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Muscle, Nerve and Synapse

Selected Publications
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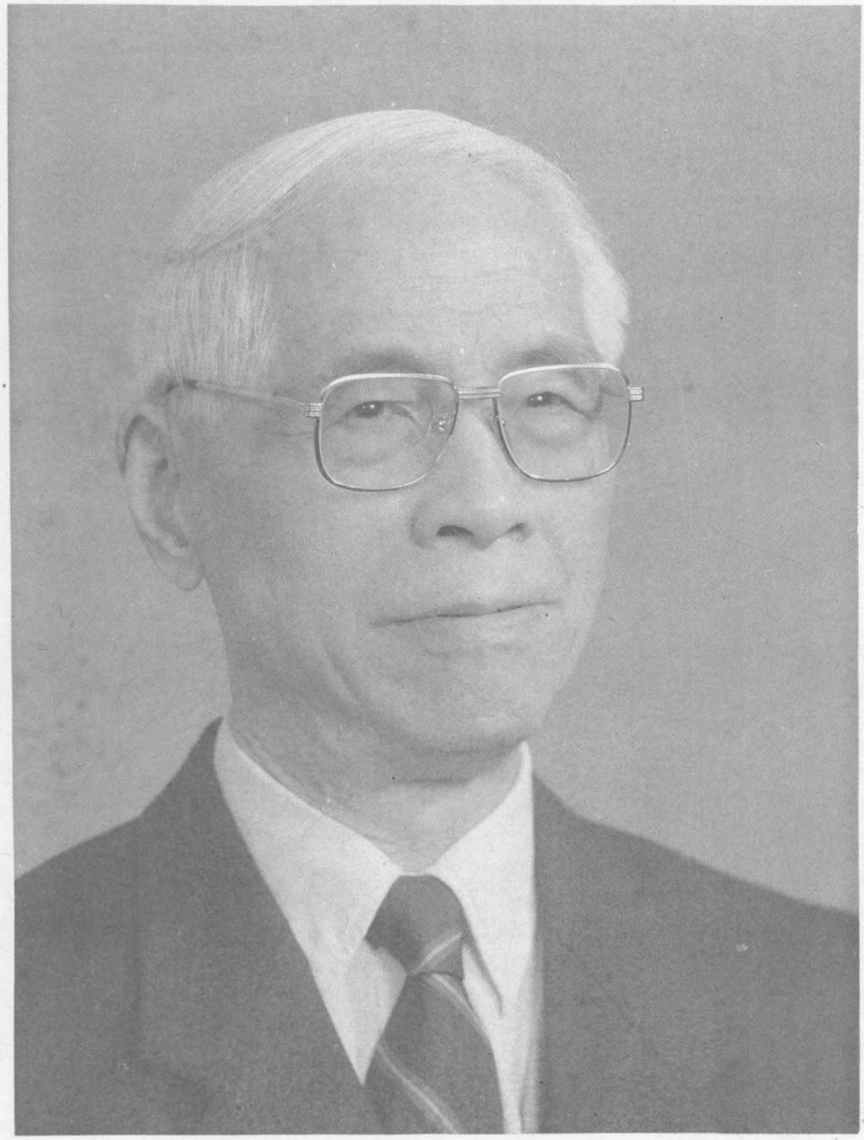
Te-Pei (De-Pei) Feng



FOREWORD

Professor Te-Pei (De-Pei) Feng is the founder and Honorary Director of the Shanghai Institute of Physiology. On occasion of the 50th anniversary of the Shanghai Institute of Physiology which happily coincides with the 60th anniversary of Prof. Feng starting as a fully independent research worker to develop neurophysiology in China, it is appropriate to issue this collection of selected works by Prof. Feng as one token of celebration.

When he was eighty, Prof. Feng was invited by the Editor of Annual Review of Neuroscience to write a Prefatory Chapter; the result was his paper "Looking Back, Looking Forward", which is a summary account of his scientific journey from youth to the age of eighty. This paper forms a natural introduction to all the other papers in the present collection, and so is placed at the beginning. All the other papers are arranged in their original chronological order of publication to correspond in a general way with the narration in "Looking Back, Looking Forward" as well as to indicate the successive paths of research in neuromuscular physiology which Prof. Feng has followed.

