Szent-Györgyi, Albert Imre. (*b*. 16 Sept. 1893, Budapest, Hungary; *d*. 22 Oct. 1986, Woods Hole, MA) biochemistry, cell metabolism [or bioenergetics].

Albert Szent-Györgyi (pronounced like "Saint Georgie") earned recognition for his biochemical work on vitamin C, muscle and energy in the cell. His contributions ranged from the practical, such as finding an inexpensive source of vitamin C and a method for preserving fresh muscle tissue, or designing a continuous centrifuge, to the deeply theoretical, such as conceiving cell function, cancer and the origin of life through electron flow. By portraying the wonder of science and its discoveries, he was widely inspirational, both professionally and publicly. He championed a view of intuitive discovery and scientific play, coupling the grand and the simple, and was outspoken that research funds should be unrestricted. He also gained renown for his charm, nonconformism and anti-war politics.

Formative Years and Early Career

Albert was born into modest privilege. His father, however, took little notice of the family. Albert was raised primarily by his mother in Budapest. Her brother, an established physiologist, was a frequent presence and, periodically, an austere surrogate father. Until age sixteen, Albert showed neither interest nor aptitude in academics. In the summers he enjoyed horseback riding and hunting. Szent-Györgyi felt inferior as a teenager and defensively tried to prove himself. He also developed a jealous dislike of his two brothers. At age sixteen Albert became motivated, however, apparently by the respect accorded to three generations of scientists in his mother's family, the Lenhosséks. He announced his intentions to pursue a career in medical research at dinner one night. His uncle, aware of Albert's poor schoolwork, scoffed at the idea. Yet in two years Albert was graduated from Gymnasium with honors and went on to medical school.

Albert was then allowed to work in his uncle's lab. He was initially directed to study the epithelium of the anus. (Later in life, Szent-Györgyi would turn the episode to his advantage, joking that he "started science at the wrong end.") Next, he studied the hyaloidal bodies of the eye. His published papers were well received and earned the young Szent-Györgyi—still in his early twenties—a local reputation. Albert felt vindicated: he had proven himself by continuing the Lenhossék tradition.

After receiving his medical degree in 1917, Albert was eager for more research. His first position in Poszony ended when Czechs recaptured the town and expelled all Hungarians. Other research opportunities were scarce in Hungary and Szent-Györgyi looked abroad. For the next seven years he chased temporary positions across Europe, with his new family in tow. He worked with Armin von Tschermak in Prague (measuring electric potential in cells); Leonor Michaelis in Berlin; Storm van Leeuwen in Leiden (doing pharmacology); H.J. Hamburger in Groningen (performing animal surgery in physiological experiments); and Henry Dale in Hampstead (see below). Each new position seemed to rely on chance encounters and personal recommendations. At one point, Szent-Györgyi studied tropical medicine, imagining that he might support his family with a lucrative career, but he found the work too demanding and uninteresting. It was a tumultuous period, of recurring poverty, at times the threat of starvation, with research typically done after hours and sometimes in makeshift labs in cellar rooms (Szent-

Györgyi cetainly accentuated the drama in later recountings) .

In 1926 Szent-Györgyi met distinguished biochemist Gowland Hopkins, who had read one of his papers. He transformed the fortuitous encounter into an invitation to work at Cambridge. There, with ample resources and a thriving community of biochemists, his research matured. He isolated a new compound from the adrenal glands, which earned him a Ph.D. and international recognition. In 1928 the Hungarian Ministry of Education invited Szent-Györgyi to return to his native land and, after some negotiation, he agreed to lead the medical chemistry department at the University of Szeged. He returned to Hungary with his family finally in 1931 and remained there until shortly after World War II. While his research continued, he became increasingly political, first as Naziism encroached and later when Soviet domination threatened.

Vitamin C

Szent-Györgyi is most notably associated with the discovery of vitamin C. The discovery of vitamins themselves was recognized in 1929 in a Nobel Prize to Christiaan Eijkman and Gowland Hopkins. The search for vitamin C was then well underway in several labs. Ironically, the compound had already been isolated by Szent-Györgyi. Yet no one—not even Szent-Györgyi—yet knew its identity. Indeed, the discovery cannot be fairly characterized as a single event or a single insight, or even due chiefly to a single individual.

