Albert-Szent-Györgyi, Electrons, and Cancer

Private foundation supports 1937 Nobelist in his effort to prove unorthodox hypothesis

Hungary has contributed more than her share of scientific genius to the world, more particularly to the United States—John Von Neumann, Edward Teller, and Eugene Wigner among others. One of the most outstanding has been Albert Szent-Györgyi, winner of the Nobel prize in 1937 for his discovery of vitamin C, and profilic theorizer whose contributions could easily have added up to a couple of more Nobels. In the 1930's he was discoverer with Hans Krebs of the Krebs cycle, which describes the oxidation of acetic acid in living organisms. In 1954 he won the Albert Lasker award for the first workable theory of heart muscle contraction.

Many people now don't know whether Szent-Györgyi is alive or dead. He is in fact quite alive at 85, and working at the rented laboratory at Woods Hole Marine Biological Laboratory where he has toiled for the past 18 years on a little-known and less understood "bioelectronic" theory of cancer that he has been developing for decades. He has not had a federal grant in years, and might well have been forced out to pasture were it not for the enthusiasm of a retired lawyer and businessman who took a shine to his ideas. Now Szent-Györgyi is the spiritual hub of a network of scientists around the world who are doing work related to his theory of cancer under the aegis of the National Foundation for Cancer Research.

The NFCR has confused quite a few of the many thousands of people who have received its direct mail solicitations over the past 4 years. It is a nonprofit organization entirely fueled by private contributions, founded by the enthusiastic businessman Franklin Salisbury, who has set up headquarters in Bethesda, Maryland, only a few blocks from the National Institutes of Health. Salisbury read news reports in 1972 that Szent-Györgyi—who has much in common with his contemporary, Nobel Laureate Linus Pauling, who hasn't been able to get federal money to finance investigations into vitamin C and cancer—was in danger of foundering for lack of research money. Salisbury, for reasons not entirely clear, was attracted to the man and sent him a check for $25. In response he received a warm letter of gratitude from Szent-Györgyi and went up to Woods Hole for a visit. Salisbury "has a feeling for talent—an eye for genius," Koloman Laki, longtime Szent-Györgyi associate, told *Science*. "It was love at first sight," says Laki, who is chief of physical biochemistry at the National Institute of Arthritis, Metabolism, and Digestive Diseases. Salisbury knows next to nothing about science, but like many other citizens he wants cancer cured—and fast. He decided this was the horse to back. The result was the establishment of the foundation which, since its 1974 inception, has built up a budget of close to $3 million a year.

The foundation's business is informally run. Its scientific board, the star member of which is Trevor Slater of Brunel University in Uxbridge, England, meets once a year to review applications and decide on established researchers to approach for contracts. The foundation pays for no facilities, administration, or equipment, relying instead on in-kind donations of facilities—equivalent to about $600,000 a year—from institutions where researchers are based. It operates as a "laboratory without walls" according to its pamphlets, paying the salaries of more than 60 doctoral and postdoctoral researchers who work with the investigators who get NFCR contracts.

The set-up is unusual in a number of ways. There are many groups devoted to trying to establish one thing or another as a cure for cancer. The NFCR is devoted to exploring a hypothesis about the basic causes of the disease. It is a truly international endeavor, giving support to or collaborating with researchers in about 20 laboratories, almost all university-based, in the United States, England, Scotland, Ireland, Wales, Hungary, Austria, France, Germany, Italy, Japan, and Australia.

The NFCR is not, as might be suspected, an organization committed to supporting a group of maverick scientists intent on proving an unorthodox theory about cancer. Indeed, from the sampling *Science* took, most of the investigators are interested in but skeptical of Szent-Györgyi's hypothesis. Some have little interest in it but are working in related fields of biophysics and submolecular biology that the foundation considers relevant. They are willing to associate themselves with Szent-Györgyi because of his record of accomplishments and his extraordinary scientific intuition which has long been acknowledged even by his detractors.

Sidney Fox of the University of Miami, one of NFCR's major contractors, does not believe Szent-Györgyi's theory is likely to prove out, but "I believe the hypothesis is worth working on because Szent-Györgyi had it . . . he has an uncanny ability to find his way into areas that are worth exploring . . . he has in the past been right many times when others have easily assumed he was wrong. I had to conclude that he has the intuition to see things that lesser minds do not."