Prof. Feng's long scientific career has several outstanding landmarks. The first landmark may be placed in the period 1930-1933 when he studied in the laboratory of professor A.V. Hill in University College London working on the heat production of muscle and nerve. Among his achievements during this period was his discovery of the increase of the resting heat production of muscle on passive stretch, which later became known as "Feng effect".

The second, and, we may say, the most prominent landmark of Prof. Feng's scientific career was the period 1934-1941, just after his return from abroad, when he was teaching in the Department of Physiology, Peking Union Medical College. During this period he opened a new research direction in the physiology of neuromuscular junction. He made a number of seminal discoveries; in the period 1936-41 he and his students published a long series of 26 papers on neuromuscular junction in the Chinese Journal of Physiology (English), which attracted worldwide attention among neurophysiologists. He soon became an internationally acknowledged pioneer in modern research on neuromuscular junction.

The third landmark in his research career was in the field of nerve-muscle trophic relations which he entered in 1961 with a spectacular discovery at the very beginning, namely, the discovery of the extraordinary phenomenon of post-denervation hypertrophy in the slow muscle fibers of the chick. Unfortunately his work was soon interrupted by the "Cultural Revolution". When this so-called revolution was over, he immediately resumed his researches in this field, and together with his collaborators made important contributions to the problem of the neural determination of the phenotypic characteristics of skeletal muscle fibers.

Prof. Feng has always been a forward looking man. When he reached the age of eighty, he said he would start some new research and he did: he took up the study of synaptic plasticity in central synapses, in particular long-term potentiation (LTP), a subject which is now one of the most active frontiers of neurophysiological research. For Prof. Feng, the study of LTP while a new adventure has its own historical root--LTP is a sort of extended PTP (post-tetanic potentiation) which he first described at the neuromuscular junction in the 1930s. Prof. Feng together with his students have already made significant contribution to the cellular mechanisms underlying LTP, and I think we may quite properly place the 4th landmark of his research career here.

Taking an overall view of his extraordinary scientific life, it is apparent that he worked with the greatest concentration and accomplished most impressive achievements during his youthful period 1934-1941, immediately after his return from abroad. It is also clear that since his student days, in every topic of neuromuscular physiological research he took up, he left his creative footprint. But we must also note that a large part of Prof. Feng's life was lived in a period of our country with frequent wars and political upheavals and that he had suffered from serious and long interruptions in his scientific work. Under such circumstances his unflagging devotion to science and to the development of science in his motherland is all the more remarkable and deserves the highest respect. We may expect that this volume of selected papers by Prof. Feng, besides its historical and scientific interest, will be a source of inspiration for many of the younger generation of Chinese physiological scientists.

Xiong li Yang

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LOOKING BACK, LOOKING FORWARD

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INTRODUCTION

Recently my friends both at home and abroad have urged me to write down some reminiscences of my life. While I appreciate such amiable reminders of my getting old, circumstances generally dictate that something more urgent must be done first. The invitation from the Editor to write a prefatory chapter for the *Annual Review of Neuroscience* provides the necessary additional stimulus to sway me finally to write a short summary of my scientific life. My narration chiefly deals with the circumstances and background relating to my development as a neurophysiologist.

MY INITIATION INTO NEUROMUSCULAR PHYSIOLOGY

I started my neurophysiological research in 1929 in the Department of Physiology, University of Chicago, under Ralph Gerard. Before that, immediately after my graduation from the School of Biology, Fudan University in Shanghai, China, I had been a teaching assistant in Physiology to Professor C. Tsai at Fudan University for one year (1926–1927) and then a research fellow in the Department of Physiology, Peking Union Medical College (PUMC) for two years (1927–1929) working under Professor R. K. S. Lim. The two years in PUMC were my first apprenticeship in physiological research. The work in which I took part concerned the nervous and humoral control of gastric secretion. Lim had a strong personality and was an impressive teacher. His operative skill was quite exceptional. Working with him I learned not only elaborate operative techniques for preparing different kinds of gastric pouches, but more importantly, I gained my first practical appreciation of how experimental

