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A tribute to Jack Petajan's inspiration: From goat to goat

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Abstract

Development of clinical neurophysiology, especially in neuromuscular disease investigation in the 20th century underscores the careers of two academic physician-investigators. Experimental models of neuromuscular disorders (toxic and diabetic neuropathies, myasthenia gravis, nerve transplant and repair) with emphasis on regeneration are described. Subsequent clinical application has validated the animal studies. The value of disease related support societies (Muscular Dystrophy, Charcot Marie Tooth and Myasthenia Gravis) is discussed, not only for patient information and support but also for support of research projects and clinical research fellowship training. The clinician–teacher–investigator as a role model is mentioned, particularly in relation to Dr. Jack Petajan's career, a truly renaissance man. Credit is given to the great teachers of clinical neurophysiology and neuromuscular diseases of the past 50 years.

Keywords: Jack Petajan; Clinical investigator; History; Clinical neurophysiology; Experimental neuropathy; Clinical applications

1. Introduction

In September 1962, Jack Petajan and I began our careers of clinical neurophysiology under the tutelage of the master in the United States, Dr. Edward H. Lambert. We were his special fellows at the Mayo Clinic in Rochester, Minnesota. A firm and a lasting friendship developed covering both personal and professional aspects of our lives spanning 43 years. This tribute concerns aspects of my clinical and basic research where Dr. Petajan's discussions and advice were often crucial; this material was presented at a symposium or *festschrift* honoring him at the University of Utah in Salt Lake City in June 2003. One might say that we met under the Sign of the Goat, as at an early date Dr. Lambert introduced us to his herd of "falling" hereditary myotonic goats at the Mayo farm. This was a signal year for Dr. Lambert. He had four fellows in his laboratory, all of whom became dedicated academic electromyographers. Three, including Jack, became presidents of the American Association of Electrodiagnostic Medicine (AAEM). The other two were the late Bert Weiderholt and Bill Kennedy. As a fellow, Jack helped me to design an in vitro chamber [1] for measuring nerve conduction in diabetic rats, of course emphasizing strict temperature controls, and he was a skilled arbitrator and peacekeeper in the tightly packed research room. He also risked his life in teaching me to drive an American behemoth on the right side of the road.

My research that year concerned experimental neuropathy in rats made diabetic with intraperitoneal alloxan [2]. Fifty young adult rats were treated and paired with littermate controls. We were able to demonstrate two types of neuropathy. There was an acute neuropathy in five of the alloxanized rats with a dramatic fall in conduction velocities by at least 50% during the first 36–72 h. We had established that the technique using the in vitro Lorente de No chamber [1] appeared more reliable than in vivo nerve conduction studies. Unfortunately, this did not allow in-depth serial studies. Modestly slowed nerve conduction velocities (20–30%) in the remaining diabetic animals were first observed at 3 months, with slight progression by 6 months. Electron microscopy indicated some splitting of the myelin sheaths in the five rats with acute neuropathy, but no classical evidence of demyelination was observed. Discussions then and subsequently postulated either a membrane disturbance of the Na–K ATPase system or toxic demyelination due to alloxan. A true diabetic neuropathy of the more chronic type may have occurred in the older alloxanized animals with

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either mixed or purely axonal features. These findings were presented at the 3rd International Conference on Electromyography in Glasgow in June 1967 under the presidency of Professor J.A. Simpson.

