The History of Neuroscience in Autobiography
Volume 3

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-12-660305-7

Hsiang-Tung Chang

pp. 144–166

https://doi.org/10.1016/S1874-6055(01)80009-8

Hsiang-Tung Chang

BORN:

Cheng-Ting, Hopei Province, China
November 27, 1907

EDUCATION:

National University of Peking, B.S. (Psychology) (1933)
Yale University, Ph.D. (Physiology) (1946)

APPOINTMENTS:

Institute of Psychology, Academia Sinica (1934)
Yale University, School of Medicine (1943)
Johns Hopkins University, School of Medicine (1946)
Yale University, School of Medicine (1948)
Rockefeller Institute for Medical Research (1952)
Institute of Physiology, Chinese Academy of Sciences (1957)
Shanghai Brain Research Institute, Chinese Academy of Sciences (1980)

HONORS AND AWARDS:

Academician, Chinese Academy of Sciences (1957)
Foreign Academician-Elect, URSS Academy of Sciences (1966)
Threshold Award, U.S.A. (1980)
Foreign Honorary Member, Royal Academy of Medicine, Belgium (1982)
Honorary member, International Association for the Study of Pain (1989)
Lifetime Achievement Award, International Neural Network Society, U.S.A. (1993)

Hsiang-Tung Chang carried out fundamental studies on the structure and function of the central nervous system. He was one of the pioneers in the study of dendritic potentials and among the first to recognize the functional significance of dendrites in the central nervous system. He was the first to propose a fundamental distinction between axosomatic and axodendritic synapses.

Hsiang-Tung Chang[1]

As a leaf goes with the wind, so does a life. The most careful planning and the strongest volition do not shape the course of events as much as chance and serendipity.

I was born in an extremely poor village in the north of China. It was not until the age of 14 that I could join a formal primary school. The fact that I could enter college and then university was entirely due to chance. At that time, I had never even dreamed that I could some day study abroad. This opportunity occurred in 1942 when the Japanese troops invaded my country. I was in the small town of Guizhou fighting for my life.

This fairy tale began in the 1930s. After I graduated from Beijing University in 1933, I served as an assistant to Professor Ging-Hsi Wang in Nanjing. He showed me the way to scientific research and trained me to design an experimental protocol and to write scientific articles. He was a remarkable teacher and a brilliant investigator. He continuously expounded on the importance of acquiring a strong basis in anatomy and electrophysiology. I spent 7 years in his anatomy department. This training played a major role in the formation of my intellect and in my future research.

During the summer of 1937, Japanese troops invaded Shanghai; Suzhou and Nanjing were defeated. Many members of the department fled in panic to safer regions. Determined to protect and transfer the library and our scientific equipment to a more secure place, I remained in Nanjing with one of my colleagues in our laboratory. One evening in August 1937, we were completing the difficult job of packing all the precious material when we heard Japanese airplanes bombarding the city. We rushed to the cellar. One part of our laboratory was completely destroyed. A week later we decided to leave Nanjing and join the rest of the members of the Academia Sinica based in Guilin.

[1] Chang Hsiang-tung published a recollection of his life in science titled *The Tortuous Path of Brain Discovery* (Technical and Scientific Press, Beijing, 1995). The book has been translated into French by Catherine Gipoulon (Université Paris VII). This autobiographical chapter, which covers the American period of Chang, is a short adaptation prepared by Ginette Horcholle-Bossavit and Suzanne Tyc-Dumont (CNRS, France). We are deeply grateful to Florence Ladd, Writer-in-Residence at The Radcliffe Institute for Advanced Study, Harvard University, for copyediting the English translation.

In 1940, all the large towns of the east coast and a great part of China were occupied by the Japanese. Thousands and thousands of my people had been assassinated or died of cold and hunger. I was desperate and humiliated, all hopes gone. I decided to leave the academy and travel to Yunan. I met tremendous difficulties in a country in which all means of communication were destroyed. All the cities were riddled with corruption. On the roads and the rivers, I did not find food, water, or hostels. Enemies were everywhere driving people into hiding in the mountains. I was hungry and in great distress without a penny in a town called Guiyang, where I had not a single acquaintance. One night as I was in total despair, wandering aimlessly in unknown streets, I felt a hand on my shoulder. Turning around, I discovered a smiling face: It was a classmate of mine with the nickname of 'Mussolini.' Thanks to him, I was invited for dinner. Soon afterward, he obtained for me a well-paid position at the Military Medical School of Anshun, approximately 40 miles from Guiyang.

During these times, I often visited the library of the Red Cross Association. It was the only place during wartime at which new publications from the West were available. In this library, I read *Physiology of the Nervous System* by John F. Fulton. It was the only published work on the matter at that time. I was deeply impressed by the book. At the medical school, I recommended this reading to my colleagues. I was extremely enthusiastic about it. One evening, I told them that it would be a great honor for me to have the opportunity of working in the laboratory of such a prestigious professor of neurophysiology. My remarks made my colleagues laugh at me and make very offensive comments. One of them even told me, 'if such a bloody fool like you goes and studies in the United States, this very day the sun will rise in the West.' I was hurt and profoundly shocked by such rude comments. That same evening, I wrote a letter to Professor Fulton asking for a job in his laboratory. The aim of my letter, of course, was only to remedy my melancholy. The fact that it could ever reach its recipient was of minor importance for me. I forgot about it.

Three months later, an overseas cable was brought to me by a telegraph operator. Without paying attention and without opening it, I asked him to deliver the cable to Professor Zhang Penchong in the pharmacology department because I did not know anybody abroad. One hour later the operator was back with the cable. Professor Zhang said that it was really for me! I read the telegram with only three words: 'Yes! letter follows.' I was surprised and totally excited. How could this happen to me?

The letter came 1 month later from the dean of the Medical School of Yale inviting me to come and work in the physiology department of the university. Moreover, he volunteered to help find a scholarship to support my studies in the United States.

