PCPA was not our only basic discovery during the mid-1960s. In 1965, after o-methyltyrosine (AMT) and its m-iodo derivative were reported to inhibit tyrosine hydroxylase, we learned that Pfizer chemists had coincidentally synthesized a one-step precursor to AMT for a different purpose, enabling our rapid conduct of in vivo experiments. In planning one of these, we expected that AMT would increase a rat’s sensitivity to amphetamine by what was termed denervation supersensitivity. The behavioral experiments yielded exactly opposite effects to those expected, and we were the first to report that AMT blocks amphetamine-elicted stimulation, a finding that teaches much about how amphetamine exerts its stimulant action.

These forays into the pharmacology of ring-halo-gennated aromatic amino acids also led us to a neglected literature that low doses of meta-chlorophenylalanine (m-PCPA) and m-fluorotyrosine (m-FT) are convulsant and lethal in rodents. While wondering how this toxicity could result from changes in brain amines, one of us then began a banal self-education project, found himself reading a review of fluoroacetate toxicity in volume 1 of Pharmacological Reviews. Could lethal synthesis to fluoroacetate be the mechanism of m-FT toxicity? Yes, and also of 3-fluorotyptophan toxicity, and analyzing the metabolic pathways had surprising benefits.

Our main reason for reviewing these events is to emphasize that they were not predicted or sighted in advance. We can provide many other anecdotes describing fortuitous drug discoveries. We are concerned that similarly important serendipitous discoveries seem to be less often made these days. For understandable reasons, the pharmaceutical industry now attempts to rationalize discovery research— to focus limited resources on proprietary goals, to foster teamwork, to minimize animal use, and to satisfy a widespread belief that modern drugs should be discovered and analyzed by using deductive logic. Analogous beliefs underlie the philosophies of most public and academic institutions that support research. But relying upon deductive reasoning as the sole basis for funding research, in our judgment, can undermine the possibility of just such serendipity as that we were lucky enough to encounter a quarter-century ago.