Calcium Study to Alzheimer's Therapeutics

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A Biochemist's Journey

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PREFACE

Calcium is a key molecule in organisms, carrying out vast numbers of essential functions, without which the very inception of life on Earth would have been impossible. Befitting to the driving roles in the development of life and organisms, the storage and control of calcium in organisms are the single most important task that is at the foundation of all biological mechanisms. Nevertheless, our knowledge about where cellular Ca^{2+} is stored and how they are controlled is still very limited. Although more is known about the Ca^{2+} storage and control in the cytoplasm than in the nucleus, virtually nothing was known about the nuclear Ca^{2+} until very recently. Therefore, in this book the subcellular organelles that play major roles in Ca^{2+} storage and control are introduced - the secretory granules in the cytoplasm and the nucleoplasmic Ca^{2+} store vesicles in the nucleus, and their mode of action, molecular structure, and functions are discussed. For the subjects have not been covered in the scientific community before, the contents deal with scientifically very up-to-date information even for researchers in the Ca^{2+} field.

The present works on Ca^{2+} storage and control mechanisms have been made possible through contribution of a number of past colleagues and collaborators, in particular Dr. Joseph P. Albanesi of the University of Texas Southwestern Medical Center at Dallas and Dr. Marc S. Lewis of the National Institutes of Health in Bethesda, Maryland. Through their

distinguished scientific insight, talent, and input, the project could proceed with vigor and excitement, leading eventually to development of Alzheimer's therapeutics three decades later. Upon my return to Korea and at the time of trying to set up the lab and restart the research at KAIST in Dae Jeon, Drs. Choon Ju Jeon and Chan Seob Shim were a big help during the time of transition, uncertainty, and much anxiety. While there I collaborated with Drs. Edwin Thrower and Barbara Ehrlich of Yale University on the regulatory role of granin proteins on the IP_3 receptor/Ca^{2+} channels.

I moved to Incheon a few years later, and the major chunk of the work presented in this book, including the discovery of the nucleoplasmic Ca^{2+} store vesicles, was carried out in Incheon, at Biochemistry Department of Inha University School of Medicine. Many hard-working members of the lab, including many students, have contributed to the scientific advances presented here; production of the real-life 3D shape of an adrenal chromaffin cell and determination of the subcellular volumes of the nucleus, the secretory granules, and the endoplasmic reticulum of chromaffin cells have been carried out based on dozens of serially sectioned electron microscope images of adrenal chromaffin cells. Such knowledge was essential to accurately estimate the concentrations of Ca^{2+}, Ca^{2+} storage proteins granins, and the IP_3 receptor/Ca^{2+} channels in each organelle of the cells.

Of the many who have worked in my lab at Inha, special thanks go to Yang Hoon Huh, Sei Yoon Chu, Seong Kwon Huh, Soung Hoo Jeon, and

Yong Suk Hur. It was during this time that the Korea Basic Science Institute in Dae Jeon made their super-expensive high-voltage electron microscope available to us, so that we could obtain tomograms of the small nucleoplasmic Ca^{2+} store vesicles (shown in Fig. 6-3a). And the human brain studies were done in collaboration with Dr. Sun Ha Paek of the Department of Neurosurgery of Seoul National University School of Medicine. Reflecting complex cellular mechanisms introduced here, the book contains many artworks to convey the scientific concept clearly. Although the original drawings were done by me, the drawings went through numerous modifications and fine touchups, which required long and arduous work. So many of my administrative assistants at the department diligently labored for weeks at a time for each piece.

Moreover, totally unexpectedly when I first started working in the field, the Ca^{2+} storage proteins, granins (chromogranins and secretogranins), were found to play major roles in the pathogenic process of the most devastating human disease, Alzheimer's disease. Yet fortunately, we could figure out not only the pathogenic mechanism of Alzheimer's disease but also how to inhibit the pathogenic steps so that it now appears possible to prevent and even cure the disease. So I share here not only the whole discovery process of Alzheimer's therapeutics candidates but also a bevy of relevant information regarding the disease, which should benefit Alzheimer's workers, patients, families, and interested public. In the adventure to develop Alzheimer's medicine in Songdo international city, my former student Yong Suk Hur joined the lab and contributed greatly to the project. Moreover, to help future research in the field, relevance of

secretory granules and granins to heart diseases and brain tumor glioblastoma multiforme is also introduced.