This conference was one at which lasting and, in many cases lifelong, scientific relationships were made. Some of the giants of the last century were there, including Simpson, Eccles, Buchthal, Lambert, Desmedt, Ekstedt, Hagbarth, Hausmanova-Petrusewicz, Liberson, "PK" Thomas and Struppler. Jack, now living in Alaska, gave a paper on motor unit control, a topic which was to occupy him for the next two decades, helping to lay the groundwork for contemporary motor unit number estimation (MUNE) studies in ALS. There I also first met the eminent Christian Coërs, whose book on the innervation of muscle provides a classic description of end-plate anatomy and pathological histology [3]. Five years later, I began my first sabbatical working in his department in Brussels on tissue culture preparations of end-plate development. Richard Mayer of Baltimore also described the neuromuscular defect in human botulism at the same Glasgow Meeting. Three other fellows from Ed Lambert's laboratory also presented. My fellow co-conspirator in the Mayo research room, the late Wigbert C. Wiederholt, gave a prize-winning and truly elegant paper on "End-plate noise"; H. Kaeser who began the toxic neuropathy studies in Dr. Lambert's laboratory in 1961 and the late Tony Hopkins, then working on neuropathy in animals with diphtheria in Roger Gilliatt's group, also presented. Dr. Lambert and Peter Dyck presented their work using the in vitro excised nerve chamber to study the compound action potentials of human sural nerve biopsies, including eight patients with Charcot Marie Tooth disease, three with Dejerine-Sottas syndrome and two with Friedreich's ataxia. Dr. Preswick from Australia arrived at the last moment from Sydney to present his studies on seven cases of axonal neuropathy with Freidreich's ataxia, the largest series to date. His friend, Alan McComas of Newcastle, was prominent in discussions of the motor unit, and two great Scandinavians, Werner Trojaborg and Erik Stälberg came with new papers and theses.

During the 1970s, Jack and I met frequently, often several times a year. He was becoming well established in his new home in Salt Lake City, where he directed the Neuromuscular Diagnostic Laboratory at the University of Utah School of Medicine, a position he held for nearly 30 years. During these visits, I became acutely aware of his other talents, including his entertaining and skillful violin playing. On one occasion, when he was practicing for a part in the Bach double violin concerto, we produced to his delight a record of the two Oistrach's (David and his father) performing this piece and gave it to him. This love of music was a strong bond between us and, frequently, at medical meetings, we would set aside one evening to sample the local city orchestra fare. At that time, he gave me great advice on investigating toxic neuropathies. I had been studying the neuropathy associated with long term and sometimes high dose diphenylhydantoin [4,5]; Jack suggested that I use some of the animal techniques that Weiderholt used for his end-plate noise studies. Together with M. Gonzales of Caracas, Venezuela, I modified this method and, surprisingly, showed that end-plate transmission failed before nerve conduction, with the muscle fiber being the last to lose its function under increasing toxin doses. However, we could not reproduce a chronic model in the rat or rabbit to mimic human neuropathy. Dr. Petajan suggested that I return to diabetic neuropathy and search for an islet cell toxin that was not directly neurotoxic. This led to a series of experiments with numerous fellows working in my laboratory in the 1970s, but principally Dr. Pierre Bouche of the Salpietriere, Paris. We showed that streptozotocin produced diabetes without a direct toxic effect on the nerve and that a true chronic neuropathy slowly developed affecting the whole length of the nerve as had been described in humans [6]. Serial in vivo near nerve stimulation studies were used to follow neuropathy progression. The diabetes could be sequentially cured, including improvement in the neuropathy, by transplantation of Islets of Langerhans. The diabetes could then be re-established with further streptozotocin administration, neuropathy allowed to develop again, and both neuropathy and diabetes corrected again by a second transplant. These studies were reported at the Lambert Symposium at the time of his retirement from the Mayo Clinic in 1985 [7].

During these years at the Neurological Institute of New York, we had become quite interested in experimental autoimmune myasthenia gravis. In addition to routine repetitive stimulation, both microelectrode studies of miniature end-plate potentials and tiny macroelectrode studies of end-plate noise were used. The last technique was extended to humans using monopolar electrodes inserted at the end-plate. We were able to identify some unusual cases of long standing atrophy that had features similar to botulism. Around this time, Dr. Petajan was appointed to the National Medical Advisory Board of the Myasthenia Gravis Foundation. Jack was also active with AAEM of which he became president in 1977. I visited Jack during the annual AAEM meeting, which was held in Salt Lake City, and became aware of some of his other talents: Jack as a family man and an outdoorsman. He and his family built an A-frame house in the woods and wilderness area outside the city that became known as "The House that Jack Built." Later, I heard that his wife and he had taken a trip down the Colorado River rapids in a rubber dingy, which I suppose is to be only expected in the man who survived the Alaskan earthquake in the mid-1960s. He wrote papers published in Alaskan Medicine and the Lancet about his experiences entitled "The Fairbanks Flood" [8,9].

It is therefore with some justification that I called him a Renaissance man in my recommendations for his membership in the American Neurological Association and for a Lifetime Membership Award from the AAEM. In the following decades, I shared several patients with him and