshops on Neuromuscular Medicine. Conference attendees owed a great deal of gratitude and respect to those patients who allowed themselves to be examined and their cases to be presented in a session on, "Diagnostic Puzzles".

Drs Umapathi Thirugnanam and Josiah Chai welcomed AOMC delegates to the official Opening Ceremony on the second morning of the meeting, followed by Dr. Ikuya Nonaka (AOMC President) and Guest-of-Honour, Ms Pin Xiu Yip (Singapore's first winner Para-Olympic Gold Medals). Ms Yip's inspiring speech was rewarded with a Token of Appreciation presented by the Medical Director of the National Neuroscience Institute, Dr. Wai Hoe Ng.

Dr. Zohar Argov began the morning scientific session on Inflammatory Myopathies with a lecture on Statin Myopathy in which he emphasised that while the use of statin therapy in the prevention of cardiovascular disease outweighed the risk of myopathy, nevertheless, myopathy was a significant side effect in more than 1 in 100 patients. Dr. Tahseen Mozaffar gave a presentation on Antibody Testing in Myositis in which he discussed the large number of auto-antibodies now found to be associated

with specific forms of myositis and myopathy. This was followed by Dr. Andrew Kornberg's lecture on Inflammatory Myopathy in Children stressing Juvenile Dermatomyositis and how, along with its well-known muscular and skin features, it seems invariably associated with a personality change towards irritability.

Session 2. was a symposium session considering Multi-Disciplinary Management of Patients with Chronic Neuromuscular Diseases followed by a panel discussion. There were brief reports on the value of a multi-disciplinary clinic and support groups for patients, as well, as cardiopulmonary, respiratory and orthopaedic management in neuromuscular diseases. Among surprises, the primary wishes of patients in a Thai survey were reported as being able to attend amusement parks, to have friends at school and not to be lonely rather than to be cured or to walk again.

A second Lunch Seminar sponsored by Sanofi Genzyme saw Dr. Andoni Urtizberea give an update on Enzyme Replacement Therapy in Pompé and Fabry's Disease. Pompé Disease was among the first neuromuscular diseases for which an ameliorating therapy was found.

Session 3. in the afternoon was taken up with considerations of the state of Myology in Asia, in particular, how AOMC might be able to help elevate the care of patients with muscle disease in the Asia Pacific region and improving both care and research in the region through encouraging contributions to (and the use of) International Registries of Neuromuscular Diseases. Especially concerning were reports of the lack of qualified neurologists with neuromuscular specialisation in many under-resourced Asian countries.

Of particular interest was an industry-sponsored Dinner Seminar on Spinal Muscular Atrophy emphasising the results from recently completed clinical trials using the newly developed drug, Spinraza/ Nusinersen (Biogen). For the first time, significant benefits have been seen in the treatment of infants with Spinal Muscular Atrophy Type 1 (SMA1). Where life expectancy had typically been less than two years, and, although response to treatment ranged from minimal to good, a video showed one treated two year old walking and attempting to climb onto a chair! Unprecedented improvement in motor abilities of later onset SMA2 and SMA3 patients were also seen after treatment. Unfortunately, the therapy is complex, requiring three initial intrathecal loading injections 14 days apart, a fourth 30 days later and then one maintenance injection every four months. It is also very expensive at $US625,000 to $US750,000 for the first year and $375,000 per year subsequently, if not participating in a free clinical trial or outside a clinical trial through an Extended Access Program (EAP). Access to the EAP is limited to SMA1 patients and then only to those in eligible territories, the EAP being provided through the goodwill of Biogen. It was very distressing to learn how parents of older SMA2 and SMA3 children from the Asian region were pleading for free or affordable access to the treatment. The need for a new paradigm for the treatment of diseases with a high chronic burden in under-resourced regions and countries without national health insurance was proposed.

Session 4. comprised Updates on Paediatric Neuromuscular Disorders. Dr. Andoni Urtizberea spoke on Congenital Myasthenic Syndrome and on Riboflavinopathies. An Asian Perspective on Congenital Muscular Dystrophy was presented by Dr. Ikuya Nonaka, an account of Childhood Neuropathies by Dr. Oranee Sanmaneechai and Next Generation Sequencing in Neuromuscular Diseases by Dr. Jong-Hee Chai. Dr. Urtizberea reported that ephedrine or salbutamol could improve muscle strength in Dok-7 myasthenia and that riboflavin transport deficiency motor neuron disorders could be responsive to riboflavin. "Cute looking bright eyes" in Fukuyama Congenital Muscular Dystrophy and "frightened eyes" in Ulrich Congenital Muscular Dystrophy were commented on by Dr. Nonaka in his comparison of the incidence of the different Congenital Muscular Dystrophies in Japan and elsewhere. In line with the high incidence of Charcot-Marie-Tooth (CMT) disease world-wide, Dr. Sanmaneechai pointed out that some 80 different genes were now known to be associated with the various forms of CMT and that well over 1000 gene variations had been implicated.

