

## In Memoriam



**Graham Goddard, M.D., Ph.D.**

### **Graham Goddard: An Appreciation**

Graham Goddard died on January 15, 1987, at the age of 48. He was hiking with his wife, Pat, and their 2-year-old son, Eric. He drowned apparently while attempting to cross a storm-swollen river in New Zealand's Arthur's Pass National Park. Goddard was born in England and emigrated to Canada where he obtained most of his education in Saskatchewan. He obtained his Ph.D. at McGill University under Donald Hebb. From 1963 to 1968, he held assistant and associate professorships at the University of Waterloo (Ontario). After spending a sabbatical year in my laboratory at Stanford, Goddard moved to Dalhousie University where he became full professor in 1973. In 1981, Goddard accepted the Chair of Psychology at the University of Otago. Combining great enthusiasm with common sense, he managed a large enflourishment of the department and neuroscience in New Zealand. He was instrumental in establishing a Centre for Neuroscience Research at the University of Otago, and last year became its first director. Almost immediately upon his arrival to New Zealand, Goddard surprised his many North American friends by inviting them to attend an Australasian Winter Conference on Brain Research that he had organized. He was determined not to become isolated "down under" and indeed to bring his new department and University to world-wide attention.

Goddard's main contribution was the discovery of the phenomenon to which he gave the name "kindling." The term is used both to describe a state (one may say that an animal has been kindled)

and the process (kindling) by which that state is brought about. In the original experiments, a brief (1-2 s) train of electrical stimuli of an intensity that was subthreshold for elicitation of a behavioral response was delivered to the amygdaloid nucleus of one hemisphere of the rat. After 6 to 10 trials (1/day), the animal was noted to have ipsilateral facial twitching. As further trials were given, the facial twitching became associated with rhythmic blinking and chewing movements, contralateral forelimb clonus, neck muscle contraction, and, eventually, a generalized convulsion. Electrophysiological recordings revealed that the brief afterdischarge (AD) accompanying the first few stimulations grew systematically longer with each successive stimulation and spread from the site of the stimulating electrodes to more and more distant though synaptically related regions. This progressive enhancement of the neural response to a constant and low-intensity electrical stimulus as a function of repetition is the essence of the kindling effect. Between stimulations, the rat appeared to be normal and, yet, even if months had passed since the last stimulation, a single reapplication of the initially innocuous stimulus resulted in a major convulsion. Thus, the nerve cells that had been subjected to electrical current retained their enhanced responsiveness despite months of inactivity. Indeed, further studies made clear that it was not only the cells directly influenced by the current that had acquired permanently altered responsiveness, but cells that were one, two, or more synapses away from the original cells had lowered thresholds and required a shorter time to kindle than did the initially stimulated region (transfer). Thus, the modification of neuronal responsiveness was transynaptic and slow, and it was completely dependent on anatomical connectivity. Kindling proved to be an extremely robust experimental phenomenon. It has been reproduced in reptiles, amphibians, rodents, lagomorphs, felines, canines, and several primate species. Laboratories all over the world are working on various aspects of kindling. If contagion is a true measure of the value of a discovery, then kindling has reached epidemic proportions.

One further feature of the kindling model is important in assessing the impact of Goddard's contribution, namely, experimenter control of the process. In the '60s, many investigators were seeking better experimental models with which to pursue studies of the development of focal epileptogenic

lesions. One of the major difficulties associated with the models of chronic focal epilepsy then available, e.g., freezing and alumina cream mainly, was that the frequency of interictal spiking was variable from preparation to preparation and that the occurrence of *ictal* discharge was completely unpredictable. Observing the evolution of an epileptogenic lesion was very tedious, required an enormous investment in time and animals, and sequential changes were difficult to pin down. I remember trying to convince my colleagues that putative or potential anticonvulsant drugs should be assayed in a model of chronic epilepsy (which more closely approximates the human condition) rather than the electroconvulsive shock or pentylenetetrazol challenge models commonly used. My argument went unattended to in the early '60s; the investment required was too great, the turn around time too slow. Discovery of the kindling model of chronic focal epilepsy in which electrically triggered convulsions are elicited under experimenter control made a dramatic difference; kindling is used extensively for drug assays and has made possible the rigorous investigation of the natural history of focal epileptogenic lesions.

