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Folke K. Skoog: In Memory and Tribute

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Folke Karl Skoog will be remembered as one of the major figures in plant biology in the 20th century. As the last surviving member of the small group of investigators who began plant hormone research in this country, his death on February 15, 2001, at the age of 92, marks the end of an era. His personal contributions to the field of plant hormone research were monumental. Few single discoveries have had as major an impact on a field of plant science as the isolation and identification of kinetin by Skoog and his associates at the University of Wisconsin–Madison in 1955. This discovery was the founding event in the field of cytokinin research (although the term cytokinin was not invented until somewhat later), and it shaped and conditioned research in plant growth regulation for many decades to come. In addition, Skoog was responsible for several early discoveries that helped to establish the general importance of auxin in plant growth regulation. He also investigated aspects of plant nutrition, advanced the science and art of plant tissue culture, and addressed a number of important questions in plant morphogenesis. His contributions to our understanding of the regulation of plant growth and development constitute a legacy that is rivaled by few others in the field. To this legacy must be added the many people whose lives he influenced and enriched. A number of these individuals are identified in the following account, but it is impossible to list all of those whose careers and lives were shaped by contacts with him and by experiences in his laboratory. For the many omissions, the author apologizes.

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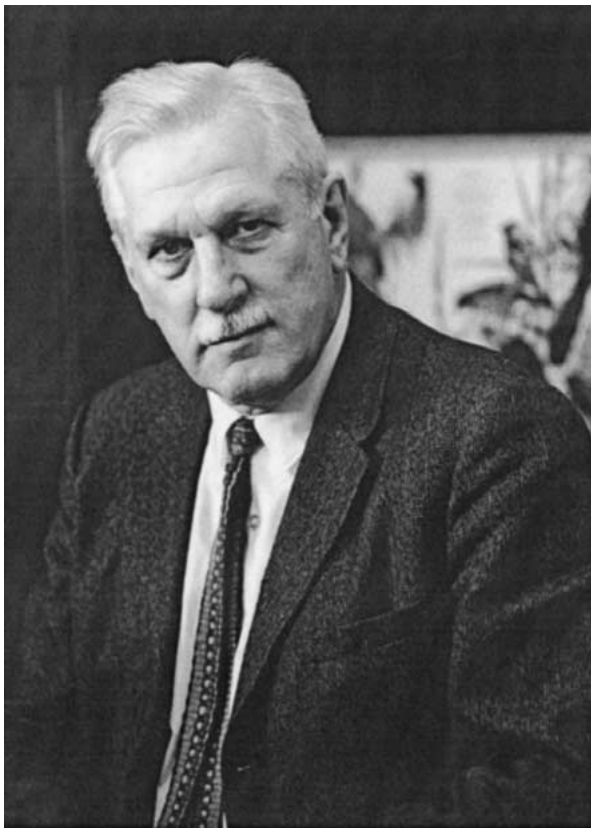
A Brief Biography

Folke Skoog was born in Halland, Sweden, on July 15, 1908. His father was trained as an agronomist, and Skoog's early years, when he was not in school in Uppsala, were spent on the large agricultural estate that his father managed. He was one of two sons, and his brother became a prominent surgeon in Sweden. When asked about the important influences in his life, his parents were the first people that Skoog mentioned.

Skoog came to the U.S. in 1925, at the age of 17, for what was originally intended as a one-year stay with his aunt, who was living in California. She appears to have been a strong-willed person, and one might guess that the youthful Skoog would have been something of an independent spirit. Therefore, it is not surprising that the relationship between Skoog and his aunt was not uniformly harmonious. Nevertheless, her help was important to his subsequent education and success.

Enrolling in high school in California, Skoog became interested in chemistry and decided to stay in the U.S. to pursue an undergraduate degree at the California Institute of Technology. He graduated from that institution with a B.S. in Chemistry in 1932 and became a naturalized citizen in 1935. By the time he received his undergraduate degree, his professional attention had turned to plant biology, but his scientific thinking over the years was strongly influenced by his early training in the physical sciences.



Folke K. Skoog (1908–2001).