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physiological research is done. During those two years, besides taking part in research on gastric secretion, I read widely in almost every field of physiology. There were two books that especially took my fancy: *Principles of General Physiology* by William Bayliss and *Protoplasmic Action and Nervous Action* by Ralph Lillie. This background prepared me for the next step in my development. In the summer of 1929, I succeeded in winning a competitive examination for the Tsing-Hua University Fellowship to study in the United States. The questions as to where in the States I should go, and what kind of study I should undertake were readily answered: I wanted to go to the University of Chicago to study general physiology under Ralph Lillie. So in the fall of 1929 I went to the University of Chicago, registered as a PhD student in the Department of Physiology, and began my studies by taking the course in General Physiology given by Ralph Lillie. At the same time I tried to learn something about the research going on in Lillie's laboratory and in the laboratories of several other professors, including Ralph Gerard. At that time Lillie was occupied with the study of the iron-wire model of nerve conduction, and Gerard with the study of nerve metabolism. When it came time to decide what research I should take up, the choice between working with a *model* of nerve or working with *real* nerves was quickly made: I wanted to work on real nerves. So Gerard became my first mentor in neurophysiological research.

The problem Gerard put me to work on concerned the mechanism of nerve asphyxiation. The specific question was whether an asphyxiated nerve could be made to recover by soaking it in an oxygen-free solution of certain oxidizing dyes like methylene blue, instead of giving it oxygen. The answer turned out to be no, and so the work was not very interesting. But the process of arriving at that answer was far from straightforward. I quickly discovered that the connective tissue sheath of the nerve was an effective diffusion barrier and prevented the methylene blue from reaching the nerve fibers. This finding invalidated the original experimental design. It took me several tense days before I could alter the design so that my experiments could continue. However, a way was soon found and the answer was obtained. This experience was exciting to me as a beginner in neurophysiology.

When I registered at the University of Chicago as a PhD student I had originally planned to stay there for three years, but an unexpected turn of events radically changed this plan. Shortly after I started working with Gerard, Robert Lim, my old teacher in PUMC made arrangements for me to go to University College London to work with A. V. Hill. I was unaware what Lim had written to Hill about me, but in the spring of 1930 I received a brief letter from A. V. Hill saying: "If you are as good as Lim says you are, come along." That settled the matter: I was to go to London to work with A. V. Hill in the fall of 1930. Before leaving I was able to finish sufficient work for a MS degree from the University of Chicago and I also took the summer course in General Physiology at Woods Hole, according to a plan approved by Lim.

I arrived in London in September 1930. I saw A. V. Hill for the first time while he was doing some work with his assistant, J. L. Parkinson, in his laboratory. My first impression of Hill was that he was rather austere, but I soon felt more at ease when I saw a galvanometer in his laboratory labeled conspicuously, "DANGER 1000 OHMS"! Hill made me start working the day after my arrival. I worked mainly on the heat production first in muscle and later in nerve. In the course of about two and a half years I either did or participated in sufficient work for nine papers, five of which I wrote up myself.

The way Hill dealt with the first paper I wrote, entitled "The Heat-Tension Ratio in Prolonged Tetanic Contractions," is worth mentioning. The problem had been suggested by him and was carried out under his direction with much assistance from Mr. J. L. Parkinson. I naturally put Hill's name on the paper as a co-author. He promptly took his name off the paper, saying: "If this is the only paper you write while you are here, it will not make much difference whether my name is on it or not, and it will not mean much to you." Another remark he made to me in a similar vein toward the end of my stay in London should also be retold. "You have done good work here and you have done most of the work quite independently. But people will still think you are under my direction. You must go back and continue to do good work all by yourself, then you will be recognized as a fully independent worker." I don't know whether A. V. Hill talked to his other students like this, but his words left a deep impression on me.

