Establishment of Biochemistry in Japan

Tatsumasa DOKE*

Biochemical studies in Japan started after the Meiji Restoration (1868) and grew up with a rapid transplantation from Europe. About twenty years latter, i.e. in1880s, the original studies of applied biochemistry full of local colour began to appear; thirty years later, i.e. 1900s, some of them were internationally recognized of their academic value in their own fields, and accordingly the more theoretical researches were brought up; and fifty years after the Meiji Restoration, i.e. in 1920s, it developed to a degree that Japanese students could attain in their Japanese institutions so excellent result that stands on the international level even in the field of pure theory. In 1922 two technical magazines on biochemistry, *the Journal of Biochemistry* and *the Acta Phytochimica* issued their initial numbers. In 1925 the Japanese Biochemical Society was established and acquired 513 members of Japanese scholars. To all appearance it seemed that thereafter Japanese biochemistry should make a rapid progress in quality as well as in quantity, and shortly should come into full blossom. But it did not. On the contrary it slowly came to a stop as the aggressive policy of Japanese imperialism proceeded, and finally fell down far behind the international progress. Since the end of the World War II it nevertheless recovered swiftly and is now running its way at full speed though facing with new difficulties one after another.

In Europe around 1868 when the Meiji Restoration broke out, a new field of biochemistry was brewing in Germany. Incidentally we may notice that in 1840 J. Liebig published a paper entitled *die organische Chemie in ihrer Anwendung auf Agrikultur und Physiologie*, in 1842 *die Tierchemie, oder die organische Chemie in ihres Anwendung auf Physiologie und Pathologie,*and in 1871 *Jahres-Berichte*

* The Tokyo Institute of Technology, Ôokayama, Meguro-ku, Tokyo, Japan.

über die Fortschritte der Tier-Chemie was born; and in 1877 Hoppe-Seyler and others started the *Zeitschrift für physiologische Chemie*.

In Japan prior to 1868, the scientific researches had been impeded under the severe feudalistic reigns. Nevertheless the productivities were rising gradually promoting the necessity of scientific researches. At the same time the studies of physiology and chemistry, two bases of modern biochemistry, were being made and accumulated in Japan, mainly by the efforts of medical practitioners though scarce in number. The European achievements were translated and introduced through the studies of Dutch learning; such as the *Seimi Kaisô* (1837-47) which Yôan Udagawa translated from a Dutch translation of *the Elements of Experiemental Chemistry* of W. Henry. Udagawa also wrote *the Shokugaku Keigen* (1833) which was the first book of systematic European Plant physiology in Japan. Even before the Meiji era, there had already existed some original and highly developed technologies for the brewery and for the medical science without which the Japanese biochemistry would have never been born and grew up rapidly. After the Meiji Restoration, Government, crying their slogans "National Industrialization First!" and "Strong Army!", intended to take in the European natural sciences rapidly by opening colleges and universities of Western style, inviting European scholars, and assisting with enthusiasm the regular "Study Abroad" system. The import of biochemistry was realized also as one of these Westernizations of learning. However, it was naturally impossible as yet to transplant from Europe her biochemistry in systematic order as it had not yet been completely systematized even in Europe immediately after the Restoration. This was a peculiar situation somewhat different from in the case of transplanting chemistry and physics.[1)]

It was in the Tokyo University (including its predecessor) that the educating of biochemical students started first. According to their own purpose and blueprint, the Colleges (Faculties) of Agriculture, of Medicine, of Technology, and of Science each made their progress, for instance, College (Faculty) of Agriculture tried to increase the agricultural productivity, College (Faculty) of Medicine to promote modernizing the medical treatment. Once the necessity of introducing modern chemistry realized, each section began to invite European chemists with sufficient knowledge of modern chemistry. To the College (Faculty) of

Agriculture came E. Kinch (U.K.), O. Kellner (Germany) and O. Loew (Germany); to the College (Faculty) of Science R.W. Atkinson (U.K.) and the College (Faculty) of Technology E. Divers (U.K.). Selected students in turn were despatched to the distinguished scholars of international authority; for instance, A.W. von Hoffman (Germany), H.E. Roscoe (U.K.), C. Shorlemmer (Germany and later U.K.), F. Hoppe-Seyler (Germany) and E.L. Salkowski (Germany). Most of them were the disciples of J. Liebig and R. Virchow. It was not incidental that Japanese biochemistry at its preparatory stage tried by all means to learn from J. Liebig.