What is this bioelectronic theory of cancer? Szent-Györgyi has explained that to begin with, it is an attempt to explore cell activity on a submolecular level, not stopping, where cancer research ordinarily does, at the molecular level. He starts out with the assertion that the abnormal growth characterizing cancer cells is a reversion to an earlier evolutionary stage of growth (he calls it the "alpha state"), where cells merely proliferate rather than perform their specific tasks. The main difference between cancer cells and normal cells that are also simply proliferative, such as those in blood and gut, is that they don't know when to stop. He believes that a substance called methylglyoxal, which has been identified but whose functions have not been firmly ascertained, is the foremost regulator of such cell growth. He believes that the extremely active glyoxalase enzymes, which destroy methylglyoxal, may be the main culprit in cancer growth. (Other scientists say the available evidence is equivocal.) What is more controversial is his belief about the conductivity of structural proteins. Most proteins tend to be insulators, not conductors of electrical charges. Conductivity is required for a cell to perform its normal functions. Szent-Györgyi contends that the methyl-

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glyoxal attached to protein molecules makes them conductive, thereby facilitating charge transfer of electrons from one molecule to another. In a problem cell the orbitals of protein molecules are "saturated," that is, electrons are paired and there is no room for the transfer of an electron from one molecule to another. If there is a shortage of methylglyoxal or an excess of glyoxalase, there is no charge transfer, and cells revert to the simple, nonstoppable proliferative state, which is cancer.

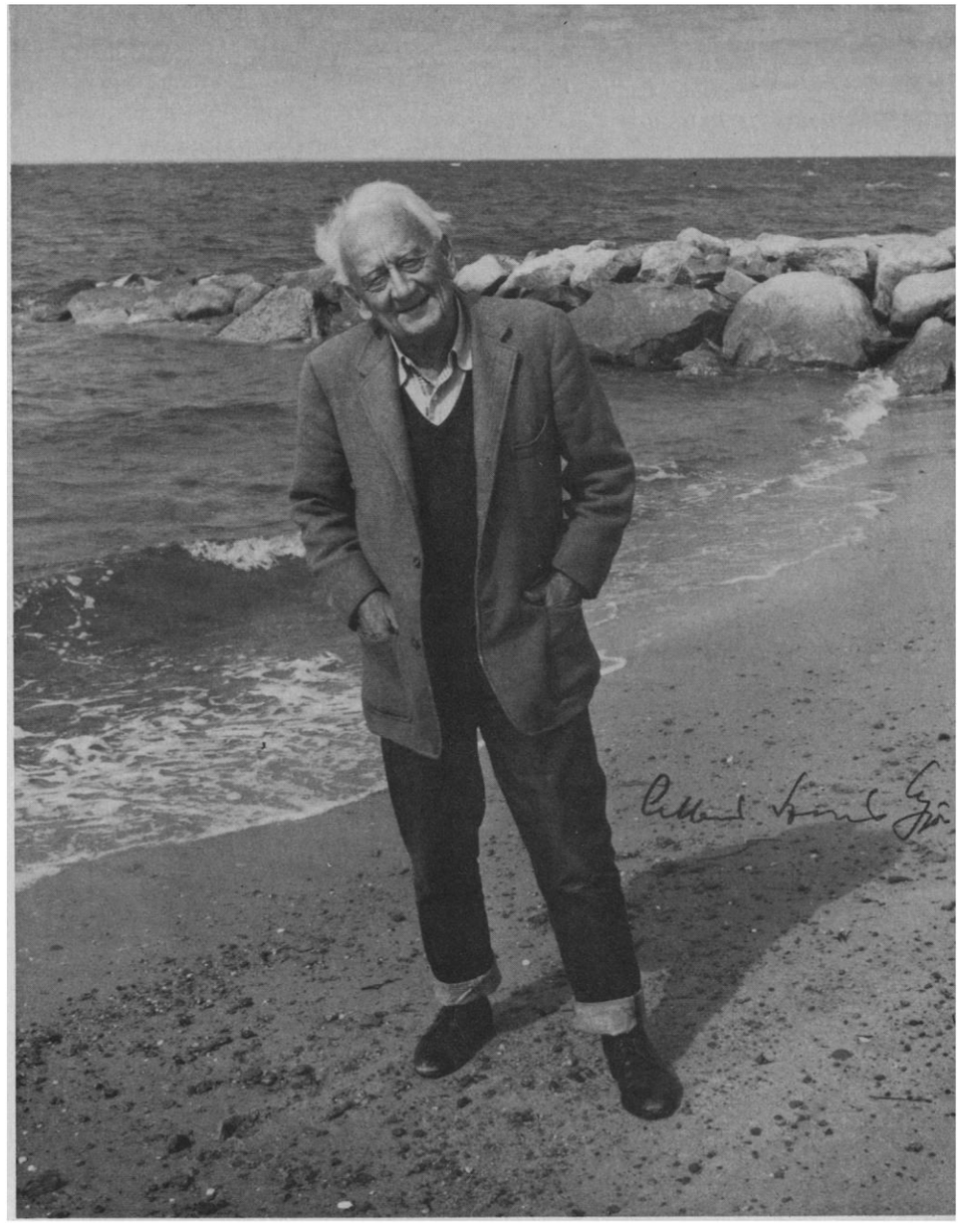
Szent-Györgyi's theory is propounded on a very basic level indeed, as he acknowledges. An obvious intellectual objection to it is that it is too reductionist. A more practical objection is that there are no data indicating that it might have validity.