The learning environment that Skoog encountered as an undergraduate at Cal Tech was truly remarkable. He had chemistry courses from Linus Pauling, physics from Robert Millikan, and philosophy from Bertrand Russell. However, it was contacts with a number of outstanding scientists in the field of biology that shaped the course of his career. During his undergraduate years at Cal Tech, he came to know and be mentored by the geneticist Thomas Hunt Morgan (who had recently been persuaded to head the new Department of Biology at Cal Tech), Carl Lindegren (then a graduate student and later to become well known for his work on the genetics and biochemistry of *Neurospora* and yeast), and notably Hermann Dolk (who was brought to Cal Tech by Morgan to initiate work in the exciting new field of plant hormone research). Dolk was one of a number of brilliant young scientists that Morgan brought to Cal Tech, including Robert Emerson, George Beadle, Kenneth Thimann, and Boris Ephrussi. Dolk had been trained in the laboratory of F.A.F.C. Went in Utrecht, Holland, and had worked alongside the latter's son, Frits Went, to define the physiological properties of the growth substance (auxin) that Frits had demonstrated was produced in the tips of *Avena* coleoptiles. Based on a recommendation from Lindegren, Skoog began working with Dolk on the regulatory effects of auxin on plant growth. Interestingly, Skoog's initial project was to attempt to obtain evidence for a second growth substance that Dolk believed moved upward from the seed during the growth of the *Avena* seedling. However, Dolk had an unfortunate penchant for fast cars, and he was killed in an automobile accident before the project was completed.

Following Dolk's death, Skoog began working with Kenneth Thimann, a young plant biochemist from England. Thimann had joined the faculty at Cal Tech at about the same time as Dolk, and he was himself destined to become a well-known figure in plant hormone research. Although Skoog was still an undergraduate at the time, this early association with Thimann began a life-long friendship between the two men. After receiving his bachelor's degree in 1932, Skoog remained at Cal Tech as a graduate student in Thimann's laboratory, where he continued to work on various aspects of auxin physiology and biochemistry. When Thimann left for a position at Harvard, Skoog finished his graduate work at Cal Tech under the tutelage of Frits Went (who replaced Dolk after the latter's death). Over the years, Skoog always remembered Went's kindness when Skoog was a young graduate student trying to survive and carry on his studies in the midst of the Depression.

Skoog received his Ph.D. in Biology from Cal Tech in 1936 and was awarded a National Research Council Fellowship (one of only two awarded nationwide in biology) to work with Dennis Hoagland in the Division of Plant Nutrition at the University of California, Berkeley. Hoagland's work on plant mineral nutrition was already well known at the time. In Hoagland's laboratory, Skoog worked on several projects, including the effects of zinc on auxin metabolism. This experience provided him with knowledge concerning mineral nutrition that he was to employ later in other venues. At Berkeley, he also worked with J.P. Bennett in investigations of the regulation of bud dormancy in woody perennials.

Skoog accepted a position with Thimann as a research associate and instructor at Harvard University in 1937. With the exception of a 6-month sabbatical in 1938 as a visiting scientist at the Pineapple Research Station of the University of Hawaii, Skoog continued at Harvard until he accepted a faculty position at Johns Hopkins University in 1941. Throughout this period, his investigations focused on auxin metabolism and action, including some initial experiments with plant tissue culture systems. While at Johns Hopkins, he contributed to the war effort by partici-

pating in an NIH study of medical problems arising from the handling of TNT in munitions manufacture, and he also developed assays to test the efficacy of various antifungal compounds. In 1944 through 1946, he served with the Quarter Master General's Office in the Defense Department, where he held the position of Chemist and Technical Representative attached to the U.S. Army in Europe. After a brief tour-of-duty in his native Sweden, he was assigned at war's end to investigate and report on Germany's war-time research on food technology related to the production and use of yeast as a food source.

Skoog returned to academic life in the U.S. at the close of 1946. After a brief stay in Carl Lindegren's laboratory at Washington University in St. Louis, he was offered and accepted a faculty position at the University of Wisconsin–Madison in 1947. There he began the work with tobacco tissue culture systems that was ultimately to lead to the discovery of kinetin and the founding of the field of cytokinin research. He remained at University of Wisconsin as a faculty member in the Department of Botany until his retirement in 1979.

During the course of his career, Skoog authored over 170 scientific publications (see the Appendix) and trained over 60 graduate students and more than 40 postdoctoral associates. His laboratory was always an international center of intellectual activity, attracting students, postdoctoral associates, and visiting scientists from around the world. Throughout his long and distinguished career, he received numerous honors and awards, including the Stephen Hales Award (the premier award of the American Society of Plant Physiologists) in 1954, the Botanical Society's Award of Merit in 1956, and election to the National Academy of Sciences in 1956. He was elected president of several of his professional societies, including the American Society of Plant Physiologists in 1957, the Society of Developmental Biology in 1970, and the International Plant Growth Substances Association in 1979. In retirement, he received the National Medal of Science, which was presented to him by President George Bush at a White House ceremony in 1991.