It was extremly difficult, however, for the early Japanese students to understand Liebig's thought that underlies his scientific system even if they had succeeded in accepting the necessary technologies in short time. Both these foreign teachers invited and the Japanese students learning from them chose at the outset the practical themes and materials full of locality as subjects of their studies rather than the pure theoretical problems. It was a national request then but at the same time these subjects were regarded as a short cut to call attentions of the international academic world to the results of their studies.[2)]

R.W. Atkinson who was invited in 1874 to Kaisei Gakko (a predecessor of the Faculty of Science, Tokyo University) made with his students researches on the Japanese wine "sake" and published *the Chemistry of Sake-brewing*[3)] in 1881, which was a pioneering and most characteristic work of biochemistry in Japan.

It dealt first with areas where rice is cultivated in Japan and the annual yield, then with chemical analysis of rice, morphology, physiology and chemistry of Koji, and quantitative study of functions of diastase at Koji, chemical analysis of each processes of Sake-brewing, further with how to prevent the putrefaction of Sake in stock. He argued all these subjects based on his own experiments and observations utilizing E. Kinch's data and in cooperation with J.A. Ewing and others. He even tried to design apparatus of new type. What is more, he expressed a great surprise to see that in Japan a germ-killing process at a low temperature had been discovered and practised by Sake-brewers nearly 300 years earlier than by L. Pasteur, and stressed that Europe had something to learn from Japan and even referred to a mutual profit born out of the intimate cooperation between science and technology. His work was quite a model worth to follow. Students

who learned chemistry from him began to engage vigorously in the chemical analysis of producing processes of Japanese products with long tradition such as "shoyu" (soy) and "urushi" (lacquer). As early as 1883 Hikorokurô Yoshida[4] made a discovery of highly scientific value about laccase from his study of hardening of the lacquer. Another masterwork was achieved by Jôkichi Takamine who studied under E. Divers at Kôbu Daigakkô, a predecessor of the Faculty of Technology, Tokyo University, and succeeded in the industrial extraction of diastase from "Koji", and in its merchandization producing a large quantity of cheap enzyme as materials for researches. This diastase was named "Taka-diastase" by Takamine. As for the Faculties of Agriculture and of Medicine, they tackled their own objects full of local colour that deserved their chemical researches.

In contrast with this, chemical studies taking up a fundamental thesis of biochemistry as its direct object, that is, the elucidation of vital phenomenon, started much more lately. Jûgô Sugiura[5] who studied under R.W. Atkinson and was ordered to study in England at the government expenses, and then moved to the laboratories of H.E. Roscoe and C. Schorlemmer, started on his return to Japan a periodical entitled *Tôyô Gakugei Zassi* (Journal of Oriental Arts) and contributed to its first issue (1881) an article saying: "To quote C. Schorlemmer, the only way to elucidate the problem of vital force should be to penetrate into the protein compounds. .....Once the chemist enabled to compose original protein, it probably must be identical with what Mr. E.H. Haeckel calls Monera." The article was so pioneering to introduce the materialistic philosophy on life and in fact it was much more years later that Japanese students began to argue among themselves about such a problem trying to verity it by experiments.

At first, biochemical studies in the agricultural and medical fields concentrated to those of application so rich in local characteristics. For instance, themes chosen in the College (Faculty) of Agriculture were : chemical research or the influence afflicted by fertilizer upon crops; chemical change in the tea-leaf when processed; chemical analysis of producing processes of rice and "miso" (bean paste). In the College (Faculty) of Medicine, studies focussed on extraction, purification and chemical synthesis of the effective components of Chinese or Japanese herbs or poisons such as of swell-fish.

The trend continued for some time thereafter but since around 1900 an epochmaking change emerged. While these applied studies full of local colour were gradually developing into fruit appreciated highly from abroad,[6] the pure biochemical studies began to take a clearer shape in parallel. In another words, a new movement to grasp the physiological processes of animals and plants from more chemical point of view began to appear among the students on the Medicine and the Agriculture. It was derived from an inner necessity that required more deepening of basic studies to gain more practical profits, accelerated further by the influence of foreign instructors. O. Loew at the Faculty of Agriculture who succeeded O. Kellner in 1893, and F. Hoppe-Seyler and E.L. Salkowski at the Medicine, started their less applied, more theoretical studies of physiological chemistry or pathological chemistry that threw a grave influence upon Japanese students working under them. Under these circumstances with inner and outer motives combined, the course of physiological chemistry was established one after another in the Faculties of Agriculture and of Medicine that yielded later so many physiological and chemical students for plants and animals. The new course called "Medical Chemistry" was set up in 1893 at the Tokyo University (Prof. Muneo Kumakawa in charge), then in 1899 at the newly established Kyoto University (Prof. Torasaburô Araki in charge).