When he first publicly announced his theory, at a 1975 meeting of Nobel laureates in Lindau, West Germany, it was greeted for the most part with skepticism. Elements of the theory are regarded as worth exploration—methylglyoxal, for example, is well known to scientists and has been shown to have an effect on cell growth. But the whole theory represented to most people a quantum leap of imagination. "A series of somewhat mystical intuitions based on simplistic analogies," was the way one scientist put it at the time. People have too much respect for Szent-Györgyi's past accomplishments to dismiss his hypothesis out of hand. However, even researchers working with NFCR money—most of them, anyway—would agree that the National Cancer Institute was perfectly justified in turning down his latest application for support in 1975. The reasons for this were apparently pretty straightforward—no literature was cited in support of his hypothesis, and no particular experiments were proposed in detail.

Szent-Györgyi has never been one to cater to the bureaucracy. He has always been impatient with those who want to know what he is going to do—for after all, if he already knew, there would be no point in doing it, would there?

Science was unable to reach him on the telephone—an assistant said he wanted the questions submitted in writing. But associates say he and a small handful of co-workers are doing electron spin resonance in order to detect free radicals in structural protein, which is to say he's trying to demonstrate that proteins can in fact act as semiconductors with the help of methylglyoxal.

The scientists associated with the NFCR are by no means an eccentric brotherhood devoted to proving the hypothesis of the master and thereby ridding the world of cancer. All appear to be investigators of good repute whose work has varying degrees of relevance to the bioelectronic hypothesis. Harold Swartz, for example, who is working on electron spin resonance at the University of Wisconsin, is skeptical of the theory but believes it is opening up productive directions for research. He notes that the ideas leading to the bioelectronic hypothesis "date back 20 and 30 years—these are not the products of a senile mind." Although Szent-Györgyi reportedly uses techniques that are not very scientifically rigorous by current standards, no one connected with NFCR appeared to feel that age had dimmed the man's judgment or damped his legendary intuition.



Although some suggest that Szent-Györgyi's advanced age is a strong factor in the government's refusal to fund him, one does not get the impression that injustice has been done. Aside from executive director Salisbury, who appears inclined to the belief that the government is a pack of fools, scientists connected with the NFCR agree with others that this is not a theory that is exactly ripe for government support. It is exceedingly unconventional, a leap into the unknown, and no one has any way of testing its validity because nothing so far has been published about it in the scientific literature other than one or two papers in the Proceedings of the National Academy of Sciences, where they are not subjected to prepublication peer review.

Szent-Györgyi's hypothesis is both attractive and officially unfundable because it harks back to the days of global hypotheses. It can probably be said that the simpler the instruments a scientist has to work with the more he compensates with his own imagination.

Americans are probably the world's most cautious and data-oriented scientists. As you move further East, there is more sympathy with fantastic ideas. Judging from the scientific board of the NFCR, there is more sympathy with the theory in Europe than in the United States, and probably more in Eastern Europe.

In fact, it appears the core group of scientists connected with the NFCR—aside from Slater in England—are Hungarians. One is Laki of NIAMDD who is associated with several NFCR-funded scientists at Washington's American University. Another is Janos Ladik who works at the University of Erlangen in Nuremberg, Germany. The third is Gabor Fodor, an organic chemist at the University of Wisconsin who got his doctorate under Szent-Györgyi and who has developed a compound of vitamin C and methylglyoxal that other researchers hope to test clinically at an NFCR outpost in Dublin. Fodor feels that Szent-Györgyi has in his career combined the best of European and American science. Before the war, he says, "he brought the free spirit of Anglo-Saxon science to Hungary when everything was being filtered through the German influence." In Hungary, he says, we have a saying: "if your sword is short, you lengthen it with your arm." That is, if you don't have fancy scientific instruments you make up for it by exercising your intuition.

