REPORT OF A SCIENTIFIC MEETING

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The Dahlem Conference
Berlin, Federal Republic of Germany

During the eventful days when the Berlin wall was opened (November 7–12, 1989), the Dahlem symposium met in West Berlin and considered the issue of "Towards a New Pharmacotherapy of Pain: Beyond Morphine." The organization of the Dahlem meeting is unusual. Sponsored by the city of Berlin and the Stifterverband für die Deutsche Wissenschaft, it was designed to draw together a group of 50 scientists and clinicians representing a number of scientific perspectives and place them in a setting of what amounts to a small pressure cooker for 5 days to address in a directed fashion specific questions pertaining to the topic at hand. The workshop, organized by A. I. Basbaum and J. M. Besson, was broken into four groups, each with its own chairman, to consider the principle issues of: physiologic and pharmacologic basis of nociceptive transmission (H. O. Handwerker); approaches to overcoming tolerance and other limitations to narcotic therapy (K. M. Foley); the molecular basis for nociception and new drug design (E. A. Barnard); and differential response of neurogenic and sympathetically maintained pains to opioid and nonopioid therapy (W. Janig). Background papers were prepared by members of each group prior to arrival and these served as the basis for discussion. The gatherings were characterized by heated discussion and, a curiosity of the meeting, no slides. On the last day, in what frequently turned out to be 24-h marathon sessions, consensus opinions were evolved by each group on their respective topics. The result of these efforts (18 position and four consensus papers) will form the proceedings of the Dahlem conference to be published in early summer, 1990.

There is insufficient space here to discuss the far-ranging subjects raised. Nevertheless, several issues appear to reflect the general tenor of the meeting.

1) Pain states originating from peripheral nerve injury can be shown to be associated with wide-spread and time-dependent changes in spinal physiology (increased spontaneous activity, decreased inhibition, change in the effective afferent stimulus in specific subpopulations of neurons) and spinal biochemistry (synaptic reorganization; alterations in local receptor systems; changes in neurotransmitter mRNA and promoter molecules). The physiology of the altered system is such that the messages generated have a pharmacology different from that associated with the input generated by high-threshold afferent stimuli. Thus, the agents such as NMDA receptor antagonists, adenosine, anticonvulsants, and voltage-sensitive calcium antagonists that alter repetitive neuronal discharge, but less so opioids, appear to powerfully modulate this facilitated activity. The parallel between this pharmacology and that associated with the so called "dysaesthetic" pain syndromes suggest possible important corollaries.

2) While the mechanisms of opioid tolerance remain unknown, there is evidence to suggest that the change in the drug-effect relationship may be modified by the use of agents acting at different receptors (*e.g.*, μ *vs.* δ *vs.* α_2 agonists) or differing in pharmacodynamic properties. Still, from a clinical perspective, the limitations to dose incrementation remain side effects. Dealing with such actions (constipation, nausea, etc.) by adjunctive therapy (a pharmacologic issue in its own right) can serve to significantly augment the utility of conventional opioid therapy. Moreover, it was emphasized that the change in efficacy of opioids in late-stage cancer may as well represent a change in the pain state to that of a neurogenic component. In this case, the loss of drug action would represent a change in the pain substrate to one that is not opioid sensitive rather than a change in true drug responsiveness.

3) While some information exists as to the possibility that different opioid receptors may be associated with different effects (*i.e.*, respiration *vs.* analgesia), there are at present no agonists that can practically address those differences. However, there is evidence that a variety of other receptor systems (*e.g.*, α_2, NPY, GABA, adenosine, etc) may also play an important role in the modulation of the "pain message." In the spinal cord, many of these analgesically effective systems have several common properties, including the ability to inhibit the release of primary afferent neurotransmitters.

4) Peripheral afferent terminals are and will be even more in the future an important point of therapeutic intervention. The majority of afferent C fibers are only activated, if at all, by high-threshold stimuli, *i.e.*, they are "silent nociceptors." There is now evidence that a pharmacologic sensitization of these nerve terminals may occur as a result of the release of agents which act at terminal membrane sites to activate and facilitate activity in these classes of silent afferents. There is a growing body of evidence to suggest that such chemically mediated changes may play a more prominent role in all types of pain ranging from postoperative to chronic malignant and nonmalignant (arthritis, pancreatitis). The hyperalgesic effects of certain prostanoids is known to account for the efficacy of cyclooxygenase inhibitors. Now the identification of the pharmacology of yet even more pervasive factors (specific products of the cyclooxygenase pathway, cytokines, kinins) may lead to highly selective and efficacious approaches to blocking the afferent message generated by somatic and visceral stimuli.

Meetings such as this suggest that our understanding of the basic physiology and pharmacology of nociceptive processing is moving ever more rapidly toward information that will yield rational advances in pain management.

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