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FERENC GUBA

Albert Szent-Györgyi's contribution to a better understanding of the living state

Honoured Guests!

With regard to the immortality of great spirits Seneca writes the following: "Those who rise to the center of attention by pure chance, those who are but a tool and a part of others' power will only flourish and receive visitors in their homes as long as they stand high. The respect for great spirits, however, grows constantly and they are honoured not just for themselves but their fame underlies everything that pertains to their memory in one way or another".

Those dealing with the living organisms (and, for his greatness of soul, others, too) will remember Albert Szent-Györgyi in the centuries to come just as they will remember Darwin, Pasteur or Watson, one of the discoverers of the double helix: Szent-Györgyi has for ever inscribed his name in the history of the theory of the living state not only because he was awarded the Nobel Prize for his activity in 1937. Of the works for which the Novel Prize has been awarded a number have proved incorrect in the course of scientific development, and many of the seemingly outstanding results have been forgotten. Perhaps it was not the most significant scientific achievement in Szent-Györgyi's research activity that was awarded the highest scientific tribute of respect. Among other facts, his greatness is reflected in the quest by his creative spirit for opening ever newer paths towards a more thorough understanding of the material organization referred to as the living state.

His unforgettable memory is essentially based on this endeavour. When we think of Szent-Györgyi's life it is Madách's words that inevitably come to mind: "I said, man: struggle and hope trustfully". Szent-Györgyi lived a full life.

Although amongst the introductory lines to his curriculum vitae written at the editor's request for publication in the yearly issue on biochemistry we find the following: "I dedicate my life to science and my only real desire has been to promote science and to live a life according to its requirements", his scientific career cannot — perhaps due to this noble purpose and high moral motivation, and amidst the controversial developments of his era — be separated from his social activities, political declarations, from his attitude towards the arts, and, perhaps, even from his private life. Albert Szent-Györgyi was a humanist in the fullest sense of the word: he was a man full of emotions and evoking emotions who would, through failure, strive to find truth and consequently live according to this truth.

His scientific publications are amazingly colourful. The results he publishes are interspersed with a train of thoughts scintillating with wit. Seemingly remote experimental data or observations become in his explanation clear correlations, new interpretations of the facts observed or assessed.

Albert Szent-Györgyi's only scientific purpose was to understand and reveal the fundamental laws of matter as a living state. A classical formulation concerning life is what he wrote in "The science of Life" in the introduction to a volume on the frog and its heart published in 1943 under his editorship. The essence of this formulation is briefly as followes: in biology, 1 plus 1 does not equal 2, but is something else, something more, something new.

During his scientific career he was mainly concerned with the organization of matter into structures disposing signs of life and their functions. Striving for a better understanding of life he proceeded through stages of descriptive morphological, physiological and biochemical investigations towards the study of electron movement.

What he was actually working on, what structural layers, or what models he was dealing with, depended always on the stage of his mental development and experience, and, of course, on the actual problems to be solved through biochemistry, as well as on the appropriateness of the model used for answering the given question, and on the efficiency offered by the different methodological approaches. In this latter respect his intuitive way and ingenuity in finding simple solutions, sometimes confined to the mere use of test tubes, amazed both his colleagues and his scientific rivals. Mention should be made of the fact that, especially in the last few decades, many specialists doing excellent research in their own field and living with the magic of refined and mechanized devices have failed to understand the revelation of essential questions by Szent-Györgyi precisely because the methodological approach seemed to be oversimplified.

For the study of most biochemical and, in general, biological problems it is of utmost importance to select the suitable model, i.e. to decide what kind of living organism or what type of biochemical function or process should be chosen for answering the actual question. Szent-Györgyi was certainly aware of this. He was a master at finding and selecting the appropriate experimental model. This was the way he evaluated the functional importance of the morphological changes based on the molecular combination of proteins with respect to blood coagulation or to the muscle proteins named "actin" and "myosin". And this was the way he used the breast muscle of the pigeon for the study of the chemical energy production of the cells, of biological oxidation, etc. Working with these models in reassuringly suitable experimental conditions, he was able to obtain definite and commensurable answers to the questions "asked of nature". His profound knowledge of the field rested, in the first place, on his inclination towards experimentation. He came to know the living state through the touch of his fingers and the keen observation of his sharp eyes so that he spent most of his days in his laboratory even when he was already old.