Investigations of Auxin Metabolism and Physiology

When Skoog was awarded the Stephen Hales Award of the American Society of Plant Physiologists in 1954, the citation for the award read: ''For outstanding contributions to research in the physiology of auxins, the development of plant tissue cultures, and the physiology of fresh water algae.'' The revolutionary discovery of kinetin in 1955 was yet to come, but he had already made major contributions to research on the regulation of plant growth and development. As an undergraduate and graduate student working with Thimann at Cal Tech, he had shown that auxin activity could be extracted from plant sources other than the tips of coleoptiles. Moreover, he found that auxin applied to the cut surfaces of decapitated dicot seedlings could substitute for the effect of the terminal bud in inhibiting the out-growth of lateral buds and thus maintain apical dominance. This result provided evidence that the role of auxin in plant growth was more general than the promotion of elongation in cereal coleoptiles and led eventually to the recognition that this substance was broadly involved in the regulation of plant growth and development. Further confirmation of a role of auxin in apical dominance was obtained by Skoog in a series of experiments using x-rays as a tool to lower endo genous concentrations of auxin in selected portions of intact plants.

To further explore the effects of auxin on bud growth, Skoog became interested in culturing excised buds, and this turned his attention to the emerging field of plant tissue culture. However, the only local expertise available in tissue culture was Boris Ephrussi, who was working on mouse cell culture, and Skoog's initial ventures into this field were with animal cells in Ephrussi's laboratory.

Skoog's early investigations of auxin metabolism continued as a postdoctoral associate, first in the laboratory of Dennis Hoagland at the University of California, Berkeley, and subsequently in Thimann's laboratory at Harvard. Hoagland had previously demonstrated that incipient effects of zinc deficiency in plants grown in nutrient solutions could be counteracted to some extent by treatment with the auxin indoleacetic acid. Skoog was able to demonstrate that auxin levels in the terminal shoots of tomato plants were rapidly reduced and virtually disappeared in plants showing incipient signs of zinc deficiency, resulting in complete secession of growth. However, the effects of zinc deficiency on plant growth were not due exclusively to effects on auxin synthesis and destruction. At Harvard, Skoog worked with Thimann on the development of methods for the quantitative extraction and estimation of free and bound auxin levels in plant tissues. As part of this work, he was able to demonstrate that cultured tissues from the plant tumors that arise spontaneously on certain hybrid tobacco plants (derived from the cross *Nicoti-*

ana Langsdorffii × *N. glauca*) produced high levels of auxin in culture.

The *Nicotiana* genetic tumor system received further attention from Skoog after he joined the faculty at Johns Hopkins University in 1941. Philip White, one of the pioneers of early research on plant tissue culture, had made the interesting observation that cultured tissues derived from the *Nicotiana* tumors sometimes produced shoots when the tissues were grown submerged in liquid culture. Skoog demonstrated that the addition of auxin to the liquid culture medium completely suppressed shoot formation. In addition, he was able to root some of the shoots that developed in culture, providing the earliest demonstration of the regeneration of a complete plant from a callus tissue. This work foreshadowed his later research on hormonal interactions in the regulation of plant growth and morphogenesis.

Auxin metabolism and physiology would continue to interest Skoog in later years. Even after the discovery of kinetin, several of his graduate students were directed to problems in auxin research. In the latter half of the 1950's, Ethel Niedergang and Geoge Keitt, Jr. investigated the polar transport of auxin and established that triiodobenzoic acid was a potent inhibitor of auxin transport. In work published in 1965, T.T. Lee conducted a detailed study of the stimulation and inhibition of auxin destruction by substituted phenolic compounds, and the interactions of auxins and cytokinins in the *Avena* curvature test were investigated by Bill Jordan as part of his thesis research published in 1971. The latter work essentially revisited (but in an altered context) the problem that Skoog had attempted to address in his initial work with Dolk.

