PATHOLOGICAL PAIN: FROM MOLECULAR TO CLINICAL ASPECTS
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Chair’s introduction

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It is my great pleasure that we are holding this symposium on pathological pain here in Japan, as part of the Novartis Symposium series, a series that has had a brilliant history for more than half a century. As Chair of this symposium, I want to express my deep gratitude to all of the participants, who are joining here from all over the world, and to the Novartis Foundation for its generous support.

Before the 1970s, we learned much about pain from publications arising from two previous meetings on pain organized by the Foundation (then known as the Ciba Foundation): namely, *Pain and itch* in 1959 and *Touch, heat and pain* in 1966 (Ciba Foundation 1959, 1966). To my knowledge, except for these two meetings, there are no Novartis symposia focusing on the subject of pain. However, from the end of 1960s until now, pain research has undergone an explosive development. As all of you know, Dr Perl, one of the participants at this symposium, has played an important role in the development of the study of pain, from the pioneering early days until the present.

Over the last three decades, there have been two core phases in the development of pain research. The first was research on pain mechanisms in the normal state, from the late 1960s through the 1980s. The second, more recent focus has been on pain mechanisms in pathological states. Neurobiological research in the first phase of this explosive development of pain research uncovered detailed characteristics of the nociceptive system in normal states, from nociceptors to the cerebral cortex, and the existence of the endogenous analgesic system. The results obtained during this period were excellent, and we can now almost fully understand the mechanisms underlying nociceptive pain or so called ‘acute pain’, which warns of potential tissue damage. But the outcome of this research, on the other hand, has also shown that the information obtained in the normal state does not by itself explain mechanisms implicated in various mysterious pains of pathological states. The subsequent investigations have demonstrated that plastic changes take place in pain systems in chronic neuropathic states, and can result in structural changes of the nervous system. ‘Plasticity’ of the nervous system is becoming the most important key word in understanding pathological pain.
The terms ‘acute pain’ and ‘chronic pain’ remain very commonly used descriptors. But should we really be using the term ‘chronic pain’ which implies a chronological basis? Recent study on pain has revealed that acute pain has a physiological, nociceptive function. On the other hand, chronic pain may be caused by pathological, plastic changes of the neural system. This indicates that the difference between acute pain and chronic pain may be more than chronological: instead, it is mechanistic. The usage and definition of the terms acute and chronic pain therefore need reconsideration.

Why has ‘plasticity’ become a key word? This may reflect the fact that the pain system is primitive and not well differentiated. From the evolutionary point of view, the pain system was built up at the earliest stages of neural development, since alarm and defence systems are fundamental for survival. This evolutionary origin characterizes the nature of the system responsible for pain. First, the pain system has a high capacity for plastic changes, because its primitive nature provides a high degree of freedom for change. Second, the pain system is intimately related to instinctive functions and other fundamental bodily functions, such as autonomic or postural regulation. Third, humoral signalling is richly implicated, since these signalling means have roots in defence systems such as immune and inflammatory reactions.

Recent advances throw light on plasticity in humoral messenger systems as well as the organization of the neural systems. These neural plastic changes may underlie pathological pain. Reflecting these recent advances, in this symposium we will discuss mechanisms focusing on plastic changes in the pain system under various pathological states, at levels spanning from the molecular to clinical.

This symposium consists of five sessions. In the first two sessions, the roles of ion-channels, receptors and chemical messengers implicated in neuropathic pain will be discussed, mainly from a molecular perspective. Plasticity of the organization of the nervous system involved in pathological pain will be considered on the basis of molecular, electrophysiological and morphological analyses in the third session. Morphine tolerance is a notorious but important problem in pain management. The fourth session will consider the issue of opioid-induced plastic changes in the signalling pathways of anti-nociceptive and pro-nociceptive systems. In the last session, the mechanisms of pathological pain, such as bone cancer pain, complex regional pain syndrome (CRPS), and other chronic pain, will be discussed on the basis of experimental and clinical studies that aim to facilitate establishment of mechanism-based medicine.

I would now like to go back to this booklet published by the Ciba Foundation in 1959 (Ciba Foundation 1959). The title of this booklet, *Pain and itch* may tell us, at that period, that scientific knowledge on pain and itch were at similar levels of development. But at present, our knowledge of the pain system is far superior to that of itch, I think. In the chair’s opening remarks of this book, Lord Adrian wrote
that ‘Although pain is one of the central problems of medicine, it is disappointing that there is still so much to investigate.’ I think that this remains very much so. He also wrote that, ‘We may think that a discharge will not give pain unless it includes impulses in the non-medullated C fibres but the evidence is scarcely conclusive.’ This point seems to have been the main interest of that conference. But at present, we know much about the receptor characteristics of C-fibre nociceptors and the whole nociceptive system. On the other hand, what we know now about itch is almost the same as it was at the beginning of the 1970s when neurophysiological studies on the nociceptive system began to flourish. As far as the pain system is concerned, the knowledge that we can obtain from this earlier symposium is quite limited at present. However, the interesting discussions included in this booklet are quite stimulating.

The Novartis Foundation Symposia have consistently attached importance to informal discussion. This is their distinctive feature and is testament to their importance. The present Symposium membership is made up of 14 speakers and nine discussants and the time scheduled for discussion is nearly 1.5 times longer than time for formal papers. To facilitate fruitful discussion, we have two excellent facilitators in each session whose role is to steer actively the process of discussion. I expect very stimulating discussions over the following three days. Thank you.

References