Armin C. Braun

1911–1986

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by Maarten J. Chrispeels and Frederick Meins, Jr.

NATIONAL ACADEMY OF SCIENCES

ARMIN CHARLES **BRAUN**

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Armin C. Braun, Professor of Plant Biology at the Rockefeller University in New York was internationally known for his research on crown gall tumors in plants and the first experimental demonstration of tumor reversal. He postulated the existence of a tumor inducing principle, later shown to be the T-DNA that is transferred to plant DNA from the bacterial Ti plasmid of *Agrobacterium tumefaciens,* the causative agent of crown gall. His research laid the groundwork for later developments in the field of plant genetic engineering and the biology of tumors in plants and cancer in animals.

By Maarten J. Chrispeels and Frederick Meins, Jr.

Training at the University of Wisconsin

Armin Braun was born in 1911 and raised in Milwaukee, Wisconsin. Unfortunately nothing is known to us about his parents or his early life as he rarely talked to his associates about his personal life. We do not know what he was like as a youth, but later in life he was rather formal. Everyone referred to him as Dr. Braun and we will refer to him as Braun in this memoir. We do know that he excelled at sports, in high school or in college, perhaps both. He entered the University of Wisconsin-Madison and in 1934 received a Bachelor of Science degree in Microbiology and Biochemistry. He entered graduate school at the same university and selected Professor James Johnson, a virologist, as his mentor. The University of Wisconsin was then one of the top institutions in the U. S. to study plant pathology.

Tobacco had become an important crop in Wisconsin, and Braun did research on the bacteria that cause wildfire and angular leafspot diseases of tobacco. His PhD thesis was published in the journal Phytopathology in 1937. Towards the end of his thesis research, during 1937-1938, he spent time in Europe that included a stay in the laboratory of

Professor C. Stapp, who was an expert in bacterial diseases of plants. Professor Stapp was particularly interested in crown gall disease. Undoubtedly, Braun already knew much about crown gall because the plant pathology department at UW-Madison included Robert Joyce Riker. Riker was the U. S. expert on this bacterial disease of fruit trees, which was a significant problem in both European and American orchards and vineyards.

The Rockefeller Institute at Princeton

Upon receiving his PhD in 1938, Braun joined the department of animal and plant pathology at the Rockefeller Institute in Princeton. In 1931, Louis Kunkel had been asked by the Rockefeller Institute for Medical Research in New York to organize a department of plant pathology that was to be located in Princeton. Diseases of various crops were a threat to American agriculture and horticulture and the country needed outstanding plant pathologists to help solve these problems. Kunkel, a virologist, discovered that several viral diseases of plants could be cured by keeping the plants at an elevated temperature of 35 to 42° C. This technique would play a role in Braun's later research. Kunkel traveled all over the country and by 1932 he had assembled a staff that included many young promising plant pathologists. Among them was Wendell Stanley, who would later receive the Nobel Prize in Chemistry for his research on crystallizing tobacco mosaic virus.

In his new position, Braun started two lines of research: he began research on crown gall and continued work with other bacteria that infect plants. In 1941 he published a short article in *Science* entitled A phytopathogenic bacterium fatal to laboratory animals. The bacterium in question was *Phytomonas polycolor,* now called *Pseudomonas aeruginosa.* This discovery probably influenced him later when he was fully engaged in understanding the cellular basis of "cancer" or neoplastic growth in plants, the formation of crown gall tumors, and found parallels with research going on in animal cancers. Based on his own research and after a careful reading of the literature, he became a strong proponent of the epigenetic basis of cancer in both plants and animals.

Understanding bacteria and plant tumors

When Braun started at Princeton in 1938 it was known that *Agrobacterium tumefaciens*, a soil-dwelling bacterium, was the causative agent of crown galls. It was not clear whether the bacteria needed to be continuously present to cause the disease. When Braun was in Germany with Professor Stapp he met a student who had trouble recovering bacteria from the tumors, as others had done. Published accounts indicated that bacteria could be isolated sometimes but not always. The presence of a primary tumor on a stem can

cause secondary tumors to be formed at some distance, but whether these also contained bacteria was not known. *A. tumefaciens* can infect a number of plants and Braun chose to work on sunflowers.

Braun in 1957, working on a grafting experiment.

