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Recent Progress in Nutrition

Interview

An Interview with Prof. Corrado I. Angelini

Recent Progress in Nutrition Editorial Office

LIDSEN Publishing Inc., 2000 Auburn Drive, One Chagrin Highlands, Suite 200, Beachwood, OH, USA;
E-Mail: rpn@lidsen.com

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Prof. Corrado I. Angelini

Corrado Angelini, MD, received his education and training as MD, at University of Padova, was Postgraduate Research Assistant and Associate at Mayo Clinic, Rochester, Minnesota, 1970-1972; had a Research Fellowship of Muscular Dystrophy Association, 1972; a Senior Fellowship of Muscular Dystrophy Association, 1978 Resident in Neurology, Mayo Clinic, Rochester, Minnesota, 1973; Assistant Professor of Neurology, University of Padova, Italy, 1973-1978; Associate Professor 1980-1994 Full Professor of Neurology 1995-2011; Coordinator of PhD Program in Neurosciences, University of Padova, Italy, 2001-2011; Director Neurology Residency Program, University of Padova, Italy, 2002- 2010; Consultant Neuromuscular Disorders, IRCCS S. Camillo, Venice, Italy, 2010-2020; Director Master in Neuromuscular Disorders, University of Padova 2011-2013; Senior Researcher, University of Padova, 2013-present.

Honors:

- Lion Club Milano Host award for Neurological Sciences, 1981
- President, Italian Association of Myology, 2003-2006
- Grands Prix Newropeans, 2004
- Gaetano Conte's Prize, Kusadasi, 2005
- Pisa Muscle Award, 2023

1. Could You Please Tell Us Your Scientific Background and Main Research Area?

I first started Myology in Italy, which reached an initial vigorous development in the second part of the 20th century in the '70 decade with the establishment of the CNR center in Padova, where I attended studying mitochondria and then myopathies. I was invited by Di Mauro to join a small interdisciplinary group dealing with muscle biopsy: a neurosurgeon was performing an open biopsy, and a neurologist was doing intravital end-plate and nerve terminal staining by Coer's technique while we took care of morphology and biochemistry.

The first stage in the '70 in neuromuscular research drove us out of complete ignorance of pathogenetic mechanisms in Neuromuscular Disorders (NMD) and it was characterized by three main discoveries: first, it was observed that substantial elevation of the serum activity of creatine kinase indicates muscle damage or destruction in both patients and animal models such as vitamin E-deficient rabbits. Then, the adaptation of modern histo-and cytochemical techniques to the study of muscle biopsies markedly improved the diagnostic accuracy since it was possible to differentiate neurogenic, mitochondrial, metabolic, and myopathic changes in muscle, while this was impossible in formalin-fixed specimens and these techniques made possible the identification of new changes, diseases and structures. Examples of this were the demonstration of nemaline rods in nemaline myopathy and ragged red/blue muscle fibers in mitochondrial diseases. Thirdly, the advent of modern biochemical techniques permitted the identification of various enzyme defects/storage diseases such as glycogen storage disorders, i.e., Pompe disease, and McArdle's disease thereafter lipid storage diseases, mitochondrial disorders due to Cytochrome c oxidase or coenzyme Q deficiency, were soon identified, and this allowed their treatment.

2. What Got You Interested in This Research in the First Place?

In London, I visited the National Hospital for Neurology and Neurosurgery, sometimes referred to as Queen Square after its location, which has been providing care for adults with neurological conditions for nearly 150 years and is one of the leading clinical neuroscience centers in the world.

The hospital provides comprehensive services for the diagnosis, treatment, and care of all conditions that affect the brain, spinal cord, peripheral nervous system, and muscles in state-of-the-art facilities.

In August 1969, I visited the Queen Square Hospital in London and worked on the phospholipid composition of the Extensor Digitorum longus and soleus muscles in rats. The laboratory I worked in was in connection with the Department of Chemical Pathology but had a location inside the Queen Square Hospital and the opportunity to study the main phospholipids, i.e. phosphatidic acid, phosphatidylglycerol, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and cardiolipin, with Ken Owens, who subsequently left for Canada.

3. Would You Like to Share with Us What Impressed You Most in Your Career Development and Research Life?

My experience at Mayo Clinic Rochester and the Medical Science Building, where I worked for two years, included a muscle lab with electron microscopy, a room for biochemistry, and a histochemistry room equipped with a liquid nitrogen freezer for muscle biopsies. I performed my experiments on Glycogenosis type 2 and discussed them with A.G. Engel.

In the second year at Mayo, Corrado Angelini, as a promising researcher in the field, with letters of recommendation by Ed Lambert obtained an MDA fellowship pursuing both the study of acid maltase deficiency (AMD or Glycogenosis type II) and performing fascinating exploration into the world of lipid myopathies to discover their biochemical cause. The research focused Mayo Clinic on a singular and rare case, where muscle fibers in the patient were found to be filled with numerous lipid-filled vacuoles. The disorder was first reported as a Lipid Storage myopathy responsive to steroids by AG Engel and Siekert. Dr. Siekert, as editor-in-chief for the Mayo Clinic Proceedings, played a seminal role in describing the case. We were able to conduct a study on fatty acid oxidation in human homogenates using radiolabeled substrates.

