Acta Biochim. Biophys. Hung. 22(2-3), pp. 141-148 (1987)

THOUGHTS ON THE LATER CAREER OF ALBERT SZENT-GYÖRGYI*

Seymour S. Cohen

Marine Biological Laboratory, Woods Hole, MA 02543, U.S.A.

(Received May 19, 1987)

I did not know Albert Szent-Gyorgyi well. We were a generation apart and I did not work in his laboratory. However, for almost forty years I observed his activities each summer in and around the Marine Biological Laboratory at Woods Hole and enjoyed his zest for science and living. I admired his past achievements as a master biochemist and listened to his joyous dramatic lectures. He had peopled the United States with bright young Hungarian biochemists, many of whom are my friends, and they and I were grateful for the pleasure of knowing a heroic scientist in our own time.

He had occasionally listened to my reports of progress on the biochemistry of virus multiplication and on the effects of unusual medicinal nucleosides. We nodded and smiled in passing, but we remained a generation apart. Biochemistry and biological science generally were pulling away from him. Some of his younger friends offered to help him in some institutional problems, but he had decided not to change his way of doing science and there was little that could be done. Nevertheless his professional problems towards the end of his career are of general interest and should be addressed.

In 1963, he wrote an autobiographical essay entitled "Lost in the Twentieth Century." Containing a paean of praise for science and its moral inquiring spirit and achievements, he directed a plea to fellow scientists to struggle for peace and prosperity, to create "a new form of life, the wealth and beauty of which cannot be pictured today by the keenest imagination."

At that time, he had lived in the United States for 15 years and had built a functional laboratory as part of a prestigious institution in the lovely seashore town, Woods Hole, in which he lived. In that new laboratory, he had discovered the interesting properties of glycerinated muscle, and the glycerination process proved to te of widespread interest and use. Many of his students and assistants from Hungary had settled in productive positions in America. The knowledge he and his colleagues in Hungary had developed on actomyosin had been transferred to the United States, and his institution, the Marine Biological Laboratory, had become a center for research on muscle and discussion of the new results.

Summers at Woods Hole were an exciting scientific and social experience in which he participated actively. Many figures of his earlier scientific life had turned up on occasion, including Otto Warburg, Carl Neuberg, Otto Meyerhof, and Otto Loewi. A biochemist-physiologist member of his generation, E.S. Guzman-Barron led a laboratory and lecture course in Physiology, to which Albert contributed, with many other distinguished scientists. Indeed, when this course was converted at five-year intervals to contemporary versions of the discipline, muscle remained a key segment. The "Prof's" lecture was popular and retained in the teaching sequence. With this transition to modernizing, also, came the emerging younger scientists who were appropriately interested in Albert's interests and concerns and applauded his vigorous way of life.

The vitality of this summer activity also reflected the state of American science, which was well supported and growing in leaps and bounds. The American leadership of this international science was a consequence of World War II, and a result of the destruction of much of

European civilization. But it also was due to the escape of many European scientists to America and to their contributions in research and help in training young American biochemists. I myself came from such a training center, the Department of Biochemistry at Columbia University, whose Faculty during the period of my studies included R. Schoenheimer, E. Brand, E. Chargaff, and K. Meyer. The language of science had become English, and the enormous flood of new results expressed mainly in this language poured into the superb Library of the MBL which now harbored Szent-Györgyi and his small group.

Nevertheless there was a fly in the ointment. Or there were flies. He had been a European and a Hungarian, and it is impossible to describe the attachments of a displaced person to his roots, to his former home, friends, familiar sights, language. I will not attempt to describe theoretical longings, with which I am not familiar, but which exist in, indeed permeate, every stratum of American society containing so many immigrants and exiles from chaotic societies all over the world. Szent-Györgyi had discovered also that the Promised Land was not merely a given good, but needed some input to preserve its Promise. He had resisted Hitler and quarreled with the Russians, only to be challenged by McCartny in this new home, his presumed asylum. He was frustrated "to see mankind on the brink of extinction," "to have spent so much life and energy in vain." Nevertheless it will be remembered that he never ceased to exhort his colleagues, his neighbors, and the youth to express their democratic will.

