

## **The Impact of Hungarian Scientists on the Development of Biochemistry**

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It may be stated, without being pompous or arrogant, that the development of biochemistry dominates most of the twentieth century medical science. Major achievements in the years between 1930 and 1960 have placed biochemical sciences in the centre of the scientific scene. Important consequences of these successes have led to the trend to describe all life processes in biochemical terms, apply biochemical methods in almost every field of medical and biological research, investigate biochemical mechanisms underlying disease conditions and utilize biochemical laboratory techniques for the diagnosis of the cause of illness.

The roots of biochemical research started in the middle of the last century. The year 1861 is considered the beginning, when the first chair of biochemistry was established in Tübingen for Felix Hoppe-Seyler. At the heroic beginning, many investigators were engaged to study an interplay of biology and chemistry, the main concept being to reveal the chemical structure of substances which occur in biological systems and to understand the chemistry of life. There were several schools mainly in Germany and to a minor extent in France. The core of their program was laboratory investigations where the analytical work was carried out. This analytical era resulted in many basic discoveries. Emil Fischer and his school established the composition of carbohydrates (sugar derivatives) and amino acids which are the building stones of proteins. Friedrich Miescher studied nucleic acids responsible for cell mitosis and characteristics of genes and heredity. Louis Pasteur's work led to the knowledge of enzymes which catalyze chemical processes essential in all cellular functions and for the maintenance of a balanced living organism. Later I.P. Pavlov described the enzymic and hormonal mechanism of digestion. The essential role of vitamins had also been discovered.

The importance of the new direction, studying the chemical composition of living organisms, was quickly recognized by the Hungarian medical public. At the beginning of the nineteenth century there was only one place in Hungary where medicine was taught, namely, the Royal University of Science in Pest, and this university wanted to adopt the results of the new progress. Although the legal rights and financial support were greatly curtailed after the defeat of the Hungarian army in the War of Independence in 1849, the school submitted a proposal to the government that a chair in pathological chemistry should be created for studying chemical changes in the living cell and in post mortem tissues. The proposal was rejected by Vienna, and only after the compromise in 1867 was the government allowed to set up a pathological chemistry department. The first was established in Kolozsvár in 1872, organized by Lajos Markusovsky and in 1874 in Budapest with the leadership of Pál Plósz. Many years later, after the First World War when the University of Kolozsvár was relocated to Szeged, a chair was created for medical chemistry in 1930 and was offered to Albert Szent-Györgyi. The biochemical departments of Debrecen and Pécs universities were set up after the Second World War between 1950 and 1960.

From the early stages of biochemical research Hungarian scientists exerted an impact on the development of this discipline. The reason for this may originate from the advanced scientific interest and outstanding intellect of several individuals such as Pál Bugát, Károly Than, Ottó Hermann, József Lenhossék, Jenő Jendrassik, Ignác Semmelweiss, just to name a few. These men excelled either in various branches of the natural sciences or medicine. Their inspiration significantly influenced the course of young people interested in studying the foundation of biological phenomena. However, since the possibilities in Hungary were limited during the last century, Hungarian scientists learned the *métier* mainly at German universities. After this training many students returned to Hungary where they continued to teach and conduct research.

Some Hungarian scientists settled in Germany and became internationally known. Many scientists left Hungary after the First World War, during the periods of religious discrimination and persecution, or after the Revolution in 1956. Several Hungarian biochemists continued to further their scientific

career and made significant contributions to the advancement of biochemical sciences in their host countries.

Two of these Hungarian emigrants were among the first Nobel Prize winners. In 1914 Róbert Bárány won the Nobel Prize for his study on the physiology and pathology of the human vestibular apparatus in the ear and cerebellum. In 1904 Richard Zsigmondy invented the ultramicroscope in collaboration with Heinrich Siedentopf. With the help of this new research tool Zsigmondy determined the movement of colloidal protein particles. He described their heterogenous nature leading to important information on the status of colloids in the cell protoplasma. For this study Zsigmondy won the Nobel Prize in chemistry in 1925.

In later years some other scientists of Hungarian origin won the Nobel Prize for biochemical or related studies. When Albert Szent-Györgyi received the award in 1937, he was the only biochemist working in Hungary. He won the Prize for his investigations of biological combustion, for the discovery of vitamin C and the catalysis of fumaric acid oxidation.

In 1943 George C. de Hevesy, who lived in Sweden, received the award; he was the first who used isotopes as tracer elements in research. In 1961 George de Békésy was recipient of the Prize for the discovery of the physical mechanism of stimulation of hearing within the cochlea (inner ear). In 1967 George Wald, a third generation Hungarian American, was awarded the Prize for his discovery of vitamin A and A-2 in the retina, and their role in the mechanism of colour vision. Imre Szörényi, who lived in the Soviet Union, also belonged among the great Hungarian biochemists. Szörényi received the Stalin Prize during the Second World War for his studies on the crystallization of muscle enzymes.