Discovery of Cytokinins

After returning from the war and accepting a position at the University of Wisconsin in 1947, Skoog turned again to cultured plant tissues as experimental systems. This time, he chose to develop a new system derived from stem tissues of *Nicotiana tabacum* cv Wisconsin 38. Skoog and Cheng Tsui, a postdoctoral associate, demonstrated that stem segments from this tobacco cultivar formed abundant callus tissue when cultured on a medium containing auxin. Although Skoog and Tsui were able to use the tobacco stem segment system to demonstrate a number of interesting morphogenic phenomena, the callus tissue that formed on the segments could not be subcultured on the same medium. Moreover, if pith tissue from the center of the tobacco stem, rather than complete stem segments, was placed on the medium, no cell division or callus formation occurred. Subsequently (in the early 1950s), J.R. Mauney and John Jablonski (both graduate students in Skoog's laboratory) were able to demonstrate that cell divisions could be induced in tobacco pith tissue and an indefinite proliferation of callus tissue achieved by addition of certain complex natural products to the medium. Thus, coconut milk, malt extract, and yeast extract were able to induce cell divisions in tobacco pith tissue when these materials were added to the auxin-containing medium.

The isolation of the substance or substances responsible for the cell division activity of yeast extract was undertaken in Skoog's laboratory by a young postdoctoral associate, Carlos Miller, who had continued Tsui's work with the tobacco stem segment system. Miller was unsuccessful in identifying the compound responsible for the ability of yeast extract to promote cell divisions in plant tissue, but he did obtain evidence that this compound had properties similar to those of purines. With this information in hand, a variety of purines and substances known to be rich in purines were tested by Miller in the tobacco pith bioassay system. As a result of these screening tests, an old commercial preparation of herring sperm DNA was found to be highly active in promoting cell division in the pith tissue. New DNA preparations did not yield the activity, but it was soon demonstrated that the cell division activity could be generated by heating the DNA preparations in weakly acid solutions in the autoclave. (The generation of this activity from deoxyadenosine by a series of complex ring rearrangements was elucidated many years later in collaborative work with Nelson Leonard's group at the University of Illinois–Urbana.)

The purification of the compound responsible for the cell division activity of partially degraded DNA preparations was achieved by Miller and Skoog late in 1954. The identification of the compound as 6-furfurylaminopurine (that is, N^6-furfuryladenine) and confirmation of the structure by synthesis was accomplished shortly thereafter in collaborative work with Frank Strong and his associates in the Department of Biochemistry at the University of Wisconsin–Madison. The trivial name kinetin was given to this compound. Kinetin has never been shown to occur naturally, but it was the first example of a new class of plant growth substances that came to be known as cytokinins. Within a few days, the first analog of kinetin (the compound N^6-benzyladenine) had been synthesized by Strong and his associate F.S. Okimura. N^6-benzyladenine proved to be even slightly more active as a cell division factor

than kinetin itself. Another 40 compounds were subsequently synthesized by Strong and his associates and tested in Skoog's laboratory. Of these synthetic compounds, 21 proved to have some degree of activity in promoting cell division in the tobacco pith bioassay system. The name kinin was originally proposed as the generic name for this new class of plant growth regulators but was later (1965) changed to cytokinins to alleviate confusion with another class of compounds that stimulate smooth muscle contraction in mammalian physiology.

The discovery of kinetin, published in 1955, initiated intensive efforts to isolate and identify a naturally occurring compound with equivalent activity in promoting cell division in plant tissues. Work in Skoog's laboratory by J.A. Zwar had detected cell-division-promoting activity in extracts of pea seedlings, and Janina Rogozinska and John Helgeson subsequently achieved partial purification of a cell division factor from extracts of pea seeds. (It is illustrative of Skoog's creative approach to problems that the starting point for the latter effort was 2000 gallons of blanch water obtained from a nearby Green Giant Cannery as a byproduct of the processing of 25 tons of peas. The blanch water was transported to the University of Wisconsin in a milk truck and taken to dryness in the powdered milk facility of the University's Dairy Department.) However, it was D.S. Letham in New Zealand and, almost simultaneously, Carlos Miller at Indiana University, who were the first to successfully purify and identify a naturally occurring cytokinin from plant material and to demonstrate that this compound was also an N^6-substituted adenine derivative. The isolation and identification of N^6-(*trans*-4-hydroxy-3-methyl-2-butenyl)adenine as the active cell division factor present in immature corn kernels was achieved by Letham in 1964. Letham gave this compound the trivial name of zeatin, and the compound that Miller had isolated from the same source was quickly shown to be identical to zeatin.