To arrange for my departure, I left for Chongquing, the capital, in wartime. There, I requested an incalculable number of appointments and

I filled out countless important forms. My feet pounded the streets of that hilly city and I knocked on all the doors of administrative offices. Very fortunately for me, I managed to finish all the formalities related to my departure in 6 months. It was a tour de force whose secret lay in the letters and telephone calls from Professor Blake. It was the key opening the doors of all the bureaus concerned.

Finally, on New Year's Eve 1943, I happened to be the only passenger on a flight to Jakarta in a troop carrier plane. Some weeks later, I embarked on a steamer named *Mariposa* to travel to California. After 30 days of tense, difficult, distressing travel, we were transferred, in the most terrible anguish, to a regular liner that sailed from Bombay through the Indian Ocean toward southern Australia to the Bashi Channel, Tasmania, New Zealand, through the South Pacific Ocean, and finally to California. After disembarking there and completing the immigration formalities, we were sent to a Los Angeles hotel and 10 days later put on a train for New York. Completely by chance, in a New York hotel I came upon some young soldiers whom I had met in Jakarta. They told me that the destroyer they had taken had been attacked by the Japanese at the mouth of the Red Sea and that it had sunk. Of the 12 military students on board, only 5 had survived. The ill-starred destroyer was the one that I should have taken at the outset.

On March 24, 1943, I took a train to New Haven, Connecticut, and the next morning John Fulton expected me in his office. The arduous and dangerous 3-month-long journey had ended successfully; another journey on the road of knowledge was beginning.

Fierce Combat at Yale University: Professor John Fulton

When I arrived in the United States in the midst of war, all aspects of the society were affected by it. The whole country was fully committed to the war effort. Young people were enlisted in military service and the professors devoted their energies to war-related projects. The laboratories in universities were a tragic spectacle of desolation. I was struck by the similarity between the situations of the United States and China. Obviously, it was not a good time to study under such increasing pressure. I thought that the United States was not a good place to stay for a long time and I decided to go home as soon as possible. Maybe Fulton and my colleagues in the laboratory suspected my feelings. They all tried to convince me to stay and register in the doctoral program.

The Qualifying Examination

My colleagues explained to me that in the Western scientific world, without a diploma of higher studies it was not possible to obtain a position with a future despite the scientific successes one might achieve. This, of course, was not rational, but that is how things were done and no one had the power to change them. They stated precisely that, if I wished, I could take the Yale University examination used to select students who want to do research. If accepted as a researcher, they could help me obtain a scholarship from student aid funds. Moreover, I would be exempted from paying the registration fees. At the time, the education costs increased each year, and at $800 per year Yale had the highest costs in the country.

Although I was exempted from the written examinations, I had to take an obligatory test in two foreign languages, except Chinese and English. I got out of this by taking German and French, in which I had some training at Beijing University. In the examination, I had to translate a text from *L'introduction à l'étude de la Médecine Expérimentale* by Claude Bernard and a passage from the 1911 book of the famous neuroanatomist S. Edinger, *Lessons on the Organization of the Nervous System in the Animal.* In choosing these two texts, which were familiar to me, the committee was kindly disposed and I succeeded easily in my two translations. I was then promptly admitted as a regular student in Yale University, enrolled in a Ph.D. program.

At Yale, the rules were rigid and severe. The first 2 years had to be dedicated to courses in fundamental biology. The first-year courses were of no interest to me. I felt like I was taking elementary courses and wasting my time. Moreover, my money was running short and my health was not very good. I decided to ask about taking the final examinations immediately, before the end of the 2 years. If successful, I would start my thesis work. If not, I would abandon my scientific project and go back to China. My plan was accepted by the authorities.

These special examinations were conducted like the examinations in ancient China. The candidates were left in an empty room with only an ink pot and a pen from 9 AM to 4 PM. Lunch was served in the same room. The examinations lasted 3 days: anatomy, general physiology, neurophysiology, biophysics, and history of physiology were the subjects. I passed them all and was permitted to start my thesis. I proposed a title: 'Segmentation, Lamination, and Topological Projections in the Central Nervous System with Particular Reference to the Tail of Ateles.' Professor John Fulton and Dr. T. C. Ruch, who were my supervisors, both agreed.

Defending My Doctoral Thesis

I defended my thesis before a distinguished panel of examiners, the names of whom I discovered only after the defense. I was extremely honored. The chairman was a famous professor in psychology who discovered that red light decreased the time period of adaptation in darkness. The second member was Harold Burr, a professor in neuroanatomy. He had a wide knowledge of a variety of related fields. He had been interested in electricity in living animals. He discovered an electrical change that occurred during the menstrual cycle at the ovulatory stage. He called the phenomenon 'the ovulatory potential,' which could be recorded at the surface of the belly. Because his findings were very popular and published in newspapers, many young women who were eager to be pregnant came to be recorded. For example, I noticed that many young girls were going in and out of his laboratory every morning. Burr was the subject of many jokes. He was a cheerful companion.

The last member of the examining board was Clinton Woolsey from Johns Hopkins University. He was one of the pioneers in the localization of the receptive fields of evoked potentials in the cerebral cortex.

After the vote of all the members of the jury, my thesis passed, Burr shook my hand and then, turning to Fulton, he said, 'I would like so much to have a researcher like this one in my laboratory.' I consider that the greatest compliment that one could give me. In fact, he had followers throughout the world. At the time I obtained my doctorate under the direction of Fulton, Theodore Bullock and Alexander Mauro obtained theirs under the direction of Burr. Bullock is a leading figure in the field of comparative physiology. He has become professor of neurosciences in San Diego. Mauro is a biophysicist who teaches at Rockefeller University in New York. Both were my neighbors at Yale.