Szent-Györgyi's part in the story began in 1924 while he was struggling to establish a career in Groningen. He had been reflecting on biological oxidations (see next section). He imagined that the browning of cut fruit, based on the oxidation of polyphenols, might offer clues to understanding Addison's disease, which darkened patients' skin (the analogy, ultimately, had no biochemical basis). He knew that other fruits that do *not* brown, such as citrus, contain reducing agents, or anti-oxidants. The disease patients, by comparison, lacked full adrenal gland function. Could they be missing an essential anti-oxidant substance from the adrenal glands? Szent-Györgyi set out to isolate such a prospective substance. After extracting a substance that seemed to show reducing activity (using silver nitrate as a simple indicator), he tested it on a single alley cat whose adrenal glands had been removed. The cat was healed, and Szent-Györgyi construed it as definitive evidence of his anti-oxidant, possibly a new hormone. (He was mistaken, we now know: the cortisol in the impure extract that must have cured the cat was no anti-oxidant.)

Szent-Györgyi sought additional support from Britain's leading physiologist, Henry Dale, and received a limited three-month fellowship. Dale's skepticism seemed confirmed when he proved unable to isolate the substance. Indeed, within six weeks, his original results were traced to a known reaction with adrenaline and iron, with the iron attributed to the meat mincer, not the adrenal gland.

Szent-Györgyi persisted. When invited to Cambridge by Hopkins in 1926, he used his newly available resources to isolate a reducing substance from adrenal glands, enough to characterize it as "a highly reactive carbohydrate derivative, isomeric with glycuronic acid." He also extracted what seemed to be the same substance from oranges and cabbages. It was named 'hexuronic acid'. At the same time, Szent-Györgyi documented the reducing activity of numerous plant extracts and suggested that the new compound was an intermediate in the oxidation system of plants. There were several clues (notably, the plant sources) that hexuronic acid might be vitamin C, the anti-scurvy nutrient. However, when a sample was sent for testing to Sylvester Zilva in London (who had worked for over a decade on isolating the vitamin), the report came back negative.

In an era when many hormones, vitamins and other biological compounds were being identified, hexuronic acid gained widespread attention. Thus, when Szent-Györgyi toured the United States in 1929, the Mayo Clinic welcomed him to work with adrenal gland specialist Edward Kendall. Using a healthy supply of glands from a nearby slaughterhouse, the two extracted a large amount (just over twenty grams) of the substance. Ten grams went to Norman Haworth in Birmingham, England, who tried to identify its chemical composition, but found the quantity insufficient. Szent-Györgyi returned home with his remaining hexuronic acid. He used a small bit to continue investigating its reducing properties in the cell and to isolate an enzyme that oxidized it.

Meanwhile, other researchers had been trying to isolate and identify vitamin C, producing highly concentrated if not pure extracts from lemons, rutabagas and other plant sources. Zilva was working at the Lister Institute and Glen King at the University of Pittsburgh. Each was equipped to test substances, only possible on live guinea pigs with induced scurvy. Many investigators noticed the similarities of hexuronic acid to vitamin C: Hopkins, Kendall, Zilva and King, at least. But the procedures to prepare a sample for testing seemed too demanding for mere speculation. Szent-Györgyi, by contrast, had a sample but did not pursue the appropriate tests. Indeed, he found research with animals distasteful. His style (exhibited throughout his career) involved chemical analyses and simple tests, such as clear color indicators.

In late 1931 (for reasons that remain obscure) Joseph Sviberly, who had worked in King's lab, returned to his native Hungary and presented himself to Szent-Györgyi, who had just settled into Szeged. Sviberly brought with him skills for testing hexuronic acid with guinea pigs (which Szent-Györgyi lacked) and, not surprisingly, was allowed to test the residual sample. When King became aware of Sviberly's success, he published his own independent work on vitamin C isolated from lemon, confident that the uncertain status of hexuronic acid was finally resolved. Sviberly and Szent-Györgyi published their own paper. A dispute over priority ensued. Vestiges of the debate would linger for decades.

Sviberly's tests had exhausted the supply of hexuronic acid. Szent-Györgyi wondered whether the native red pepper—the source of paprika—might be another source of the vitamin. His test proved richly rewarding. Soon, Szent-Györgyi's lab could produce kilograms, not mere grams, of vitamin C. A large sample went again to Haworth, who this time was able to elucidate its structure. In 1933, he and Szent-Györgyi renamed it 'ascorbic acid' to clarify its biological role. That same year, yet another team, led by Leslie J. Harris at Cambridge, confirmed the identity of hexuronic acid and vitamin C through a fuller, and critically more complete, ensemble of tests. A synthesized vitamin and proof of its efficacy followed soon thereafter. So, too, did overstated claims by Szent-Györgyi about the efficacy of vitamin C for treating many conditions unrelated to scurvy.