Although in Hill's laboratory most of my work was concerned with the heat production of muscle and nerve, there was a short period when I was otherwise occupied. I had finished the study suggested by Hill on the thermoelastic properties of muscle and had completed a related study on the effect of length on the resting metabolism of muscle, which described a discovery that I called the "stretch response" (Feng 1932a) but that Hill later dubbed the "Feng effect". Hill then asked me to look into Lapicque's controversial theory of isochronism to see whether I could make something of it. I spent about a month measuring the chronaxies of nerve and muscle under various conditions. I was soon convinced that my results did not support Lapicque but felt that they were not otherwise of much interest, so I was inclined to discontinue the work. I told Hill how my experiments on isochronism had gone and indicated my intention to move on to something else. I had in mind using iodoacetic acid as a tool to address the question of whether lactic acid might play some role in nerve activity. After inquiring as to how I arrived at this idea, Hill encouraged me to go ahead with my proposed experiment. The result was a paper entitled, "The Role of Lactic Acid in Nerve Activity" (Feng 1932b), showing that frog's nerve is capable of utilizing lactic acid by oxidation and that the formation of lactic acid, though not essential to nerve conduction, enables normal nerves to perform long hours of continuous function.

Altogether I stayed with Hill for three years, obtaining my PhD degree in 1933. During those three years, I spent one summer in Plymouth working on the heat production of crustacean nerve, and, for about two months in each place, Hill sent me to E. D. Adrian's lab in Cambridge and then to C. S. Sherrington's lab in Oxford to broaden my research experience. Upon my arrival in Cambridge in 1932, Adrian gave me a problem to solve by myself. A little earlier, he, Cattel, and Hoagland had noticed that if the surface layers of a frog's skin were scraped away, the tactile responses of the cutaneous nerves ceased for a time but eventually returned. How was this reversible inexcitability of the tactile endings in skin to be explained? After about a week's work on the phenomenon, I convinced myself that it was simply due to the release of potassium from the skin by the injury, and that recovery was due to the subsequent removal of potassium by washing. When I told Adrian about this simple solution to the problem he was initially skeptical, saying that it sounded too simple to be true, and adding if I had told him it was due to some complex organic substance he could believe it more readily. He took the trouble to repeat my observations on frog's skin and then extended them to cat's skin before finally accepting my conclusion (Feng 1933). From that experience in Adrian's lab I learned two things. One was the seriousness and carefulness that one should cultivate in scientific work. Adrian set an admirable example of this. The other was the advantage of bringing people with different backgrounds together in scientific research. Coming from A. V. Hill's laboratory, I was already familiar with the reversible inexcitability of muscle due to potassium, and it was a simple matter for me to extend this knowledge to the problem of injured frog's skin.

I should mention that during my stay in Adrian's laboratory, I had the benefit of contact with Bryan Matthews, Rushton, Roughton, Adair, and Willmer. Barcroft was then the head of the Cambridge Physiological Laboratory, and I had frequently met him at the regular afternoon teas.

Hill sent me to Oxford with the remark: "Go to Sherrington and learn how to keep a cat alive." Unfortunately, shortly before I arrived in Oxford, late in 1932, Lady Sherrington died. Sherrington therefore made arrangements for me to work with J. C. Eccles, and I had only occasional contacts with Sherrington himself. Eccles was then working on spinal reflexes in cats, using mainly myographic recordings. I learned various surgical and technical procedures from him and assisted him in minor ways with his experiments. Eccles impressed me as a most energetic worker. During my short stay in Oxford I also had the pleasure of getting acquainted with Ragnar Granit.

My scientific association with A. V. Hill did not end with my stay in London. In 1936, about three years after I had left him, Hill was asked by *Ergebnisse der Physiologie* to write a review on the heat production of nerve. Instead of writing the review himself he recommended that I do it (Feng 1936). Last summer, Professor R. O. Keynes told me that he is planning to write a new review on the heat production of nerve, saying: "You wrote the first review, and I am going to write the last review on the subject."