Lastly, I'd like to thank my wife Sue who has patiently endured long hardships and stood by me through all the difficulties and hurdles encountered while I have been seeking the solution to Alzheimer's disease. My great appreciation also goes to our family friends, Mr. and Mrs. Chang Seob Kwon, Dr. and Mrs. Thomas Constable, and Mr. Frank Carmical for their continued prayer support during my unscrupulous-looking adventure to develop Alzheimer's medicine.

Seung Hyun Yoo

INTRODUCTION

As one of the atoms in the dawn of the Universe and Earth, calcium took its position as the foundational atom of subsequent development of material world, and so established as the key molecule in the development of life-forms on Earth. Due to this historical background, calcium (Ca^{2+}) has been an essential player in virtually all the important biological reactions in organisms, and the Ca^{2+} storage and control mechanism is at the center of vast numbers of cellular functions. So misfunction of Ca^{2+} storage and control in cells is fatal to the health of the organisms. Reflecting such background, the origin, and the history of calcium's role in biokingdom are discussed in one chapter (chapter 4).

Regarding the question of where cellular Ca^{2+} is stored and how it is controlled, recent scientific advances have shown that the storage and control of Ca^{2+} in the cytoplasm are primarily handled by secretory granules (focus of chapter 2) while those in the nucleus are by the numerous small nucleoplasmic Ca^{2+} store vesicles (focus of chapter 6). Accordingly, combined with the historical origin and the scientific significance of the role of calcium in biosphere, the first half of the book covers the historical account of scientific discoveries related to Ca^{2+} storage and control role of secretory granules in the cytoplasm and of the new nucleoplasmic Ca^{2+} store vesicles in the nucleus.

And in connection with the crucial roles of Ca^{2+} storage proteins granins and secretory granules, the latter half of the book deals with their implication to neurodegenerative diseases with focus on Alzheimer's disease. Since all the key brain cells (neurons, astrocytes, and microglia) are secretory cells that contain secretory granules and secrete granin proteins, Alzheimer's disease is directly affected by granins - the major proteins in the cerebrospinal fluid of the brain. Therefore, the detailed connection between granins and Alzheimer's disease is introduced in the latter half of the book. Moreover, the discovery process of potential Alzheimer's therapeutics is also extensively explained along with, 1) the underlying molecular mechanism of pathogenesis, 2) insight into the methods to inhibit the progress of disease, and 3) relevant and helpful information related to the current status, symptoms, diagnosis, treatment schemes, and prospects of Alzheimer's disease.

Since secretory granules and granin proteins have also been shown to be closely linked to major human diseases such as diabetes, heart diseases, and brain tumors, the relevant data on heart diseases and brain tumors are also introduced. To our great surprise, astrocytes of the brain cancer glioblastoma multiforme expressed explosively increased granin proteins and secretory granules in them, which indicated a strong cause-effect relationship between the players of Ca^{2+} storage and control and the brain tumor. Furthermore, heart cells, both atrial and ventricular cardiomyocytes, have also expressed secretory granules and granins, thus not only identifying themselves as secretory cells but also strongly linking the inositol 1,4,5-trisphosphate (IP_3)-sensitive Ca^{2+} store and control

organelles and granin proteins to heart failures and cardiac hypertrophy. Accordingly, the relevant information is added at the end as a future avenue of research.

In addition, since the contents of the book are a culmination of my 30 plus years of scientific research on Ca^{2+} storage and control mechanisms in cells and granin proteins, I structured the book in a biographical format to reveal the details of the scientific reasoning and the process, thus sharing my personal history beginning from the Korean War (1950-53). My personal life coincides with the spectacular modern history of Korea which transformed from a rock-bottom poor, war-torn country in the mid-20^{th} century to one of the most advanced countries in one generation and a half. With the rapidly increasing popularity of K (Korean)-culture, -food, and -arts on world stage these days, I felt that the historical account of my experience as a person who has lived through such a breathtakingly transforming country from its starting block to a state-of-the art science/technology leader that also developed Alzheimer's therapeutics would be worth recording for readers of various backgrounds.

