

In Memoriam: W. King Engel, MD (1930–2025)



William King Engel MD died peacefully at his home in Ann Arbor, MI, at the age of 94. Born in St. Louis, MO, Dr. Engel graduated from Johns Hopkins University, earned his medical degree from McGill University and completed his neurology residency at University of Michigan and the newly formed National Institute of Neurological Disease and Blindness (NINDB) at NIH. Inspired by Dr Milton Shy, the first Clinical Director of the NINDB, Dr Engel began an in-depth investigation of Neuromuscular Diseases (NMD), becoming in 1963 the Chief of the Medical Neurology Branch where he established the first in the world comprehensive training and research program in NMD. In 1981, he left NIH to join the University of Southern California (USC) where, along with Dr. Valerie Askanas, his esteemed wife and life-long coinvestigator, co-founded and co-directed another neuromuscular program until retiring in 2015.

Dr Engel's outstanding legacy started with the urgent need to define the various clinically different, and histologically heterogenous but poorly recognized, NMDs. His inspiration to study muscle enzyme histochemistry as a means of appreciating the precise changes within the muscle fibers, is best highlighted by his creation of the first cryostat, writing: "*my first cryostat was a makeshift; it was a food freezer from Sears, lid unscrewed, into which I put an ordinary microtome with a self-designed anti-roll plate*".¹ His pioneering observations, including his own "modified trichrome stain", defined many muscle-specific disease pathologies, like central core disease, nemaline and

lipid-storage myopathies, or target fibers due to denervation.^{1–6} When one of his key papers published in Neurology in 1962 had been previously rejected by several pathology journals that did not appreciate his enzyme-histochemical approach, King characteristically advised the young investigators "*when encountering philistines, persevere!*".¹ His teaching on how to diagnose a NMD became a uniquely effective and enjoyable event. During his weekly NINDS meetings when projecting the patients' muscle enzyme histochemistry slides to a packed room, he asked each of the trainees for a diagnostic opinion. He was never critical of those who were wrong, but supportive and encouraging with stimulating, often humorous remarks, characteristic of his candidly impactful teaching style. He saw the muscle biopsy as a living tissue: "*look at the lymphocytes invading the sarcolemma*" or commenting that the muscle fibers were "*ragged and red*", hence his term "*ragged-red fibers*".⁶ Every unusual histological observation was further explored by electron microscopy, highlighting the depth of his pioneering clinicopathological science and the reasoning that attracted many brilliant fellows. His love for understanding mechanisms is exemplified by concurrently pursuing cultures from every muscle biopsy, inspired by Dr Valerie Askanas, his future beloved wife. We vividly remember the first nerve biopsy cultures from patients with CIDP exploring the living Schwann cells,⁷ based on which he had proposed that CIDP should be called "*dysimmune dyschwannian neuropathy*".⁸

Dr Engel pioneered multiple new therapies in NMD including the use of corticosteroids in myasthenia and every other day prednisone as effective but safer maintenance therapy.^{9,10} He had a strong compassion for patients with evolving disability exploring new therapeutic options, like carbonic anhydrase inhibitors in periodic paralysis^{11,12} or splenic radiation for refractory myasthenia and polymyositis^{13,14}; his articles with photos of improved patients were

emotionally stimulating. He published more than 700 scientific articles and seminal books that shaped the field, attracting more than 200 trainees from all over the world. At USC, along with Dr Askanas's pioneering contributions, his research focused on inclusion body myositis (IBM)¹⁵ while continuing to teach muscle histopathology and clinical reasoning. He spent significant time throughout the day seeing patients, eating only small chocolate-peanut snacks, stating that “*they are sufficient to re-fuel him*”.

King was driven by the well-being of his patients, earning their deepest trust and respect, projecting hope even to those with progressive degenerative NMDs. Patients sought him out because they believed in his genuine efforts to never give up trying to reverse their progressive disability. He believed that a neuromuscular expert should combine expertise in clinical exam, correct interpretation of laboratory findings, especially muscle biopsy, and familiarity with all current or promising options, a legacy that drove most of his mentees to establish their own centers modelled after him. King's breadth of intellect in connecting neurology with humanity witnessed during our 50-year interactions, is best highlighted by key neuro-philosophical articles or commentaries with catching or humorous titles in prestigious journals, like: “*Dagen des oordeels*” on the pathokinetic and molecular mechanisms that characterize the “*assassinations or suicides*” of muscle-fiber death¹⁶; the “*further fond farewell to Shy and Drager*” illuminating the importance of “the three men I knew well, Drs Shy, Drager and also the patient for this syndromogenesis”¹⁷; the “*ponderous-purse disease*” describing cervical stress-pains due to heavy feminine purses, “destined to remain endemic”¹⁸; the “*Wartenberg wheel-and-flair reaction—a prickly problem*” regarding neurosensory testing¹⁹; “*abolish boxing*”, arguing that “we forbid our pitbulls and our cocks to fight, why not our fellow men?”²⁰; or “*Unicorns, dragons, polymyositis, and other mythical beasts.*” to highlight what is not polymyositis.²¹

At a personal level, he was humble, with genuine love for his patients, trainees, and his wife, Dr. Valerie Askanas, who has been a stimulating collaborative force in exploring key NMD mechanisms and fulfilling his scientific and personal dreams. While Dr Engel often expressed his respect to his collaborators and friends with smart and pleasant, even amusing, but rather laconic comments, Dr Askanas was always providing wider supportive and consensual loving sentiments. Their presence at national and international NMD conferences was inspiring to the new generation of fellows who pursued meeting them even for a greeting, a photograph, or just to exchange pleasantries from such a long-standing and admired legend.

