

# 25 Years Ago in the Canadian Journal of Neurological Sciences

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## KINDLING A SYMPOSIUM ON BASIC RESEARCH IN NEUROSCIENCE

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University of British Columbia, Vancouver, Canada

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### SECONDARY EPILEPTOGENESIS IN FROG FOREBRAIN: EFFECT OF INHIBITION OF PROTEIN SYNTHESIS

F. Morrell, N. Tsuru, T.J. Hoepfner, D. Morgan and W.H. Harrison

**Summary:** Secondary epileptogenesis was induced in the hippocampal cortex of the paralyzed bullfrog by means of localized, unilateral, intermittent electrical stimulation (kindling). Stimuli were designed to yield a brief but definite after-discharge. In control animals a progressive increase in after-discharge duration occurred at the 1<sup>o</sup> (stimulated) site and then at the 2<sup>o</sup> site (contralateral hippocampus). Spontaneous epileptiform potentials (SEPs) occurred between stimuli, eventually independently on both sides. Cycloheximide (50mg/kg) caused 88-99% reduction in protein synthesis, measured by <sup>14</sup>C-leucine incorporation into brain protein. Cycloheximide-treated animals revealed no evidence of progressive prolongation of after-discharge duration when subjected to the kindling procedure ( $p=0.1205 \times 10^{-7}$ ). SEPs were reduced in the cycloheximide-treated animals, and confined to 1<sup>o</sup> hemisphere ( $p=0.6 \times 10^{-10}$ ).

Since cycloheximide did not disturb normal electrogenesis or disrupt the after-discharges, this experiment distinguishes processes dependent upon electrical events from those requiring macromolecular synthesis. Protein synthesis seems critical to the emergence of spontaneous and autonomous epileptiform behavior of neural aggregates.

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### PRIMARY AND "TRANSFER" SEIZURE DEVELOPMENT IN THE KINDLED RAT

W. McIntyre Burnham

**Summary:** An investigation was made of both primary and "transfer" kindling as they occur in ipsilateral limbic sites. Primary kindling was found to involve progressive growth of after-discharge (AD), propagation and convulsive behavior. It was noted that AD growth did not take place gradually but occurred in sudden, large increments. "Transfer" (a significant acceleration of secondary kindling) was found at every secondary limbic site. It was associated with the early appearance of full-blown ADs, super-normal propagation, and well-developed seizures. The post-transfer interference of primary site function previously reported by Goddard et al was also found, but it occurred in significant amounts only after transfer kindling of the amygdala. It is believed that the data offer some support for both of the hypothetical mechanisms of transfer which have been proposed.

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## SPLIT-BRAIN RAT: TRANSFER AND INTERFERENCE OF KINDLED AMYGDALA CONVULSIONS

Dan C. McIntyre

**Summary:** Rats were subjected to varying degrees of commissurotomy, followed by implantation of a bipolar electrode into each amygdala. After the kindling of six convulsions at one electrode (primary site), the procedure was applied to the contralateral amygdala (secondary site). Convulsions were observed to develop more rapidly, independent of the degree or kind of transection. After six secondary site convulsions, the primary site was retested and convulsion-triggering was blocked, except in animals with transection of the rostral portion of the corpus callosum (CC).

Collectively, the data indicate: (i) amygdala kindling develops a lasting trace which operates through the midbrain or brainstem; (ii) kindling from a second site utilizes this trace; (iii) a series of six convulsions produces negative after-effect which manifests itself at the convulsion level via the anterior CC; (iv) the anterior CC is important in determining the laterality of the forelimb clonus; and (v) the inter-amygdala propagation of after-discharge is blocked by the combined sectioning of the anterior CC and the anterior commissure.

Can. J. Neurol. Sci. 1975;2:(Suppl 2):429

**New seizure-free dosage data on Neurontin as add-on therapy**

**During the storm of epilepsy**

**two studies highlight Neurontin's\* improved efficacy as add-on therapy at higher doses.**

**Neurontin\* was effective when titrated to individual effectiveness<sup>1,2</sup>:**

	NEON Study* (n=141)	STEPS Study* (n=1055)
Average % Decrease in Seizures	N/A	60%
% Seizure-Free	46%	46%
≥50% Improvement	71%	76%

\*Last 8 weeks of study. Study included patients with complex partial seizures and was a prospective, open-label, 20-week, multicentre study.

†Last 4 weeks of study. Study examined patients with partial seizures with or without secondary generalizations. STEPS was a prospective, open-label, 16-week, multicentre study.

**Doses higher than 1200 mg/day may increase the efficacy in some patients; however, higher doses may also increase the incidence of adverse events.<sup>3</sup> The maximum recommended dose is 2400 mg/day.<sup>3</sup>**

**To help them through the storm – consider moving patients to a higher dosage of Neurontin\***



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<sup>3</sup>In previous fixed dosage studies somnolence and ataxia appeared to exhibit a positive dose-response relationship. Patients treated with 1800 mg/day (n=54) experienced approximately a two-fold increase as compared to patients on lower doses of 600 to 1200 mg/day in the incidence of nystagmus (20.4%), tremor (14.8%), rhinitis (13%), peripheral edema (7.4%), abnormal coordination, depression and myalgia (all at 5.6%). Neurontin is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.<sup>3</sup>