It was fortunate that Philip White, a pioneer of plant tissue culture, worked in the same department at the Rockefeller Institute in Princeton. White was an expert at plant tissue culture and Braun was an expert at grafting. Braun first confirmed that when *Agrobacterium* causes the formation of a primary tumor on sunflower stems, secondary tumors can arise at some distance. He cultured ten of these secondary tumors and performed some 2000 tests, but not a single one showed the presence of bacteria. The conclusion was inescapable: the bacteria did not need to be present for tumors to proliferate. Furthermore, Braun showed that these tumors could be grafted onto healthy plants and would continue to grow. White had devised a medium that would allow plant organs such as roots or shoots to grow in axenic culture. The same medium would not support the growth and multiplication of differentiated plant cells. Braun collaborated with White and found that White's basal medium allowed the tumor cells to grow and multiply and do so year after year. They concluded that normal cells had been *transformed* into neoplastic cells. Together they wrote three important papers, one of them in 1942 in *Cancer Research*. The papers are an excellent example of Braun's meticulous experimental approach.

Around the same time Braun made another important finding. It was known that an attenuated strain of *Agrobacterium* (Strain A66) produced very slowly growing tumors when compared to the wild type strain (A6) from which it was derived. It had been found earlier that cultures of *A. tumefaciens* secreted the plant hormone indole acetic acid (IAA). When these slow-growing tumors were supplemented with the synthetic

auxin naphthalene acetic acid, they grew as fast as the tumors elicited with the A6 strain. The same result was not obtained with IAA, the natural auxin, because it was unstable in culture. The experiment showed very clearly that tumor initiation and tumor growth were steps that could be separated.

The Tumor Inducing Principle (TIP)

Some plants tolerate elevated temperatures that are lethal to bacteria. *A. tumefaciens* is a soil dwelling species that is quite sensitive to temperature, and Braun started a program aimed at using higher temperatures to disrupt the transformation process. He started work with the Madagascar Periwinkle (Vinca rosea), which, Louis Kunkel had shown, could withstand temperatures of 46°C for a week or more, conditions that killed *Agrobacterium*. By transferring the plants at different times after infection at 25°C to the higher temperature (46°C), Braun was able to once more separate tumor induction from tumor growth. This demonstrated again that live bacteria were not essential for tumor growth, as they did not survive the 46°C treatment. Subsequently, Braun and a colleague showed that transformation occurred when plants that were inoculated and kept at 32°C—a temperature that was too high to permit transformation to take place—for 24-48 hours and then transferred to 25°C. The plants had to be kept at 25°C for as little as 10 hours before being transferred again to a higher temperature. These experiments showed that a conditioning of the wound site was necessary before transformation could take place. They postulated the existence of a Tumor Inducing Principle (TIP) as the agent responsible for transformation. In a 1947 paper, Braun postulated four possibilities for the nature of TIP: (1) a metabolic product of the crown-gall bacterium; (2) a host constituent converted by the bacterium to a tumor-inducing substance; (3) a chemical fraction of the bacterial cell, such as a DNA molecule, that is capable of initiating in the host cell a permanent developmental alteration; and (4) a viral or other agent present in the crown-gall organism. Including DNA as a possibility illustrates Braun's advanced thinking: this was only three years after O. T. Avery's classic experiments, when few people even accepted the idea that DNA was the genetic material. Many years passed before it was established that TIP was a foreign DNA derived from the *Agrobacterium Ti* plasmid.

Next, Braun became interested in the physiological basis of tumor growth. The temperature shift experiments showed that the rate of tumor growth depended on the length of time the tissue was exposed to TIP. If exposure was for 36 hours, the tumors grew slowly. If it was for 48-72 hours, the tumors grew moderately fast. Exposure for 4 to 5 days produced the fastest growing tumors. What was changing in the cells? Using

different tissue culture media, Braun showed that the slowest growing tumors could be made to grow faster in a medium supplemented with auxin and various organic compounds. Fewer additives were needed for the moderately fast growing tumors and none for the fastest growing tumors. Braun concluded from his experiments that the neoplastic state involved the gradual activation of different metabolic pathways that synthesized molecules necessary for rapid cell division and cell expansion.

Braun showed that *Vinca* tumor extracts contained a growth substance or substances that could supplement auxin in sterile media to bring about rapid growth of plant cells. These results strengthened Braun's belief that the crown gall system could serve as an experimental model to research the changes in metabolism that underlie neoplastic growth in plants and, by extension, to research cancer in humans.

