Recollections of Vitamin Research by Suzuki Umetaro

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SUZUKI UMETARO

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RECOLLECTIONS OF VITAMIN RESEARCH BY SUZUKI UMETARO

IN RETROSPECT, animals were thought for a long time to grow and develop entirely from nutrients that included proteins, fats, carbohydrates, as well as inorganic elements like calcium, phosphorus, iron, and iodine. Moreover, no one had any doubt.

I demonstrated that animals could not maintain life with only the above four components, proposed the existence of substances in trace amounts that support life, discovered one of these mysterious substances contained in rice bran, extracted and analyzed this substance, and named it *Oryzanin* (vitamin B). In the winter of 1910, I published a paper for the academic world, but, at that time, it went unnoticed for the most part. Around 1918 or 1919, fervent research on vitamins that had developed in the academic worlds of Europe and the United States reverberated in Japan. Finally, the eyes of Japanese scholars had been opened. Today, no one would discuss nutrition without vitamins, just as no one would discuss life science without knowledge of vitamins. Considering this, it feels like a completely different world.

My research on vitamins began immediately after I returned from Germany in 1906 and has lasted 24 or 25 years. I've spent nearly half a lifetime on this research, and, perhaps, will continue on for a lifetime. Although various motivations for this research could be imagined, my primary motivation was the acute realization of the poor constitution of the Japanese people when I studied abroad. Although Japanese people had competed against and studied with foreign scholars and, for the moment, had not been defeated, this would not continue indefinitely. I pondered the cause endlessly.

At the University of Berlin in those days, Professor Emil Fischer had embarked on the study proteins. As his student, I assisted the Professor with his work for over two years. We first determined the differences in the nutrition provided by various proteins. Since rice is a major food of the Japanese, the

surrounding questions were whether rice protein is bad, and whether the nutritional values of rice protein and meat protein differed significantly.

Before I returned to Japan in 1906, I consulted with Professor Fischer about what kind of research I should pursue upon my return. He stated, “If you tackled the same problems as European scholars, you would not be able to compete with the well-equipped facilities and the many people doing formidable work. A better course would be to find a problem particular to Asia.” Since I thought this probable, I decided to research the current problems of rice.

Upon returning to Japan, I was appointed as a professor at the Agricultural High School of Morioka where I first collaborated with Yoshimura Kiyohisa (currently, President of Kagoshima Agricultural College). We investigated the properties of the proteins of white rice, brown rice, and bran; extracted a phosphorous compound (phytin) from bran; and discovered proteins in bran that contained iron.

Simply analyzing a protein to determine its nutritional value is inadequate. Animal tests must also be performed. As a researcher in agriculture, I’m familiar with fertilizer testing methods with plants. In water cultivation, plants absorb plant nutrients, for example, ammonia, phosphoric acid, potash, and lime, dissolved in appropriate amounts in pure water and healthily grow. However, if even one nutrient is missing, the plant may stop growing or die. For example, if phosphoric acid is missing, the leaves will turn yellow and wither.

Similar tests are available for sandy soil cultivation, when the plants are planted in clean sandy soil and given various nutrients. Similarly, with animals, it should be possible to collect pure proteins and fats, carbohydrates and inorganic components, and to produce an artificial formula feed for raising animals. I believed that animals would develop differently if given different types of rice proteins or meat proteins and tested this hypothesis with pigeons and rats. Animals fed compound feed similar to the one described above died unexpectedly after several weeks. Despite repeated trials, the outcomes were the same, but I could not determine the cause. I did determine that bran

contained a special component and tested for healthy growth by adding bran to the compound feed.

In those days, bran like lees was only used as livestock feed or as fertilizer, and was never considered to be food for people. I found that adding bran in the form of an alcohol infusion was as effective. I then applied various chemical manipulations to obtain a single product and found a previously unknown component, namely *Oryzanin* (vitamin B).