Structural Studies of Cytokinins

Following the structural characterization of kinetin, Skoog and Strong had shown that several other synthetic N^6-substituted adenine derivatives had similar biological activity. As the search for a naturally occurring cytokinin was proceeding, a group in France claimed that they had observed cell-division-promoting activity in tests of a naturally occurring 3-substituted adenine derivative known as triacanthine. Triacanthine had been isolated and characterized by Nelson Leonard (a well-known natural products chemist at the University of Illinois–Urbana) in 1962. Leonard and his co-workers obtained triacanthine from young leaves of *Gleditsia triacanthos* (honey locust), where it occurs in very high concentrations. Triacanthine is 3-(γ,γ-dimethylallyl)adenine. Samples of triacanthine, provided by Leonard, were tested for cytokinin activity in Skoog's laboratory and found to be inactive, but the compound was observed to be converted to an active compound by autoclaving. More interestingly, a related compound synthesized by Leonard, 6-(γ,γ-dimethylally)aminopurine, proved to be the most active compound tested to date, with activity in the tobacco bioassay approximately ten times that of kinetin. [It should be noted that the nomenclature commonly applied to this compound has changed several times. It was referred to in the early literature as 6-(γ,γ-dimethylallyl)aminopurine and somewhat later as 6-(3-methyl-2-butenyl)aminopurine. More recently, it has been termed N^6-(Δ^2-isopentenyl)adenine. All of these names, and others, refer to the same N^6-substituted adenine derivative. The name N^6-(Δ^2-isopentenyl)adenine will be used in the remainder of this review.] When zeatin was subsequently isolated, its structure was found to differ from that of N^6-(Δ^2-isopentenyl)adenine by only the presence of a hydroxyl group in the N^6-side chain.

The interaction between Skoog and Leonard that began with studies of triacanthine developed into a long and highly productive collaboration and friendship. Over the years, more than 200 compounds were synthesized by Leonard's group and tested for cytokinin activity in Skoog's laboratory. A graduate student, Hamzi Q. Hamzi, conducted one of the early studies in this effort, but the individual who became central to the on-going structure–activity work in Skoog's laboratory was Ruth Schmitz. Dr. Schmitz was one of Skoog's early graduate students at the University of Wisconsin. She returned to Skoog's laboratory in the 1967, after a prolonged sabbatical to raise a family. In the years that followed, her careful work contributed to a steady stream of publications that described in detail the structure–activity relationships of cytokinin-active compounds. Additional products of this collaborative effort were compounds that functioned as cytokinin antagonists (at least in the tobacco bioassay) and both cytokinin and auxin analogs suitable for photoaffinity-labeling studies.

The collaboration between Skoog and Leonard also yielded the structures of a number of naturally occurring compounds and resulted in the demonstration of the natural occurrence of N^6-(Δ^2-iso-

pentenyl)adenine. This compound was isolated from cultures of the plant pathogen *Corynebacterium fascians* by Dieter Klambt, a postdoctoral associate in Skoog's laboratory, in 1966. (In later work by Emanual Scarbrough and others in the laboratory, several other cytokinin-active compounds were isolated and characterized from the same source.) When cytokinin-active ribonucleosides were discovered to occur in certain transfer RNA (tRNA) molecules (as described elsewhere in this review), the collaboration between the two laboratories resulted in the isolation and identification of a number of cytokinin-active molecules from this source, including compounds not previously described.

Hormonal Regulation of Plant Morphogenesis

One of the important outcomes of the work in Skoog's laboratory was the demonstration that plant growth and morphogenesis were controlled by complex interactions of multiple plant hormones, interactions in which both the relative and the absolute amounts of these substances were important. This theme first emerged in Skoog's early work on the control of shoot formation in plant tumor cultures (described above). Further development of this basic concept occurred in the early work at the University of Wisconsin that utilized cultures of tobacco stem segments. In addition to the callus formation that was stimulated by treating these stem segments with auxin, Skoog and Tsui found that adventitious shoots occasionally formed on the stem segments. Shoot formation could be suppressed by increasing the auxin concentration in the medium, and, under these conditions, roots sometimes developed. Moreover, at low auxin concentrations, the addition of adenosine or adenine to the medium greatly increased the number of shoots formed on the segments. Similar results were obtained with cultured segments of roots from horseradish. (The addition of adenosine, and later adenine, to the culture medium was based on the suspicion that energy metabolism might be involved in hormonal regulation.) In discussing these results in a 1951 publication, Skoog and Tsui noted that Sach's old concept of specific organ-forming substances had enjoyed a recent revival, but: "The results we have obtained are in disagreement with such concepts. On the contrary, our findings suggest that both organ formation and subsequent development are brought about by quantitative changes in amounts and interactions between nutrients and growth factors which are essential for growth of all cells, so that the pattern of development is determined by the relative supplies...of these materials at particular loci."