Session 5. on Myology Updates included Asian Perspectives on Periodic Paralyses covered by Dr. Raymond Rosales, a report of an attempt at Autophagic Manipulation in a clinical trial of Trehalose

for the Treatment of Oculopharyngeal Muscular Dystrophy (OPMD) by Dr. Zohar Argov and a presentation on VCP-Associated Multisystem Proteinopathy (MSP) by Dr. Tahseen Mozaffar. That Periodic Paralyses in Asia can result from certain infections, autoimmune thyrotoxicosis and a wide variety of conditions other than the usual channelopathies with differing prevalence in males and females was pointed out by Dr. Rosales. Although Dr. Argov's clinical trial of trehalose was ineffective in alleviating the limb-girdle muscular weakness in OPMD it did seem to improve swallowing ability in drinking tests. Of particular interest was Dr. Mozaffar's account of developments for the potential therapy of MSP, a particularly nasty disease affecting muscle, bone and the central nervous system.

A third Lunch Seminar was sponsored by A. Menarini in which Dr. Argov discussed the Treatment of Myasthenias: From Basic to Advanced. Special issues relate to all immuno-suppressive therapies and the new monoclonal antibody (mAb) therapies, including the occurrence of opportunistic infections and the unmasking of novel autoimmunity disorders.

Session 6. comprised the usual greatly appreciated clinico-pathological conference. On this occasion, 11 cases were presented. A final diagnosis for a number of these stumped both the panel of experts and the audience despite extensive discussion and divergent opinions pending further clinical and laboratory investigation. Sets of original microscope slides relating to these cases were available for viewing throughout the meeting.

Also, on this occasion, some 40 posters were submitted for display covering most areas of Neuromuscular Disease. During coffee breaks, these were individually the site of considerable animated discussion as crowds of interested viewers and anonymous judges moved from poster to poster. Two prizes each of $500, donated by Dr. Ikuya Nonaka were awarded for the best posters to Dr. Nalini Atchayaram (Bengaluru, India) and Ms. Miriam Rodrigues (Auckland, New Zealand).

In addition to the above-mentioned meeting sponsors, the organisers also acknowledged the support of Cadwell, DanMedik-Natus, Euroimmun, Grifols, the Lee Foundation, Neurostyle and Nihon Kohden.

At its Executive Board meeting, AOMC members agreed to accept Dr. Ikuya Nonaka's resignation as President of AOMC, to accept his nomination of Dr. Raymond Rosales to succeed him as President and subsequently of Dr. Ichizo Nishino to succeed Dr. Rosales as Vice President. Dr. Andrew Kornberg was then nominated to succeed Dr. Nishino as Secretary, Dr. David Hutchinson to succeed Dr. Kornberg as Assistant secretary and Dr. Satish Khadilkar to succeed Dr. Shin'ichi Takeda as Treasurer. The proposal from Malaysia to host the 17th annual scientific meeting of AOMC from 27th to 29th July, 2018 to be organised by Drs Khean Jin Goh and Kum Thong Wong was also accepted.

17th Meeting, Kuala Lumpur, Malaysia 2018

The 17th Annual Scientific Meeting of the Asian and Oceanian Myology Center (AOMC) was held in Kuala Lumpur, Malaysia, on 27th to 29th July, 2018 with the venue for the meeting being the Mahkota Room and neighbouring meeting rooms at the Istana Hotel.

Drs Khean-Jin Goh and Kum-Thong Wong (AOMC Executive Board Members) from the Departments of Medicine and Pathology, respectively of the University of Malaya organised the meeting with administrative support from the Malaysian Society of Neurosciences (MSN), which is the main body representing neuroscience professionals (both scientists and clinicians) in Malaysia. Overall delegate registrations for both the pre-conference workshops on the 27th July and the conference itself totalled 683 (513 from Malaysia) with 170 international participants from 24 Countries and Autonomous Regions, some, such as, Azerbaijan were represented for the first time. The AOMC meeting ran alongside the 28th Annual Meeting of the Malaysian Society of Neurosciences.