On the recommendation of A. V. Hill, after leaving London in the summer of 1933, I returned to the United States to spend a year in the newly established Johnson Foundation for Medical Physics in Philadelphia, directed by Detlev Bronk, before returning to China. That new organization with a research staff composed entirely of active young scientists provided a lively and congenial atmosphere, quite different from that prevailing in the old university laboratories in England. During my stay there I was able to see at first hand a rather wide range of biophysical research relating especially to nerve and muscle (Robert Hodes), sympathetic ganglia (Detlev Bronk, M. G. Larrabee), and vision (Keffer Hartline). I did not concentrate on a specific research project, but spent my time mainly learning to make electronic apparatus under the guidance of John Hervey, in preparation for setting up my own laboratory in China.

THE NEUROMUSCULAR JUNCTION 50 YEARS AGO

For my initiation into neuromuscular physiology, I had the good fortune of having eminent men as my teachers. Their example and their generous encouragement were formative influences in my development. In the summer of 1934, I returned to China to take up a teaching position in the Department of Physiology of the PUMC, where I had previously worked as a research student. As no other space was available, Lim, the head of the department, provided me with a long, windowless basement room, isolated from the rest of the department, for my laboratory. Since the teaching duties assigned to me occupied only about six weeks a year, I could devote the rest of the time to research. In planning and doing my research, Lim left me entirely alone; and because of my location in the faraway basement, I was effectively left alone also by everybody else. This solitude turned out to be a good thing, minimizing distractions and interference. Under these circumstances I proceeded to build my own laboratory, partly with equipment purchased and partly with equipment that I had made myself and which I brought back from abroad.

It was clear that I was to do research in neuromuscular physiology. But what, specifically? I expected that I would have to grope about for some time before I could settle down to what I would regard as a serious program of research. I had at my disposal a couple of stimulators capable of delivering stimuli over a wide range of frequencies. The first exploratory experiment I undertook was to give the frog sartorius muscle a one-second tetanic stimulus at increasing frequencies up to about 2000/sec (the stimulating electrodes being placed on the tibial half of the muscle) to see how the tension response recorded on the kymograph varied. I had expected the tension response to decrease progressively and smoothly after a certain maximum, with increasing frequency. To my surprise, the response varied in a periodic manner, i.e. it showed periodic decreases and increases with the progressive increase in stimulus frequency. I then ascertained that this periodic pattern of response was only obtained when the stimulating electrodes were on the nerve-containing tibial half of the sartorius muscle, and not when the electrodes were on the nerve-free pelvic end of the muscle. With nerve stimulation the periodic pattern appeared even more strikingly. Further experiments, with combined nerve and pelvic end muscle stimulation, finally established the important fact that the contraction elicited by direct muscle stimulation could be inhibited by additional nerve stimulation at certain frequencies. This immediately impressed me as something quite new about the neuromuscular junction—something for which I had no ready explanation, but something whose study might disclose other new features of the neuromuscular junction. This intuition led to a quick decision to make the neuromuscular junction the subject of a continuing program of research, and a period of concentrated work followed. In the course of the next six years (1936–1941) after the first exploratory experiments, in collaboration with a series of students, I published no fewer than 26 papers on the neuromuscular junction in the *Chinese Journal of Physiology* (in English). This work was terminated only by the outbreak of the Pacific war and the closing of the PUMC.

At the time I started my research, the theory of chemical transmission at the neuromuscular junction was still in the formative stage. I was led to my own views by the outcome of my own experiments, without any theoretical preconception. It soon became clear that most of my results fitted well with the new chemical theory of neuromuscular transmission and, indeed, provided support for it. When I was in London working in Hill's laboratory, I had visited the National Institute for Medical Research at Hampstead on several occasions and had the opportunity of getting acquainted with H. H. Dale (then Director of the National Institute for Medical Research), J. H. Gaddum, W. Feldberg, G. L. Brown, and others. I often heard Hill speak of Dale with great respect, much as he did of Sherrington and Adrian. But I could not then imagine that I would later work in an area of research so closely related to that of Dale's group. Some of the more significant findings of my studies on the neuromuscular junction may be briefly summarized here.

