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PREFACE

A Tribute to Professor Ji-Sheng Han

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Dr. Ji-Sheng Han

We dedicate this special issue to Professor Ji-Sheng Han, a dear friend of mine, a great scientist, a dedicated teacher and above all, an inspiring individual to his colleagues and students. To mark his 80th birthday occasion, we bring together highlights of his works and milestone achievements that shaped China's burgeoning era of modern neuroscience. My role here is to provide you all a flavor for the importance of this man, not only for his works and studies of the neurobiology of pain and analgesia conducted under the challenging research environment in China, but also the positive influence he bestowed on innumerable lives he came in contact with.

Professor Han was born in Hangzhou, China in 1928. His childhood aspiration was to become a surgeon but instead, he developed a passion for physiology during his research career in medical science. During 1965, under the designation of China's former prime minister En-Lai Zhou, he concentrated his efforts to study acupuncture mechanisms, especially its analgesic effect, aiming to bestow Chinese traditional therapy to a deserved position in the international medical treatment arena. Forty years on, his devotion to explore the neurochemical basis of acupuncture analgesia has resulted in findings that have deservingly received worldwide recognition.

Among his early achievements, Professor Han became the first to discover the spatio-temporal character of the analgesic effect triggered by acupuncture at a certain point by systemic observation in healthy human body. He

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demonstrated that acupuncture increased pain threshold with a peak increase occurring 20–40 min after the needle insertion at a single point (Heku, LI-4). After the withdrawal of the needle, the pain threshold gradually returned to the preacupuncture level with a half-life of 16.2 min. When two or more points were stimulated simultaneously with acupuncture, a greater increase in pain threshold was produced than that from stimulating on one point alone [1]. His discovery not only confirmed the analgesic effect of ancient Chinese acupuncture, but also provided the experimental basis for its clinical utility, such as application during a surgical procedure where doses of anesthetics and postoperational analgesics could be significantly reduced.

A large part of Professor Han's study has focused on the mechanism of acupuncture analgesia drawing across principles of neurochemistry. His studies suggested that acupuncture analgesia shared, at least in part, similar mechanism with morphine analgesia, in which opioid receptors in different nuclei mediated analgesic effects of both treatments. By means of microinjection of β-endorphin antibodies into selected brain area—the Periaqueductal Gray, he demonstrated that while morphine acts directly on opioid receptors to produce an analgesic effect, the effect of acupuncture is mediated by β-endorphin [2–4]. Furthermore, he revealed that different kinds of endorphins are released by electro-acupuncture (EA) with different frequencies of electrical stimulation. Two hertz enhanced the secretion of β-endorphin, enkephalin [5, 6], and endomorphin [7], while 100 Hz enhanced production of dynorphin [8–11]. Meanwhile, the site specificity of the neuropeptides in mediating analgesia induced by EA was also illustrated in his study. He confirmed that the action site of endorphin is mainly the nuclei in brain and that of dynorphin is spinal cord, whereas that of enkephalin is both brain and spinal cord [3]. Since different endorphins have different biological activities, his study on understanding the selectivity of acupuncture on the release of endorphins in the central nervous system (CNS) presented great clinical advantage. His work on acupuncture analgesia unveiled the molecular mechanism of the Chinese traditional acupuncture theory [5, 12, 13] and explained why different modes of needle manipulation at the same acupoint may result in various therapeutic effects, even for the treatment of different kinds of diseases.

What impressed me the most is that his research extends into the area of tolerance to acupuncture analgesia, i.e., a gradual decrease of the acupuncture effect when applied repetitively or continuously for several hours. This tolerance has been a big problem in confusing the therapeutic values of acupuncture. He discovered that a repeated acupuncture could induce a bulk production of endogenous opioids, which brought forth the anti-opioid substances ameliorating the analgesic effect of these endogenous opioids. This was actually a negative feedback mechanism. Professor Han discovered and confirmed Cholecystokinin octapeptide (CCK8) being the most effective physiological antagonist of endogenous opioids in the CNS, and further elucidated its anti-opioid mechanism at the cellular and molecular level [14–18]. Through this discovery, he successfully diminished the tolerance by altering the CNS CCK availability and potentially increased the therapeutic effect of acupuncture.

Professor Han is among the pioneer leading scientists who exemplified what applications can emerge out of research. He has made great effort to translate his basic research findings into medical applications. The Han's Acupoint Nerve Stimulator (HANS) was a portable multiple-purpose EA apparatus he developed and successfully applied to many therapeutic purposes, including managing chronic pain and incidental pain attack of chronic pain patients, controlling occasional craving and withdraw symptoms of drug addicts. The clinical application of HANS on the treatment of withdrawal syndrome (physical dependence) in heroin addicts showed that HANS reduced more than 90% of the amount of buprenorphine needed by drug addicts to complete the detoxification procedure [19–21]. HANS can also effectively reduce opiate craving (psychic dependence), hence reducing the chance of relapse after detoxification [19, 22]. The success rate of keeping the former heroin addicts' drug free for 1 year has been increased from $<5\%$ to $>20\%$. These clinical observations have been validated by his recent brain imaging work elucidating the mechanism of EA treatment of drug addiction. These findings confirmed the clinical observation that EA/HANS may serve as a potential therapy in decreasing drug craving and drug relapse.

