

SPECIAL ARTICLE

Acupuncture Research Is Part of My Life

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ABSTRACT

Acupuncture has been used in China for more than 3,000 years. Although the clinical application of acupuncture is very popular, its mechanisms of action are still unclear. Beginning in the middle of the 20th century, a boost of research on acupuncture emerged in China, and I was one of the researchers involved in this episode. With the help of modern neuroscience, the mechanisms of acupuncture for pain management have been unraveled at least partly. This article describes my decision as a young medical graduate to devote my life to research on acupuncture and pain medicine; it has since been my life's journey—one full of challenges and happiness, pitfalls and achievements.

Key Words. Acupuncture; Pain; Drug Addiction

Introduction

Acupuncture has been used in China for more than 3,000 years. Although the 53 years I have spent working in this field amount to only one-sixtieth of this span of time, they constitute the majority of my life. My experience in this field affords me the opportunity to share stories that may be of interest to scientists in pain research.

My First Encounters with the Western World (1979)

The 1979 International Narcotics Research Conference (INRC) took place in Cape Cod near Boston. At age 51, it was my first trip abroad to attend the conference in place of Professor C.Y. Song who was invited by his former PhD advisor Dr. Eddy Liang Way. Professor Song asked me to attend the conference because he knew that I was involved in endorphin research to study the mechanism of acupuncture. At the time, which was only a few years after the first United States Presi-

dent Nixon's visit to China, it was a rare opportunity for a Chinese scientist to come abroad for scientific exchange.

Before heading to Cape Cod, I made a stop in Washington, DC to visit Dr. Emino Costa who then worked for the National Institute of Mental Health on neuropharmacology of various kinds of classical neurotransmitters. Dr. Costa was delighted with my talk as he had never heard of any research on acupuncture with a neurochemical approach. For the rest of the day, he gave me his top treatment by showing me around Washington, DC, and finishing with a dinner in the Cosmos club. The weather in July was hot and I had only a shirt on without a tie. I was surprised to learn that Dr. Costa had to borrow a jacket for me in order to dine in the club. I thought I was misled to think that "Americans are casual in clothing." The next morning, I was in Cape Cod wearing my suit for breakfast only to find that everyone else was in T-shirt and even in shorts.

Having had an unexpected success for my presentation (chaired by Dr. Eric Simon of NYU) and having made so many new friends, I was filled with satisfaction when I started my return trip. However, I found myself stranded in San Francisco (SF) for a week because I did not reconfirm

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my flight in advance. This was a hard reality for me to take as I had only \$100 in my pocket that would not be enough for me to survive more than a couple of days in SF. Luckily, when I called the Counselor of the Chinese embassy, they were so kind to introduce me to an overseas Chinese, Mr. Xie, who agreed to take care of me while waiting for my next flight. Staying in Mr. Xie's house with free accommodation and meal, I grew anxious to know if there was anything that I could do for him in return for his kindness. Immediately, a chance came up. When Mr. Xie got to know that I came to the United States for an international conference to present my research on the mechanisms of acupuncture, he was overwhelmingly delighted. He asked if I could give a talk about my work to the Chinese acupuncturists in the SF area. I said "Of course!" and thought that this was perhaps the easiest thing I could do in the situation.

However, I soon found out that the task was not as easy as I thought it would be because of the language barrier the early Chinese immigrants had. Most of the overseas Chinese in SF area spoke Cantonese, not Mandarin and English, whereas I spoke Mandarin and not-so-fluent English, but not Cantonese. Luckily, Mr. Xie invited a medical doctor who was able to translate between English and Cantonese. I wondered, but never asked, how the interpreter translated those technical terms such as endorphins and catecholamines into Cantonese. Nonetheless, the lecture was so well received that many of the audiences came up to shake my hands with tears on their faces. Many said that they would display my article in their clinic to show that acupuncture does have its scientific basis. For losing 1 week of time, I gained such an experience that the memory would last for the rest of my life.

Stepping into the Field of Acupuncture Research (1965)

I dreamed of becoming a surgeon when I was a medical student around the time when the communist party took over power. But being a citizen in the new China, one's destiny had everything to do with what the country needed at the time, rather than the individual's wish. I never had problem accepting my assignments even when they were not in my best interest, trusting that they were the best for the country. In the 1950s, the country was in desperate need for educators in basic medical sciences. I was assigned to teach physiology in one medical institution after

another, for years before I settled in Beijing Medical College (now Peking University Health Science Center).