Although unstated by him, there had also been very real changes in the structure of science, changes which had already affected his ability to make discoveries and which could only increase his difficulties in that activity. Indeed he had referred to undefined "personal limitations,", but he might also have noted changes in the structure and institutions of biomedical science, which were to affect his future work.

Szent-Gyorgyi made his important discoveries at a very early stage in the evolution of biochemistry. Although Buchner's discovery in 1897 of glycolysis in a yeast extract had established the perspective of separating cell components and analyzing the metabolic activity of purified fractions, for some time washed minced tissues remained as major biological materials for the study of catalytic properties. Only 27 years after Buchner, i.e., in only 1924, Szent-Györgyi had used washed muscle to demonstrate the activation of both hydrogen and oxygen in cellular oxidation. A few years later, in 1928, using effective techniques now considered primitive, he found a factor in adrenal cortex and inplants which could serve as a catalytic hydrogen carrier in selected reducing systems. This eventually proved to be ascorbic acid or vitamin C. It is instructive to note that, despite the growth of biochemical skills and human activity, many aspects of the functions and metabolic relations of ascorbic acid have not yet been clarified. His important work in 1934 to 1937 on the four-carbon dicarboxylic acid cycle employed rapidly respiring minced pigeon-breast muscle. Although he elected in 1941 to work on a muscle protein called myosin, and, with his collaborators, discovered the presence of two proteins, actin and myosin, in the functional complex of actomyosin, his research career demonstrates that cell fractionation and work with purified enzymes and proteins was not the approach he deemed most comfortable or most promising.

We note that he did not use isotopic methods in the exploration of metabolism, or explore changes in the actomyosin structure by the sophisticated physical methods introduced in the 1920's and 1930's. Viscosimetry was available in war-torn Hungary, but how does a biochemist expert in the use of minced muscle switch late in life to the most modern gear? In short, Szent-Györgyi, like every other scientist trained and experienced in one era, had problems with the new theory of related disciplines and with the tools of a subsequent period. How do most of us do it, if we do it at all?

In the 1930's major laboratories had concentrated on the fractionation of cell extracts and the purification of proteins and enzymes, even of viruses. Powerful physical tools, ultracentrifuges, apparatus for electrophoresis, had improved the characterization and, in some cases even the isolation of macro molecules. Electron microscopy and X-ray crystallography were adjuncts to the difficult problems of describing proteins in isolation and in situ. Enzymology had become a fine art for the mathematically inclined students of catalysis and in its cruder aspects was essential in the analysis of reaction sequences. Isotopic methods had enormously expanded our metabolic catalogue and knowledge of catalytic mechanism. Biochemistry, in its reductionist aspects, had become the work of specialists, and the contributions of all of these had become necessary to understand the integration of the separate bits. These directions of the discipline had become evident even before the addition of the developmental disciplines in the evolving construction of the superdiscipline of molecular biology.

Szent-Györgyi thought (hoped?) that the new knowledge on the plethora of small metabolites and the ungainly macromolecular cellular components might prove to be too complex to account for the functionality of living tissue, as well as of the origin of cells. The whole system might possess simpler mechanisms to permit, to support, biological activity, might possess short-cuts to bypass the stuff of thousand-page textbooks, the long lists of intermediary metabolic reactions. If such a primitive simplicity had existed and had been retained Szent-Györgyi himself could bypass this complexity and stride like a giant past the epiphenomena Described in decades of accumulated trivia. I have seen other men in physics and biology searching for new rules with which to link these disciplines, expecting (hoping?)-to bypass the awesome complexity of growing biochemical knowledge. Obviously this search has failed. After World War II, physicists came in flocks to biology to demonstrate the power of their discipline, their magical skills. In virology at least, a field with which I am familiar, almost all of these prideful searchers were silenced by primitive mouth-filling pipettes. The search for short-cuts is always with us, and Szent-Györgyi needed one to solve the problems of his "personal limitations."