Soon after the isolation and identification of kinetin, Miller and Skoog demonstrated that it was possible to control organ formation in tobacco tissue cultures by manipulating the auxin and cytokinin levels in the culture medium. At intermediate concentrations of auxin and cytokinin, the tobacco tissue grew as an undifferentiated callus tissue. On the other hand, high concentrations cytokinin, accompanied by low concentrations of auxin, promoted the formation of shoots in the tobacco tissue cultures, while high concentrations of auxin, accompanied by low concentrations of cytokinin, were found to promote root formation. Thus, depending on the balance and absolute amounts of auxin and cytokinin in the medium, the tissue could be shifted from one morphogenic program to another, and, with appropriate sequential manipulation of the culture medium, it became possible to regenerate whole tobacco plants from undifferentiated callus tissue. This result has proven to be applicable to a number of other tissue culture systems as well, and it finds important applications today in many of the strategies for modern genetic engineering of plants. Moreover, similar auxin and cytokinin interactions have subsequently been shown to regulate morphogenic events *in planta.*

Skoog's interests in plant morphogenesis were quite broad and continued throughout his professional career. In the 1960s, he explored the regulation of morphogenesis in several new systems. One of his graduate students, Michael Bristow, investigated the factors controlling the differentiation of fern callus tissue into gametic or sporophytic tissues. William Wardell examined the regulation of floral bud formation in excised tobacco stem segments, and Alvin Engelke studied the interaction of cytokinins and gibberellins in the regulation of leaf shape in tobacco. A postdoctoral associate, Michael Schneider, investigated the regulation of differentiation in moss protonema, and Ola Heide, a visiting scientist from Norway, analyzed the *in vivo* changes in cytokinin associated with regeneration in *Begonia* and *Bryophyllum.* As these examples illustrate, at any one time, a number of different systems and problems were under simultaneous investigation in Skoog's laboratory. Over the course of his career, he worked with algae, moss, ferns, bacteria, fungi, and even some animal systems, as well as a variety of seed plants and the tobacco tissue culture system for which he is best known.

Studies on the Mineral Nutrition of Algal Cultures and Plant Tissue Cultures

The citation for the Stephen Hales Award given to Skoog in 1954 alluded to his contributions to plant tissue culture and the physiology of fresh water algae as well as to his auxin work. Although the algal studies are not as well known as other aspects of Skoog's work, they represent a fairly substantial body of work at the University of Wisconsin, extending over the years 1950–1957. This work grew out of problems related to algal blooms occurring in association with eutrophication of the lakes that form a prominent and attractive feature of the landscape in the immediate vicinity of Madison, Wisconsin. In collaborative studies with Gerald Gerloff and George Fitzgerald (two other members of the University of Wisconsin faculty), Skoog participated in investigations of the nutritional requirements and possible methods of control of the blue–green algae responsible for the local blooms. A particularly noteworthy outcome of this collaboration was the demonstration in 1954 by Holm–Hansen, Gerloff, and Skoog that cobalt was an essential element for the growth of blue–green algae.

Skoog's contributions to plant tissue culture are numerous and substantial, and his most important achievements in this field were to come sometime after he received the Stephen Hales Award. Aspects of this work that relate directly to the discovery of cytokinins and subsequent studies on the interactions of cytokinins and auxins in the regulation of growth and morphogenesis in plant tissue culture systems are described above. However, Skoog's contributions to plant tissue culture as a technique also include one of the most systematic and extensive investigations of the general nutritional requirements of a plant tissue culture system ever performed. The inorganic nutrients required by tobacco tissue cultures were examined and optimized by Toshio Murashige, a graduate student in Skoog's laboratory, in work published in 1962. One result of this investigation was the demonstration that much of the growth stimulation observed when extracts from various natural sources were added to tissue culture medium could be attributed to relatively nonspecific effects arising from the use of suboptimal levels of inorganic nutrients in the tissue culture medium. The Murashige and Skoog medium is now a standard commercial product that is widely utilized for plant tissue culture. Murashige's work was followed by a painstaking and detailed examination of the organic nutrients required by tobacco tissue cultures in a study conducted by Elfriede Linsmaier, a postdoctoral associate in Skoog's laboratory.