The toxin of *Pseudomonas syringae pv tabaci*

While this research with *Agrobacterium* was going on mostly in the 40s, Braun also made progress with his investigations on wildfire disease of tobacco. As part of his PhD thesis he had compared *Bacterium tabacum* and *Bacterium angulatum*, now known to be different forms of a single species called *Pseudomonas syringae pv tabaci*. The bacteria that cause wildfire (*B. tabacum*) and angular leaf spot (*B. angulatum*) were thought to be two different species, because the disease symptoms are different. Both types of bacteria are pathogenic, but only the wildfire bacteria produce a toxin. The symptoms, lesions on the leaves, differ for the two forms. When wildfire bacteria infect a leaf, a small necrotic lesion develops with a large yellow halo around it, caused by the diffusion of the bacterial toxin. Braun's PhD thesis work showed that mutants of the toxin-producing *tabacum* strains, which produced no toxin, could not be distinguished from the *angulatum* strains. Braun's later research showed that the toxin inhibits the growth of *Chlorella* and that its action can be antagonized by methionine. In the 1950s Braun teamed up with a colleague named Woolley, also at the Rockefeller Institute, to purify and determine the structure of the toxin. But the correct structure—a novel β-lactam— was finally established only much later, in 1971.

Cell division factors in tumors

As early as 1954, Braun and Naf produced evidence that crown gall tumors contain cell division-inducing factors. They were able to induce growth of tobacco pith parenchyma cells on a medium containing auxin and filter-sterilized tumor extract. Somewhat later Braun showed that there were two factors involved. These he termed cytokinesins I and

II, describing them as nicotinamide derivatives. The methods available to characterize such natural compounds were, of course, quite limited at the time. About the same time Carlos Miller working with Folke Skoog discovered that kinetin (furfuryladenine), obtained from partially degraded herring sperm DNA, was a potent cell division factor. Later, molecules with similar activities—now called cytokinins—were found in plants. Subsequently Braun turned his attention to the physiological basis of tumor growth, but the matter remained unresolved: were cytokinesins different from cytokinins? In 1969, Braun's lab teamed up with Hans Kende's lab from Michigan State University. Kende was a hormone expert and a neutral party in the debate about the identity of the cell division factors in tumor tissue. Their research showed that the cytokinesin preparations were not contaminated with cytokinins. Not content to let the matter rest, one researcher, Carlos Miller, examined *Vinca rosea* crown gall tumors supplied by the Braun lab and found that a cytokinin, ribosyl-trans-zeatin, was present in the tumors and accounted for a major portion of the cell division activity. The Braun lab then re-examined the issue and reaffirmed that the chemicals they had identified earlier were indeed cell division factors as claimed. However, the two labs used different methods of extraction. The unusual and provocative title of the paper contributed to the *Proceedings of the National Academy* by Braun was "A comparative study of cytokinesins I and II and zeatin riboside: A reply to Carlos Miller."

Braun's insistence that he was right isolated him more from the plant biology community to which he had never really belonged. He did not publish in *Plant Physiology,* where much work on plant hormones was being published at the time. The issue was settled much later after Braun retired by studies of Andrew Binns, Braun's last postdoc, in a collaboration with David Lynn. Using more sophisticated methods of purification and analysis, the cell division factors were found to be dehydroconiferyl glucosides that can replace cytokinins in cell division assays but not in organogenesis assays. A second paper showed that in the presence of auxin, cytokinin stimulates the accumulation of these cell division factors in the culture medium soon after tobacco pith is put into culture and before the first wave of mitosis. Finally, it turned out, both Carlos Miller and Armin Braun were right! There are additional cell division factors—other than cytokinins—in tumors, but they were not nicotinamide or hypoxanthine derivatives as originally proposed.

Plant tumor reversal and suppression

Certain strains of *A. tumefaciens* on certain plant species such as tobacco (*Nicotiana tabacum*) incite complex tumors called teratomas consisting of highly abnormal leaves and buds. As early as 1948 Braun had proposed, based on grafting experiments, that individual teratoma cells are pluripotent and that complete recovery from the cancer state might be possible. Braun finally tested this hypothesis in 1959 by using a cell-cloning method recently developed by Muir. He obtained numerous single, tobacco-teratoma cells by shaking tissues vigorously in liquid culture. A very few of these cells survived and grew into tissues when cultured and separated by filter paper from a nurse tissue of *Nicotiana glutinosa*.

Seven of the 11 resulting cloned lines were capable of hormone-independent growth and exhibited the typical, teratomatous phenotype. When serially grafted onto the cut-stem tip of tobacco plants, the cloned teratoma tissues gradually developed more normal appearing shoots, lost their ability to grow on hormone-free medium, and eventually formed normal shoots that flowered and set fertile seed. This work, part of which was done in 1957 when Braun was a visiting professor at Cornell University in the laboratory of F. C. Steward, led him to conclude that transformation in crown gall was a gradual, fully reversible progress and, hence, unlikely to result from somatic mutation such as deletion or irreversible rearrangement of nuclear genes.

