From Rats to Monkeys to Man—The Neurophysiology of Alcoholism: A Tribute to Henri Begleiter

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THE SECOND ENTRY in Henri Begleiter's extensive curriculum vitae was entitled "Changes in Auditory Evoked Responses Induced by Alcohol" (Gross et al., 1966). It signaled a 4-decade-long scientific career dedicated to the understanding of the actions of acute alcohol on the brain, the consequences of alcohol abuse and alcoholism, and the genetic determinants rendering individuals at risk to develop alcoholism. While his research took many and varied paths, he was at heart a neurophysiologist who sought to understand brain function by interrogating the electrical activity observable from probes inside the brain or noninvasively from electrodes outside the brain. Here I have selected a few of Henri's neurophysiology-based publications to trace the development of his thinking about alcohol and the brain as it encompassed three species—rats, monkeys, and man.

In his 1975 paper "Evoked Potential Changes During Ethanol Withdrawal in Rats" (Begleiter and Coltrera, 1975), a skull screw electrode over visual cortex and an implanted electrode in the ascending reticular function were used to record the EEG response to light flashes in Long Evans rats after alcoholization and subsequent withdrawal. The methodology in those days relied on the dedicated computer of average transients (the CAT), analog plotting of averaged evoked potentials on graph paper, and manual estimation of response amplitudes and latencies. The results indicated CNS hyperexcitability 24 hours after the last of several days of intragastric alcohol administration in the rat, consistent with human observations. Later (1977) with his career-long colleague Bernice Porjesz, persistence of this hyperactivity in the rat at least 5 weeks after withdrawal was demonstrated (Begleiter and Porjesz, 1977). Using a postwithdrawal alcohol challenge they observed progressive increase in brain electrical activity rather than the depression seen in control animals, consistent with a subacute postwithdrawal syndrome and with implication for mechanisms of craving.

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In 1980 Henri and his colleagues repeated the rat studies in Bonnet monkeys using implanted electrodes in several brain regions (Begleiter et al., 1980). The animals were made alcohol dependent with large intragastric doses (5.0 g/kg) daily with the animals reaching peak blood alcohol concentrations of >300 mg%. As with the rat studies the monkeys were then challenged with alcohol (2.0 g/kg) 5 weeks after withdrawal. Using visual evoked potentials, persistent CNS hyperexcitability was reactivated with reexposure to alcohol. The pattern observed in the rat was demonstrated in the monkey.

Henri was a pioneer in alcohol translational research long before the term became popular. The rat and monkey withdrawal CNS hyperactivity studies were prompted by observations in human alcoholics. He and his colleagues were the first to demonstrate direct electrophysiological evidence of hyperexcitability in human alcoholics during withdrawal (Begleiter et al., 1974), and the animal studies completed a full cycle of translation.

The thrust of his electrophysiology work progressed from examination of withdrawal hyperexcitability to the use of evoked potential to examine persistent brain alterations in chronic alcoholics. In 1979 he and Bernice demonstrated amplitude reduction in visual evoked potentials (N1-P2) in detoxified alcoholics (Porjesz and Begleiter, 1979), and at the 1978 International Symposium on Biological Research in Alcoholism in Zurich (the precursor to ISBRA and the occasion of my first meeting with Henri) they presented data on P300 (a cognitive—rather than sensory-based event-related potential component) deficits in chronic alcoholics (Porjesz et al., 1980). Shortly thereafter came the demonstration of brain stem evoked potential deficits in alcoholics (Begleiter et al., 1981).

His proposal that the electrophysiological alterations seen in chronic alcoholics might antedate their use of alcohol was tested in 1984 when he published the results of his study of preadolescent boys at risk for developing alcoholism, i.e., the nonalcoholic sons of alcoholics (Begleiter and Porjesz, 1984). Like the chronic alcoholics he had previously studied, these boys also had smaller P300 amplitudes than their controls although they had not yet been exposed to alcohol. This was the seminal observation that would drive the rest of Henri's scientific career, ultimately leading him to initiate one of the first large-scale cooperative genetic study of a major disease in the world: the Collaborative Studies on the Genetics of Alcoholism (COGA).

The COGA began with Henri's notion that the relative amplitude decrement of the P300 component of the human event-related potential could serve as an endophenotype for the genetic liability to the development of alcoholism (Alexander et al., 1994; Cohen et al., 1994). The ensuing success of the COGA, for which Henri was principal investigator from its inception until his death and to which many talented investigators have contributed, can trace its origins to the heart of a neurophysiologist.

REFERENCES

Alexander JE, Polich J, Bloom FE, Bauer LO, Kuperman S, Rohrbaugh J, Morzarati S, O'Connor SJ, Porjesz B, Begleiter H (1994) P300 from an auditory oddball task: inter-laboratory consistency. Int J Psychophysiol 17:35–46.

Begleiter H, Coltrera M (1975) Evoked potential changes during ethanol withdrawal in rats. Am J Drug Alcohol Abuse 2:263–268.

Begleiter H, DeNoble V, Porjesz B (1980) Protracted brain dysfunction after alcohol withdrawal in monkeys. Adv Exp Med Biol 126:231–249.

Begleiter H, Porjesz B (1977) Persistence of brain hyperexcitability following chronic alcohol exposure in rats. Adv Exp Med Biol 85B: 209–222.

Begleiter H, Porjesz B (1984) Event-related brain potentials in boys at risk for alcoholism. Science 225:1493–1496.

Begleiter H, Porjesz B, Chou CL (1981) Auditory brainstem potentials in chronic alcoholics. Science 211:1064–1066.

Begleiter H, Porjesz B, Yerre-Grubstein C (1974) Excitability cycle of somatosensory evoked potentials during experimental alcoholization and withdrawal. Psychopharmacologia 37:15–21.

Cohen HL, Wang W, Porjesz B, Bauer L, Kuperman S, O'Connor SJ, Rohrbaugh J, Begleiter H (1994) Visual P300: an interlaboratory consistency study. Alcohol 11:583–587.

Gross MM, Begleiter H, Tobin M, Kissin B (1966) Changes in auditory evoked response induced by alcohol. J Nerv Mental Dis 143:152.

Porjesz B, Begleiter H (1979) Visual evoked potentials in brain dysfunction in chronic alcoholics, in *Evoked Brain Potentials and Behavior* (Begleiter H ed), pp 277–302. Plenum Press, New York.

Porjesz B, Begleiter H, Garozzo R (1980) Visual evoked potential correlates of information processing deficits in chronic alocholics, in *Biological Effects of Alcohol* (Begleiter H ed), pp 603–622. Plenum Press, New York.