Kindling was an accidental discovery. Goddard had been using electrical stimulation of the amygdala in an effort to disrupt learning in a task to which rats were exposed once a day. After 10–14 days, he noticed that some rats had convulsions when the current was turned on. The latter rats were dropped from the experimental population comprising his Ph.D. thesis, but the observation was not dropped from his mind. A couple of years later, he returned to the problem and succeeded in defining the experimental circumstances responsible for this unexpected "complication" of his thesis work.

Goddard was an intuitive, thoughtful, and insightful investigator. He was also not afraid to gamble on a hunch. He spent 5 years in a fruitless attempt to identify ultrastructural alterations in the kindled amygdala. Despite the lack of success, the experimental design was an elegant one—something on which graduate students should model their own designs. It is a pity that because of the negative result, the paper will not be widely read. Indeed, many of Goddard's experiments were brilliantly designed and deserve to be characterized as classics in this field of research. One thinks especially of his studies of the role of hippocampal long-term potentiation (LTP) in the evolution of kindling and his demonstration of the coactivation of afferents involved in LTP as paradigms of careful and concise experimental reasoning.

Graham Goddard had a knack for biology. By that I mean that he had an extraordinarily prescient sense of what *ought* to be true, how nature *should* have honed and designed the system. Sometimes he was wrong, but he was right more frequently than can be attributed to chance. And he was not dismayed by trivial "facts" that "seemed" to contravene his main hypothesis, although he took careful note of contrary evidence. He was not afraid to speculate, or better, one might say, he went at speculation with a zest. One afternoon of a meeting day, Janice Stevens asked him to consider the implications of kindling for behavioral disturbances. The result was a walk that Goddard, Stevens, and I took along the Hudson, almost from one end of Manhattan to the other. Goddard's conversation ranged from the Galapagos, to temporal lobe epilepsy through the "dyscontrol syndrome" (a concept he disparaged) and predatory behavior in cats, to synaptic plasticity (his favorite subject). In fact, Goddard's zest as a symposiast was widely recognized, not least of all by his many students. He didn't allow anyone simply to do an experiment and then go home to cultivate a garden. A clear requirement for any student who worked with Goddard was to be prepared to extend the experimental ideas until either they could be chopped to pieces or the subsequent experiment suddenly jelled. His long-time friend and colleague, Ron Racine, tells me that Goddard was still at it "down under." He held a weekly seminar at his house in a room under the eaves where everyone sat on the floor, teacup in hand, during which his students were required to consider how their own projects contributed to the understanding of behavior.

These largely theoretical discussions represented only one aspect of his approach. The other aspect, equally important to him, had to do with the clinical implications of his research. Goddard was convinced that man would not prove to be immune to a process so universally characteristic of other complex nervous systems as was kindling. He believed that the abnormal electrical activity generated in a primary epileptic focus in, for example, the human posttraumatic lesion would influence surrounding nerve cells in the same way that the artificial electrical stimulus effective in kindling did. He was especially impressed with Racine's demonstration that the discharge pattern of nerve cells subjected to an effective kindling stimulus in the rat was similar to the pattern seen in more orthodox primary epileptic foci. Always one to translate thought into action, Goddard became a strong advocate of the use of prophylactic anticonvulsant drugs in those at risk for posttraumatic seizures. He argued that pre-

vention of kindling by suppression of abnormal electrical discharge in the early stages of recovery before seizures occurred, and before the healing or gliotic process was complete, would likely reduce the incidence of posttraumatic epilepsy. He advocated extensive clinical trials of such a concept.

In this summary of Goddard's contributions, kindling and its implications for epilepsy have been stressed because of its obvious importance to the readership of this journal. But Goddard was equally aware that kindling was an important model system in which to study learning and memory. Indeed, it was this latter aspect of kindling that provided the occasion for us to meet. And the circumstances of that meeting convey something of the flavor of this extraordinary individual in a way that the recitation of his scientific accomplishment cannot do.

The man had style. It was a style that pervaded his work in the laboratory as well as the way he lived. I rarely saw him sleepy. He conveyed a sense of intense energy and attentiveness that seemed the same whether he was at an afternoon picnic or the two of us were hunched over the brain of a cat at 2 a.m. He had a kind of clear, limpid intelligence, and he applied the same cautious reasoned approach to discussions of politics as to science. But he was ever alert to the main chance, and when one pierced the outer shell of conventional behavior, there was a swashbuckler and a gambler not very far underneath. The story of how he arrived at my laboratory at Stanford is a good example.

