

Epilogue

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The history of the natural sciences tells us that the detailed examination of an appropriate and valid model has always been helpful in obtaining insight into the nature of the phenomenon under study. The desirability of such a model through which the theoretical framework of the elusive processes of learning and memory and the pathophysiology of epilepsy can be rigorously examined cannot be over-emphasised.

Yesterday, we heard that kindling is analogous to normal learning. Goddard showed us evidence of the lasting potentiation of EPSP. There was some suggestion of enlarging axon terminals in the kindled synapses of the amygdala but no electron microscopic evidence of alteration at the receiving end has been identified. Racine has told us of durable electrophysiological changes in his series of elegant studies but, again, he was unable to find evidence by Golgi's method of morphological alteration which might be attributed to kindling. The lack of morphological changes is reassuring and supports the contention of Goddard, thereby making this preparation really comparable to many of the epileptic conditions found in man. However, it is unsettling for those who believe that physiological manifestations should have visible correlates in the neurobiological substrate. In this regard, the preliminary studies presented by Morrell of the effect of protein synthesis inhibition; by Sato, of cerebral catecholamine depletion; and by Tanaka of possible GABAaminergic involvement in the modulating kindling process, all appear

to suggest promising avenues leading to a very fertile area of further inquiry. Rigorous experimental verification of Phillip's statement on catecholaminergic organisation and kindling, for example, may herald the dawn of a new era, with unifying conceptualization of many previous observations on the catecholamine system and epileptic seizure.

From Burnham we heard about the intriguing phenomenon of transfer and post-transfer interference which may well represent both sides of the coin. Supporting my previous observations with split brain cats and rats, we learned from McIntyre of further dynamic processes involved in the inter-hemispheric interaction using forebrain bisected animal preparations. We heard about the effect of sleep upon the behavior of interictal discharge and kindled seizure susceptibility, and about the effect of kindling upon sleep organization which, as mentioned by Daly, reminds us of the close association of circadian rhythm and epileptic seizure manifestation in human epilepsy, as well as the intriguing physiological role epileptogenic discharges may play in the patterning of the expression of clinical seizure. Adamec told us of evidence of a causal relationship between limbic epileptic excitability, neurosensory responses and behavioral measures, which further suggests that investigation of this type may help us understand the subtle impact that "experience" may play upon our brain. This morning, Pinel discussed the wider clinical implications of kindling. Finally the frontal lobe was revisited by my laboratory demonstrating a complex picture of frontal participation in amygdaloid kindling and the diffe-

rential features of frontal versus amygdaloid kindling among three different species.

The significance of a warning which emerged from this Symposium regarding electrical or chemical stimulation of the human brain requires further emphasis. According to our survey, more than 200 cases of spontaneous recurrent epileptic seizures following repeated electric shock treatment have been reported in the literature since 1946, (still an accepted treatment in psychiatry.) On the other hand, the degree of technological sophistication of our "scientific" medicine is such that the significance of utilization of direct electrical and at times chemical brain stimulation as a diagnostic or therapeutic approach has not been questioned. We are also aware of the widespread use of many potent drugs, whose action is obscure and yet clearly dependent upon their capability of modifying brain function. Are we certain that there will not be any long-term deleterious effect? I believe each one of us dealing with the kindling phenomenon has a responsibility to warn the medical profession and the public of such a possibility.

As far as I am aware, Watanabe, (1936) who was interested in verifying Spielmyer's vascular spasm theory as the pathogenesis of epileptic seizure, was the first to observe and describe in 1936 the phenomenon of progressive epileptic seizure development by daily cortical stimulation of freely moving dogs, culminating in spontaneous status epilepticus. Subsequently, many investigators must have observed similar phenomena as has been repeatedly mentioned during this Symposium. However, it was Goddard's fresh perception which

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enabled him to investigate this phenomenon systematically.

This reminds us all of the nature of discovery and the way discoveries are made. If we look back we find, for example, the very familiar story of Fleming who went after the blue mould which grew in his presumably pure culture when many of his contemporaries and distinguished colleagues were throwing the mould away or closing their laboratories, in order not to jeopardize their reputation as microbiologists. I think that every discovery is made to order for the one who can look at a phenomenon with a detached eye, with perspective, and without excessive, immediate or categorical pre-occupation, so that one can penetrate the non-essential mossy or glossy layers covering the fact facing him. This would require a process of "unknowing" which can reject conformist ideas. We would be better to lift the transparent but often tinted "scientific" blinds from our eyes if we hope to significantly contribute to the area of one's endeavour, and be able to experience the real joy of research. I know this is not easy at a time when one has to struggle in a highly competitive jungle for research funds. However, when I look back on my past thirty years, I do not believe I have ever experienced a single period in which research funds were easy to come by, and I do not think there ever will be a paradisaical situation for the support

of research. We do need adequate financing, and there is no doubt about that. I only wish the funding agencies could adopt a more enlightened and flexible philosophy towards aspects of the "art" of science, which I believe to be an integral part of doing research. But, more importantly, we need to cultivate and maintain a balanced posture and perspective for the art and science of research, since without either one of them, I predict that the possibility of a real breakthrough is very slim. I think we owe Dr. Goddard a great deal in reminding us of how a blending of the art and science led to his discovery, and for the quality of his subsequent investigations, which I am sure all of us agree, opened up the fascinating and tantalizing vistas of neurobiology.

Not surprisingly, more questions than answers have been generated by this Symposium. I think, however, we are all convinced that we have now enough information to make a thrust for further enquiry. At the same time I am mindful of Livingston's comments on the implications of this Symposium; that is, this meeting was fruitful since it brought together physiological psychologists, neurologists, neurosurgeons and psychiatrists, to discuss the various dimensions of the kindling phenomenon. That alone motivates me to look forward to a second Symposium. Hopefully, the kindling phenomenon might be

considered as one of the key topics for the Epilepsy International Meeting in Vancouver in 1978. The study of kindling is still in its embryonic stage but we have gathered considerable data upon which we can base our future work. Whatever one's special interest might be, we have more reasons to believe that the kindling model will continue to be a source of very productive work. Probably in three year's time we should have gathered enough new information to reassess our progress critically and, hopefully collectively.

I would like to take this opportunity to thank all the guest speakers, discussants and participants who came from afar and contributed to our knowledge; and, finally, I would like to thank my colleagues and staffs who worked long hours helping me to bring this meeting to a successful conclusion. I am particularly grateful to Ms. Sue Calthrop for her careful and conscientious editorial assistance.

REFERENCES

- SATO, M. and WADA, J. A. Review on the Kindling Preparation: A New Experimental Model of Epilepsy. *Brain and Nerve*, 27: 257-273, (1975).
- WATANABE, E. Experimental Study on Pathogenesis of Epileptic Convulsive Seizures. *Psychiatria et Neurologica Japonica*, 40: 1-36, (1936).