1. PERSONAL HISTORY

1-1. Family Background

I was born in Shin Mak, Hwang-Hae Province, Korea (presently north Korea) - which is located on the very train route the Gyung-Ui Line that links Seoul to Shin Ui Joo, the border city between Korea and China - in late November 1950 at the height of the Korean War (1950-1953) to a family who has lived in Hwang-Hae Province for at least hundreds of years. My family genealogy traces back thirty-six generations from me, spanning about 1,100 years to the period when the Koryo dynasty (918 AD – 1392 AD) had just been inaugurated with its capital in Gae Sung (ancient name Song Ak) near where my ancestors had lived and I was born. My ancestral hometown is Pyong-San Goon, Hwang-Hae Province, and my mother was from a town called Do Jeo Wool, Han Po, near Gyung-Gi Province. Incidentally and to my extraordinary interests, Pyong-San Goon and neighboring Hae Joo, which are in the southern region of Hwang-Hae Province near Gae Sung, are also hometown of several prominent recent leaders of Korea, including Ahn Joong-Geun who was the most distinguished Korean independence movement leader at the turn of the 20th century when Korea was on the verge of being annexed by Japan, Dr. Rhee Syng-Man who was the founding president (1948-1960) of the republic of Korea and had laid the firm foundation of Korea to be what it is today - an advanced, democratic, prosperous, and freedom-loving country, and Kim Goo who had led the Korean government in exile for

dozens of years in China during the Japanese colonial rule (1910-1945).

After the end of World War II and the surrender of Japan in 1945, the north Korean side (north of the 38th parallel (latitude) line) was occupied and ruled by the communists who had been backed by the Soviet Union (present Russia) whereas the southern side of the 38th parallel line of Korea was initially administered by the US military with the aim of building a democratic country. During the communist-ruled period (1945-1950) in north Korea, my parents and the family have severely been persecuted due to my parents' staunch anti-communist attitude. Before the outbreak of Korean War my parents have tried to escape north Korea on several occasions to move to democratic south Korea. At one time the family has even moved to a town called Yeo Hyun, which is located barely on the northern side of the 38th parallel line, looking for an opportunity to cross the 38th parallel line, yet they could not find a right opportunity to cross the line because the communist authorities had always kept keen vigilant eyes on my family's move.

In face of such hostile suspecting eyes, my parents had to give up their hope of escape to the south and returned to Shin Mak, near their original hometown, to work for the north Korean national railway system. For Shin Mak is located on a key strategic railway route, linking Seoul to Shin Ui Joo (the Gyung-Ui Line), all the trains that run on the route made a routine stop there. Moreover, there was a major train maintenance and repair plant in the city that my father started to work as a machinist after returning from Yeo Hyun near the 38th line. Therefore, with little choice left my

family had to settle down in Shin Mak, and my father started to work at the train maintenance and repair plant. My mother conceived me in early 1950 when the north Korean leader Kim Il-Sung was secretly, but intently, preparing the whole north Korean side to invade the unsuspecting south. Since my family has been living in a city that served as a key logistical locale in supplying the wartime materials to the frontline, the 38th line - just a short distance directly due north of Seoul - my family had witnessed the endless caravans of supply trucks, trains, and human carriers, moving toward the south under the cover of darkness at night during the months leading up to the sudden, unannounced June 25 invasion of the south.

1-2. The Korean War

While Kim Il-Sung and the communist north Korea were preparing for the blitzkrieg invasion of the south, they conscripted their soldiers by force from all walks of life in north Korea regardless of the conscripts' age. Living in the north at the time, such madness also forcefully disrupted my family's life and as a result my parents ended up forfeiting their first child, a son, who was a high school junior at the time, to the communists. The north Korean social mood at the time, leading up to the June 25 invasion at the start of the Korean War, was highly ominous to families like ours whose staunch anticommunist attitude had already been widely recognized by the communist authorities. My parents and other like-minded families began to sense that the communist authorities are intent on conscripting male youths, regardless of ages, to the communist army, so many youths, including the first child of my parents who was only a high school junior, had to leave their homes and hide somewhere in remote mountains.

During this period of escape and hideouts, my parents had to bring food and clothing to their son who had been hiding in a remote mountain cave while the communist authorities were frantically searching for the hideouts. One of the mountain hideouts my brother had hidden was among the mountain ranges of Gam-Ak San (Mt. Gam-Ak, height, 674 m), as they were called by the local people.

While this hide and seek has been going on for a while, the school authorities in Shin Mak have been demanding all their hiding students to come to school, ostensibly for fear of their students losing out on their precious education at school. But they were trying to deceive the students so that when they return to school the communist authorities can snatch them up and conscript them into the communist north Korean military. In the meantime, owing to the indefinite length of time to hide with no end in sight and the burden to provide daily supplies and foods on foot to the students who had hidden in the far-out locations by the caring parents and relatives, the hiding students started to leave the hideouts and visit their homes once in a while.