Altogether, for the AOMC's clinico-scientific presentations and symposia there were 50 invited speakers, 29 from Malaysia and the remainder being international invitees. As well, representatives from patient care organisations and charitable trusts and foundations, from pharmaceutical companies,

and manufacturers of equipment for people with disabilities, for research, for diagnosis, etc., provided industry displays during meeting breaks. Travel awards (supported by the Ayaka Foundation) were given to 6 young doctors from under-resourced regions: Dr. Kiran Polavarapu and Dr. Veeramani Preetish-Kumar (India); Dr. Shuang Cai (China); Dr. Yan Lynn Aung (Myanmar); Dr. Luh Ari Indrawati (Indonesia); Dr. Si Tri Le (Vietnam).

As in previous meetings, a day of pre-conference educational lectures and workshops was held for the benefit of nurses, allied health workers and trainee clinicians. Here the knowledge and skills of experts, including Dr. Ikuya Nonaka, Dr. Jun Kimura, Dr. Alberto Dubrovsky, Dr. Jantima Tanboon, Dr. Andoni Urtizberea, Dr. Wen-Chen Liang, Dr. Sanjeev Nandedkar, Dr. Ichizo Nishino, Dr. Khean-Jin Goh and Dr. Umapathi Thirugnanam, were utilised. Conference attendees were greatly indebted to those patients who participated in hands-on demonstrations of their conditions.

Delegates were welcomed to the main meeting by the organisers, Dr. Khean-Jin Goh and Dr. Kum-Thong Wong and the AOMC President Dr. Raymond Rosales. At this conference Drs Shin'ichi Takeda, Andoni Urtizberea and Yuh-Jyh Jong presented extremely exciting developments in Translational Medicine. At least three pharmaceutical companies, Sarepta, Solid Biosciences and Pfizer, have current clinical trials under way using Adeno-Associated Viruses (AAVs) to transport mini-dystrophin genes into muscles to treat Duchenne Muscular Dystrophy (DMD). By the time of the July AOMC meeting, Sarepta had reported three patients (more recently, four patients) with significant improvements in time to stand from lying down, time to climb four stairs and time to walk 100 metres. Likewise, Audentes Therapeutics has shown remarkable results using AAVs to transport the *MTM1* gene into the muscles of infant boys with Myotubular Myopathy. Elsewhere, the AveXis pharmaceutical company has demonstrated significant benefit in survival and positive functional motor milestones achieved using AAVs to transport the human *SMN1* gene in cases of Spinal Muscular Atrophy. While these are stunning advances and have the potential to be therapeutic no matter what mutation is present in the respective genes involved in these particular diseases, the cost of treatment, unless participating in a clinical trial, is likely to be in the million dollar range. Among other accounts of clinical trials, the orally-administered, steroid-like compound, Vamorolone, has been found to have the disease-progress-halting (anti-inflammatory) benefits of the corticosteroids (prednisolone and deflazacort) in DMD but without the adverse steroid side effects. In the meantime, deflazacort has been found to be as effective as prednisolone but with less severe side effects. Two small molecule, orally-administered drugs have been developed for the treatment of Spinal Muscular Atrophy. They are the Roche (Genentech) drug RG7916 and the Novartis drug LMI070. Both are in early phase clinical trials. As of October 2018, RG7916 (risdiplam) was being reported to have very promising results in each of SMA types 1, 2 and 3. Of course, as potential neuromuscular disease (NMD) therapies, both exon skipping that uses antisense oligonucleotides (AONs), and read-through of stop mutations remain in contention. Among these are Sarepta's Eteplirsen (Exondys 51) and PTC Therapeutics' Ataluren, respectively, for DMD. Sarepta's other exon skipping drugs for DMD such as Golodirsen (exon 53 skipping) and Casimersen (exon 45 skipping) are somewhat more promising than Eteplirsen (exon 51 skipping) but, so far, apart from Nusinersen in the treatment of Spinal Muscular Atrophy, these have not resulted in the more dramatic outcomes seen with AAV gene transport. In perhaps even more of a potential breakthrough, Dr. Giampietro from University College London presented his research on axoplasmic transport. In particular, retrograde axoplasmic transport is slowed in the motor neurone disease ALS, in Charcot-Marie-Tooth (CMT) disease and in Alzheimer's disease. Not only this but, in laboratory experiments, this defect can be rectified by treatment with a specific chemical called "compound A1" that could be a lead agent for discovering a therapy for these serious diseases.