Foundation Hungarians have so far developed two related compounds, containing methylglyoxal (which is toxic alone) and ascorbic acid, whose purpose is to stop the cancerous proliferation of cells and, by facilitating charge transfer, return them to their normal state of functioning. One compound was tried out at the University of Debercen in Hungary and appeared to arrest mouse tumors until it was purified, at which point it became ineffective. The other compound, informally dubbed "oncostatin," has been used in animal studies at Brunel University under the direction of Slater, with no definitive results. Despite this fact, NFCR publicity talks optimistically of imminent clinical studies with oncostatin to be conducted at its "clinical arm" by Douglas Thornes, professor of experimental medicine at the Royal College of Surgeons in Dublin. Thornes himself, when contacted by *Science*, was duly cautious, saying that "I'm at the end of the line" (that is, the clinical application) and that he was waiting for the animal studies. It seems that oncostatin does work when tested against cancer cells in test tubes but no way has been found to deliver it in a live organism. So far, it has only been tested on mice, which manufacture their own vitamin C. Now it is thought that it will be more appropriate to test it on guinea pigs, which like humans must get their ascorbic acid from outside.

Well. Should one send in a donation to NFCR if one gets a fund-raising letter from Franklin Salisbury inviting one to add cancer to the list of "almost-forgotten disease plagues of the past"?

The American Cancer Society, which like NFCR wants to end cancer "in our lifetime," is mildly perplexed about the foundation. "They are competing with us in fund-raising and they're creating a great deal of confusion," says Congdon Wood of the ACS, who says he spent a half-day in conference with Salisbury and still doesn't understand what it's all about. The NFCR may be creating more confusion in the future. It claims to have 300,000 members, and there are plans to establish fund-raising arms in Europe. Wood says: "The unfortunate thing about people like Szent-Györgyi and Linus Pauling is that when they start to taper off there is the danger that people will start to use them." He has no evidence that dubious scientists are trying to ride on the coattails of the greats and agrees that it would be very difficult to ascertain if this were so. But it's a question, he says, he has been asked more than once by members of the press.

The personal Salisbury presentation is not particularly reassuring. His fund-raising letter scoffs at government red tape involved in grant-getting while omitting mention of the fact that all Szent-Györgyi's cancer grant applications have been turned down. He told *Science* that Sloan-Kettering Institute for Cancer Research was interested in the theory, although several calls to Sloan-Kettering did not uncover any interest. He said NCI's peer review system had approved the 1975 application and the reason it wasn't funded was because it held too low a priority. In fact, the NCI study group did not approve it. He also said the theory has now achieved a "new scientific respectability" as witness the conference held last September by the CIBA Foundation in London to honor Szent-Györgyi. It is true that the CIBA conference attracted a number of English scientists curious to learn about Szent-Györgyi's work and may have consolidated new directions for research. But several American scientists (who did not attend the CIBA meeting) contacted by *Science* expressed as much mystification and skepticism about the theory as was expressed when it was presented to the world in 1975.

Nonetheless, were it not for a gung-ho American businessman, a scientist of monumental achievements might have found himself becalmed in his later years for lack of money.

George Weber, Hungarian-born biochemist at Indiana University Medical School who is a generation younger than Szent-Györgyi, strongly feels that there should be some way for scientists with a "track record" such as Szent-Györgyi's to be assured of support for their work until they retire or die. "Such people should be cherished," he says. "If he were in Hungary or Germany the government would consider him a national treasure and continue supporting him so he could be an inspiration to younger scientists." Weber expresses unqualified approval of the NIH peer review system, which he called "the best system ever devised." But he believes some mechanism, perhaps an endowed professorship, should be created for people like Szent-Györgyi and other outstanding scientists now past retirement age, whose productivity has been curtailed for lack of money. Says Weber, "our obsession with youth and equality of opportunity is fine, but there should be some channel for recognizing the truly towering figures."

—CONSTANCE HOLDEN

Barbara Culliton Named News Editor of *Science*

Barbara J. Culliton, editor of the News and Comment section since 1977, has been appointed the first news editor of *Science*. The new post combines responsibility for Research News and News and Comment.

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