I decided to publish the 300 pages of my thesis in separate papers in scientific journals. Two papers were published in the *Yale Journal of Biological Medicine*, three in the *Journal of Anatomy*, two in the *Journal of Comparative Neurology*, and one in the *Journal of Neurophysiology*. One of these papers that deserved consideration was dedicated to the 'representation of muscles in the motor cortex of the macaque.' For the first time, experimental evidence was obtained showing that voluntary muscles were all represented in the motor cortex.

The controversy over the question of the representation of movement or muscles in the motor cortex was the subject of heated debates for decades. The dominant opinion was that movements were represented in the motor cortex and not the muscles, as stated, for example, by the well-known English neurologist Walsh. In contrast, Fulton supported the idea that only muscles or groups of muscles were locally and precisely represented in the motor cortex. Fulton, who was eager to find experimental evidence for his theory, suggested that I apply local electrical stimulation to loci in the motor cortex to record simultaneously the muscular contractions at the periphery. Each cortical locus could thus be associated with the contraction of a single muscle. Fulton was participating in the experiments with me, and Arthur Ward joined us later. These results were published in the *Journal of Neurophysiology* in 1947 and had a strong impact on the world's scientific community. In 1987, George Adelman published a book, *Neuroscience Encyclopedia*, in which the researchers who contributed to the progress of knowledge on the nervous system between 1300 BC and 1950 were represented. Our work on the cortical representation of the muscle was quoted and listed as one of the contributions. In fact, it was not a major contribution but rather a correction of erroneous beliefs and misinterpretation.

A Fruitful Collaboration

In the summer of 1946, I had just completed my thesis and was on my way to Baltimore for postdoctoral training in electrophysiology. David Lloyd, whom I used to meet very often at Yale in the laboratory next door, had just left for New York. He invited me to visit for a weekend. He met me at the airport, and on our way to his home we discussed many questions about the study of afferent fibers in muscle nerves. The subject was important and could be a matter of collaboration. David Lloyd had demonstrated the monosynaptic nature of the stretch reflex. He showed that the afferent fibers that trigger the reflex arise within the muscle. He wished to further investigate the nature of these fibers and to establish the distribution of the fibers with respect to diameter. He suspected that we could discover differences in populations of afferent fibers. He was undoubtedly the world expert in the field of the physiology of nerves, but he spoke modestly about his training in neuroanatomy. In particular, he claimed not to have the skill to carry out a histological study of the nervous tissue. He knew that my Yale training in anatomy was broad and thought that I was the best candidate for the research. He proposed that we collaborate: I accepted immediately. I even suggested some possible projects and protocols. I would perform the experiments and prepare the histological sections in Baltimore, and the data would be processed at the Rockefeller Institute in New York.

The experiments consisted of sectioning the ventral root of the spinal cord at the level of the lumbar segments. After 3 months of survival to produce the atrophy and a complete degeneration of the muscles, the 28 muscle nerves from the hindlimbs were carefully dissected and fixed in vinegar to be processed for histological sections. A double-blind examination of the histological sections under a Zeiss microscope at high magnification was then done by both of us. The muscles were innervated by 4000 to 5000 nerve fibers, which meant making about 10,000 measurements. The amount of work necessary to accomplish this experiment was enormous, but we refused any help. Nobody in the laboratory was allowed to touch the precious histological preparations. At the end, we could say with complete confidence that our data were 100% reliable. These important results were published in the *Journal of Neurophysiology* (1948). They showed that (i) the diameters of the sensory fibers of the thigh were larger than those of the leg; (ii) the diameters of the fibers controlling the extensor muscle were larger than those of the fibers controlling the flexor muscle; and (iii) the diameter of the fibers of pale muscles was larger than the one of red muscles. Moreover, our data demonstrated that the fiber diameters of each muscle were distributed into three groups. This classification became a general rule and can be found in all textbooks.

A Postdoctoral Year at Johns Hopkins: Why This University?

When I was at Yale, I passed my examinations and completed my thesis in an unexpectedly short time. It was unusual and I was congratulated by the professors, my colleagues, and my friends. However, I did not let myself become intoxicated by praise. I understood perfectly that my success was limited and I realized that I was resting on my laurels. In fact, I had no reason to be proud. A general survey of the trends in neurophysiology of the time, together with examination of the reality of my situation, was enough to convince me that I was lagging in the scientific world. The experiments performed for my thesis as well as the questions I had posed were out of date and all the techniques that I had used in China were old-fashioned. It was clear that if I wanted to make a name for myself in neuroscience, I needed to master the modern technology recently developed for electrophysiology. In other words, electrical events were the major manifestations of nervous activity. In order to understand the physiological functions of the nervous system, they had to become the principal object of my research.

Two men were in my life in important ways during this period of my scientific development: David P. C. Lloyd and Clinton Woolsey. They were both brilliant and prominent electrophysiologists. Fulton thought that I should broaden my proficiency in these new domains by spending some time training in electrophysiology. With this in mind, he wrote to Philip Bard, who was the dean of the Medical School of Johns Hopkins, and arranged for me to be a postdoctoral fellow under the direction of Professor Philip Bard and Dr. Clinton Woolsey.

A Happy Time in Woolsey Laboratory

Woolsey was trained under Philip Bard, who was a charismatic person with a wide knowledge of physiology. He had recently received a doctorate from Johns Hopkins and had remained there as a professor. He was already known for his research dedicated to the localization of the primary areas of the cerebral cortex. Using electrophysiological techniques, he localized precisely the function of the cortical areas. As with many pioneers in scientific fields, he began with an old and simple laboratory.

The new technology required the development of a range of new equipment, most of which was not commercially available. He built his own electronic equipment, such as amplifiers and stimulators. The cathode ray oscollograph was a prototype of the 1940s built by the Grass company. The camera for recording cathode ray tube traces was a secondhand Leica. Sometimes, the breakdown of the system left us in the middle of an experiment rapping on the table and reeling with a long string of swear words. We used to call for help next door, where specialists in electronics were working. We badly needed to broaden our proficiency in electronics. A special course was organized for us by the university. I enrolled in the course and attended the classes with care and dedication. What I learned regarding electronics very much helped me in my career.