The exploration of Szent-Györgyi's scientific activity, of its values and far-reaching effects, will take many years of work. The revelation of his heritage including his scientific results is one of our future obligations. It goes without saying that in this commemoration I can only refer to fragments, — sparks lighting torches in scientific life.

I will briefly throw some light on Szent-Györgyi's contribution to a better understanding of the living state by mentioning three seemingly unrelated topics of his scientific activity. They are as follows: biological oxidation, the physiology of the motion and the problem of cancer.

When Szent-Györgyi realized that one must go at least as far as the level of biochemical processes in order to reach a better understanding of the living state, the burning question of modern biology at the time (in the 1920's) was the problem of chemical energy production obtained by biological combustion. (By the way, it seems that a final solution to this problem was reached only in the sixties, for which Mitchell, and of course, others in the meantime, were awarded the Nobel Prize.) At that time two research groups were taking an interest in the question and had rather unusual debates with each other: one of the groups (led by Wieland) considered the enzyme activation of nutriment hydrogen to be inseparable, whereas the other group (led by Warburg) claimed the enzyme activation of air oxygen to be inseparable, as evidenced by precise experiments. (As is well-known, although the combustion of nutriments is coupled with CO_2 expiration, the chemical energy relevant to the biological system is obtained from the union of hidrogen and oxygen, i.e. the formation of water.) Szent-Györgyi's ingenious experiments, the majority of which were carried out in collaboration with his colleagues in Szeged, produced evidence that both types of activation are necessary: the hydrogen of nutriments reaches air oxygen through different stages. The stages are represented by well-defined C_4 organic molecules oxaloacetic-, succinic-, fumaric-, and malic-acids. Through this observation (which meant, along with the discovery of vitamin C, the Nobel Prize for him), Szent-Györgyi put an end to a long-lasting debate and opened the way for a detailed description of energy production in the cells of most higher organisms. This fundamental observation by Szent-Györgyi and his colleagues led first to the exploration of the Tricarboxylic Acid Cycle (the Szent-Györgyi — Krebs cycle, as we Hungarians refer to it), and later to that of electron transportation.

It is worth noting that finding a relatively quick answer to the problem was due to the selection of the appropriate model. It was Szent-Györgyi who introduced sectioned breast muscle of the pigeon in analyzing cellular respiration. Now we know that this muscle can do its job (i.e. provides for the long-time flight of the pigeon) because it is rich in mitochondria, which are the organelles of cellular respiration.

And now I shall turn to the second topic. In Szeged, the investigations with muscles began with the application of pigeon breast muscle. But Szent-Györgyi was not interested in muscle tissue either in this study of the muscle with a view to motion and its related phenomena in all living beings, or in other studies to be mentioned later on. In this case, too, he made use of the muscle to answer one fundamental question in biology. Muscle, again, was used as a model due to its specification as an organ of motion. (It should be added that Szent-Györgyi had brought over a specialist in muscle physiology, Jenő Ernst — lest some trivial set-back should occur — who kept on working in the laboratory in Szeged in his own field.) The study of muscle motility (muscle contraction and relaxation, mechanical work done by muscle) began in Szeged in 1940 and was continued in Budapest under his guidance till 1947, when Szent-Györgyi left the country. This work involved almost all his colleagues in Szeged and Budapest. After he had settled in America he went on doing research in this field for a while, but the fundamental observations had been made in Szeged, and I think I am right in saying that these latter results by Szent-Györgyi's outdo in importance his previous investigations. Had he been luckier, he might have been awarded a second Nobel Prize. Switching over to the study of muscle movements had firm roots in the past: thanks to his activity, the mainstreams of the study of energy production had already been formed and it was time for the details to be described.