The nutritional studies of Murashige and Linsmaier were significant because they were particularly thorough and broke new ground in that regard. However, problems related to the nutrition and metabolic activities of plant tissue culture systems occupied the attention of a number of other students and associates of Skoog. Robert Sanstedt investigated the effects of various amino acids on the growth of tobacco tissue cultures. The nutritional requirements of tissue cultures derived from woody species were the subject of separate studies by graduate students Carol Steinhart, Karl Wolter, and Jakob Lowenberg. Machteld Mok examined the genotypic control of carotenoid synthesis in carrot tissue cultures. Various metabolic activities of tobacco tissue cultures were investigated, including uronide metabolism (by Curtis Wilson), the metabolism of phenolic compounds (by John Sargent and Edgardo Montaldi), and the regulation of thiamine biosynthesis (by John Digby and Dzintar Dravnieks). Within Skoog's professional lifetime, and due in large measure to his efforts, plant tissue culture progressed from a technique restricted in application to a few special tissues to today where it finds routine applications with almost any plant species of interest.

Hormonal Regulation in Relation to Nucleic Acid Metabolism

Skoog was one of the first to recognize and suggest that plant hormones might be affecting growth and morphogenesis by mechanisms associated with nucleic acid metabolism and protein synthesis. As early as 1953, he had Julius Silberger, a graduate student, examine auxin-induced changes in the DNA and RNA content of tobacco pith tissue, and James Naylor, in 1954, observed that auxin caused mitosis in cells of the same tissue without accompanying cell division. In 1956, 1957, and 1958, Skoog collaborated with Nirmal K. Das and Klaus Patau (from the University of Wisconsin Medical School) in a series of microspectrophotometric and autoradiographic studies of the interaction of kinetin and auxin in the control of DNA synthesis in tobacco pith cells. The relationships between growth rates and nucleic acid content in root tips of inbred corn lines were investigated by Lowell Woodstock and Skoog in work published a little later.

In the early 1960s, Skoog became convinced that understanding the mechanism of hormonal effects on differentiation would require the application of new technology capable of measuring changes in nucleic acids at the level of single cells. He invested considerable energy and capital in an attempt to adapt to plant systems the procedures for microanalysis of nucleic acids that had been developed by Jan-Erik Edström (University of Gothenburg, Sweden) to measure RNA and DNA changes in single nerve cells dissected from rat brains. Edström's technique employed micromanipulation for the enzymatic extraction, hydrolysis, and quantitative estimation of RNA and DNA from isolated single cells, followed by analysis of the base composition of these molecules by microelectrophoresis on a single cellulose fiber. During the time I was a graduate student in Skoog's laboratory, Edström visited the laboratory to train several of us in the procedure. Somewhat later, Michael Schneider, a postdoctoral associate in the laboratory, was successful in applying Edström's technique to an analysis of the cellular changes in nucleic acids associated with the initiation of gametophore structures in protonema of the moss *Funaria hygrometrica*. However, in spite of the elegance of the technique, it did not provide the molecular distinctions needed to answer the questions of interest in plant systems, and the emphasis in the lab shifted quickly with the discovery of the presence of cytokinin-active nucleosides in certain tRNA molecules.