During this short period in Baltimore, the amount of work that was accomplished was impressive and the results were interesting. Moreover, most of the people in the laboratory came from all over the world and were full of energy and enthusiasm. Our efficacy was impressive. For example, the question of the cortical distribution of the responses evoked by electrical stimulation of the pyramidal tract was discussed at a tea-time meeting. The experiments started that very evening. The first results were very encouraging and we continued day and night. This investigation had been a pioneering attempt to apply the technique of antidromic activation of nerve cells to the study of cortical neurons. One month later, we had managed to accumulate important data showing that the distribution of the neurons of the pyramidal tract spread out largely beyond the so-called specific motor area, contrary to the evidence available at that time. Our findings emphasized the contribution of parietal cortex to the pyramidal tract. In the monkey, this contribution seemed largest from the rostral portion of the postcentral gyrus, but the whole parietal lobe contributed. In the cat and rabbit, a particularly strong contribution was made by the second somatic area in the anterior ectosylvian gyrus. Woolsey gave an oral communication on these provocative results at the 27th meeting of the American Society for Mental and Nervous Disease 2 months after the end of the experiments. He wrote a paper that was published in *The Frontal Lobes* in 1947.

Not all the projects were as successful. For example, concerning the functional organization of the sensory area of the cerebral cortex of the macaque, we were supposed to do the experiments and the writing during my stay at Johns Hopkins. It was our purpose in these investigations to map out the distribution and boundary of the cortical areas for the representation of cutaneous tactile sensibility of different parts of the body, especially of the tail of the spider monkey. The experiments, which were executed by many collaborators, were time-consuming. The experimental reports were contradictory and needed more discussion, and new experiments were also probably needed. Leonardo E. Harcho and Elwood

Henneman, both of whom were visiting fellows in the department, participated in some of the experiments. Shortly after my return to Yale, Woolsey took up the professorship in neurophysiology at the University of Wisconsin, Dr. Henneman was recalled to Harvard University to take up an assistant professorship in physiology, and Harcho was appointed as professor of clinical neurology at the University of Utah. Our original research team was completely disbanded and the publication of the paper was delayed indefinitely. The data from this project remained at the bottom of a pile of old books. When I went back to the United States in 1981, I met my colleagues again. They suggested that I should write a paper with the old results, but eagerness is declining with age. Maybe somebody will find them in 100 years time!

My year in Baltimore was formative and provided fruitful collaborations. There, I met many distinguished scientists who became my friends. Their influence played a major role in my life. Some of them have passed away, but their work will remain in the history of neuroscience. Besides meeting a wide cross section of people, the opportunities to learn new technical tools were golden.

I remember an interview with the dean of Johns Hopkins University, who had been interested in the physiology of the hedgehog. I told him about my own involvement in the auditory reflex of this animal, which I had previously studied in China. He revealed to me a peculiar anatomical feature of the 'paniculus carnosus' in the hedgehog. In all the animal tissues that he had examined in his lifetime, none displayed such a high density of spindles as the hedgehog's paniculus carnosus. This special muscle, largely responsible for the general contraction reflex when the animal was exposed to danger, was activated by exposure to high-frequency noise. This information, I think, was never mentioned in books.

Back to Yale

My skill in operating a wide range of new electronic equipment was greatly improved during my training in Baltimore. I also gained new knowledge in constructing experimental protocols in electrophysiology. I was prepared to go back to Yale and use the setup of the electrophysiology laboratory left by David Lloyd. In fact, the first owner of this laboratory was the famous neurophysiologist Dusser de Barenne, who had built the first experimental equipment. Dusser de Barenne had a charismatic personality whom I had admired very much when I was young. In 1938, Dusser de Barenne and Warren McCulloch postulated a strong functional connection between the receptive area of the cerebral cortex and the sensory centers of the thalamus suggesting afferent and efferent connections between the two structures. This hypothesis inspired me. I was very excited to occupy the same laboratory 10 years later. I even found writings and recordings in an old cupboard that were the property of Dusser de Barenne.

The Reverberating Thalamocortical Circuits

According to the general belief of the time, sensations such as vision, audition, and touch were related to the evoked potentials recorded in the cerebral cortex. The duration of the event could be observed on the cathode-ray tube trace with an adequate fast sweep rate. However, the potentials following the evoked responses were blurred by the sweep rate of the trace of the oscilloscope. Good fortune intervened when we decided to decrease the sweep rate of the oscilloscope. We discovered that the evoked potentials were followed by a sequence of late waves that had never been noticed. This series of regular oscillations lasted for more than 1 second. We attributed this phenomenon to the activity of the thalamocortical connections already suspected by Dusser de Barenne. We decided to focus our research on the reverberating circuits between the thalamus and the cerebral cortex. Fulton was fascinated by the subject, which he strongly supported both materially and financially. We quickly obtained major results.

At this time, the idea was generally believed that the thalamus was a one-way relay station with the function of transferring passively the nervous information received from the environment to the cerebral cortex. In neuroanatomy handbooks the thalamus was described as a so-called relay center. However, this notion was questioned at the beginning of the century by clinicians who had noticed that patients with cortical lesions showed disturbances of sensory perception such as hyperesthesia and paresthesia. These clinical observations led to the assignment to the thalamus of an important role of continuous secondary control. Our recording of the late waves that followed the evoked auditory potentials led us to postulate feedback circuits between the cortex and the thalamus. The afferent volley from the thalamus after arriving at the sensory cortex would return to the corresponding thalamic nucleus, from which the impulse would again ascend to the cortex to start another cycle of activity along the same neuronal circuit. This cyclic activity would repeat a number of times. After careful experiments, we managed to find evidence that indicated our intuition was not a dream but reality.