Furthermore, it became evident that a unique phosphate organic compound, the "big source of energy", i.e. adenosine triphosphate (ATP) is an outcome of energy production. It was in these years that the Soviet scientists Engelhardt and Lyubimova discovered that ATP and myosin, the fibrous protein of muscle fibre interact: while ATP hydrolases, myosin threads become deformed. According to Szent-Györgyi's ingenious insight, we have now arrived at an appropriate model for the study of the energy source synthesized in energy production as it is in its biological function, i.e. motion. It took only a couple of years of intensive research to identify the biochemical mechanism underlying the physiology of motion. It appeared that this necessitates the presence of two proteins, myosin and actin (both were isolated in a pure form during these investigatios), which interact with each other in the presence of ions that can be found in muscles cells. The rate of consumed energy of ATP during motion is proportionate to the extent of motion. Since research continued in a country which was separated from the outer world during the war scientific community learned the sensational results only after the liberation of Hungary in 1944. It would be no exaggeration to state that the many volumes summarizing the achievements of Szent-Györgyi and his colleagues, caused a world-wide sensation among biologists. These volumes are a treasure in every self-respecting biochemist's library. Following the investigations started in Szeged, there are a number of countries where high-level biological experiments are at present being carried out that relate to the study of the physiology of motion at the molecular level. Along the path made by Szent-Györgyi it is now evident that any cell motility, any change in cell shape, and even a major part of matter transportation (e.g. in the nerve cells) takes place according to the principle formulated in Szeged thus providing a subtle proof for Szent-Györgyi's idea: "nature is economical, it will not invent a new mechanism for the solution of the same problem". I think we should pay attention also to the fact that the cognitive process initiated by Szent-Györgyi almost 50 years ago, which linked a relatively complex physiological phenomenon to molecular and submolecular interactions; opened a new way towards the interpretation of mechanisms of biological control. The first results of these studies now appear to be bearing fruit.

In the sixties Szent-Györgyi's attention gradually turned towards the malignant transformation of cells, which was preceded by the recognition of the fact that in the case of the living state the fundamental laws should be detected on the submolecular and, indeed, on the subatomic level. He thought that some special kinds of substance, tree radicals which are difficult to analyse, can play a role in cell transformation and, consequently, in the formation of malignant tumours. He had an ever-growing confidence in the idea that malignant transformations can be explained only after an understanding of normal changes in the cell. In America, in the maritime biological laboratory of Woods Hole he and some of his colleagues started wearisome research into the biochemical processes of tumoruos tissues. He dealt with the metabolism and effects of compounds similar in properties to ascorbic acid which he had isolated and studied at the beginning of his scientific career.

Although his contribution to a better understanding of cancer has not as yet developed into significant results, he did, on the one hand, call attention to such unique states of substantial systems which seem to open new paths in field of physics and biophysics, and, on the other hand, he created a special form of scientific collaboration named "the Laboratory without walls", which is sponsored by voluntary contributions and involves many scientists all over the world collaborating not only in interdisciplinary fields but also in intercontinental dimensions.

The above glimpse of Szent-Györgyi as a scientist reflects his admirable individuality. The formation of his personality is, according to him, connected with his education and the atmosphere of his parents' home, particularly his mother, Josephine Lenhossék, who showed him the best of humanitarian values. Apart from his genius, it was the education at home that played a decisive role in his scientific attitude:

— he saw everything others saw, but he thought about it as no one else did,

— he was extremely accurate, precautious and disciplined during experimentation (just remember, among other facts, the isolation of ascorbic acid in crystalline form, the isolation of myosin, actin and ATP),

— he never chose the easy way, but achieved his results and discoveries through failures,

— thus, everything concerned himself with opened new pathways and far-reaching horizons for research.

He arrived at his universally significant results while working within a community.

An efficient collaboration cannot be maintained without extraordinary personality. Those working with Szent-Györgyi could not withdraw themselves from his influence. This influence was especially manifest in the community in Szeged, where Szent-Györgyi's most significant discoveries were made. The colleagues he had chosen to work with admired and followed his train of thoughts and carried out hard and accurate work. This is how the "Szeged School of Biochemistry" emerged providing for successful team work along with a healthy spirit of emulation.

We can pay due respect to his genius and preserve a faithful memory of him by acting in accordance with the path he showed.