An intriguing aspect of this condition was that the fatty acids in the patient's muscle homogenates were oxidized at a slower pace compared to the normal rate seen in 11 control cases. The exploration, however, doesn't end here. Luckily, we were able to introduce carnitine into the scenario and observed that it elevated the oxidation rate in the patient's muscle, equalizing it with the control group. Therefore, the presence of carnitine was essential. Diving deeper into the patient's condition, we examined five separate muscle samples, mostly working on weekends. The findings were startling. The carnitine levels in these samples averaged less than 20 percent of the levels observed in 42 control samples. Since two critical enzymes in fatty acid metabolism, carnitine palmitoyl transferase and palmitoyl thiokinase, displayed normal levels in the patient's muscles, carnitine was the missing factor. I left at this point for summer vacation, but unfortunately, further control experiments, led to a denouncement for using muscle homogenates without proper consent. We left experiments and published our discovery in *Science* [1].

4. Where Do You Get the Latest News about Your Research Area, or Where Do You Take Inspiration From?

I have participated in meetings of the European Neuromuscular Centre as a scientific advisor since 1999 and contributed to several workshops. Both congenital muscular dystrophy and its defective protein product, were identified.

The European Neuromuscular Centre (ENMC) was a great innovation in the early 1990s through the foresight of several clinicians and scientists active in the Parent Support Groups in various European countries, such as Victor Dubowitz, Giovanni Nigro and Reinhardt Rudel, who saw the need for a forum to promote collaborative research in Europe. Alan Emery, as the first scientific director, was the driving force in the early years and personally read up on the topic of each workshop, presided over it, in addition to the organisers, and tried to promote and encourage debate. The principle ENMC followed in several workshops, which I participated in, was that there were only the participants and no passengers. Thus, with the first corticosteroids workshop in 1996, there were only 7 centres in the whole of Europe with experience of it. Similarly, for the first ENMC workshops on Congenital Myasthenia, calpainopathy, or LGMD-R1 and dysferlinopathy or LGMD-R2 [2, 3], the character of many workshops has changed with few of the conveners having had no previous experience with the interactive workshops, so they have taken the format of symposia with more formal presentations and minimal debate and discussion and in contrast to the one or two in the early days are more in the format of reviews with large numbers of references. Since the early days, they have been regularly published in *Neuromuscular Disorders* as the new classification [4].

5. Considering the Progress in Your Research Area, Could You Please Share with Us What Challenges and/or Developments You Think May Be Encountered in the Coming Years?

For over 20 years, I directed the Padova biobank (NMTB), supported by Telethon, and then founded a EuroBiobank and another Bank for biomarkers at S Camillo IRCCS Lido. Both biobanks in Padova and Venice are part of BBMRI. Several discoveries on new diseases, i.e., LGMD due to sarcoglycanopathy [2] and dysferlinopathy [3] or LGMD-D2 (transportinopathy) were made with NMTB specimen and on disease biomarkers with the biobanks in Padova and Venice.

Several examples have always illustrated how access to large numbers of biospecimens and associated data plays a pivotal role in the identification of disease genes and the development of pharmaceuticals. Hence, allowing researchers to access significant numbers of quality samples and data, genetic biobanks are a powerful tool in basic, translational, and clinical research into rare diseases. Recently, demand for well-annotated and properly preserved specimens is growing at a high rate and is expected to grow for years to come. The most effective solution to this issue is to enhance the potential of well-managed biobanks by building a network.

We reported a 5-year experience of the Telethon Network of Genetic Biobanks (TNGB), a non-profit association of Italian repositories created in 2008 to form a virtually unique catalog of biospecimens and associated data, which presently lists most neuromuscular diseases [5]. The EuroBioBank (EBB) network (www.eurobiobank.org) was created by Cecil Jaeger as a network of Banks, and met regularly in Paris. A catalog was made by Fabrizia Bignami and Anne-Marie Bodin of all the specimens available and represented an excellent model of the European Organization as an infrastructure for research on rare and neuromuscular disorders.

6. What Do You Think of the Future of *Recent Progress in Nutrition*, an Open-Access Journal?

In case of rare metabolic disorders, publishing the diagnosis and nutritional and dietary prescriptions will be welcomed. However, unlike in other medical disciplines, nutritional treatment of patients presenting with a genetic disease is only possible in a small minority of cases, but can be

followed for metabolic myopathies such as glycogen storage disorders, i.e., Pompe disease, and McArdle's disease thereafter lipid storage diseases, mitochondrial disorders due to Cytochrome c oxidase or coenzyme Q deficiency, when identified, this allows their treatment.

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