Fulton was very enthusiastic about our results, reporting that an afferent–efferent neuronal circuit between the cortex and the thalamus was demonstrated for the first time. This was a major finding that deserved immediate publication. Fulton gave an oral communication at the second meeting of the EEG Society held June 13 and 14, 1948, in Atlanta. The paper was published later in the *Journal of Neurophysiology* (1950).

Subsequently, I sent the manuscript to the outstanding neurophysiologist Lorente de No and asked him for criticisms. He was a follower of Ramon y Cajal, who had stressed that the ventral nucleus of the thalamus and the internal and external geniculate bodies, which transmitted cutaneous, auditory, and visual information, respectively, had not only nervous fibers contacting the cerebral cortex but also fibers arising from the receptive area of the cortex. This was a consistent anatomical condition supporting our idea of reverberating circuits.

The reason for sending my manuscript to Lorente de No was because he had a reputation of being an uncompromising person and not offering compliments lightly. I was surprised to receive such a cordial answer:

> Dear Chang,
>
> I have just finished reading 'The Repetitive Discharges of Reverberating Cortico-Thalamic Circuits.'
> I thank you for sending me your work. Without hesitation, I can readily say that your article is a masterpiece. Your deep and systematic analysis of the experimental data and your observations are of a great importance. Moreover, I must congratulate you for the clarity of your presentation and your impartial view of the state of previous works. Your article set a good example to us all.
> I thank you for giving me the opportunity of reading it. As your elder, I am happy to say that you are one of the key figure of contemporary physiology. I wish you many other successes.
>
> Yours
> Lorente de No

It was an unusual letter but not so unexpected. Lorente de No had proposed long ago that the activity of the central nervous networks might contain information that persisted and did not vanished instantly. This could be the basis of memory. He developed this idea when working on the structure of the olfactory cortex in 1934. He further elaborated the notion of reverberating circuits in the olfactory bulb using electrophysiology. At that time, however, the proof of reverberating circuits in the higher regions of the central nervous system was lacking. His interest in my paper was obvious.

His letter greatly boosted my morale, however, and I felt very honored, although I was conscious of the reason for this admiration. I knew that any new scientific theory provoked criticisms and violent debates. I was ready to react. As I expected, the paper had a large audience in the scientific community. The specialists in electroencephalography had perceived at once that the notion of reverberating circuits between the thalamus and the cerebral cortex could explain the electroencephalogram. My Belgian friend Frederic Bremer thought that the neurons were like cardiac muscle with automatic activity. For him, the regular oscillations that followed the evoked potentials at the cortical level revealed a kind of pacemaker activity that was not related to the operation of the reverberating circuits. We exchanged a rich correspondence that strengthened our friendship without lessening our points of disagreement. The English neurophysiologist D. Burns had previously shown that section of the nerve fibers, which isolated an area of the cortex but kept intact its blood supply, suppressed all spontaneous electrical activity. For me, this was the proof that the so-called pacemaker activity was not spontaneously operated but was the result of nervous transmission.

Among the numerous letters that I received, there was one from an American physiologist, Robert Galambos, an expert in the auditory system. I found the letter impolite, abrupt, and in bad taste. I convinced myself that feelings must never take over reason in scientific matters. One must respect different opinions in whatever way they are expressed. I answered with a long, serious, quiet letter. I objected to his questions and criticisms one by one. I stressed the fact that his animals were anesthetized with chloralose. These experimental conditions, without suppressing pain, could induce a general excitation of the brain resulting in spontaneous activity of the neurons. He should take this fact into account in interpreting his results. I never received an answer from Galambos.

In the fall of 1958, I was invited to the Moscow colloquium 'The Cerebral Maps and Reflexes.' Galambos was a member of the U.S. delegation. We met there and had several warm discussions. One afternoon during an excursion, we sat together on a bus. I discussed with him dendritic function and especially the dendritic potential. He spontaneously described his laboratory and his conditions of work at Harvard University, and he told me about cultures of neurons. He opened new horizons and I must say that it was upon his suggestion that, when I returned to Shanghai from Moscow, I worked hard to create the first laboratory of cultures of neurons in China. Galambos' idea of cultivating neurons was the starting point of a new direction in my research.

My Lifelong Association with Dendrites

For someone who has been interested in the anatomy of the cerebral cortex since his university years, the structural complexity of the dendrites was a subject of admiration and interrogation. This fascinating structure had been described by Ramon y Cajal beautifully with the Golgi method. In the summer of 1947, I decided to learn the technique of silver staining with Lorente de No. It was an outstanding piece of luck to be taken as an apprentice by the follower of Ramon y Cajal. He stated that only a few persons in the world were mastering this technique. For 4 months, I commuted every day between New Haven and New York, traveling on the early morning and late night trains. I remember this extraordinary period as full of many interesting things. During the histological procedure, we used a rose essence to clear the sections. Our bodies and clothing smelt of this perfume. In the evening when I was in the subway on my way to Central Station, I was surrounded by women who came to sit next to me. I felt awkward. Sometimes things happen unexpectedly!

The extraordinary structural richness of the brain stained with the Golgi method may be viewed as one of the reasons for my interest in dendritic function. My work started in 1949.