When the Nobel Foundation honored Szent-Györgyi's work in 1937, it did not cite his discovery of vitamin C, as has been reported in many places. The award was mainly for his work on biological energy reactions "with especial reference to vitamin C." Haworth was recognized separately for determining the structure of vitamin C.

Biological Oxidations

What ultimately became perhaps the central theme in Szent-Györgyi's research also emerged while he was in Groningen. In reporting his modest investigations of potato respiration in 1924, he suggested how to resolve a debate about energy reactions in the cell. In these reactions, akin to combustion and known as oxidations, food is broken down chemically. Each step leads to a lower energy level. In some steps, the energy released can be "captured" to help fuel other reactions in the cell. Chemically, this occurs primarily through the exchange of protons and electrons between molecules. In the 1920s, two perspectives dominated. In Heinrich Wieland's view, the process was primarily about how protons, or hydrogen ions, move to lower energy states. The chemist's objective was thus to interpret where protons originated and how they were tranferred to another molecule. Otto Warburg approached the process from the other end. Oxygen was primary, he claimed, due to its receptive low energy state. For him, the aim was to understand how oxygen contributed to "oxidation" by taking electrons. In Szent-Györgyi's gentlemen's compromise, the roles of "activating" oxygen and "activating" hydrogen ions were complementary. The hybrid view also opened the possibility of intermediate stages. Szent-Györgyi had started to conceive biological oxidations primarily in terms of the flow of protons and electrons.

When Szent-Györgyi established his own lab in Szeged six years later, he turned again to biological oxidations. A first challenge was having ample material for studying energetic reactions. He shifted from potato to pigeon breast muscle: the tissue—used for flying—was energetically quite active, and a cheap supply of pigeons was easily available. The pragmatic method was widely adopted by other researchers.

Szent-Györgyi, as he did in venturing into new topics, repeated classic studies. He observed that certain molecules, notably malic, fumaric and succinic acid, increased the use of oxygen. But he also observed that they did not deplete themselves. They seemed not to act like a foodstuff, or source of fuel, simply being burned. Szent-Györgyi reasoned that he had found a series of catalysts. They seemed to function as successive hydrogen carriers, accepting protons in one reaction and releasing them later elsewhere. They might link the hydrogen ions and oxygen in the scheme he had imagined earlier. But it was left to others, notably Hans Krebs, to interpret fully the role of these compounds as intermediary metabolites and to identify the cycle that accounted for their regeneration.

In 1937 Szent-Györgyi received the Nobel Prize in Medicine "for his discoveries concerning the biological combustion processes with especial reference to vitamin C and to the fumaric acid catalyst." Ironically, fumaric acid was later characterized as an intermediate, not just an unaltered catalyst. Szent-Györgyi had also erroneously interpreted vitamin C, as well as vitamin B_2, as similar intermediates. Szent-Györgyi had further proposed succinic acid as a treatment for diabetes. His fundamental discovery of the role of the intermediates was coupled with many errors.

Szent-Györgyi's interest in protons, electrons, and "bioelectronics" deepened. Decades later, after he had established himself in the United States, he applied his views further by suggesting that a disrupted flow of electrons triggered cancer. His views on "free radicals" and oxidants in disease provoked considerable discussion, although firm evidence for their role did not develop.

Chemistry of Muscle Contraction

Szent-Györgyi seemed depressed following the Nobel Prize, but his enthusiasm rebounded after reading a 1939 paper by Vladimir Engelhardt and Militsa Ljubimova describing how the muscle protein myosin could split adenosine triphosphate, or ATP: myosin was an enzyme, not merely a structural element. Szent-Györgyi was excited by the prospect of explaining movement, a hallmark of life, biochemically. In addition, he may well have been intrigued by the report that myosin's behavior seemed similar to an enzyme he had recently studied as part of the intermediate energy reactions, the "yellow enzyme" (later NADP dehydrogenase). First, he and associate Ilona Banga confirmed the Soviet couple's work. Then, one evening, they allowed a protein extract to sit overnight while they attended a lecture. The preparation unexpectedly gelled. Addition of ATP, however, restored the original viscosity. That seemed an indirect clue to contractile properties. Using the new form of myosin, they extruded threads of myosin gel, added ATP and watched, amazed, as the thread contracted. They had recreated the vital property of animation just by mixing chemicals! Szent-Györgyi later remarked that it was "the most beautiful experiment I ever witnessed".