Parallel to this research, medical doctors were confronting the problem of beriberi. At that time, Dr. Christiaan Eijkman of the Netherlands was conducting research on beriberi in Java, the Dutch East Indies, and fortuitously discovered that chickens would become unsteady and die when fed leftovers from hospital meals. He then fed the chickens white rice and observed that all of them experienced the same weakness and leg paralysis, which closely resembled the symptoms of beriberi in people. However, when fed brown rice, the chickens did not become sick. This effect was also observed when the chickens were fed a mixture of bran and white rice.

Dr. Eijkman thought that the chickens were poisoned by microorganisms that adhered to the white rice and multiplied in the chicken's bladder, and that some substance in bran neutralized the toxins.

During that time, doctors in Japan also took note of rice. Takaki Kanehiro, a medical officer in the Imperial Japanese Navy, was troubled by the deaths of sailors who developed beriberi while on long voyages and surmised that there may be a link to food. He conducted tests replacing Japanese food with western-style food or white rice with barley. The test results confirmed that beriberi became rare when barley was mixed with rice, and eventually led to improved Navy food. However, he could not explain why barley mixed with rice was better.

Soon after returning from Germany, I presented a lecture about protein at Sankaido in Akasaka that was attended by Dr. Takaki, who said, "Your talk was interesting. This is the first time I've heard that the nutrition differs with the type of

protein. I would like to see research on how the properties of the proteins differ in rice and barley."

At that time, medical doctors who believed that white rice caused beriberi had a variety of explanations, such as toxins in white rice or harmful microorganisms attached to the rice. Many elite doctors in the medical world disagreed with Dr. Eijkman's theory; they thought beriberi was an infectious disease. Another theory was that beriberi was caused by eating blue fish, like mackerel.

THE DISCOVERY OF ORYZANIN

MEANWHILE, I CONTINUED to study the components of rice and conduct animal tests from the perspective of pure nutritional science unrelated to the cause of beriberi. Naturally, my initial thought was that animals given white rice would die. I soon found by analyzing white rice that it contained 7% protein, 90% starch and fiber, an extremely low 1% amount of fats, and an even smaller minute 0.5% amount of inorganic components. The animals did not have to be raised entirely on their favorite foods. I believed that adding the missing components to white rice would be beneficial and performed tests in which casein or lard, phosphorus, iron, and lime were added at various ratios. Unexpectedly, the animals weakened and died which was almost identical to when they were fed a diet consisting only of white rice.

If the percentage of bran added to white rice was just 3%, the animals grew up healthily as Dr. Eijkman had observed. Therefore, I conducted tests by adding *phytin* collected from bran, iron-containing protein, or bran ash. However, the results were not the same. But when a simple alcohol infusion of bran was added, I observed an effect. Around the same time as the compound feed tests described above, I investigated the components of this alcohol infusion and eventually discovered *Oryzanin*.

Shimamura Torai alone was in charge of the animal tests in the discovery of *Oryzanin* and did not take a day off for two years. Otake Satoru provided substantial assistance. By the winter of 1910, we had become increasingly confident in our findings that animals fed white rice soon died due to a lack of *Oryzanin* and presented these findings to the Chemical Society of Tokyo. I stressed that *Oryzanin* was a previously unknown, new nutrient and was essential to all animal growth. This is the foundation of today's vitamin theory.

My announcement presented no problems for the most part to chemists and medical doctors at that time because few were aware of nutrition. Only Dr. Ikeda Kikunae of Tokyo Imperial University commented, "If this is true, it is very interesting..."

I continued to be engrossed by this research and reported results to the Beriberi Investigative Committee of the Imperial Japanese Army in April 1911. I also informed the Chemical Society of Tokyo of the properties of *Oryzanin* and the essential components of the nutrients about five times by February 1912. Unfortunately, these also failed to attract any attention.

In January 1911, I applied for and received a patent for a method for manufacturing *Oryzanin*. I then had Sankyo & Company manufacture samples and offered them to the medical community to conduct extensive experiments. Unfortunately, these samples were largely ignored and viewed with caution by the company.