To bypass the enormous range of substances present in the cell and their numerous reactions, observed in extracts, Szent-Györgyi asked if essential electron transfers had not found shorter routes. Indeed ascorbic acid, in reaction with nicotinamide and quinones, has been found to participate in such transfers, and could be isolated in "charge-transfer" complexes. Such phenomena, if they existed, were detectable in the electron spin resonance (ESR) of the complex, and he and his young collaborators sought such evidence in one of the first instruments used in this country to measure ESR. His ideas elicited much discussion among biophysicists and a certain amount of work. However, no major discoveries have been made or exploited, and the postulated direct path of Szent-Györgyi has not been placed in the textbooks containing his many other achievements. I have myself made a solid yellow complex of ascorbic acid and nicotinamide, all too readily dissociable in water, and have wondered about its possible physiological significance.

All maturing and mature biochemists who have made even a single discovery, face the problem of having more to do than he or she possibly can handle himself. To solve the problem of an expanding program of work in the United States he has technical assistants, students and postdoctoral fellows. He develops a division of labor, which in modern times at least soon drives him to his desk, examining data, writing papers, and justifying and applying for financial support. The development of a research team, made possible by the prosperity of the country and his own success, inevitably separates him, at a greater or lesser rate, from the bench at which the amazing tissue, cell or substance is being examined. Very few are able to stay as close to the work as they once did. Szent-Gyorgyi rejected this solution and had decided to organize his laboratory, his working space and working life to avoid the transformation of scientist to manager. Nevertheless this very laudable decision contributed to his falling behind.

His "modest" course was possible with meager funds, possible until the funds were inadequate to maintain his self-limited needs. By this time, by 1963, many private foundations in support of research had closed this aspect of their efforts, unwilling to compete with the much larger funds made available by the United States government. In its initially enlightened policy, the government began to support Albert's work and that of many others. As requests for government support of basic research proliferated, the bureaucracy developed an enlightened theory and system of making awards in which the scientists themselves assessed and screened grant applications. The form of grant application became more and more elaborate. Young unknowns had to convince the review panels of their worth. Szent-Gyorgyi, whose discoveries had achieved world-wide recognition and honor, was now in a race for funds with worthy young applicants eager to succeed and willing to accept tasks Albert had rejected. He was not competing with these eager aspirants who for the most part were extending the past and their own recent work, to seek new and previously unsuspected biologically significant phenomena. Had not his previous record of discovery entitled him to the unextravagant support he needed?

Albert no longer fit within the categories, the rules established by government agencies. Actually few members of the review panels appreciated an elderly gentleman, who refused to abide by the rules within which they had to function. He was over seventy, why didn't he quit just as did almost everyone at that age? Why didn't he work in a field we could understand, i.e., a known field? Why didn't he publish his work in the way the other applicants had to? To make a long story short, the combination of unappreciative scientists and a fearsome bureaucracy did not support his work. After a series of wearing rejections, he turned to a special agency which helped him almost until his death.

Is there a moral from all this, are there lessons to be learned? They might be stated as follows. Young biochemists, despite an "advanced" education of a certain kind, can be ignorant and frequently unkind. Older biochemists, despite status and position, have generally adopted and accepted the standards of the society in which they have succeeded; they do not often support their older colleagues in need. Historic elderly surviving figures do not receive special consideration, nor should they expect to. The bureaucracy is predictable; rules are rules.

Albert Szent-Gyorgyi lived an extraordinary life. His work and career were like the bright burning breathing candle, whose description by Seguin and Lavoisier in 1789 illuminated biochemistry at the very beginning of our discipline. Towards the end the bright flame of his science flickered, and was extinguished as his substance was consumed. We did not know how to help him as he grew old, nor did we try to do so sufficiently. The different generations living side by side in our society seem to be living on different planets.