OBITUARY

Hans Kosterlitz (1903–96)

HANS Kosterlitz, who died on 26 October in his beloved Aberdeen, often remarked that he had really wanted to be a mathematician but that medicine offered a more certain living. His mathematical grasp of problems stood him in good stead, however, over a scientific career which spanned more than 50 years, and which culminated in the development of a quantitative *in vitro* bioassay for morphine and its congeners and its use to discover the brain's own 'opiates', the enkephalin peptides.

Pharmacologists have always claimed bioassay as their own, and it was perhaps ironic that one of its most triumphant applications should come at a time when the new receptor-binding assay technology was changing the face of pharmacology. The race to isolate and identify the opioid peptide enkephalins was eventually a contest between bioassay as practised by Kosterlitz's group at the University of Aberdeen, and opioid-receptor binding, originally developed by the groups of Avram Goldstein, Eric Simon, Lars Terenius and Solomon Snyder, and vigorously exploited by Snyder. But the discovery and its impact on neurobiology was much more than a triumph of technique — it was rooted in assiduous scholarship and the careful testing of hypotheses arrived at by reason and experiment, virtues that Hans passed on to generations of students and colleagues.

Although not a Jew himself, Kosterlitz foresaw where Nazi policies were leading and left his clinical assistantship at the University of Berlin in 1933 to work with J. J. R. Macleod in the Department of Physiology at Aberdeen. Macleod, who had shared the Nobel prize for the discovery of insulin, had offered Kosterlitz the opportunity to pursue his interest in liver glycogenesis and the role of insulin.

Almost immediately, however, with the unexpected death of Macleod in 1935, Kosterlitz was faced with a dilemma — should he stay on in Aberdeen without a mentor or move south to Oxford? He chose to stay, a decision which in private he sometimes regretted. Aberdeen at that time was rather insular and it could be difficult for foreigners (which included anyone from south of the River Tay). Kosterlitz's abilities were quickly recognized, however, and he coped with any xenophobia by becoming more Scottish than the Scots, not least in his love of the country's culinary products.

Nevertheless, his academic progression was slow, and he was bitterly disappointed to be passed over for the chair of physiology in 1959 despite his manifold contributions to the department. That might have been the end of the story but for Alaistair MacGregor, who had recognized the need to develop both the clinical and basic aspects of pharmacology in the medical curriculum. Thus it was that Kosterlitz returned to a clinical department as professor of pharmacology at the age of 65.

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Kosterlitz continued to work on the glycolytic pathways after Macleod's death and succeeded in isolating galactose-1-phosphate as an intermediary metabolite. This might have received greater recognition if he had gone to Oxford. But it was not to be; the war intervened and Kosterlitz took up nutritional research to support the war effort. This not very exciting period of his career ended in the 1950s with a sabbatical period at Harvard with Otto Krayer to work on the effect of the veratrum alkaloids on the autonomic nervous system.

This change in direction was typical of Kosterlitz, who had recognized the growth of autonomic pharmacology and its potential. His research on gut reflexes led him inexorably to study the effects of morphine, which had been reported by Paul Trendelenburg to inhibit myenteric reflexes in the ileum. Kosterlitz refined this observation into a quantitative assay, involving the guinea-pig longitudinal muscle–myenteric plexus, and with Louise Cowie and Angela Waterfield he showed that the analgesic activity of a wide variety of opiates could be predicted from their activity in this bioassay.

When, in 1969, I joined Kosterlitz in Aberdeen, the interest in opiates was intense. MacGregor affectionately called us the cat doctors and it was the cat nictitating membrane which brought our two lines of research together. Together with Graeme Henderson, we showed that noradrenergic transmission in that tissue was morphine-sensitive; this stimulated the search for new adrenergic models, resulting in the discovery of the mouse vas deferens as a new bioassay. Kosterlitz recognized the importance of reducing the complexity of morphine action to its simplest elements, which meant getting away from the complications of working with the brain that had led numerous workers into unproductive paths.

Our group established without doubt that morphine and its congeners acted as agonists at stereoselective receptors to modulate neurotransmission. When all other possibilities had been eliminated, the inference was clear — some undiscovered neurochemical system must use an endogenous opiate. It has been assumed that the discovery of opiate-receptor-binding sites in 1973 played an important role in establishing this hypothesis. But it was only a confirmatory one, because Kosterlitz and I had already agreed on the endogenous opiate hypothesis in 1972 and made plans to test it in the Unit for Research on Addictive Drugs formed upon Kosterlitz's retirement in 1973.

For 12 years this unit was an international leader in opiate research. Discovery of the enkephalins and other opioid peptides opened up the new era for neuropeptides, whose physiological and therapeutic implications are still being vigorously explored. The rigorous classification of the κ-opioid receptor, for instance, and the discovery of the δ-opioid receptor, opened up new therapeutic avenues.

Kosterlitz won widespread recognition and many honours, including a Lasker Award in 1978, for these and other seminal studies. It was controversy over the Lasker, awarded at the same time to Snyder and myself, that perhaps deterred the Nobel committee from recognizing the opiate work. A student of Snyder claimed that she should have shared the award. Kosterlitz and I found the incident distasteful, and supported Snyder, who has continued to make major contributions to neuroscience.

Hans Kosterlitz could sometimes appear fierce and intimidating, but those who chose to meet him on equal intellectual grounds usually found a colleague and friend for life. Hans was a physician, scientist, teacher, *bon viveur* and friend — he will be sorely missed, but his work will endure. John Hughes

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