Generally, in the early years of biochemistry the Hungarian contribution was very modest, due to inadequate state support. Still, there were valuable contributions: István Bugarszky and Leo Liebermann described for the first time in 1898 that the surface of the egg white protein contains electric charges. This measurement was so accurate that even with the utilisation of modern methods, half of a century later, their data proved to be correct.

The second important period in the history of biochemistry was the investigation of metabolic processes and energy requirement of the cell. In this direction in Hungary Ferenc Tangl and Pál

Hári were outstanding. Tangl was first appointed to the chair of pathological chemistry, at the University of Budapest in 1903, Hári was his docent who became professor in 1915. The Tangl-Hári school was really the first in establishing biochemical research in Hungary. The central theme of their investigations was how metabolism regulates cell function, how this is connected with energy circulation and heat production and through this with the maintenance of health. Hári was also known for his spectrophotometric measurements of hemoglobin.

The application of isotopes, first introduced by Hevesy, represented a revolutionary advancement. The attention of biochemists turned to changes constantly occurring in the cell. It became known that the properties of the living matter are dynamic and ever changing, special qualities of life are associated with continuous turnover and modifications. This was the period when Szent-Györgyi started working in Szeged. He laid down the basis of modern biochemistry in Hungary. A brilliant and original investigator, his personality created a stimulating atmosphere and he trained many enthusiastic pupils. Most of the present generation biochemists learned from Szent-Györgyi or from his pupils the art of scientific thinking and investigations. Szent-Györgyi produced significant results in three areas: mechanism of cellular oxidation, identification of vitamin C, and the role of actomyosin and adenosine triphosphate, a high energy containing molecule in muscular contraction. A number of basic discoveries are attached to the achievements of the Szent-Györgyi group, including the isolation of myosin and actin, and the contraction of the actomyosin complex by the action of adenosine triphosphate. One of Szent-Györgyi's best pupils was F.B. Straub who discovered the actin. As a young assistant to Straub, I was the first who found that the actin contains adenosine triphosphate and that this compound is metabolised when actin filaments were formed.

The scientific activity in Szent-Györgyi's laboratory was various. Ilona Banga was involved in biological oxidation studies and later became interested in the synthesis of collagen, an important protein in connective tissue. Kálmán Laki's major contribution was related to the blood coagulation process and to the maintenance of hemostasis.

The roots of biochemical research was strongly planted by the Szent-Györgyi school and its merits were awarded by the Nobel

Prize. After this promising start, however, circumstances spoiled the smooth development. World War II scattered the members of the Szent-Györgyi group and after the revolution even more scientists left Hungary. Szent-Györgyi emigrated to the United States, and some of his co-workers followed him. In his eighties, Szent-Györgyi still works at the Marine Biological Laboratory in Woods Hole, Massachusetts.

Meanwhile the focus of biochemical research has changed. In this new period it seemed to be important to investigate the following: "what regulates the dynamic processes in the cell and what is the relationship between the cell and its surrounding?" Biological studies have established a principle that the living organism forms a unit with the environment and its existence can only be assessed by considering the interaction. With the recognition of the dynamic status of cell composition, biochemistry extended this principle to every constituent of the cell. Earlier the properties of isolated proteins, carbohydrates, and lipids have been studied, now researchers began to explore how these components manifest themselves in the unity of an organ and how various organs are interrelated by affecting the status of the living body.

This direction was recognized by Szent-Györgyi when he started studying the function of the muscle and the mechanism of muscular contraction. Following this tradition some investigators still continue research in this direction, Endre Biró in Budapest, John Gergely in Boston, Mihály Bárány in New York. Other investigators have been studying the processes of blood coagulation, the function of hemoglobin and role of abnormal hemoglobins in disease, Kálmán Laki in Washington, László Loránd in Chicago, and Zsuzsa Hollán in Budapest. Some investigations have attempted to reveal the biochemical mechanisms underlying brain functions. Maria Wollemann and myself, while working in Budapest at the Institute of Biochemistry, Hungarian Academy of Sciences, became interested in the problem of how energy producing processes are connected with the function of the brain cell and transmission of neural messages. Attila Fonyó and his co-workers investigated the association of adenosine triphosphate with subcellular particles of the nerve cell, particularly the characteristics of the mitochondrial transport adenosine triphosphatase enzymes. Maria Wollemann continued her interest in neurochemistry: at

the Szeged Biological Centre she has been working on biochemical changes occurring in brain tumors and on the molecular mechanism of how tranquilizers and sedatives affect the nerve cells. Meanwhile in London, I had been studying what is the biochemical basis of our emotional responses and how behavioural changes are connected with different emotional expressions such as cowardice and courage. We have found that these are regulated by hormones produced by various endocrine glands.