Braun was quite cautious in interpreting his results. He recognized his findings did not rule out a role for self-replicating elements—later shown to be DNA sequences of bacterial origin—or cell-heritable epigenetic changes. Braun's 1959 paper was especially important for two reasons. First, at the time cancer in animals was still widely believed to be an irreversible process. This was the first experimental demonstration of tumor reversal. It provided strong evidence for Braun's view, forcefully argued in his 1969 book, *The Cancer Problem,* that cancer is a potentially reversible process generally.

Second, Braun was fully aware that the regeneration of entire plants from the progeny of single teratoma cells implied that at least some somatic plants cells were totipotent. The Principle of Totipotency—later established by others for specialized cells of numerous plant species and certain animal species—is fundamental to modern thinking in developmental biology and the basis for important applications in biotechnology. Over time, more and more hints accumulated that tumor formation in crown gall was linked to the transfer of genes from the bacteria and not just the activation of metabolic pathways as shown by Braun.

This interpretation resulted from different lines of research, but most strongly from the discoveries in the laboratory of Georges Morel in France. In 1957, Lioret observed that crown gall tumor cells contain unusual amino acids not found in normal cells. Further characterization in Morel's lab showed that these novel chemicals, called opines, are condensation products of an amino acid and a keto acid. Different strains of *A. tumefaciens* were found to induce the synthesis of different opines. Because normal plant cells do not make opines, this finding could not be reconciled with a purely epigenetic model.

By the mid-to late 70s it became clear from a series of experiments in different labs that virulent *A. tumefaciens* strains contain a large plasmid and that a small piece of this Ti-plasmid, T-DNA, is transferred to the plant genome. This transfer causes neoplastic growth because the T-DNA carries genes needed for the multiplication of normal cells including genes for auxin and cytokinin biosynthesis. Braun was well aware of earlier, discredited claims that TIP was a DNA molecule (Braun and Stonier, 1958) and did not readily buy this explanation for neoplastic growth. Nevertheless after Mary-Dell Chilton (elected to the Academy in 1985) visited his lab and patiently explained her careful experiments, he did accept and embrace the new explanation. Understanding of T-DNA grew rapidly in the late 70s and early 80s and many of the experiments carried out earlier by Braun began to make sense.

While the discovery of T-DNA didn't detract from the conclusion that teratoma cells retain the potential for normal development, it raised the possibility that tumor recovery might simply result from the loss of part or all of the T-DNA. Between 1976 and 1981 Braun and his collaborators Henry Wood, Andrew Binns, and Robert Turgeon addressed this issue using numerous, cloned, tobacco teratoma lines induced by *A. tumefaciens* strain T37. They found that the grafted teratoma shoots, while capable of normal differentiation and development, produced the opine nopaline and grew when cultured on hormone–free medium. This suggested that the neoplastic properties of these teratoma cells encoded by T-DNA genes is somehow suppressed, but not lost, in the grafted shoots. In contrast, plants raised from the seeds produced by flowers on these shoots were unable to produce nopaline and cells were unable to grow when cultured on hormone-free medium. Molecular experiments by others summarized in Braun (1982) confirmed that suppressed teratoma shoots contain T-DNA, but that T-DNA or those parts of the T-DNA required for neoplastic growth have been lost in the seed-grown plants. This implied that the presence of T-DNA is necessary but not sufficient for expression of the teratoma phenotype. Loss of tumorous growth can occur by suppressing

expression of T-DNA genes and by the loss of these genes, presumably after meiosis and before fertilization.

Epigenetic models for cancer

In his 1969 book, Braun already clearly favored the idea that tumorous growth was under the same types of epigenetic regulation as normal development. Braun came to believe that epigenetic models provide a unifying concept for understanding cancer. Once again, this view was strongly influenced by studies of plant tumor diseases. Braun's tumor suppression experiments had shown that even when neoplastic growth is caused by foreign genes, tumor cells have the capacity for normal growth and differentiation. He drew similar conclusions for tumors resulting from the interaction of genomes in hybrids. In Kostoff Tumor Disease, hybrids obtained by crossing two plant species, such as *N. glauca* and *N. langsdorffii*, are tumor prone. Whereas young plants grow and develop normally, older plants consistently form autonomous, transplantable tumors at sites of wounding. Nevertheless, individual Kostoff tumor cells were shown to be toti-potent and capable of normal growth and development. Finally, epigenetic activation of pathways required for neoplastic growth can occur without apparent changes in the cell genome. Acquisition of cytokinin-independent growth is a key, early step in plant tumor transformation. Normal plant cells in culture sometimes spontaneously lose their requirement for growth hormones by a process called *habituation*. Habituation of tobacco cells for cytokinins is a cell-heritable, but potentially reversible epigenetic change in cytokinin production. The key point is that these epigenetic changes could fully compensate for T-DNA deficiencies in cytokinin pathways that are necessary for neoplastic growth.