King will be missed and remembered forever not only by his friends and colleagues but also by his hundreds of

trainees throughout the scientific neuromuscular community and his many patients who have experienced his sincere dedication to their care. He is survived by his beloved wife, Dr Askanas, as well as his children, and grandchildren.

Acknowledgment

The publication of this article in OA mode was financially supported by HEAL-Link.

Author Contributions

Marinos C. Dalakas: Conceptualization; writing – original draft; writing – review and editing. **Steven P. Ringel:** Writing – review and editing; conceptualization.

Marinos C. Dalakas^{1,2} and Steven P. Ringel³

¹Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA, ²Neuroimmunology Unit, Department of Pathophysiology, Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece, and ³Department of Neurology, University of Colorado, Boulder, CO, USA

Address correspondence to Prof Dalakas, Department of Neurology, Thomas Jefferson University, Philadelphia, PA. E-mail: marinos.dalakas@jefferson.edu

References

- Engel WK. The essentiality of histo- and cytochemical studies of skeletal muscle in the investigation of neuromuscular disease. *Neurology* 1998;51:655–717.
- Engel WK, Foster JB, Hughes BP, et al. Central core disease—an investigation of a rare muscle cell abnormality. *Brain* 1961;84:167–185.
- Shy GM, Engel WK, Somers JE, et al. Nemaline myopathy. A new Bcongenital myopathy. *Brain* 1963;86:793–810.
- Engel WK, Vick NA, Glueck CJ, Levy RIA. A skeletal-muscle disorder associated with intermittent symptoms and a possible defect of lipid metabolism. *N Engl J Med* 1970;282:697–704. <https://doi.org/10.1056/NEJM197003262821301>.
- Engel WK. Muscle target fibres, a newly recognized sign of denervation. *Nature* 1961;191:389–390.
- Engel WK. Fiber-type nomenclature of human skeletal muscle for histochemical purposes. *Neurology* 1974;24:344–348.
- Askanas V, Engel WK, Dalakas MC, et al. Human Schwann cells in tissue culture: histochemical and ultrastructural studies. *Arch Neurol* 1980;37:329–337. <https://doi.org/10.1001/archneur.1980.00500550031001>.
- Dalakas MC, Engel WK. Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. *Ann Neurol* 1981;9:134–145.
- Warmolts JR, Engel WK, Whitaker JN. Alternate-day prednisone in a patient with myasthenia gravis. *Lancet* 1970;2:1198–1199.
- Engel WK. Myasthenia gravis, corticosteroids, anticholinesterases. *Ann N Y Acad Sci* 1976;274:623–630. <https://doi.org/10.1111/j.1749-6632.1976.tb47720.x>.
- Griggs RC, Engel WK, Resnick JS. Acetazolamide treatment of hypokalemic periodic paralysis. Prevention of attacks and improvement of persistent weakness. *Ann Intern Med* 1970;73:39–48. <https://doi.org/10.7326/0003-4819-73-1-39>.

12. Dalakas MC, Engel WK. Treatment of “permanent” muscle weakness in familial hypokalemic periodic paralysis. *Muscle Nerve* 1983;6:182–186. <https://doi.org/10.1002/mus.880060303>.
13. Engel WK, Lichter AS, Dalakas MC. Splenic and total-body irradiation treatment of myasthenia gravis. *Ann N Y Acad Sci* 1981;377:744–754. <https://doi.org/10.1111/j.1749-6632.1981.tb33772.x>.
14. Engel WK, Lichter AS, Galdi AP. Polymyositis: remarkable response to total body irradiation. *Lancet* 1981;1:658.
15. Askanas V, Engel WK. Inclusion-body myositis: muscle-fiber molecular pathology and possible pathogenic significance of its similarity to Alzheimer’s and Parkinson’s disease brains. *Acta Neuropathol* 2008;116:583–595. <https://doi.org/10.1007/s00401-008-0449-0>.
16. Engel WK. Dagen des oordeels. Pathokinetic mechanisms and molecular messengers (a dramatic view). *Arch Neurol* 1979;36:329–339.
17. Engel WK. A further fond farewell to shy and drager. *Ann Intern Med* 1997;126:334.
18. Engel WK. Ponderous-purse disease. *N Engl J Med* 1978;299:557. <https://doi.org/10.1056/NEJM197809072991024>.
19. Engel WK. Wartenberg wheel-and-flair reaction – a prickly problem. *N Engl J Med* 1992;327:1397. <https://doi.org/10.1056/NEJM199211053271923>.
20. Engel WK. Abolish boxing. *N Engl J Med* 1982;307:761. <https://doi.org/10.1056/nejm198209163071227>.
21. Askanas V, Engel WK. Unicorns, dragons, polymyositis, and other mythical beasts. *Neurology* 2004;63:403–404.

DOI: 10.1002/ana.78176