1. Accompanying the inhibition produced at the neuromuscular junction by high-frequency indirect stimulation which was mentioned above (and is now generally called junctional inhibition), we found a local contraction surrounding the nerve endings. This local contraction could be greatly exaggerated and could become a prolonged contracture if the muscles were treated with various agents that either inhibited AChE (eserine or prostigmine) or enhanced the sensitivity of the muscle to ACh (barium, methyl alcohol, ethyl alcohol, acetone) or both. The occurrence of this local contraction (or contracture) provided a ready explanation for the inhibiton of directly elicited contraction by high-frequency nerve stimulation—it would interfere with the propagation of the muscle action potential. At the same time, it gave a direct demonstration of the stimulated release of ACh by the motor nerve endings, in keeping with the chemical theory of neuromuscular transmission. It may be noted here that Brown, Dale & Feldberg (1936) had shown that eserine greatly potentiates the twitch response of mammalian muscle to maximal single stimuli applied to the nerve, but stated that Z. M. Bacq in their laboratory was unable to find similar twitch potentiation in frog muscle. When I found the proper experimental conditions for demonstrating eserine potentiation of twitches with the amphibian nerve-muscle preparation, I wrote to inform Dale of my experience, and this resulted in a pleasant correspondence with him.

2. Calcium was shown to have various striking effects on the neuromuscular junction. Raising the calcium concentration in Ringer's solution was first found to greatly intensify the junctional inhibition. Then calcium was found to be a universal "decurarizing" agent, removing or diminishing the neuromuscular block produced by such diverse agents as the following: (*a*) drugs: curare, eserine, veratrine, nicotine, atropine, ergotoxin, strychnine, pilocarpine, and novocaine; (*b*) fatigue and long survival; (*c*) acid, strontium, magnesium, and barium; and (*d*) extreme temperatures. Calcium was also found to increase the local contraction or contracture produced by high-frequency nerve stimulation. In an attempt to give a unifying explanaton for all of these various effects, I considered several

possibilities and came to the conclusion that the best hypothesis is that calcium causes each individual nerve impulse to liberate a larger or more concentrated amount of ACh from the nerve terminal.

3. Much effort was spent on the study of the facilitation of neuromuscular transmission during and after prolonged nerve stimulation at various frequencies, and the post-tetanic facilitation or potentiation of the endplate potential, which could last many minutes, was described for the first time.

4. In mammalian muscles the spontaneous twitchings as well as the potentiated twitches due to stimulation, in the presence of eserine, could be shown to be accompanied by repetitive discharges from the motor nerve endings. Likewise the post-tetanically facilitated or potentiated twitches could be shown to be also accompanied by such repetitive activity. In both cases the repetitive activity was readily suppressed by curare. A new prejunctional aspect of the eserine and curare effects and the post-tetanic effects was thus brought to light.

Throughout my research on the neuromuscular junction during the period 1935–1941, I kept an open mind as to the mechanism of neuromuscular transmission. Although there was no doubt that the weight of my experimental evidence was on the side of chemical transmission, I regarded all my interpretations as tentative. This seemed appropriate because the neuromuscular junction was then still a "black box." Microelectrophysiology and electron microscopy, to say nothing of molecular biology, had not yet been applied to its study, and we still knew nothing about how the postulated neurotransmitter was released by the prejunctional motor nerve endings and how it acted on the post-junctional membrane. New, rapid development in the study of the neuromuscular junction soon followed after the end of the Second World War, which served to make the neuromuscular junction a prototype of chemical synapses. The enormous advances achieved during the last three to four decades through the efforts of many people has largely opened up this black box, and analysis is now becoming more and more molecular. There is now a new basis for understanding each of my earlier observations. Yet I feel there is still room for further elucidation, and, if circumstances permit, I would like to make a renewed study of some of these in light of our present-day knowledge.

THE EPISODE OF THE NERVE SHEATH CONTROVERSY

After the interruption of my research on the neuromuscular junction by the War and after my departure from the PUMC at the end of 1941, I eventually made my way to Zhongqing, the War-time capital in the interior of China. I was appointed first as Professor of Physiology in the Shanghai Medical College, which had migrated to Zhongqing, and subsequently as the Acting Director of the Medical Research Institute (Preparatory) of the Academia Sinica. In this latter capacity I visited the United States in 1946 to purchase equipment and books for the new institute and also to look into a number of new scientific developments that were of interest to me. On my arrival in New York I went first to see Dr. Herbert Gasser, then Director of the Rockefeller Institute, to seek his advice about possible arrangements for my stay in the US. He told me that since the War had just ended, most laboratories in the States were not yet fully operational. However, Lorente de Nó's laboratory at the Rockefeller Institute was an exception, as Lorente de Nó had worked uninteruptedly throughout the War. Gasser suggested that I might work for a while with Lorente de Nó, at the same time using the Rockfeller institute as my base while I gathered equipment and books for my own institute. I did as Gasser advised, and I should add that Lorente de Nó was very kind and helpful to me. I ended up spending about a year with him.