As a result, when the students showed up on the day the school authorities demanded, the communist authorities rounded up all of them and brought to the military camp that very day, thereby leaving the parents in the dark for many days until they were finally told that all their sons were conscripted into the communist military. Once all the students were driven away to an unknown place, the parents have been kept in the dark for many months and never been told what is happening with their sons, until

my parents heard a rumor one day that a division of north Korean army to which their son belongs is marching through the town at night, apparently heading south toward the frontline. It was in September of 1950, about three months after the breakout of the Korean War. Upon hearing this surprising, yet long-awaited welcoming rumor, my parents hurriedly prepared some food to pass on to their son in case they could get hold of him and went out into the streets the soldiers were rumored to pass in the middle of the night.

After several hours of anxious waiting in the streets, columns of soldiers indeed came marching on and passed in front of the crowds who had been waiting for them. Luckily, my parents could notice their son among the marching soldiers, but since they were in marching orders not to be disturbed, only my mother rushed out from among the crowds and quickly approached her son to pass the home-made food package to him. Although she had succeeded in passing the food package to her son, she could not have even for a moment to exchange words with her son because he was among the marching soldiers and was not allowed to stop. His only words to her mother at the time was, "mom, don't worry about me, and stay healthy!" The columns of marching soldiers kept moving and disappeared into the darkness, and that was the last time my mother saw or heard from him.

After the dramatic encounter with their firstborn son, my parents have never seen him nor heard about him again during the war, which lasted for three years. But he was last seen in Geo Je Island prison camp that was in

the South Sea of Korea right after the war by one of his high school friends. Although not known at the time, many thousands of anticommunist prisoners were later known to be slaughtered secretly by communist prisoners in the prison camp. It was during this dark period in the prison camp that I suspect my brother who was a staunch anticommunist and a leading figure among anticommunist prisoners might have been killed by communist prisoners. Such scenario is a very likely possibility judging from the account of my brother's high school friend who had seen my brother in the camp, survived the prison camp, and told my parents of his experience at the camp after he had been freed from the camp.

When the democratic south was in real danger of being overrun by the communist north, the UN and Korean forces led by US Gen. Douglas MacArthur had successfully conducted the Incheon Landing operation and began to push back the invading forces. After the successful Incheon Landing operation, the communist north Korean soldiers were forced to retreat, and were driven back all the way to the northern end of Korea. During the period from the days of Incheon Landing to the retreat of the communist north Korean forces from the middle region of the nation, Shin Mak the city my family has been living in was a major target of attack by the UN forces because it was not only a key city positioned in the Gyung-Ui Railway line, connecting Seoul and Shin Ui Joo - a border town between Korea and China - but also a strategic town with a major railway plant that has maintained and repaired railway trains.

1-3. Birth in North Korea

Soon after such horrible war-time experiences, the communists in the north were forced to abandon the town and retreat to the further north, and the UN and south Korean soldiers began to arrive in the town. Although the UN and Korean forces have pushed back the communist invaders to the north and advanced to the Ap Rok (Yalu) River, the Korea-China border, the war was nonetheless far from over: The UN forces were ordered not to cross the border to Manchuria, China to defeat the fleeing communists who escaped to Manchuria by the then US president Harry S. Truman although that was a sure way of wiping out the enemies. While the UN and Korean forces lingered around the border, the Communist Chinese army soon joined the war with an overwhelming number of soldiers, forcing the UN and Korean forces to retreat. It was during this brief period in which the UN and Korean forces advanced to the border between Korea and China that Shin Mak was freed from the communist rule. I was born during this brief period of peace and freedom in late November of that year, 1950.

However, it was not long before my family heard the news that the UN and Korean forces that had reached the Ap Rok (Yalu) River are now retreating, which caused a massive migration of anticommunist, peace-loving north Koreans to flee the communist north. While my mother had been recuperating from the childbirth in Shin Mak, my family has witnessed endless streams of refugees from the north moving toward the south through Shin Mak. It was therefore plain clear that my family also had to move to the south soon unless they risked being ruled by the

communists again. Realizing the stark reality, my father, who has been a leading figure among the anticommunist families in the rail train maintenance plant, had organized a group of families who wanted to move to the south and arranged specific departure plans for the south. Accordingly, my father and others repaired a locomotive that had been partially destroyed during the UN air-attacks and bombings, and also had several freight cars ready for the evacuation trip. After loading whatever belongings and possessions they could muster to the freight cars, they hurriedly left for the south on a frigid-cold early December day. I was barely ten days old at the time, and the temperature back then stayed often at -20^{o}C or lower during the winter in north Korea.