Professor Han's research accomplishments are supported by numerous funding he received from China. Perhaps the most striking aspect of scientific academia is that Professor Han is probably the only Chinese neuroscientist who has received funding for 12 consecutive years by the US National Institute of Drug Abuse (NIDA), for research on "neurobiology of acupuncture analgesia". Today, his work is also funded by the US National Center for Complementary and Alternative Medicine (NCCAM), for research associated with drug addiction.

As an academician of Chinese Academy of Sciences, Professor Han is an outstanding neuroscientist and a role model to many scientists who have built their career on the roots of ethics and courage as exemplified by the man himself. His contributions and integration into the forefront of modern neuroscience send ripples of impulse to China's development. In 1997, he established the Neuroscience Research Institute of Peking University, one of the country's most active neuroscience research groups in China. In 2001, China's Ministry of Education turned the research institute into the nation's Key Laboratory along with the establishment of the Department of Neurobiology, School of Basic Medical Sciences of Peking University. As a great

contribution to the development of neuroscience in China, Professor Han is the editor-in-chief of the comprehensive textbook of Neuroscience for three consecutive editions (1993, 1999, 2008).

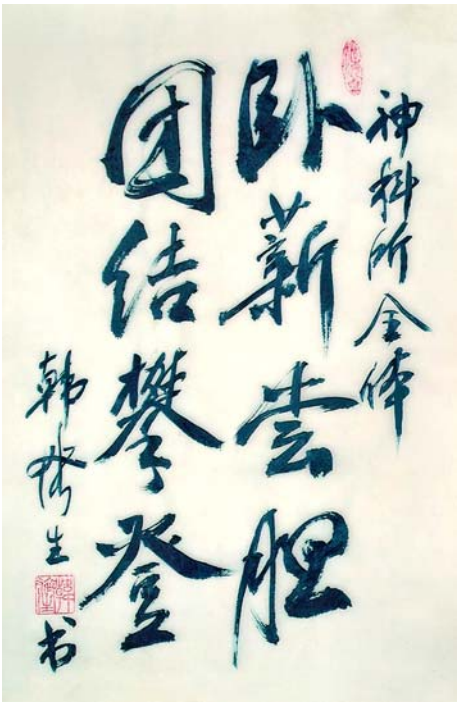
Professor Han founded the Beijing Society for Neuroscience in 1988, the Chinese Association for the Study of Pain (CASP) in 1989, and the Chinese Neuroscience Society in 1991. In his 40 years of research and doing science, he would hit the road to give more than 200 invited lectures on the neurological basis of Chinese acupuncture therapy all over the world. He used his considerable political talents to encourage the government to place more focus on pain research and better clinical pain management. In July 2007, the Chinese government ordered [WeiYiFa(2007) No. 227] that a Department of Pain Medicine shall be included in the general hospital of the second and third level throughout the country, putting China at the forefront of the world in the area of pain therapy and management for pain sufferers.

Professor Han's time and energy spent on putting forward pain research at both the national and international levels, earned him high acclamation that led to the recognition of acupuncture therapy as an applicable method in many countries. In 1997, the US National Institute of Health (NIH) invited Professor Han to give a lecture on the Consensus Conference on Acupuncture sponsored by NIH. Based on his and others' data presented, NIH Consensus Conference confirmed the effectiveness of acupuncture for pain treatment and acknowledged its great potential for future development. The Austrian Acupuncture Society also expressed their appreciation to Professor Han for his research and works that led the Austrian government to accept acupuncture as an official pain therapy.

Professor Han is described by many, a teacher and a mentor, synonymous in one statement. He has trained 68 Ph.D. students and 16 postdoctoral fellows; most of whom continues to work in the neuroscience field. Professor Han's love of science is also deeply rooted in his family. His wife, Professor Xiu-Yuan Zhu, a renowned pharmacologist became the first to artificially produce Musk, an important ingredient in Chinese medicine. His son and daughter, both of whom are scientists in the biomedical field currently working in the United States of America.

At the age of 80, Professor Han is still working everyday in the laboratory. He is highly praised by many of his peers, scholars and friends for the generosity and time that he continues to share to this day. Above all else, he still devotes time for his love of Chinese calligraphy. He has written many of them as gifts to fellow neuroscientists whom have participated in neuroscience meetings that we organized together in China.

This special issue of *Neurochemical Research* comprises of work and review from those who love him and praise him. This is the least we can do for a great man, a great scientist and a great philosopher on his eightieth birthday. Salute to Professor Ji-Sheng Han!



A piece of Chinese calligraphy by Professor Ji-sheng Han:

For all members of the Neuroscience Research Institute:

To undergo self-imposed hardships so as to strengthen our ability in research;

To hold together and solidarize, so as we can reach a higher ground.

Han Ji Sheng

A piece of Chinese calligraphy by Professor Ji-sheng Han:

To relieve pain for people is an holy mission
Han Ji Sheng

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