The courses of the first (N. Matsui in charge) and the second (O. Loew in charge) "Agricultural Chemistry" was set up in 1893 at the College of Agriculture, Tokyo University, and Umetarô Suzuki succeeded O. Loew in 1907. The second Agricultural Chemistry was called "Biological Chemistry" as the common name.

M. Kumakawa was dispatched to Germany in 1884 for the study of internal medicine, worked under Salkowski of University of Berlin and returned to Japan fully conscious of the importance of biochemistry under the strong influence of an independence movement of biochemistry from physiology then flaring up in Germany. Fortunately his masters at the Tokyo University, Kenji Ohsawa (Physiology) and Hiizu Miyake (Pathology), were also aware of the significance of physiological and pathological chemistry and acted in favour of setting up the new course of Medical Chemistry. Then T. Araki, a desciple of Ohsawa, sent to study under Hoppe-Seyler, came back to Japan. From then on, a number of biochemists were hatched and fledged out of the laboratories of these two scholars.

Kumakawa, studying the fat metabolism, discovered as early as 1904 a new quantitative method for fat, for which Araki advanced his research in haemoglobin and nucleic acid.

Takaoki Sasaki (Kumakawa's pupil) studied under E. Fisher, F. Hofmeister, E. Abderhalden, E. Friedman et al., and made researches for protein chemistry, micro-biological chemistry in 1910-1920s,[7] and pathological chemistry in 1930s in his private institute Sasaki-Kenkyu-Sho which was built by the found of his grand-father Tôyô Sasaki. Yashirô Kotake (Araki's pupil) studied under M. Jaffe, A. Ellinger (Germany), and research for amino-acid metabolism in animal body at the Medical College of Osaka.

O. Loew, who once in Japan was immediate to commence a basic study of synthetizing function of protein, brought up many students in cooperation with Yoshinao Kozai, the favourite disciple of O. Kellner. Out of this team work sprang a most distinguished follower, U. Suzuki, who reported as early as 1898 about the biosynthesis of protein in plants and went to study under Emil Fischer, then on his return to more practical research in the Japanese foodstuffs like rice and fish and discovered "Phytase"[8] and "Oryzanin" (Vitamin B_1). His laboratory also yielded many students, and they engaged in the studies of Vitamin A.B.C.D.L. in the "Rikagaku-Kenkyu-Sho (Institute of Physical and Chemical Research)".

In parallel with these movements, the course of Plant Physiology (Prof. Manabu Miyoshi in charge) was set up in 1895 at the Faculty of Science in Tokyo University. His follower, Keita Shibata, deepened the study of plant physiology and organic chemistry working under W. Pfeffer and M. Freund in Germany, and then established and supervised the course of Physiological Chemistry of Plant at the Faculty of Science, Tokyo University (1924). Numerous distinguished experts in the field were to be born there. Keita Shibata and Yûji Shibata studied with Flavon in plants and metal complexes and published *Katalytische Wirkungen der Metall-Komplex verbindungen* (1936). Yûji Shibata, K. Shibata's brother, a chemist (Prof. of the Faculty of Science, Tokyo University.), studied under Kohichi Matsubara (Organic chemistry), then went abroad and worked under A. Werner (Switzerland), A. Hantzsch (Germany) G. Urbain (France).

On the other hand, the course of Biological Chemistry at the Faculty of

Science was set up in 1919 in Tokyo University, for the purpose of promoting the theoretical study of biochemistry by efforts of U. Suzuki, Kakiuchi & others, and was presided over first by Samurô Kakiuchi, and then by Tokurô Sohda. After two years the course of Biological Chemistry was set up in 1921 at the Faculty of Science, Kyoto University and presided over by Shigeru Komatsu.

S. Kakiuchi, who studied under Kumakawa and Kikunae Ikeda (physical chemistry), went to U.S.A. and studied biology (under Mendel, Harrison, Petrunkewitch, J. Loeb, Folin, Cawdray, Lillie, Herrick, Child, Benselay, Moulton, Wilson, Morgan, Calkins) and also physics and physical chemistry (under Moulton, Michelson, Bancroft). After he came back to Japan, he sucseeded Kumakawa and worked as the organizer of a group of students of basic biochemistry thus brought up in each field.