One day in 1965, the dean of Beijing Medical College called me to his office. He said to me, "Something new is happening in the medical field, called Acupuncture Anesthesia. Believe it or not, by inserting needles into the acupuncture points and twisting them, you do not need to use anesthetics for surgical operations!" He encouraged me to find out why it works. My first reaction was "It can't be true!"

The next day I was brought to a hospital specializing in chest surgery. In front of my eyes was a young lady lying on the operating table, about to undergo pulmonary lobectomy (to surgically remove one lobe of her lung). She had 10 acupuncture needles inserted in each limb, with four acupuncturists each working on one of her limbs. After 30 minutes of needle manipulation (the "induction period"), the surgeon started to make the skin incision. I was so surprised to find no sign of suffering on her face! I approached the patient who was drinking juice from a straw to verify my observation.

"Do you feel any pain?" I asked.

"No", she answered.

"Is there any uncomfortable feelings?" I asked, still finding it hard to believe.

"I feel something happened on my skin, but not painful," she answered.

I was advised by the anesthesiologist not to ask too many questions at the moment, because the patient needed to perform abdominal respiration in order to best cooperate with the open chest surgery.

Upon witnessing the miracle, I was determined to take on the challenge of unraveling the mystery of acupuncture anesthesia, which is now more adequately called acupuncture analgesia (AA).

Insights From the Study on Human Volunteers (1965)

Working together with me was a small group of graduate students and young researchers in the Department of Physiology to explore the mechanisms of AA. Among them were Tang Jian, Fan Shao-Guang and Zhou Zhong-Fu.

In practice, acupuncture is used to treat pain that already exists, whereas in the case of acupuncture anesthesia, acupuncture is used to prevent pain caused by the upcoming surgical procedures. If this is true, then normal volunteers can be used to test whether acupuncture is able to increase the

pain threshold by a standard procedure such as pinprick or heat contact.

After an exhausting exploration we decided to use potassium iontophoresis method, which is to introduce an anode current to the skin through a sponge of 5 mm diameter saturated with potassium chloride solution. Several interesting findings emerged from this experiment.

While the average minimal current to induce a pain sensation is around 1 mA, it increased to 2 mA after the volunteers received an acupuncture treatment. That was a 100% increase in the pain threshold! In addition, the effect did not happen immediately after the acupuncture started. It took about 20 minutes of needling to reach its maximal level. This agrees with the clinical experience that it needs a 30-minute induction to reach a full expression of the analgesic effect. Once the analgesic effect is established, it sustains as long as the needles are being twisted continuously. When the needles are withdrawn, the analgesic effect starts to decline exponentially with a half-life of about 16 minutes. We found that, whether the analgesic effect was strong or relatively weak by stimulating different points, the characteristic of the declining pain-threshold after the needle withdrawal was the same, with a half-life of 15–17 minutes. This finding inspired us to think that there might be a neurochemical factor involved in mediating the effect of AA [1].

According to Traditional Chinese Medicine (TCM) theory, there are three Yin and three Yang meridian channels passing through the arm and hand, there is no meridian channel passing through the point between the second and the third metacarpus. What would happen if a needle was inserted in this “nonacupoint”? The results showed that stimulation of the “nonacupoint” can also produce a deep sensation called “deqi,” as well as an analgesic effect similar to that produced by stimulating the adjacent “HeGu” acupoint located between the first and the second metacarpus. Both the “deqi” sensation and the analgesic effect can be abolished by local anesthetics injected deep into the point. It seemed that the correct manipulation of the needle in order to induce strong deqi sensation was more important than the accurate insertion of a needle into a specific point.

The Rabbit Cerebrospinal Fluid Transfusion Study (1972)

How to validate the idea of neurochemical involvement in mediating AA? We performed a

cerebrospinal fluid (CSF) transfusion experiment to test the hypothesis. We perfused the brain ventricle of a donor rabbit while performing acupuncture. The perfusate was infused into the brain of a recipient rabbit. As was expected, the recipient rabbit showed a significant increase in pain threshold as measured by the heat-induced head avoidance response. On the other hand, the perfusate obtained from the donor rabbit without acupuncture did not induce such effect [2].