THE COINING OF VITAMIN

JUST ONE YEAR after I discovered *Oryzanin*, Casimir Funk of the Lister Institute in England reported that he had extracted the same effective components that I had already extracted (February 1912). Because the term vitamin he coined was in common use worldwide, it was easy to erroneously believe that Dr. Funk had been first. At that time, Dr. Funk believed these components cured a disease resembling beriberi in birds, but neither conducted experiments nor discussed whether this substance had any nutritional significance. He attracted the world's attention because he had announced the extraction into the crystalline form. However, he was mistaken, that crystal was nicotinic acid, which I had previously discovered, and not the effective component. I compiled papers encompassing several dozen of my results reports published in Japan over the previous few years and published them in the *German Journal of Biochemistry* in August 1912. People outside of Japan had not seen these original papers because they had been initially published only in Japanese journals. Thus, they appeared to follow Dr. Funk's paper.

As I explained earlier, I produced compound feed to confirm the effectiveness of *Oryzanin* by using white rice. I also planned tests involving many animals; in addition to pigs, cows, dogs, cats, doves, domestic fowl, and mice, the tests included fungi and yeast bacteria. I demonstrated that *Oryzanin* is needed by all higher animals with the exception of particular filamentous fungi and bacteria. This work was accomplished with the assistance of many researchers.

Because of the need to conduct tests involving humans, in 1914, Suzuki Bunsuke (formerly, Araki) and I gave *Oryzanin* to a sub-group of 20 children, who had been hospitalized in a Tokyo asylum, for a full year in order to study the growth of these children and the others who had not received *Oryzanin*. The results were encouraging. (We were assisted by Dr. Itami of the asylum.)

THE MOCKERY SURROUNDING BERIBERI

WE FIRMLY ESTABLISHED the need for *Oryzanin* in people, and believed the lack of *Oryzanin* to be the cause of beriberi in people because white rice contains absolutely none. However, not being a medical doctor, I felt particularly ill-suited to conducting experiments involving people.

When I first sent *Oryzanin* to a young doctor at Izumibashi Hospital and requested that he conduct tests, after just one month, he stated, “When I tested one patient, a workman, he reported having energy after three days and never returned. Another patient was seriously ill, but said that he became very energetic after taking *Oryzanin* for several days, and left the hospital although the symptoms had not entirely disappeared. I believed that *Oryzanin* was probably effective. However, because beriberi is cured by other methods, I cannot say that it is a wonder drug. I'll have to decline to conduct further tests because the chief of staff will not allow it.”

Next, I asked a doctor in private practice in my district, Nihonbashi, but he sent a letter of refusal. I was dumbfounded by his reason of absolutely no confidence.

At the Chemical Society of Tokyo, when a newspaper reporter asked an eminent doctor in the medical community at that time about my explanation that “*Oryzanin* should be effective against beriberi,” he stated, “Suzuki has said that bran is effective against beriberi, but that is simply nonsense. It’s amazing what some people will believe. If beriberi were cured by bran, then drinking urine should also be a cure....”

When I later met this doctor, he said, “Someone told me that you discovered the cause of beriberi. That was probably a joke.” I probably was not thought of as a medical doctor nor a chemist, but as someone with some familiarity with beriberi.

A little later, on my way to teach at an agricultural college in Aoyama, I came across a student carrying another student on his back. I asked what

happened. He said the other student had a test that day but could not move because of beriberi, so he was carrying him to school. I told him that I had a treatment, and immediately ordered two bottles of *Oryzanin* from Sankyo & Company. Two or three days later, the students came to my home and the ill student drank the *Oryzanin* and recovered inexplicably fast. I live in 4-chome in Aoyama and today he came to thank me. His gait matched that of a healthy person. Since there were no trolleys at that time, he surely had to walk over two miles round-trip. The student had been cured by taking a bottle and said that he had the other bottle in safekeeping.

Another time, a young man from my hometown came down with beriberi and set out for home. He experienced heart failure while on the train and had to disembark and be hospitalized in Odawara. A telegram stating that his condition was critical and to come immediately was sent to my neighbor's home. I took two bottles of *Oryzanin* and consulted with the hospital director to ask him to administer this medicine. In two to three days, the young man was energetic and returned home in just a week. The patient was surprised by the unexpected effect and sent a note of thanks. But it seems that the hospital director did not say that the medicine I had provided was effective.