1-4. Childhood in Busan

The evacuation train had finally arrived after a month on the road at Cho Ryang railway station in Busan, the southeasternmost port city of Korea, where my family and all the refugees disembarked from the train. But since there was no place to go, my family and others had remained in the open areas of Cho Ryang railway station for a few days. Since it was still January, the coldest month in Korea, the refugees from the north had a very difficult time to keep warm or preparing food to eat in the open yard. Yet sympathizing with the hardships of the refugees who had just arrived, some native Busan residents from the surrounding areas kindly brought some movable earthen cooking stoves that are fueled by charcoals or log embers, which helped relieve the pains and hunger of my family and other refugees. Soon, they moved from there to one of the serene agricultural suburbs in northern Busan, near the foot of Mt. Baek Yang (height, 642 m),

not far from Seo Myun, where my family settled down, and I spent my entire childhood there until I left for college in Seoul after high school.

By growing up in a village that was surrounded by mountains at the foot of a large mountain (Mt. Baek Yang) I could also fully enjoy the nature that the mountainous environments have richly provided: In clean meandering streams of valleys, there were many kinds of small fish, aqueous insects, crayfish, and frogs, whereas on the above ground near the creeks and on the rolling hills and mountains, there were a wide variety of animals and plants that thrive and disappear in cycles, following the change of seasons. Among the clean streams, there were occasionally good-sized pools that were deep enough so I and other children could swim in during summers, and wildflowers that seasonally bloomed on the fields and mountains were pleasant greeters to welcome me every time I paid a visit - which I used to do often, alone or with friends - on Saturdays and Sundays from spring to fall. Only during my high school senior year did I miss the opportunity to visit and enjoy such places so I could concentrate more for the upcoming college entrance exam. But in contrast to enjoying natural beauty from spring to fall, in winters I have spent major chunk of my spare time sledding in creeks.

1-5. College Life in Seoul and Move to the US

I began my college in March 1969, with a high anticipation and hope for the unexplored future, without any real clue about what lies ahead. Unlike the relatively balmy March climate of Busan, the early March in Seoul still felt biting cold for me who had still kept the memory of balmy March in

Busan. Embarrassingly though, I realized soon that I had not been adequately dressed for Seoul's cold early March weather. In particular, the campus for the first-year class from the four colleges of my university – liberal arts and sciences, engineering, business, and law – was in the campus of engineering college, which was in a far-out open area of northern outskirts of Seoul. So the wind there appeared stronger and the temperature lower than the central regions of Seoul where I lived. It took about an hour and half each way to commute, yet the newly started college life in Seoul nonetheless seemed to proceed normally during the early part of the spring semester.

But after a few months into the first semester, the college life was interrupted by political turmoil of the nation that was caused by the authoritarian government of then President Park Chung-Hee, and the classes were stopped before the semester was over. This interruption continued, on and off for the remainder of the first year, crippling the normal academic year. After the first year, each of us first-year students moved to our own colleges for the remaining education, so I moved to the college of liberal arts and sciences for the sophomore year and onward. Yet the political turmoil of the nation did not subside throughout my college years, and this has severely crippled my college life. Even though I had spent 4 years, 8 semesters, in college, the actual time of education seemed to be only for about 3 semesters due to lengthy interruptions caused by political instabilities of the nation during the period, which surely ended up hurting me academically in my subsequent scientific career.

I left Korea in the summer of 1975 for graduate study in the US. For Korea was still recovering from the Korean War and there was no strong industrial base in the nation – the per capita income of Korea in 1975 was US$617. The nation's economy was export-driven, and all the economic activities were focused on earning dollars for a better future. Consequently, any activities that require spending dollars overseas were strictly regulated. This policy also affected those who wanted to study overseas so the government had tightly controlled the number of students who can even apply for government's passport, without which the prospective students could not apply for visas of the host countries. In those days, ordinary Korean citizens were not allowed to apply for a passport nor issued one, so the privilege of applying for issuance of a passport by the government was permitted only to those who had passed the overseas-study qualification exam that had been sponsored by the Ministry of Education of Korea.