We performed this experiment in 1972, 3 years ahead of the discovery of endorphins. Without the slightest idea that the brain would be able to make its own morphine-like substance, we started our search among the known substances with pain killing activities. We first studied the possible involvement of the serotonergic and catecholaminergic transmission in mediating acupuncture mechanisms. Dr. Li, then the vice secretary of the World Health Organization who watched our CSF transfusion experiment during his visit to Beijing, was so kind to help us to obtain the chemicals necessary for our neurochemical exploration.

The identification of serotonin (5-HT) both in the brain and spinal cord as one of the key neurotransmitters in mediating AA provided us with a huge sense of success. With a bigger effort, we subsequently discovered that while noradrenalin in the spinal cord mediates AA, in the brain it plays an opposite role.

These results constituted the main part of my talk presented in Dr. Costa's lab in DC and in the INRC conference in Cape Cod [3]. However, despite our excitement about these results, they were dwarfed by the findings of the possible involvement of opioid peptides in mediating AA.

From Monoamines to Opioid Peptides (1975)

The Science article of John Hughes et al. on the discovery of enkephalins in pig brain injected a mega dose of excitement to the neuroscience field. Everyone seemed to be able to find some connection between enkephalins and their own work. It was so in particular for the research on the mechanisms of AA.

A rational thing to do was to check whether AA can be blocked by naloxone, the opioid receptor antagonist. While the result on rabbits was a clearcut success with 50% reduction in AA by naloxone, the result for rats was not as obvious at first glance. From a methodological point of view, the traditional manual needling used in humans and rabbits can hardly be used in rats. The delicate

extremities of rats rendered needle manipulation a source of trauma. We custom designed an acupuncture treatment for rat by fixing to the leg a thin needle that is connected to an electronic stimulator generating electrical pulses of selected frequency, intensity, and pulse-width. This was named electro-acupuncture (EA) to be distinguished from manual acupuncture.

Among the three EA parameters mentioned above, frequency has the widest range of variations (from 1 Hz up to 100 Hz). We discovered in the rat that while the analgesic effect induced by 2 Hz EA could be blocked by 50% using naloxone at 0.5 mg/kg, the effect induced by 100 Hz EA seemed resistant to naloxone, with a 50% blockade dose as high as 20 mg/kg. Considering the findings of Avram Goldstein's group in Palo Alto, CA, that the dose of naloxone needed for blocking κ opioid receptors can be 10–20 folds higher than that for μ receptors, could it be that low- and high-frequency EA-induced analgesia was mediated by μ - and κ -opioid receptors, respectively? Our finding that the 50% blockade doses of naloxone for 2, 15, and 100 Hz EA were found to be 0.5, 1.0, and 20 mg/kg, respectively, supported the hypotheses [4].

This result agrees with the fact that in traditional acupuncture practice, different types of needle manipulation at the same acupuncture point can result in different therapeutic effect. In our studies using various kinds of animal models and clinical observations, we found that neuropathic pain responded preferably to 2 Hz EA (mediated by enkephalin) than that of 100 Hz, whereas the pain caused by muscle spasm in patients suffered from spinal cord injury responded preferably to 100 Hz EA (mediated by dynorphin) but not to 2 Hz EA [5–7].

As acupuncture induces the release of endogenous opioids, can it be used in treating the withdrawal syndrome (physical dependence) and craving (mental dependence) for narcotics? It was already established that the κ -receptor agonists are more effective for treating the narcotic withdrawal syndrome, whereas the μ -receptor agonists are more effective in treating the craving for narcotics. If this is the case, one may expect that 100 Hz EA should be more effective for the treatment of withdrawal syndrome upon the abstinence of morphine or heroin, and 2 Hz EA should be more effective in suppressing the opiate craving. These were demonstrated on animal models using jumping and writhing for acute withdrawal syndrome [8] and conditioned place preference for

craving. Results obtained in animal experiments were also verified in humans. In a study using heart rate as one of the indices for withdrawal syndrome, it was found that the 100 Hz EA was significantly more effective than the 2 Hz EA in normalizing the heart rate. Another study was conducted on detoxified heroin addicts. A visual analog scale (VAS) was used as the subjective index for craving. The results showed that it was the 2 Hz EA, not the 100 Hz EA that produced a significant decrease in VAS score for craving [9].