Another time, a research student in my laboratory visited a barbershop that was in an uproar and inquired about the reason. The proprietor said that he had experienced heart failure caused by beriberi and was in distress. The student who had *Oryzanin* in his pocket said, “This is excellent medicine for beriberi. You should take some right now,” and had the proprietor drink half of one bottle. In less than half an hour, the sickly man who had been in great distress became calm and composed. By the next day he had taken all of the medicine, had completely recovered, and was extremely grateful.

I have collected many similar reports, but cannot publish them because I am not a medical doctor.

THE CAUSE OF BERIBERI IS ESTABLISHED

IN 1908, THE Special Beriberi Research Council was established in the army. Around 1912, tests were conducted to determine whether bran was truly effective. However, some doctors conducted tests involving patients with beriberi using a boiled aqueous infusion of bran and reported that an equivalent effect was not obtained.

In this climate, there was no resolution at all to this argument. Ultimately, it was evident in retrospect that a potent form of vitamin B could not be manufactured because the amount provided was small. If a large amount of the potent product could be provided, the effect was remarkable.

Around 1918 and 1919, vitamin research was flourishing in Europe and the United States; this resonated again in Japan. Doctors in Japan perhaps thought that this problem would allow them to demonstrate their true abilities. Above all, Professor Shimazono Junjiro, who was then at Kyoto University, used my manufacturing method to produce *Oryzanin* and conducted tests involving many patients with beriberi. He obtained good results in tests involving seriously ill patients with wet beriberi and was increasingly led to the conclusion that the main cause of beriberi was a lack of vitamin B.

Around this time, Professor Omori Kenta of Keio University attracted the attention of the medical world by giving several assistants and nurses foods containing little vitamin B to artificially induce beriberi and tested whether providing a vitamin B preparation cured them. Previously in 1913, Dr. Max Moszkowski, an assistant of Professor Zuntz of the Agricultural University of Berlin, ate food containing little vitamin B, and in less than 200 days became seriously ill with a beriberi-like disease. He recovered by drinking a bran infusion and later published the clinical report.

However, his diet was not completely free of vitamin B. Additionally, his symptoms differed from those of beriberi found in Japan. Consequently, Japanese doctors were skeptical.

Nonetheless, the beriberi problem has weathered many storms and eventually returned to the theory of a lack of vitamin B. Thus, preparations of vitamin B have emerged over time to reach the several dozen varieties available today.

A TRIUMPH FOR CHEMISTS

THE POTENT *Oryzanin* I manufactured in 1911 was still not chemically pure. The cure for the beriberi-like disease of pigeons required 5 to 10 milligrams. To extract the crystalline form, I actively conducted research with the assistance of Otake, Shimamura, Suzuki (formerly, Bunsuke), and many others. However, we were unable to reach the goal.

During that time, World War I erupted in Europe in 1914 and the supply of raw materials and medicines to Japan was stopped causing great disruption. We chemists could hardly bear the suspension of *Oryzanin* research, but our lab mobilized to successfully produce antiseptic salicylic acid, raw alcohol, and lactic acid or Salvarsan (No. 606), and even tried to create antipyrine and synthetic indigo. This situation lasted four to five years. During that time, I became seriously ill twice.

Around 1920, we were able to resume research on *Oryzanin.* With Mr. Odake in charge, we extracted a large number of crystalline components with the aspiration of categorizing all of the components of bran and yeast. Although many of these substances were novel, none of the crystals was the vital B. In 1929, we first obtained just 2 centigrams of the crystals, but gained ample courage. About one year later in the summer of 1930, we produced a splendid crystal, a mere 0.3 grams, but we confirmed its effectiveness through animal tests.

A crystal of 0.02 milligrams was strong enough to cure a beriberi-like disease in pigeons. Therefore, we believed that one milligram would be effective in people. In November 1930, Dr. Odake announced these results at the Japan Society for Science. He then performed elemental analysis and tested other chemical substances.

