

## Commentary

---

# Forty years neuromuscular experience

In 1968, as a second-year neurology resident, I attended a neuromuscular conference in Detroit organized by Max Newman, M.D., a Detroit physiatrist and Muscular Dystrophy Association clinic director. The presentations concerned the classification of dystrophies and the utilization of electrophysiological studies and biopsies. Two years later, I went to another MDA-sponsored electromyography course in New York City, where demonstrations on volunteers were eagerly viewed and the learning curve for electrodiagnostics more easily developed.

For the next two years, my fellowship at Children's Hospital of Philadelphia and the University of Pennsylvania provided me the most incredible experience of my career with regular MDA clinics, participation in semi-quantitative EMG procedures, conferences on neuromuscular pathology, and the presence of people like Lewis (Bud) Rowland, M.D., Salvatore (Billy) Di Mauro M.D., and Don Schotland, M.D., who was using freeze fracture techniques to try to explain the pathogenetic mechanisms of muscular dystrophy. We were able to evaluate and understand patients with what were then ill-defined mitochondrial disorders. Later at Wayne State University, we helped define the genetic and biochemical features of mitochondrial cytopathies [7].

After completing my fellowship, I began practice and was involved with the MDA clinics of southeast Michigan for thirty-five years and directed the clinic for thirty of those years. The clinic, with nearly full patient participation, evaluated and treated common and rare neuromuscular diseases in a teaching forum. What changed over that period of time was paradoxically both immense and minute. The knowledge base was exponentially advanced and new approaches to treatment heralded as patients were, and still are, affected in profound ways.

From the beginning of my career in neurology until the present, the emphasis on dealing with neuromus-

cular patients has remained the same. Although we could not cure such patients, we learned we could and should be aggressive in treating them. Myasthenia had not yet been defined as an autoimmune disorder; CIDP was barely recognizable; but Duchenne Muscular Dystrophy, myotonia, FSH, limb-girdle, and a few mitochondrial and congenital myopathies were well known. All lent themselves to some type of treatment, whether it was range of motion, strengthening, bracing, diet, mobility aids [5], or orthopedic surgeries.

Irwin Siegel M.D., a Chicago orthopedist and MDA director, perfected Achilles' percutaneous tenotomy followed by immediate bracing and ambulation and was able to sustain standing and ambulation in boys with Duchenne's beyond what other physicians were able to achieve [9]. Despite this accomplishment, few other physicians followed this route.

While corticosteroids have since been used by many physicians treating boys with Duchenne Muscular Dystrophy [6], the limited benefits and significant side effects have precluded the acceptance of its application by all today. Nevertheless, boys are living longer, going to college, and enjoying wheelchair-active sports and summer camps, all without a cure, but with much meaning in their lives because of devoted families and MDA staff and volunteers. Yet, the complex multi-systemic problems of the dystrophinopathies [4] require reevaluation and remain a challenge as witnessed in this month's journal.

The discovery of the dystrophin gene in 1987 by Hoffman et al. [2] was a turning point in knowledge of the pathogenesis of the dystrophies that heralded a way to definitive diagnosis and treatment. DNA analysis made muscle biopsy unnecessary in many instances, and, when necessary, a needle muscle biopsy for dystrophin staining could easily be undertaken. Myoblast transfer was the first meaningful effort at a scientific treatment for the dystrophies, but proved subsequently to be a stunning disappointment [8]. The promise

of gene therapy since has remained unfulfilled, but the likelihood of its success seems nearer now than ever [3].

Basic pathogenic mechanisms of the dystrophies continue to be enumerated many times each year, and definitive classification are made more readily and precisely by DNA analysis. This advance has been more informative and has resulted in minimizing the need for invasive studies. To diagnose Myotonia Dystrophica only requires CTG repeat analysis that avoids even an EMG, and spinal muscular atrophy no longer requires a biopsy. Mode of inheritance (recessive, dominant, x-linked), specific altered protein (caveolin, calpain, dysferlin, sarcoglycan etc), and DNA analysis have identified particular types of limb-girdle dystrophy. Muscle biopsy still has its place in providing definitive diagnosis and in the reclassification of myopathies and dystrophies that no longer fit into our preconceptions.

The rare carnitine and CoQ10 responsive mitochondrial disorders have **encouraged** us as we sought treatment for disorders that were once rare and difficult to diagnose but are more readily evaluated today. And yet it is apparent that so much more is to be discovered about these metabolic myopathies and multisystemic conditions we thought were fully categorized thirty years ago. DiMauro and Schon certainly have helped clarify the complex issues of mitochondrial disorders [1].