1-6. Arrival in Honolulu and Reunion with Jerry Dubuque

With the award of a full scholarship by graduate schools in the US, I could obtain the entry visa to the US and left Korea in the late afternoon on July 4, 1975. I landed in Honolulu, Hawaii, *via* Tokyo, in the morning of July 4, the Independence Day of the US, where I was greeted by my American friend Gerald "Jerry" Dubuque whom I had befriended when he was a Peace Corps volunteer in Busan several years ago. Jerry has been studying Korean Studies as graduate student at the East-West Center of the University of Hawaii at the time, and I spent a week with him at his dormitory room before heading to Texas, where I was supposed to enroll at the University of Texas Health Sciences Center in Houston for graduate study.

Being out of Korea for the first time and especially from a country that had not yet recovered from the destruction and ravages of a big war and remained a poor country, the air and scenery I have experienced in Hawaii were so other-worldly beautiful and refreshing that it seemed there was no air to see or feel in the air. In addition to such an impressively clean and transparent air, the beauty of flowers, plants, and trees in surrounding natural setting was so impressively exotic and pretty that it made me feel that Hawaii is a paradise transplanted on earth. Moreover, the frequent but brief showers - which are characteristics of a subtropical climate, seen even in the presence of shining sun in the sky, were surprising enough to me who had never experienced such a phenomenon in Korea before.

But this feeling of wonders in a new world was soon pushed aside temporarily when Jerry and I went outside of the campus - after leaving the luggage in his dorm room - to eat lunch because the university cafeteria remained closed to observe the Independence Day. When Jerry took me to a local Asian restaurant, which was not a Korean-style one, a couple hours after I arrived in Honolulu, I was at a loss what to order for lunch because the menu was totally unfamiliar to me. I ended up eating just a bowl of steamed rice after splattering it with soy-sauce, because I had no idea what else was available at the restaurant. Being an American from Seattle, Washington, Jerry was also not prepared for such an unexpected turn of event and felt very embarrassed, although he might have thought that a local Asian restaurant might be able to provide a suitable meal for me.

Once Jerry found out that my food choices have a long way to be Americanized, he escorted me to a supermarket that sold kimchi, a representative Korean food. Though it was in Hawaii, the very availability of kimchi in the US grocery store was quite a surprise because I have never imagined finding typical Korean food in the US market. Yet, the very existence of kimchi in the US grocery store has greatly relieved me of the deep lingering fear of not being able to eat the kind of foods that are familiar to my taste in the US, which I felt was an uncompromisable condition for me to survive in the new world.

In stark contrast to the world-popular K-food fame of the 21st century in which kimchi is now loved by so many people in the world as one of the premier health foods, in addition to its superb salad-like taste, kimchi was an unknown food back then, and people did not like the strong smell. But I carried the kimchi bottle with me every time Jerry and I went to the university cafeteria. So we had to eat at a table sufficiently separated from other tables in the cafeteria so other diners would not be bothered by the kimchi smell. While I have stuck with the kimchi bottle and the steamed rice at the cafeteria during my stay in Honolulu, Jerry would often choose sour milk products, which, when I tasted a little bit of it, tasted like inedible, terribly spoiled rotten milk. Ironically, after several years of living in the US, I began to like and enjoy those sour rotten milk products (yogurt) Jerry used to eat back in Hawaii.

1-7. Graduate Study at the University of Texas Health Sciences Center in Houston

After a week with Jerry in Hawaii, I flew to Fort Worth, Texas to spend a month with an exceptionally loving American host family, the Van Vlakes, who had arranged to have me come and live with them before I went to graduate school, which turned out to be an invaluable transition to a typical American society. So in Fort Worth I spent a month of wonderful and warm time with the Van Vlake family, after which I flew to Houston for graduate study at the University of Texas Health Sciences Center, which is located in the campus of the Texas Medical Center. The graduate scholarship stipend at the time was US$319 a month which was sufficient for me to live and study in the US. For the University of Texas Health Sciences Center did not have dormitories for students, I had to rent a room of a private citizen's house which was located five miles from the campus and commuted to the school by bike. Though the lodging was solved by renting a room, preparing food was still a formidable task for me in a completely new world, who had never cooked at home in Korea because the food had always been prepared by my mother or others. Even while I lived with the American host family in Fort Worth for a month, I have not done any cooking but eating the food prepared by them.

Notwithstanding such a troublesome culinary issue in Houston, the one year I spent in Houston was essential in my learning biochemistry, physical chemistry, and many laboratory techniques, which served me well in my later study in Austin and beyond. Being a part of the modern medical center in the US, the University of Texas Health Sciences Center