The Design for a “Needle-Free Acupuncture” Device (1980)

The traditional acupuncture treatment has certain obvious limitations such as lack of reproducibility and accessibility. We wanted to design an electric acupuncture device based on the scientific findings, to standardize the treatments and to make the treatment readily available for more patients. Our idea of an EA device would have the following features:

1. Able to induce the release of neurotransmitters in a predictable manner.
2. Provide needled (percutaneous) or needle-free (tanscutaneous) options.
3. Easy to operate by patients following doctor's instructions.
4. Portable in size, which is especially advantageous for chronic pain patients for controlling incidental pain attack and to drug addicts in managing occasional craving and withdraw symptoms.

In collaboration with Liu Yi-Ming, an aerospace engineer, a device was constructed named Han's Acupoint Nerve Stimulator (HANS). In contrast to a constant voltage output designed for conventional nerve stimulators, HANS has a constant current output. This way, the users do not have to adjust the voltage in order to compensate for the gradual fading of the stimulation intensity.

The small size is especially convenient for drug addicts. In a study conducted in Shanghai, the success rate for 1-year drug-free among the detoxified former drug addicts was 32% compared with 0–5% in those without a HANS in their pocket.

As the release of neurotransmitters is frequency-dependent, we decided to use alternating frequencies shifting between 2 Hz and 100 Hz with an optimal cycle of 3 seconds each. This was termed dense-and-disperse (D/D) mode. We

found that the D/D mode produced a much more potent analgesic effect than that produced by a single frequency of either 2 Hz or 100 Hz. This alternating frequency is especially ideal for treating narcotic addiction. While 100 Hz is best for treating withdrawal syndrome and 2 Hz for craving, the D/D mode works well for both. Dr. Paul White at the Department of anesthesiology, Washington University in St. Louis, MO in the United States, conducted a series of clinical trials with HANS. In 5-year period, Dr. White and his colleagues published five articles to show that D/D mode of EA was indeed significantly more effective in analgesic efficacy than either low or high frequency stimulation, tested in various pain modalities such as postoperation pain, low back pain, and diabetic neuropathic pain.

How does the needle-free EA compare with the needled EA? My post-doc John Q. Wang conducted a series of experiments on rats to compare the analgesic effect of EA either via needles inserted into the leg (percutaneous) or via electrodes applied on the skin (transcutaneous). The results indicate that the transcutaneous delivery was at least as good as the percutaneous delivery, if not stronger. The underlying mechanisms for the needled and needle-free EA seem to be the same, as evidenced by cross tolerance study and receptor analyzing study [6]. HANS has also been used for research on the treatment of inflammatory pain [10], neuropathic pain [11,12], heroin abuse [9], alcohol abuse [13], smoking [14], Parkinson's disease [15], and obesity [16] with considerable success.

Validated by Brain Imaging Study (1998)

Up to this point, all of the neurochemical experiments were done on lab animals, mostly rats. How would the findings on rats translate into humans?

Since 1998, we started to perform brain imaging studies in humans to show changes of the brain activity as a result of acupuncture stimulation. In the first brain imaging study, we used functional magnetic resonance imaging (fMRI) scanning to compare high responders with low responders of AA for their brain activity. EA of 2 Hz or 100 Hz was applied to the Hegu point during the fMRI scanning. Within 1–3 days, the same subject was given an EA session for 30 minutes and the thermal pain threshold was measured before and after the EA session. The percent change of the pain threshold after the EA was taken as the index for AA. The extent of the fMRI

signal change was then correlated with the analgesic effect of EA. A positive correlation was found in eight brain areas and a negative correlation was found in two brain areas. AA responders showed a stronger activation or inhibition in the 10 brain regions of interest, as compared with that of the nonresponders, indicating certain functional basis underlying the efficacy of AA. In addition, the changes induced by 2 Hz and 100 Hz were partially overlapping but not identical, which indicates a separate but related mechanisms [17].

Sorry, I am a Nonresponder for Acupuncture Analgesia

Over the years of my lecturing in 26 different countries and areas, one of the most frequently asked questions has been “Does acupuncture work for everyone?” My answer is always “No. For example, it doesn't work for me”. While the answer always triggers a burst of laughter, it is sincere. In mid-1980s, I had a severe low back pain. HANS provided little help. The same is true for rats. In about 10–15% of the rat population, a standard 30-minutes EA produces no analgesic effect.