Braun's 1981 article, "An epigenetic model for the origin of cancer," published the year of his retirement, drew heavily on the up-to-date animal cancer literature to argue strongly for the optimistic view that independent of the proximal cause—such as somatic mutation, viruses, and developmental abnormalities—expression of the neoplastic state is ultimately under epigenetic control, and, hence is potentially reversible. It would have pleased Braun to know that the current view of cancer is so much closer to his view more than 30 years ago. It is now widely recognized that tumor cells generally have some capacity for differentiation and that epigenetic mechanisms have a key role in tumor progression.

Armin Braun the man

Other than being a meticulous experimental scientist, who was Armin Braun? As noted earlier, we know little about his beginnings. He was a bachelor whose private life was a complete enigma to his collaborators. Peter Wolk, who was in his laboratory for four years in the mid-sixties, commented that at the end of his time with Braun he only knew three things about him: that he had a nephew, a tractor, and a swimming pool. During lunch Braun told Peter a horror story as to how his nephew had driven his tractor into his swimming pool! A few also knew about Braun's athletic exploits, because he kept a scrapbook about his triumphs and occasionally showed it to his collaborators. Apparently, in his early days Braun was a star football player nicknamed *Crazy legs Braun* as well as a golden gloves boxer. In 1938, when he started at the Rockefeller in Princeton, Braun moved there not just by himself, but with his widowed mother and his widowed sister Irma who was 8 years older than he and had three school-age children, two boys and a girl. They all lived together in a house at number 8 Hartley Avenue at the edge of the Princeton campus. Later they would move to two adjacent properties on Hopewell Road outside Princeton. In 1948, when the Princeton lab was closed by Detlev Bronk, the president of the Rockefeller Institute, and the unit had been transferred to New York, Braun kept his house in Princeton and commuted by train to the city. He would have much preferred to stay in Princeton. He cared for his widowed sister and her three children, Lois, Erwin, and Gene. We must assume that one of these two young men was the nephew who drove the tractor into the pool. For his summer vacations Braun went back to Wisconsin.

Although Braun was rather formal, which was not unusual in those days, he was very approachable. Lunch was a time to discuss science with his collaborators, either in the Rockefeller Institute dining room or in his small office. When lunch was in his office he was constantly smoking his pipe and relighting it as listeners all choked on the smoke. In earlier years he would go to the dining room, where lunch was formal and a coat and tie were required. This was not a problem, since he came to work every day with coat and tie. The number of people in his lab was always quite small. He gave his students free reign to do whatever they wanted and strongly believed that a PhD project should be independent of the research of the professor. He was extremely generous and would not put his name on the papers of his PhD students. His name only appeared on a paper if he had done some of the experimental work.

Braun spent much time in his office reviewing the literature—he had a remarkable command of the cancer and genetics fields—and writing the manuscripts of his research papers, reviews, and three books. While doing so he chain-smoked a pipe, which was undoubtedly the cause of his respiratory illness later in life. His long-time secretary was very devoted to him and had a much bigger office than he. She kept his professional life in order and typed his lengthy manuscripts. Similarly, a devoted, long-time technician was responsible for the day-to-day maintenance of his extensive tissue culture collection. Nevertheless, Braun was very much hands-on when it came to testing his ideas, and personally made the technically demanding cloning and grafting experiments needed for studies of tumor reversal.

Awards and Honors

During his career Braun garnered a number of honors. In 1949 he received the Newcomb Cleveland Award of the American Association for the Advancement of Science. In 1960 he was elected to membership in the National Academy of Sciences, and in 1965 he was made a Fellow of the American Phytopathological Society. In 1966 he was elected to membership in the American Academy of Arts and Sciences, and in 1982 he was a co-recipient with Nobel Laureate Barbara McClintock of the *Grand Prix Charles Leopold Mayer of the Academie Française de Sciences*. By the late 1970s his respiratory problems were worsening and in 1981, at the age of 70, he retired to his house in Princeton. He continued to follow scientific advances in the *Agrobacterium* field and his last paper was published as a book chapter in 1986, the year he passed away.

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