To produce one gram of *Oryzanin* crystal, at least several hundred *kanme* (1 *kanme* = approx. 3.75 kilograms) had to be extracted from bran. Fortunately,

Sankyo & Co. could provide a large quantity of potent *Oryzanin* for injection. The ingenuity of Dr. Odake's tests and his patience were astounding.

In the future, we will determine the chemical structure of the vitamin B crystal and synthesize it, but have no idea how long this will take. Nevertheless, the crystalline form is a major triumph for chemists.

Apart from the beriberi problem, there was much debate over whether or not *Oryzanin* was actually a new nutritional component. The conditions supporting vitamin B's role in the nutrition of animals were abundant. However, various questions remained unanswered. Is it a type of protein? What is the dose? Is it a minute quantity of an overlooked substance in inorganic components? Or are lipoids needed or not?

As late as 1914, Dr. Osborne and Dr. Mendel in the United States declared that there was no need for vitamins. Dr. Abderhalden, a colleague during my years in Berlin, conducted tests over several years to provide counterevidence. Dr. Roman strongly opposed vitamin theory until 1917. In any case, it has never been easy to obtain broad consensus for any theory.

VITAMIN A AND OTHER DISCOVERIES

THE DISCOVERY OF vitamin A came several years after the discovery of vitamin B. When Dr. Osborne and Professor McCollum raised white rats with artificial compound feed, the animals grew very differently when butter rather than lard or vegetable oil was added to the feed. They surmised that some substance or active component was present in butter but not in the other ordinary fats. This was tentatively called a fat-soluble vitamin.

Takahashi Katsumi captured the true form. Takahashi studied this component at the Komaba laboratory around 1919 and extracted the component in a nearly pure state in 1922 and named it *biosterin*.

To date, we have confirmed that two elements are included in *biosterin*; one is the so-called vitamin A, and the other is vitamin D. An effect similar to that of vitamin A was confirmed in carotene pigment found in plants by Professor Euler of Sweden. Professor Windaus showed that ergosterin could be obtained from yeast or ergot by irradiating with ultraviolet light. Perhaps, carotene is reduced in the animal's body and stored in the liver. Currently, Kawakami and Washimi, my assistants at The Institute of Physical and Chemical Research, are primarily conducting this research.

Vitamin C is the most problematic substance. We do not know what to do because vitamin C is immediately destroyed when exposed to air or heat. It is also difficult to store. We currently have no idea how vitamin C crystallizes.

The late Dr. Miura Masataro discovered that green tea contains an abundance of vitamin C. Long ago, when merchant ships from the Netherlands came to the East, many people developed scurvy during the voyage. Based on records indicating that they had purchased tea from China to prevent scurvy on the return voyage, Dr. Miura tested Japanese green tea and found that it contained an extremely large amount of vitamin C.

The Chuo Tea Association widely publicized this finding and is expanding its tea market. The domestic demand is definitely high. For the past two to three

years, they have exported green tea to Russia, which exceeded 6 million pounds last year. There have also been orders from Norway.

In addition, for two to three years, I have conducted tests on vitamin E, which is needed in reproduction. A large amount of vitamin E is contained in wheat germ oil and closely mimics vitamin A, but its physiological effects are completely different. We have not yet produced a pure crystal of vitamin E.

Vitamins of all varieties play important roles and are indispensable. Vitamin B is the one most likely to be missing from the Japanese diet, probably followed by vitamins A and D. Vitamin B is not a problem in the United States, but the lack of vitamin D for children has led to many discussions. Vitamin C poses a problem in Russia. Interestingly, countries are distinct in this respect.

Vitamins have many applications in the industrial world. I believe that vitamins will be useful in many fields. Although true for any research, this kind of research demands continued perseverance. Even with considerable effort, research that is stopped prematurely will result in nothing. Fortunately, I have many research collaborators at the Komaba campus of the Institute of Physical and Chemical Research. If we don't tire of this research, the future holds intriguing possibilities.

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