At present the biochemical research field is divided into two areas. Classical biochemistry is interested in the molecular basis of cellular function and how this molecular arrangement is connected with the structure of the cell and its subcellular components. Briefly, molecular biochemistry is concerned with the molecular mechanism of the regulation of life processes. The second direction is related to disease, it is called clinical biochemistry, aiming to reveal what kind of abnormalities or derangements of the normal molecular association represent the underlying mechanism of disease conditions. Briefly, what are the molecular changes leading to cell impairment and disease?

Our body is built of molecules, mainly simple or complex protein macromolecules, and it is logical to assume that all biological reactions have to be molecular, making life a molecular phenomenon. In 1950, the Hungarian Academy of Sciences created an institute for furthering biochemical investigations and training of post-doctoral students. The first director of this institute, Imre Szörényi, initiated studies on the structure and function of enzymes which remained the major direction of research under the directorship of F.B. Straub. The major achievements of this institute were to reveal the primary structure, and the effect of proteolytic modifications of the structure on enzyme activity. They found that enzyme action fluctuated in association with amino acid side chains but restricted when the prosthetic group of the enzyme became bound to the protein. The scientists involved in this program were Gertrud Szabolcsi, Tamás Keleti, Pál Elödi and Tibor Dévényi. Other investigations on molecular aspects of biochemistry included the regulation of enzyme action by Géza Dénes and his associates, alteration of the active centre of enzymes by L. Polgár, stereospecificity of hydrolytic enzymes by L. Ötvös, elucidation of the substrate specificity of some

proteolytic enzymes by T. Vajda, hormonal control of protein synthesis by F. Antoni and structural and functional studies on polypeptide hormones by G. Cseh.

An essential factor in the existence of higher organisms is the formation of cells and subcellular structures. The structural organization of the living matter into functional units provides the vital framework for survival. Considerable parts of cellular processes and regulation are connected with biomembranes. György Gárdos and his group have been investigating the importance of electrolyte transport through erythrocyte membranes. Recently, with my research team, I have been studying the role of a particular subcellular membrane, the endoplasmic reticulum of the liver cell; this cell particle is involved in the detoxication and elimination of foreign compounds. It is a puzzle why this membrane responds to the action of certain drugs or several foreign compounds by rapidly metabolizing them, while other compounds destroy these membranes leading to liver disease. The development of certain tumors caused by chemicals is also connected with the function of these particles. The results of this and similar investigations permit the fundamental conclusion that many if not all diseases originate from an impairment of the biochemical organization of the cell. This is mainly reversible but if the abnormal process does not turn back to normal level, it results in chronic disease and death.

There are many more brilliant immigrant Hungarian scientists who have participated in outstanding discoveries towards the advancement of biochemistry such as Mihály Polányi, who studied the crystalline structure of molecules and reaction kinetics, the basis of enzyme function. Paul György discovered riboflavin, vitamin B-6 and the role of growth factor in the development of the cell. Mihály Somogyi was a pioneer of abnormal carbohydrate metabolism and established an excellent method for the measurement of blood glucose. Hans Selye made a fundamental contribution to our present understanding of the onset of disease when he described the effect of stress as an important factor in the development of abnormal life conditions.

In this short paper I have attempted to illustrate the impact of Hungarian scientists on the development of biochemical research. The list is far from complete, and I may have unintentionally omitted valuable results and eminent

Hungarians. I had to restrict myself, however, to thematic selections as associated with the major directions and advancements of biochemistry.

#### BIBLIOGRAPHY

Friedrich, P. "Biochemistry in Hungary: A Review," *International Journal of Biochemistry*. 4, No. 1, 1973.

Fruton, J.S. *Molecules and Life*. New York-London-Toronto: Wiley-Interscience, 1972.

Hári, P. *Az élet és kórvegytan tankönyve*, 3rd Edition. Budapest, 1929. .

*Les Prix Nobel, 1901-1981*. Imprimerie Royal, Stockholm: P.A. Norstedt and Söner, 1904-1982.

Liebermann, L. and Bugarszky, I. *Chemia*, 2nd Edition. Budapest, 1908.

*New Encyclopaedia Britannica, Micropaedia*, 15th Edition. Encycl. Brit. Inc., 1980.