In 1941 former student Bruno Straub returned to Szeged. He soon isolated a new protein from the second form of myosin. It could transform the original myosin into the contractile form. Accordingly, the protein was named actin. Szent-Györgyi then showed how ATP preciptated actin from the hybrid form, now called actomyosin. The critical step in contraction, it seemed, was the dissociation of two muscle proteins, actin and myosin, by ATP.

Meanwhile, Naziism had been advancing across Europe. Szent-Györgyi became politically outspoken. Eventually at risk, he went into hiding. After World War II, the promise for freedom under the Soviets diminished, and to ensure his personal safety Szent-Györgyi emigrated in 1947. He re-established himself in Woods Hole, Massachusetts and organized his own foundation, eventually known as the Institute for Muscle Research.

War had disrupted scientific communication and Szent-Györgyi's publication of *The Chemistry of Muscle Contraction* in 1947 helped inform the West of the Hungarians' work. One speculative chapter conveyed Szent-Györgyi's continued thinking about the flow of electrons, now in interpreting changes in muscle proteins. In 1949 Szent-Györgyi discovered that fresh muscle could be preserved chilled in a 50% solution of glycerol for study at a later date — another valuable research tool widely adopted. Szent-Györgyi's lab hosted much important research on muscles. For example, his cousin Andrew Szent-Györgyi investigated the unit structures of myosin and Delbert Philpott did electron micrographic studies. The relevance of Szent-Györgyi's own work, however, waned with the emergence of the sliding filament theory of muscle contraction, developed by H.E. Huxley in the early 1950s. In 1954 Szent-Györgyi received the prestigious Lasker Award for his work, "including the discovery of actomyosin, the essential contractible element of muscle."

The Man and his Politics

Szent-Györgyi ultimately became a legendary personality in science. He impressed people wherever he went. Popular journalist Studs Terkel lauded him as a "maverick" and a "poet." Fellow Nobelist Linus Pauling called him "the most charming scientist in the world". He inspired colleagues, young researchers and the public alike. He was profiled in such popular magazines as *Time*, *Reader's Digest* and *Saturday Evening Post*.

One element in Szent-Györgyi's wide influence was his sheer charisma. His biographer, Ralph Moss, noted that he had "brilliant blue eyes and a very loving expression." He was "very interested in whatever person he was engaging with". Szent-Györgyi had a hearty sense of humor and self-effacing wit that pleasantly belied the image of the serious and studious scientist. He exuded vigor, impressing others with his energy even in old age. He was an avid sportsman, from tennis and volleyball to swimming and fishing. He inspired great loyalty and, despite his love of play, a strong work ethic, as well. His associates affectionately called him "Prof," even after he abandoned his academic positions.

Szent-Györgyi's writing was fluid and his lectures memorably entertaining. He used homespun analogies with great flair, portrayed the ordinary as extra-ordinary, and dramatized his presentations with vivid examples or colorful demonstrations. He could also turn a phrase worth quoting. For example, he expressed his credo as: "be modest in everything except your aims". He rendered scientific discovery poetically: "to see what everybody else sees, to think what nobody else thinks".

Moreover, Szent-Györgyi espoused—and seemed to embody—science as imaginative play, a romantic ideal that fellow scientists could respect, and non-scientists admire. Szent-Györgyi also coupled this view to a principle of autonomy for researchers. “Scientific research is a passion," he wrote in 1943. "The real scientist is driven by this passion and is ready to bear privation and, if need be, starvation, rather than let anyone dictate to him which direction his work must take”. He famously spurned standard grant applications, claiming that no one could properly predict genuine discovery. He also ennobled "long-shot" ideas. Analogously, when fishing he used a big hook because, he said, he would rather not catch a big fish than not catch a small fish.

Szent-Györgyi fostered an image of scientific discovery—especially his own work—as intuitive. His retrospective accounts, however, were often at odds with the record of earlier events. For example, he initially rejected Krebs account of the citric acid cycle as theoretically misguided, yet would later depict it as an elaboration of the "Szent-Györgyi cycle". Simliarly, he amplified successful guesses into inspired insight, while saying little about bold proposals that led nowhere. Among the many erroneous ideas he promoted (in addition to those noted above) were: megadoses of vitamin C for miscellaneous ailments; a new vitamin P; and treating cancer with ultrasound or mushroom juice. Historically, blind guesswork, chance and resources seemed more important than any special intellectual ability.