Lorente de Nó was then intensively engaged in the study of nerve. His monograph, *A Study of Nerve Physiology*, in two large volumes, was then in the process of publication. He expressed interest in my earlier work on the effect of barium on the neuromuscular junction, and suggested that we do some further work together on the effects of barium on nerve. Lorente de Nó was a very energetic worker, who had very strong opinions on most scientific questions. During my stay at the Rockefeller Institute, I was witness to an especially pointed encounter with Kenneth Cole at a small scientific conference on excitable membranes held at the Institute. But on the whole he and I got along together well, probably because I was a good listener, and avoided getting drawn into arguments where I knew that argument would serve no useful purpose.

There was, however, one question in which I was personally involved. I referred above to the discovery I made in Gerard's laboratory of the connective tissue sheath of the nerve as effective diffusion barrier. Lorente de Nó had written in his book, and also told me pointedly that "it is utterly impossible to believe that the connective tissue sheath of frog or bull-frog nerve could act as a diffusion barrier" (Lorente de Nó 1947). It was evidently useless to be drawn into a verbal argument about a scientific opinion so forcibly expressed. On my return to China in 1947, I and my assistant, Dr. Y. M. Liu reexamined the issue experimentally. We managed to finish two papers (Feng & Liu 1949a,b) reporting our new experiments that supported the original conclusion of Feng & Gerard (1930) about the nerve sheath as an effective diffusion barrier, just before the Liberation of

Shanghai in 1949 as a result of the Civil War, which closely followed the Sino-Japanese War. The papers were sent to the *Journal of Cellular and Comparative Physiology*, and copies were sent to Lorente de Nó at the same time. These papers elicited a long reply from him, published in the same journal (Lorente de Nó 1950). During the following two to three years we published several more papers on the question in a Chinese journal. Space does not permit a full account of the controversy that ensued, but I should put on record the fact that throughout it all Lorente de Nó remained friendly toward me.

When later I was a Regent's Professor in the Department of Physiology, at the University of California, Los Angeles in 1981, Lorente de Nó was in the Department of Anatomy. At an official lunch party given in my honor by the Dean of the Medical School, I had the pleasure of meeting Lorente de Nó again. He told me quietly that it was he who had recommended me for the Regent's Professorship—a piece of news that really made me feel pleased.

FROM THE NEUROMUSCULAR JUNCTION TO NERVE-MUSCLE TROPHIC RELATIONS

After the founding of the Peoples Republic of China (PRC) and the establishment of the Chinese Academy of Sciences, my adminstrative and organizational duties and social activities multiplied and kept me distracted from continuous application to scientific work. During the first 30 years of the PRC there were frequent political upheavals, culminating in the so-called "Cultural Revolution," which upset all normal life throughout the country. This "revolution" was bad in every sense, but it had the dialectical virtue of preparing the country for a radical change. This change came in 1979, ushering in a new age in China characterized by far-reaching reforms in all spheres of our national life and opening the country once more to the outside world.

In 1961, after the disturbances of the preceding period—during the so-called "Great Leap Forward Movement" had subsided and the Institute of Physiology of the Chinese Academy of Sciences where I worked seemed to be ready to resume normal scientific life, I planned to start a new research program. The neuromuscular junction which I had studied before had by that time become an active field of research in which many people were engaged. The neuromuscular junction is the locus of the brief, fast events associated with neuromuscular transmission and it was with these that most researchers in the field were concerned. However, it is also the site at which the slower events or trophic transactions between nerve and muscle take place, and at that time these events were receiving much less