In the same year of 1975 when the discovery of enkephalin was reported, an article was published discussing the possible existence of antiopioid substance (AOS) in the brain. The result from one of our rat experiments done in 1978 agreed with this hypothesis. In the experiment, a 30-minute EA was administered followed by a 30-minute break, and the pattern was repeated for six sessions. We found that the analgesic effect went down gradually over the 6-hour course. We termed the phenomenon acupuncture tolerance (AT). A subsequent recovery of the analgesic effect was detected after 8–12 hours; and a complete recovery was reached within 24 hours.

During the period of AT, there is a concomitant reduction of the analgesic effect in response to morphine, suggesting a cross tolerance to morphine. From the brain extracts of the tolerant rats we found a component that had an anti-opioid activity. It has a molecular weight of approximately 1,000 Da. Unfortunately, we were unable to completely purify and characterize this component due to our lack of adequate technology in the 1970s. Since then, we followed closely the advancement in AOS research, and confirmed that cholecystokinin octapeptide (CCK-8) is most likely the AOS responsible for the development of AT. Indeed, AT can be reversed by CCK receptors

antagonist proglumide and by the antiserum against CCK-8 administered intrathecally or intracerebroventricularly.

Thus, a nonresponder to acupuncture can be converted to a responder by central administration of 1) CCK-B receptor antagonist L-365264, 2) antibody against CCK-8, or 3) CCK antisense oligonucleotide to down regulate the gene expression of CCK [18]. On the other hand, a good responder to acupuncture can be converted to a nonresponder by central administration of a CCK vector resulting in an over expression of CCK in the CNS. CCK seems to play a role in a negative feedback system against excessive opioid activity. This feedback control is achieved by multiple mechanisms, 1) high levels of opioids (whether exogenous or endogenous) promote CCK gene expression, 2) CCK-8, upon binding to CCK receptor induces allosteric changes in the nearby opioid receptors, and 3) CCK mobilizes intracellular calcium storage that cancels out the ability of opioids to lower calcium influx.

Could the relationship between opioids and CCK be an example of what the TCM theory described as Yin and Yang? How do we restore the homeostasis when it is out of balance? From a practical point of view, a CCK antagonist, provided it is nontoxic to humans, would serve as a good supplement for acupuncture therapy for pain and drug addiction. This thought constituted the main body of the plenary lecture "Molecular Events Underlying the Anti-Opioid Effect of CCK-8 in the CNS" that I presented in the 12th Congress of the International Union of Pharmacological Sciences (IUPHAR) held in Montreal, Canada in 1994 [19]. Three pharmacologists from my family—my wife, son, and daughter-in-law—were also on the floor.

My Unforgettable First Visit to Taiwan of China (1990)

At the 9th IUPHAR Congress held in London in 1984, I chaired a symposium on Neuropharmacology and gave a talk at the symposium on acupuncture mechanisms. Also present at the symposium was Dr. C.Y. Lee from Taiwan, the pharmacologist who purified and characterized the snake venom α bungarotoxin. During a tea break, Dr. Lee approached me very politely. After a pleasant chat, we both expressed a wish that someday we would visit each other across the Taiwan Channel.

The 10th IUPHAR Congress was held in Sydney in 1988. Dr. Lee and I met again. I intro-

duced my wife to him. A year later, in 1989, C.Y. Lee came to Beijing with his wife to meet with us. During the home dinner, he made a bold proposal: "My wife and I wish to invite both of you to visit Taiwan. If you agree, we have a fund already in place to support your trip." This was unbelievable, no less unbelievable to me than 10 years ago when Professor C.Y. Song asked me to visit the United States. Despite the fact that the relationship between Taiwan and mainland China was almost frozen at the time, my wife and I looked at each other for a full second, and burst out in unison: "Yes, of course!"

Dr. Lee's invitation was soon sent to the Chinese Ministry of Health. If this were approved, it would be the first time in 40 years that a scientist from Mainland China was officially permitted by both sides to visit Taiwan. It was entirely out of our expectation that this ice-breaking-visit proposal was approved within a week!

