L-Glutamate as Neurotransmitter—
Origin of the Concept
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During my senior year at Harvard College, I began a project under William C. Van der Koot, instructor in biology, on the effect of picrotoxin, a convulsant, on the function of the inhibitory neuron to the opener muscle in the crayfish claw. I finished the project during a summer fellowship from the College of Physicians and Surgeons in Bill’s laboratories at the Australian National University in Canberra, also reported in 1959 the excitatory activity of L-glutamate on spinal neurons in the cat, but they considered the activity "nonspecific" and not that of a transmitter.

These 1959 publications by three independent laboratories launched the field of excitatory amino acid research. My paper and those of Van Harreveld2° led others (notably A. Takeuchi, N. Takeuchi, J. Dudel, and P.N.R. Usherwood) to establish L-glutamate as an excitatory transmitter in invertebrates. Furthermore, Watkins has stated that our observations concerning L-glutamate in the crayfish, together with his and his coworkers’ observations in the cat, led to the synthesis of N-methyl-D-aspartate, which provided a foundation study of L-glutamate by defining its most important receptor in the mammalian nervous system.

The conflict concerning the transmitter status of L-glutamate, which raged for two decades before being resolved, has been reviewed by Usherwood,5 who commented on how “...sections of the scientific community react to a new concept which threatens to undermine established ideas.” He recounted how “...against a consensus view... in the early 1970s the concept of...metabolites such as L-glutamate and L-aspartate serving a neurotransmitter role seemed distinctly untenable if not outright heretical.” Today, L-glutamate is the likely transmitter at the majority of excitatory synapses in the mammalian central nervous system and, in excess, may be responsible for neuronal dysfunction or death in a variety of human neuropsychiatric disorders.

I left the field of invertebrate neuropharmacology to complete my medical education and training. However, my subsequent research has led to another hypothesis concerning the human nervous system, namely, that DNA repair is required for neurons to survive and that some neurodegenerations (e.g., Huntington's disease, Alzheimer's disease, amytrophic lateral sclerosis) are due to defective DNA repair in neurons. How ironic it is to find that one of the most attractive competing hypotheses is that neuronal cell death in some of these diseases is due to L-glutamate!