In 1922 there were three big events for biochemistry in Japan:

(1) In 1922 Kakiuchi organized a circle called "Tokyo Seikagaku-sha Yoi-no-kai (Society of Tokyo Biochemist Evenings)" where everyone could talk quite freely regardless of his academic status. At the feudal sciety of academism in Japan, this event was revolutionary. While on the other hand S. Kakiuchi issued at private expenses a technical magazine for biochemistry entitled *Journal of Biochemistry* in close cooperation with his masters and seniors and his colleagues (U. Suzuki, K. Ikeda, T. Araki, T. Sasaki, Y. Kotake, Kôji Miyake, Katsuji Inoue etc.). In the forward of its first issue, S. Kakiuchi said, "During the last decade the number of published works in biochemistry in our country has greatly increased. Until the beginning of the World War of 1914-1918 a large number of the graduates of our universities and colleges went abroad for their post-graduates research work. During the war, however, the number of research students in each of our laboratories has been increased many fold, and the status of science now in our country has passed so to speak from the exclusively educational stage into that of laboratorial research. As a result there is now an increasing demand at home and abroad for an organization for publishing our works internationally. On the one hand, owing to the situation of our country remote as it is from the centres of science abroad, there are always some difficulties in contributing our reports to foreign journals, causing a delay in publication at times of more than half a year. On the other hand, as most of our reports are published in our mother

tongue, many friends abroad regret the inaccessibility of some of our valuable works. Stimulated by these increasing demands we have decided with the cooperation of certain of our biochemists to issue this journal in the interest of biochemistry. May this little Journal of Biochemistry have a prosperous future and be a contribution, though small, toward the promotion of true knowledge."

(2) In the same year Keita Shibata, also in co-operation with his disciples, established a private laboratory the "Iwata Institute of Plant Biochemistry" 1921 and published from there a magazine *Acta Phytochimica*. A series of studies promoted by Shibata's group on the cellular respiration contributed to advance the research in the chemical process of respiratory function by joining in a scientific dispute with O. Warburg, and D. Keilin. Rikô Majima, Yasuhiko Asahina, and others contributed their works with organic chemistry of Japanese plants to this Acta.

(3) In the same year, L. Michaelis (Germany) came to Japan as the lecturer of biochemistry of the Aichi College of Medicine (Nagoya), and lectured physical chemistry at biochemistry (ex: the theory of pH).

The explosive energies of these vigorous and voluntary students culminated in the establishment of "The Japanese Biochemical Society" in 1925 that mustered so many biochemist coming from each different fields. With the opening of the Society, Japanese biochemistry was also firmly established as a section of natural science. It was a dawning of the new stage for the biochemical studies in Japan. Everyone felt happy in the highest spirits. Few people foresaw a speck of black cloud of the Japanese fascism gathering over them that would eventually doom all of their works not more than fifteen years later.

Literatures and Notes

1) Minoru Tanaka: Hundert Jahre der Chemie in Japan, I, II. *Japanese Studies in the History of Science*, No. 3, S. 89 (1964). No. 4, S. 162 (1965).

2) To quoate H. Miyake (later, the head of Medical College, Tokyo Imperial University): "If we succeeded in the chemical analysis of Oriental plants and minerals and reporting how to utilize them properly, it would not only contribute to the academic progress of medical science but also serve greatly for Japan by introducing all over the world the advanced level of Oriental Art." (*Tokyo Kagakukai-shi*, 4, 41, 1883).

3) R.W. Atkinson, *Memoirs of the Science Department, University of Tokio* No. 6, (1881).

4) H. Yoshida, *J.C.S.*, 43,472 (1883).

5) However, Sugiura immediately abandoned the studies in the field and went into the general education based on the oriental and later on the nationalistic philosophy peculiarly enough, few Japanese know that once he had been engaged in biochemical studies.

6) Extraction of first hormon Adorenalin by J. Takamine (1900), Extraction of Rotenone by K. Nagai (1901), Extraction of "Aji-no-moto" by K. Ikeda (1908), Extraction of Tetrodotoxin by Y. Tawara (1909), Extraction of Oryzanin (Vitamin B_1) by U. Suzuki (1910).

7) Über den Abbau einiger Polypeptide durch Bakterien. I. *Biochem. Zeitshr.* 41, 174, 1912.
Über die biochemische Umwandlung Primarer Eiweiss Spaltprodukte durch Bakterien. I. *Biochem. Zeitschr.* 59, 429, 1914.
Über die Bildung der Anthranilsaüre aus L-Tryptophan durch Subtilis-bakterien. *J. Biochem.* 2, 251, 1923.

8) An enzyme which splits phospholic acid from phytin (Ca, Mg salt of inositol hexaphosphate). Suzuki, Yoshimura, and Takaishi, *Tokyo Imp. Univ. Coll. Agr. Bull.* 7, 503, 1907.

9) Articles were written in English, German and French, and continued to 1944 (vol. 36) when Kakiuchi abolished it in a desperate mood because of the World War II.