Visual Evoked Potentials and the Transmission of the Three Colors

In our analysis of the primary cortical response to electrical stimulation of the optic nerve, we paid attention to the configuration of the evoked response that consisted of several deflections. The primary cortical response displayed six typical successive events on the screen of a cathode-ray oscillograph with a fast sweep speed of the beam. We investigated the latency of each wave and the effects of stimulus strength, of the local application of strychnine and Novocain, and of mechanical pressure on each of the six waves. Our concluding remarks proposed an interpretation of the successive spikes and the broad wave. The first fast potentials represented the activity of three conducting pathways in the visual system. The fact that optic nerve fibers and geniculate neurons could be classified into three distinct groups according to their sizes provided an anatomical basis for our electrophysiological findings. The slow waves following the spikes represented the activity of cortical neurons because they were the only ones that could be attenuated or augmented by agents affecting cortex. These observations naturally led us to think of the possible correlation of the triple conducting system and the multiplicity of visual sensations implied in the recognition of light of different wavelengths. The three optic pathways mediated chiefly the impulses of one of the fundamental components of trichromatic vision. This supposition was supported by Piéron's observation that the rise time of sensation was different in the appreciation of different fundamental colors, implying that impulses carrying different chromatic qualities are conducted at different velocities.

Sometime after obtaining these results, I met by chance the editor of the French review *Journal de Psychologie* published in Paris. He was also an adviser for the *Journal of Neurophysiology*. Fulton agreed that I should submit a paper on the transmission of the three colors. This article was published in the French review in 1951 in the *Volume Jubilaire en Hommage à Henri Piéron*. Piéron was delighted.

The Discovery of Photic Potentiation

During our investigation on the nature of visual evoked potentials, there were enormous technical difficulties and our morale was continuously up and down. One evening in 1950, I was working alone in the laboratory when I incidentally observed that the response vanished promptly when the ceiling light was turned off for the purpose of taking a photographic record. At first, I thought that the disappearance of the response was due to an accidental dislocation of the recording electrodes. However, when the light was turned on and the preparation was examined, no change of electrode position could be found and the response returned. However, when the attempt was made once again to photograph it by turning off the room light, the response again disappeared. Repeated trials by turning the light on and off were followed by the presence or absence of the response. This incidental observation marked the beginning of new experiments on what is called the 'potentiation effect of light.'

Diverging points of view emerged, however. In 1954, in his book *Receptors and Sensory Perception*, Granit mentioned the effect of photic potentiation by the name of 'Chang effect.' The interpretation of the phenomenon was under debate. My friend Granit was visiting Yale when I was in the middle of my experiments on the visual system. When he returned to Sweden, he wrote a letter telling me that although my experimental results were beyond question, he thought my interpretation was wrong. He stressed the fact that I was working on anesthetized animals with barbiturates that had curious excitatory effects on the retina. He advised me to proceed with more experiments and ended his letter by quoting Henry Dale: 'One must always consider the less exciting explanation.' He suggested that my results were simply due to an aftereffect related to fatigue.

This is an example for young researchers. They must always remind themselves that criticisms by colleagues must be taken into account with sufficient humility, and one must acknowledge one's imperfections. The publication of an article does not always mean the end of an experiment but sometimes the beginning of it. Before publication, one must show a very cautious attitude, as described by David Lloyd: 'When I submit a manuscript for publication, I send also my reputation and all the rest!.' Also, before sending an article, it is necessary to weigh each word and to revisit the work several times until it is perfect. Once the words are printed, one's reputation is at stake.

Dendritic Function Revisited

For those who attempted to understand the mechanism of cortical function by means of electrical stimulation of the cortical surface, it was important to remember that in the cerebral cortex at least one-third of the total neural substance is composed of dendritic processes. The cortical surface was undoubtedly the best place in the central nervous system for the study of the properties of dendrites because of the accessibility and the homogeneity in distribution of the apical dendrites of the pyramidal cells in the superficial layer of the cortex. Our investigation was an attempt to establish the existence of dendritic potentials in the cortex in response to weak electrical stimulation and to differentiate the dendritic potentials from the potentials accompanying the activity of intracortical neurons. We wanted to inquire about the properties of dendrites compared with those of axons. Our results led us to conclude that the first component of the local cortical response was the potential produced by the passage of the nerve impulse along the apical dendrites. These findings constituted evidence that (i) the dendrites were excited by electrical stimulation, (ii) the dendrites were capable of transmitting impulses, and (iii) the dendritic potential differed from the axonal potential in that it was not an all-or-none response. It was suggested that the intensity of the stimulation induced graded responses.

Our article, which was published in the *Journal of Neurophysiology* in 1951, won recognition from the scientific community along with various negative reactions. The most frequent criticism was that the direct cortical stimulation was not selective and that many neurons could be excited as well in the deeper cortical layers. We performed more experiments with different protocols to find the answer, the results of which were published in the *Journal of Neurophysiology* in 1955.

Among the nine articles dedicated to the question, the last one concerned two types of synaptic contacts in the central nervous system. The results of this research were reported at the Conference of Quantitative Biology at Cold Spring Harbor, New York, in 1952. In this paper, I postulated a hypothesis about the roles played by the different types of synapses in the performance of central nervous transmission. The synaptic relations between cortical neurons were classified into two categories: the pericorpuscular (axosomatic) and the paradendritic (axodendritic) synapses. According to the principle of synaptic stimulation as a local process, the activity of the pericorpuscular synapses was most effective in initiating a postsynaptic discharge, whereas the paradendritic synapses could only create electrotonic changes so as to modify the state of excitability of a neuron. The former executed faithful and prompt relay transmission where reflex movements were required. The latter mediated higher nervous activity, such as consciousness, perception, and

NATIONAL ACADEMY OF SCIENCES

OFFICE OF THE PRESIDENT
2101 CONSTITUTION AVENUE
WASHINGTON 25, D. C.

4 June 1952

Dear Hsiang-Tung

Just a note to tell you how pleased I was to have the privilege of seeing a copy of your paper for the Cold Spring Harbor Symposium. It is the best scientific paper I've ever read. John Fulton agrees with me on this and adds that it is of Nobel Prize calibre.

At any rate, Hsiang-Tung, I wish you the very best time possible at Cold Spring Harbor. I am proud to know you!