In May 1990, my wife and I were at the Taoyuan Airport of Taipei. Under the flash lights from the press, we were received by Dr. C.Y. Lee and Professor J.F. Chen, the director of the Institute of Chinese medicine and Pharmacy, who would accompany us for our week-long visit in Taiwan. The press conference held at the airport was immersed with a friendly atmosphere. As my wife Dr. X.Y. Zhu is a pharmacologist studying the anti-inflammatory ingredients of Musk, and I was in acupuncture research, the headlines of the Taiwan newspapers in those days were "Han and Zhu, a Couple of Traditional Chinese Medicine," "Revitalize Traditional Chinese Medicine by Modern Research on Physiology and Pharmacology," etc.

One of the most touching moments was the meeting with one of my high school classmates, Dr. B.N. Jiang, director of the central VA hospital in Taiwan. He recognized me from the news and insisted on having dinner with us. As all the dinners were pre-arranged for the whole week, we had breakfast together instead. The reunion of high school classmates after 43 years (1947–1990) of separation across the Taiwan channel felt truly historical. We embraced each other without a single word uttered. The memory of that moment can never be erased from our heart.

One week of time passed by too quickly. An officer at the airport customs recognized us and said: "We have been seeing you every day on TV and newspaper. We wish to see you again!" We said, "Surely, we will come again!" Indeed, my wife and I paid three more visits to Taiwan in the 5

years to follow. Professor J.F. Chen came to Beijing even more often.

The Best “Present” for My 79th Birthday (2007)

The night before my 79th Birthday when I was in a sabbatical leave in Harvard University, I was informed that the Ministry of Health of the People’s Republic of China has approved our proposal and issued a document to have major hospitals in China establishing a Pain Management Department. It was indeed the best “birthday present” I have ever had.

In 1989, I founded the Chinese Association for the Study of Pain (CASP) with 164 founding members. The organization has since developed tremendously with an official magazine “Chinese Journal of Pain Medicine” inaugurated in 1995. Being in the center of pain study, and from my years of direct contact with patients, I saw the desperate need for having a Pain Department to specialize in pain management. Acute pain can be a common manifestation of many diseases. But chronic pain lasting for more than 3–6 months has often been regarded as a disease entity. Physicians specialized in certain disease discipline may not have the adequate skill to treat various kinds of chronic pain. As a result, patients often have to visit one doctor after another in one hospital after another but find no end for their suffering due to lack of proper treatment. Therefore, to establish a specialty in pain management has long been on my wish list. After years and years of efforts, this dream has finally come true. On the 2007 Global day against pain, a press conference of the CASP was held in Beijing, where Drs. J.P. Wu and Q.D. Han, the leaders of the People’s Republic of China as well as the leaders of the Ministry of Health officially announced the inauguration of Department of pain management in major hospitals of China. Over 500 pain researchers and physicians witnessed the historical event, which would mark a turning point for the development of pain medicine in China. In a letter to CASP, Dr. T.S. Jensen, the president of the International Association for the Study of Pain wrote: “In this respect China may be a leading example for other countries to follow to advance pain treatment throughout the world.”

What Else on My Wish List? (2008 and Beyond)

When I close my eyes and allow my dreams to fly, I can see many targets in front of me. Being

a chief scientist of a central grant issued jointly by the Ministry of Science and Technology and the Bureau of Traditional Chinese Medicine, I have made the commitment to answer the questions of “What is the real benefit of using AA in clinical practice?” “What are the optimal conditions for a full expression of AA?” “What are the mechanisms of AA at genetic and cognitive levels?”

I would also like to extend the use of HANS for the treatment of stress related disorders such as insomnia, anxiety, and depression, which are suffered by hundreds of millions of people. These disorders often reflect a failure in the excitation-inhibition balance of brain functions. To the bottom line, restoring natural homeostasis (the yin-yang balance) is the ultimate goal of acupuncture therapy.

At this moment when I am about to close this review, I feel a deep sense of gratitude to many, many people in my life. I would like to thank my parents and teachers who taught me how to deal with challenges in life, to my family and friends for their years of nurturing, support, and sharing of happiness with me. I would like to thank my patients, students, colleagues, fellow scientists in the field and grant providers who worked together in finding better ways to fight against pain and suffering [20].

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