As clinic director, I always felt that the role of rehabilitation – physical, occupational, and respiratory therapy along with psychiatry played critical roles. The functional capabilities of these patients is critical and can thoroughly be addressed by adhering to a team approach. This concept has clearly evolved over time and should be considered for

So what have some of learned over these past 40 years?

1. Diseases have not changed and patients are affected as they always were, but our ability to diagnose them has become easier and more definitive.
2. Patients' needs are the same, albeit modified by longer life spans.
3. The splitters are able to neatly identify and delineate specific subtypes of dystrophy.
4. A single web site like the Washington University neuromuscular page (<http://neuromuscular.wustl.edu/>) is more definitive and descriptive than the accumulative texts we read in the past, and is more readily updated. It offers the student an immediate tutorial while seeing a patient in the clinic.
5. Standard occupational and physical rehabilitative therapies are just as effective as ever, but need to be implemented earlier and more consistently.
6. There is no substitute for a willing patient and family to make the sacrifices necessary to maintain functional capabilities.
7. Technological advances have improved mobility through bracing and lightweight wheelchairs; communication, through speech aids; and respiratory function, through efficient light weight BI-PAP and CPAP.
8. Early integration of additional services, such as cardiology, pulmonology, orthopedics, and dietary to name but a few, minimize the complication of medical conditions.
9. Patients need to be fully informed and active in all decision-making processes and always afforded the dignity they deserve.
10. Students today will be the practitioners of tomorrow and have to be diligently taught, nurtured, and encouraged to care for patients with neuromuscular disease.
11. What breakthroughs occur will never be enough.

Michael A. Nigro, D.O. FACN  
 Professor Emeritus Neurology and Pediatrics  
 Wayne State University,  
 Detroit, MI, USA  
 School of Medicine  
 Professor of Neurology  
 Michigan State University College of Osteopathic  
 Medicine  
 East Lansing, MI, USA  
 E-mail: mnigro01@comcast.net

## References

- [1] S. DiMauro and E.A. Schon, Mitochondrial Respiratory-Chain Diseases, *New Eng J Med* **348** (2003), 2656–2668.
- [2] E.P. Hoffman, R.H. Brown Jr. and L.M. Kunkel, Dystrophin: the protein product of the Duchenne muscular dystrophy, *Cell* **51** (1987), 919–928.
- [3] E.P. Hoffman, Skipping toward Personalized Molecular Medicine, *New Eng J Med* **357** (2007), 2719–2722.
- [4] J.S. Lee, Z. Pfund, C. Juhasz, M.E. Behen, O. Muzik, D.C. Chugani, M.A. Nigro and H.T. Chugani, Altered Regional Brain Glucose Metabolism in Duchenne Muscular Dystrophy: A PET Study, *Muscle Nerve* **26** (2002), 506–512.
- [5] M. Liu, K. Mineo, K. Hanayama, T. Fujiwara and N. Chino, Practical problems and management of seating through the clinical stages of Duchenne's muscular dystrophy, *Arch Phys Med Rehabil* **84** (2003), 818–824.
- [6] A.Y. Manzur, T. Kuntzer, M. Pike and A. Swan, Glucocorticoid corticosteroids for Duchenne muscular dystrophy, *Cochrane Database Syst Rev* **23**(1) (23 Jan. 2008), CD003725. Review.
- [7] M.E. Martens, P.L. Peterson, C.P. Lee, M.A. Nigro, Z. Hart, M. Glasberg, J.S. Hatfield and C.H. Chang, Kearns-Sayre Syndrome: Biochemical Studies of Mitochondrial Metabolism, *Annals of Neurology* **24** (1988), 630–637.

- [8] J.R. Mendell, J.T. Kissel, A.A. Amato, W. King, L. Signore, T.W. Prior, Z. Sahenk, S. Benson, P.E. McAndrew, R. Rice, H. Nagaraja, R. Stephens, L. Lantry, G.E. Morris and A.H. Burghes M, Myoblast transfer in the treatment of Duchenne's muscular dystrophy, *New Eng J Med* **333** (1995), 832–838.
- [9] I.M. Siegel, Prolongation of ambulation through early percutaneous tenotomy and bracing with plastic orthoses, *Isr J Med Sci* **13** (1977), 192–196.