All the very best
yours truly –
Bob Livingston

thinking. After the conference, I promptly received a note from Bob Livingston, who was assistant to the president of the National Academy of Sciences:

At the time of these investigations on the function of the dendrites, the limited technology of the laboratories did not permit a direct approach to the problem. Obviously, new preparations that would offer direct optical access to single neurons with their arborizations were mandatory but still a dream. Some hope appeared when Pomerat claimed in 1955 that he had obtained a culture of neurons, but a German cytologist argued that the cells were only glial cells.

On My Way Back to China

To my great surprise, when I decided to leave the United States and return to China, I was asked by the editor of the *Annual Review of Physiology* to write a paper on the physiology of vision. I accepted immediately, although I was not prepared to write such a synthesis of the data and review different ideas on the physiology of vision. I spent my summer vacation consulting the bibliography to present a historical view on the subject together with the most recent results. It was the first time that I submitted a manuscript to such a prestigious review and I was inexperienced. One should be careful not to provoke controversy and not to upset anyone. Therefore, after having sent the article, I was restless and daily I awaited the editor's response. My review was published in 1953.

Shortly thereafter, I was invited to contribute to the new *Handbook of Physiology* edited by John Field, H. W. Magoun, and Victor E. Hall. My motivation for accepting was in the interest of writing experimental results of my own and in presenting my theoretical approach to the problem. I began writing the article 'The Evoked Potentials' on January 9, 1956. The neuronal mechanism underlying the evoked potential was formulated on the basis of the histological organization of the cerebral cortex and the general principles of neurophysiology. Although the evoked potentials in different systems were independent processes, they showed interaction probably due to the overlapping of their fiber distributions, the convergence of afferent impulses on the common neurons, or through the integration in a general activating system such as reticular formation. I defended the idea that such interaction of afferent impulses on the cerebral cortex made it possible for the constant afferent inflow in any particular sensory system to modify the level of cortical excitability as a whole.

I wrote the essentials of the paper in Copenhagen, where I spent some time in the laboratory of Professor Buchthal on my way to China via Europe. I am deeply indebted to him for the facilities of his library and very comfortable material conditions during my stay. Without his help, the article would have never appeared in the *Handbook of Physiology*.

Many years later, in 1991, I traveled to Xian to attend a scientific meeting. The famous neurophysiologist John G. Nicholls was visiting. One day at lunch he introduced me to a Brazilian friend who, hearing my name, said with surprise, 'Are you the author of the article on evoked potentials? Congratulations! When I was a student your paper was our bible.' After such a long time, I had never imagined that my contribution would deserve such recognition. I was deeply moved.

The rest of my trip back was much more difficult. I had left a well-equipped Yale laboratory in which I had spent more than 10 years working days and nights and was heading to another laboratory that was not built yet. I looked to the future with great anxiety. My future was obscure. My projects were unclear and I could not elaborate on my plans for research. I worried about my intellectual status as well as my daily life. Moreover, during my journey, I encountered tremendous difficulties. There were some alarming incidents. On the physical and moral level, I had to endure inconceivable difficulties and turmoil.

Back in Shanghai

Upon my return to Shanghai in 1956, my heart and spirit were full of enthusiasm and determination to continue my research on the physiology of the nervous system. I had always entertained the dream of building a modern research center for the study of the brain, with laboratories for experiments in neurophysiology and rooms for the culture of nerve cells. I wanted to continue the research I started abroad and, particularly, studies related to the function of dendrites. However, very often the reality of circumstances separates us from our hopes. After 6 years of painful struggle, interference, and various difficulties, in 1962 it was possible to build the first laboratory for the study of nerve cells in culture in China. Moreover, we succeeded in keeping alive neurons from a human cortex to study its development for 142 days. In addition, the setup of our electrophysiology laboratory enabled us to study directly the dendrites. However, just at that time, the *Journal of Neurophysiology* (March 1962) published an article by a Japanese physiologist. This work described a mass of data on cultures of nerve cells with the aim of studying the dendritic function. The results showed the capacity of excitability and propagation in the dendrites and gave an evaluation of their conduction velocity of 0.1 m/sec, a value that was very close to that which we had obtained.

That disturbed me greatly, making me aware of the point at which scientific progress happens quickly; the competition was ferocious and heartless. If one did not hurl oneself into the contest, one would be eliminated. Once I returned to my country, I thought of continuing my research on the function of dendrites, but because of the circumstances it was not possible. There was nothing left to do but to abandon this field and to find other projects. However, the course of history and its upheavals always overtakes us.

Studies on Pain and Acupuncture

At the start, I was not destined to study the mechanisms of pain. The first time I encountered the problem was in 1946 when I was writing my Ph.D.

thesis at Yale. My supervisor, T. C. Ruch, was writing a chapter on the physiopathology of pain for a textbook of physiology edited by John F. Fulton. I often discussed the problem of sensation with him. Once we debated the notion of referred pain. I suggested an explanation that was based on Sherrington's neuron pool concept. Rush found the hypothesis interesting and asked me to draw a diagram to illustrate my theory, which I did immediately. I named my hypothesis the 'convergence-projection theory.' My drawing was published in Fulton's textbook and was assumed to be the best rational explanation of the referred pain (Fig. 1).

When I was young, as a hobby after my working hours, I made sketches from landscapes with a black pencil. I made a practice of signing these sketches in a well-hidden place. Of course, I did the same in my diagram depicting the mechanism of referred pain. However, only motivated readers, using a magnifying glass, could detect it. Each time I look at this universally famous figure, which was widely distributed, I am deeply moved.