As well as the especially exciting news about gene therapy using the AAV viral vectors, there were updates on a variety of NMDs. In a Plenary Lecture and Symposium on Inflammatory Myopathies, Dr. Werner Stenzel spoke on the diagnosis, pathology and pathogenesis of these conditions, especially Inclusion Body Myositis, Dr. Ichizo Nishino on serological and pathological correlations in immune-mediated myopathies, Dr. Swee-Ping Tang on Childhood Inflammatory Myositis and Dr. Chong-Tin Tan on parasitic infections in muscle with a special focus on muscular sarcocystosis in Malaysia. It is suspected that the infections by *Sarcocystis nesbitti* resulted from consuming unboiled water contaminated with

snake faeces as the source of the protozoan parasite. In respect to a Plenary Lecture and Symposium on Translational Medicine – Physiology and therapeutics of neuromuscular disorders, Dr. Ikuya Nonaka, gave an historical account entitled, "Important discoveries and progress in Myology – What I have learnt from muscle research", Dr. Raymond Rosales spoke on recent advances in botulinum therapy while Dr. Giampietro continued on this theme with his predictions on the use of botulinum toxin in future therapies, Dr. Shin'ichi Takeda gave a review of the basic science of gene therapy in muscle diseases, Dr. Satish Khadilkar spoke on muscular dystrophies in India and Dr. Andoni Urtizberea on clinical trials in muscular dystrophies. The second day of the conference saw one Plenary Lecture by Dr. Giampietro on defects in axonal transport in ALS and Charcot-Marie-Tooth disease models and another by Dr. Rahul Phadke who discussed the role of muscle biopsy in the era of Next Generation Sequencing. These were followed by a Symposium devoted to Paediatric Neuromuscular Diseases. Here, Dr. Andrew Kornberg spoke on the clinical aspects and management of neuromuscular junction disorders, Dr. Yuh-Jyh Jong gave an update on Spinal Muscular Atrophy and its treatment, Dr. Rahul Phadke warned about pitfalls in muscle biopsy diagnosis of paediatric neuromuscular disorders and Dr. Chuanzhu Yan spoke on Pompé disease in China. Other major highlights of the clinico-scientific meeting were the Lunch Seminars sponsored by the pharmaceutical companies, Sanofi-Genzyme on Myozyme for the treatment of Pompé Disease and, Ipsen Pharma on Dysport (botulinum toxin-botox) for the treatment of dystonias, spasticity and pain. It is worth noting that many of the new therapies mentioned in this report have already been granted orphan drug status by the United States FDA. This means that their development is considered worth expediting and that administrative barriers to their progress towards utilisation are reduced.

The importance of patients signing up to National and International Registries of their specific diseases was again strongly emphasised. Now that numerous drug therapies for different NMDs are under development or in clinical trials, being on a Registry would ensure that patients could be involved in clinical trials of new therapies and be informed as and when the new treatments become available in their countries.

In addition to the Plenary Lectures and Symposium Presentations there was again a Clinico-Pathological Conference, this time with eight submissions of clinical and biochemical data, scans and histopathology slides, the slides being available for viewing throughout the meeting. Both novices and experienced NMD experts enjoy the detective work as they attempt to determine a diagnosis from the clues provided. During breaks in proceedings, delegates were able to inspect 54 posters (attended by their authors) that covered most aspects of NMD. Prizes were awarded for the two best posters, to Dr. Lin Ge and co-authors from China for their paper entitled "A New Titinopathy: Recessive TTN variants cause a novel form of early-onset multi-minicore disease without cardiac involvement", and to Dr. Kyonwon Seo and co-authors from South Korea for their paper "Dysferlinopathy was recovered by readthrough therapy through ataluren". The awards were sponsored by MSN.

At its Executive Board meeting, AOMC members agreed to the proposal from India to host the 18th annual scientific meeting of AOMC in Mumbai, from May 31st to June 2nd 2019 to be organised by Dr. Satish Khadilkar.

Further information on AOMC and future meetings may be obtained by visiting the web site: www.aomc.info

Allan H. Bretag

School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia
email: a.bretag@unisa.edu.au

REFERENCE

1. Bretag AH. Neuromuscular disorders in Asia and Oceania: a history of the Asian and Oceanian Myology Center (AOMC). *Neurol Asia* 2019; 24(1): 83-6.