It was just about midnight when the telephone rang in my laboratory (and therefore 3 a.m. in Eastern Canada where the call originated). A telephone call at that hour is an unlikely event to begin with, and, still more unlikely, that the person on the other end would not be one of my children, but a man who introduced himself as Graham Goddard. It seems that Goddard had just then recognized the kindling phenomenon for what it was and had perceived immediately that it was related to investigations pursued in my laboratory for many years. He called to tell me about it. It was a long and excited conversation, the first of many, and the upshot of it was that Goddard would spend the following year on sabbatical leave to work in my lab.

The voyage from Waterloo to Stanford was also an adventure. Goddard and his wife, Pat, decided to make the 3,000-mile journey by motorcycle. They encountered a rough stretch of road, had an accident, were injured (fairly seriously I learned later), were hospitalized in the burn unit of a small Pennsylvania hospital, refused an offer to be flown to Stanford, and, eventually, they made it to the west coast. It was an August afternoon when

Graham Goddard, dusty, still slightly bandaged, black jacketed, jack-booted, and with an enormous, luxuriant black beard walked into the laboratory. The man who had discovered kindling made a debut that was worthy of Douglas Fairbanks.

Goddard's death deprives us of one of the major talents in contemporary neurobiology. We shall miss his keen, curious, and quirky mind. We shall miss his surprisingly subtle sense of humor. Most of all, we shall miss his panache.

Frank Morrell



**Bruce S. Schoenberg, M.D., Dr. P.H.**

**Bruce S. Schoenberg  
1942–1987**

Bruce Schoenberg died July 14, 1987. He had been Chief of the Neuroepidemiology Branch at the National Institute of Neurological and Communicative Disorders and Stroke since 1975. Following graduation from the Yale University School of Medicine (1968), Dr. Schoenberg joined the National Cancer Institute (1968–70). He then went to the Mayo Clinic for internship (1970–71) and a Neurology residency (1971–75). A Master of Science Degree in Neurology was awarded by the University of Minnesota (1976) and he received a Doctorate of Public Health from Johns Hopkins University School of Hygiene and Public Health (1980).

Dr. Schoenberg was past president of the Pan American Society of Neuroepidemiology, chairman of the World Federation of Neurology's Research Committee on Neuroepidemiology, founding editor of the journal *Neuroepidemiology*, and author of over 350 scientific papers and the text *Neurological*

*Epidemiology.* Because of his expertise, Dr. Schoenberg was frequently invited as a guest lecturer throughout the world.

In recognition of his outstanding work in the neuroepidemiology of epilepsy, which included establishing centers for neuroepidemiological study in Asia, Africa, Europe, and North and South America, the International League Against Epilepsy in 1985 presented him with the distinguished Ambassador Award in ceremonies at Hamburg, Germany.

In June 1987, U.S. Surgeon General C. Everett Koop presented Dr. Schoenberg, a captain in the U.S. Public Health Service, with the Surgeon General's Medallion, the Public Health Service's highest honor. Dr. Schoenberg is only the seventh person so honored. Captain Schoenberg was laid to rest, with military honors, at Arlington National Cemetery.

Onset of symptoms in late April 1987 forced Dr. Schoenberg to return from a trip to Uruguay, and the diagnosis of terminal abdominal carcinoma led to almost continual hospitalization at the Bethesda

Naval Hospital. Words from the Talmud, read at his memorial service, describe his few final months:

Though it is not incumbent upon you to complete the work,

You are not free from doing all you possibly can.

With a special rededication, Dr. Schoenberg intensified his efforts to disseminate his scientific findings and continued to write from his hospital bed with support from his wife Devera.

It is a special tragedy when a man as talented as Bruce Schoenberg dies so young. He died with the same quiet dignity that characterized his life. But his significant contributions to the neurological community, and especially to the epilepsy community, remain.

In this spirit, Dr. Schoenberg was asked in late June to prepare a paper on some aspect of epidemiology and epilepsy for *Epilepsia*. He chose to outline the history, current research, and future prospects for the control and prevention of epilepsy in developing countries, which follows.

James J. Cereghino