In the 1960s, my country experienced great difficulties. Drugs were lacking. Moreover, when people were sick, they tended to turn to

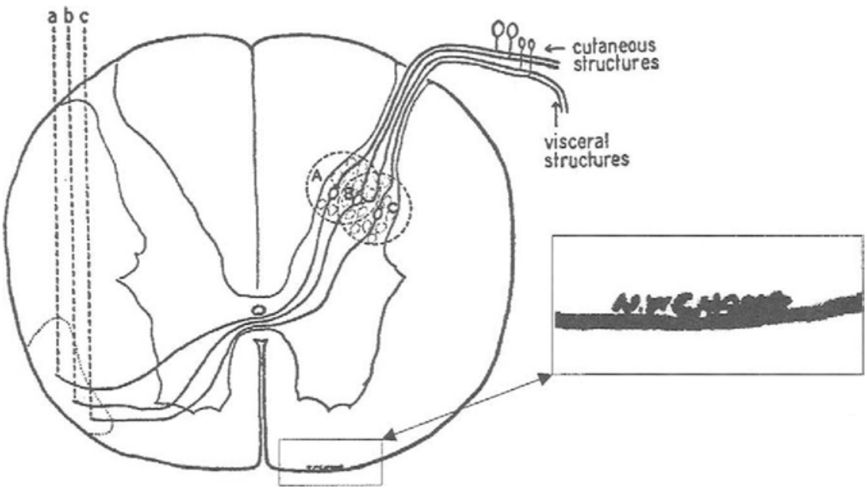

Fig. 1. Convergence-projection mechanism of referred visceral and somatic pain based on Sherrington's neuron pool concept. A–C represent a neuron pool consisting of all the spinothalamic tract fibers originating in one segment of spinal cord. (A) The field of neurons having connections only with afferent fibers from cutaneous sense organs. (B) The field of overlap constituted by neurons that receive impulses from both visceral and cutaneous afferents, and impulses in b will give rise to pain referred to skin. (C) Those neurons of pool that connect only with afferent fibers from visceral cavities and give rise to unreferred or true splanchnic pain. Only one neuron in each category is represented; others are indicated by 'ghost cells.' (a–c) Fibers in the spinothalamic tract having cell bodies in fields A–C, respectively (reproduced with permission from Fulton, *A textbook of physiology*, 1955).

traditional medicine, which was more accessible, less expensive, and often more effective. In addition, an increasing number of medical personnel trained in Western medicine were using acupuncture to replace anesthetics used in surgical operations. Throughout the country, a great number of people began to secretly experiment with anesthesia by acupuncture. Some succeeded and other failed.

I have dedicated many years of my scientific life to gaining insight into the problem of anesthesia by acupuncture and its mechanisms. All these long years, from beginning to end, have been devoted to research on the neurophysiology and the mysteries of the function of the nervous system, higher centers of perception, and human thought. In order to understand this scientific truth, I navigated far and wide on the ocean of learning about the brain, encountering serious obstacles and enduring painful difficulties. What we can gain is so infinitesimal that it is unimportant. We can only carry forward our hope to the future.

Selected Bibliography

Chang Hsiang-tung. An auditory reflex of the hedgehog. *Clin J Physiol* 1936;10:119–124.

Chang Hsiang-tung. High level of decussation of the pyramids in the pagolin (*Manis pentadactyla dalmanni*). *J Comp Neurol* 1944;81:333–338.

Chang Hsiang-tung. The repetitive discharges of cortico-thalamic reverberating circuits. *J Neurphysiol* 1950a;13:235–258.

Chang Hsiang-tung. Functional organization of central visual pathways. Pattern of organization in the central nervous system. *Proc Assoc Res Nervous Mental Dis* 1950b;30:430–453.

Chang Hsiang-tung. Dendritic potential of cortical neurons produced by direct electrical stimulation of the cerebral cortex. *J Neurophysiol* 1951a;14:1–21.

Chang Hsiang-tung. Observation on the effects of strychnine on local cortical potential. *J Neurophysiol* 1951b;14:23–28.

Chang Hsiang-tung. Changes in excitability of the cerebral cortex following single electric shock applied to the cortical surface. *J Neurophysiol* 1951c;14:95–112.

Chang Hsiang-tung. Triple conducting pathway in the visual system and trichromatic vision. L'annėe *Psychol Vol Julaire Hommage Henri Piéron* 1951d;135–144.

Chang Hsiang-tung. Cortical neurons with particular reference to apical dendrites. *Cold Spring Harbor Symp Quant Biol* 1952;17:189–202.

Chang Hsiang-tung. Interaction of evoked cortical potentials. *J Neurophysiol* 1953a;16:133–144.

Chang Hsiang-tung. Similarity in action between curare and strychnine on cortical neurons. *J Neurophysiol* 1953b;16:221–233.

Chang Hsiang-tung. Physiology of vision. *Annu Rev Physiol* 1953c;15:373–396.

Chang Hsiang-tung. The evoked potentials. In *Handbook of physiology*. American Physiological Society, 1959;299–313.
Chang Hsiang-tung, Fulton JF. The repetitive discharges of the cortico-thalamic reverberating circuits induced by afferent stimulation. *EEG Clin Neurophysiol* 1949;1:249–250.
Chang Hsiang-tung, Kaada B. An analysis of primary response of visual cortex to optic nerve stimulation in cats. *J Neurophysiol* 1950;13;305–318.
Chang Hsiang-tung, Rush TC, Ward AA Jr. Topographical representation of muscles in motor cortex of monkeys. *J Neurophysiol* 1947a;10:39–56.
Chang Hsiang-tung, Woolsey CN, Jarcho LW, Henneman E. Distribution of cortical potentials evoked by electrical stimilation of dorsal roots in *Macaca mulatta. Fed Proc* 1947b;6:230.
Lloyd DP, Chang Hsiang-tung. Afferent fibers in muscle nerves. *J Neurophysiol* 1948;11:199–208.
Ruch TC, Chang Hsiang-tung, Ward AA Jr. The patterns of muscular response to evoked cortical discharge. *Res Proc Assoc Nervous Mental Dis* 1946;26:61–83.
Woolsey CN, Chang Hsiang-tung. Activation of the cerebral cortex by antodromic volleys in the pyramidal tract. *Frontal Lobes A. R. N. M. D.* 1947;27:146–161.