Another significant feature of Szent-Györgyi's personality was his nonconformism, egalitarianism and pacifist ideals. All reflected a sense of anti-authoritarianism or anti-establishment perspectives that may well have developed from his relationships with his father and uncle. He regarded everyone as peer and friend both. He played sports with students, to the dismay of some senior colleagues in Hungary. He stridently opposed fascism as it advanced in Hungary in the 1930s. He wrote to Hans Krebs, warning him, and helped guide him to a position in England. He stopped publishing in German as protest. His public statements, amplified by the fame of his Nobel Prize, made him a leader. Eventually he became a target for arrest by the Nazis. After World War II, Szent-Györgyi's anti-elitism earned him favorable treatment from the communists. Yet he was equally prepared to oppose the threat of Soviet oppression. Later, in the U.S., he denounced the Vietnam War and the use of nuclear weapons made possible through science. In his 1970 book, *The Crazy Ape*, he expressed his agonized sentiments, which resonated with the spirit of the era. Szent-Györgyi's views were well reflected in the lifestyle he established in Woods Hole. Work in the lab paused every afternoon (as it had in Hungary) for tea and convivial discussion. At his home, "Seven Winds" — dramatically set overlooking the ocean — he and his wife hosted many parties and other intellectual gatherings. For Szent-Györgyi, freedom and universalism were guiding ideals, whether in science or society.

The complexity of Szent-Györgyi's character was often less public. For example, he served as a medic in the first World War. Amid fear and despair, he shot himself in the arm to escape duty. He nonetheless accepted a Silver Medal of Valor and maintained the deception even while serving as a member of the Hungarian Parliament after World War II. Szent-Györgyi's career was also likely shaped as much by personal insecurities, a desire for validation through science and aversion to accountability, as by ideals about research. While he was able to secure substantial funding from many sources — the Rockefeller Foundation; the National

Institute of Health; the Armour meat company; the American Heart Association; and even a wealthy couple who led a national fund-raising effort for over a decade on his behalf — in every case the relationship ended in disillusionment. Events fell short of perhaps overidealized expectations.

For Szent-Györgyi, personality, science and politics interacted, as exemplified in his relationship with the enigmatic Hungarian entrepreneur Itsvan (Stephen) Rath. Rath seems to have approached Szent-Györgyi in 1945, and provided funds for his new biochemical institute, probably in exchange for long-term business interests. Later, due to his capitalist activities, Rath was taken into Soviet custody. Szent-Györgyi, leveraging his notoreity, secured Rath's release and assisted him escaping the country. He had been severely mistreated for two weeks and was probably rescued from a far worse fate. Here was Szent-Györgyi's sense of loyalty. Once in the U.S., Rath helped establish a foundation devoted exclusively to funding Szent-Györgyi's research. Little seems known about Rath's business associates. Such was Szent-Györgyi's devotion to research that he seemed not to care how the funds were raised. Later, Rath shepherded a collaboration between Szent-Györgyi and the Sorvall Corporation in designing a continuous centrifuge. Here, again, was Szent-Györgyi's skill in developing important scientific tools. The patent proved immensely profitable. When Rath died in 1962, however, irregularities surfaced. Substantial payroll taxes and taxes on royalties for more than a decade were due. Government grant funds were unaccounted for. Szent-Györgyi quietly assumed the deep financial burden, which extended over many years. Such was his idealism and faith that they had eclipsed repeated cautions from his daughter, to his own unfortunate cost.

Ultimately, Szent-Györgyi's legacy in science was as much about his persona and style, as any idea, method or finding he introduced. He had a special gift for evoking an appreciation of science, echoing his own devotion, and so inspired many others to achievements of their own.

DOUGLAS ALLCHIN

Works about Szent-Gyorgyi

Moss, Ralph W. *Free Radical: Albert Szent-Gyorgyi and the Battle over Vitamin C*. Paragon House (New York, 1988). A comprehensive, although largely non-scientific biography with a sympathetic perspective.

Albert Szent-Gyorgyi Papers. Woods Hole Marine Biological Laboratory, Massachusetts. Papers from 1894 to 1995, including photographs, oral histories, published articles, video recordings and lectures. Summary and exhibit available online, URL: profiles.nlm.nih.gov/WG/Views/

Works by Szent-Gyorgyi

Major research papers are listed, and copies available online, at "The Albert Szent-Gyorgyi Papers: Articles (Chronological Listing)," URL: profiles.nlm.nih.gov/WG/Views/AlphaChron/date/10001/

Szent-Györgyi, Albert. *The Crazy Ape*. (1970). Plaintive epistle on war, pollution and overpopulation.

Szent-Györgyi's own accounts of his life and work should be regarded cautiously, as personal perspectives, not always commensurate with well documented history.