The presence of the cytokinin-active nucleoside N^6-(Δ^2-isopentenyl)adenosine adjacent to the anticodon in serine tRNA from yeast was reported in 1966 by Hans Zachau and his coworkers in Germany as part of their work in determining the total sequence of this tRNA molecule. At about the same time, Ross Hall at Rosswell Park Memorial Institute in Buffalo, New York, isolated the same modified nucleoside from hydrolysates of crude tRNA preparations from yeast and calf liver. When this information came to Skoog's attention, he quickly mobilized the lab to investigate these observations. Bioassays of hydrolysates of tRNA prepared from a wide range of plant, animal, and microbial sources revealed that cytokinin-active nucleosides were almost universally present as constituents of crude tRNA preparations. John Burrows (a postdoctoral associate from Northern Ireland) and I (then a graduate student and later a postdoctoral associate in Skoog's laboratory) were particularly active in the initial efforts of the laboratory in this area, but a number of other students and postdoctoral associates were to contribute to the ongoing work, including Norimoto Murai, Hendrick Vreman, John Einset, Barbara Taller, Satoshi Matsubara, and Santhanam Swaminathan. Working in collaboration with Nelson Leonard, the cytokinin-active constituents of a number of tRNA preparations were isolated and identified in Skoog's laboratory, including the previously unreported 2-methylthio derivative of i^6Ado (first isolated from *Escherichia coli* tRNA) and the corresponding derivative of *cis*-zeatin nucleoside (obtained from wheat germ tRNA). The distribution of cytokinin-active nucleosides in individual tRNA species was examined in yeast (in collaboration with the laboratories of Robert Bock in the Department of Biochemistry at the University of Wisconsin and Gordon Tener at the University of British Columbia), in *E coli* (in collaboration with Dieter Söll, Yale University), and in *Staphylococcus epidermidis* (in collaboration with Jack Strominger, then in the Department of Pharmacology at the University of Wisconsin). The results of these studies, together with results obtained independently by S. Nishimura in Japan, established that the distribution of cytokinin-active nucleosides with respect to individual tRNA species was related to the genetic code. Cytokinin-active nucleosides were found to be restricted to tRNA species that responded to codons beginning with U, although individual organisms differed in the distribution of cytokinins in the tRNA species within this group. Subsequent results with plant tRNA preparations and with tRNA preparations from yeast and *Drosophila* (the latter in collaboration with Bradley White, Queens University, Canada) established that the distribution was more restricted in eukaryotes than in prokaryotes, but the cytokinin modification was always present adjacent to the anticodon in serine and leucine-tRNA species responding to U codons. Although attempts to link these observations to the mechanism of the hormonal action of cytokinins in plant systems proved unsuccessful, this body of work contributed substantially to our knowledge of the occurrence and distribution of hypermodified bases in tRNA molecules.

The tRNA effort represented one of the last major initiatives in Skoog's laboratory prior to his retirement. This effort was interrupted briefly in the late 1960s as a result of the damage suffered by the laboratory when an adjacent building housing the Army Mathematics Research Center was demolished by a late-night explosion engineered by a small group of militant antiwar protesters. Considering that Skoog's laboratory was frequently occupied at all hours, it was fortunate that no one in the group was injured, although one person in the Math Center was killed. In spite of the trauma of this event, the laboratory was

returned to serviceable condition rather quickly, and a steady stream of publications continued from the group until Skoog's retirement in 1979.

Other Studies

The productivity of Skoog's laboratory, as measured by his publication, was enormous, but the list of his publications falls far short of reflecting all of the people who were trained in his laboratory. For a variety of reasons, a number of interesting studies by his students failed to produce manuscripts, and many of these studies survive only in thesis form. Particular examples that have remained in my memory include C.E. La Motte's investigation of the effects of tyrosine on the growth of tobacco callus tissues (a study that set the stage for later work by both R. Sandstedt and T.T. Lee), the work of James Iglehart on the physiological and biochemical effects of auxin analogs, Alan Mackenzie's application of Edström's technique to a study of pollen development, and Beth Taylor's work on cellulose digestion by the unusual thermophillic organism, *Clostridium thermocellum*. There were many others. All of this work was an important part of the internal heritage of the group, and it was discussed and passed on to newcomers as part of the intellectual framework in which the group operated. It is an interesting measure (although a somewhat unfortunate outcome) of the productivity of Skoog's laboratory that it was possible to leave unpublished a quite substantial body of work that was significant but not central to the primary questions that occupied the attention of the laboratory.

A Personal Remembrance

To bring this account to a close, I hope I may be forgiven a few personal comments concerning a man who was my mentor and friend for 30 years. His was the most original and interesting mind I have had the pleasure of encountering in this profession. Whether the topic was science, society, politics, or philosophy, Folke always brought unique perspectives and a penetrating analysis to the discussion. Even when one failed to agree, his reasoning illuminated the discussion. He was also known for his love of intellectual battle, and he was never slow to engage the opposition. He had little patience for those in the profession he regarded as pompous or too much impressed with their own stature, and nothing delighted him more than to deliver a humorous line that punctured the arguments of the pretentious. However, the repartee was almost always in good humor, and, in private, he was surprisingly modest about his own achievements. He was also an enormously kind individual, and I, and others who were associated with him, benefited greatly from his concern and assistance.

Humor was always close to the surface with Folke. The quick mind was never short of quips and humorous associations. As a native of Sweden, he had a particular fondness for obscure ethnic jokes about Norwegians, and he delighted in bringing these to the attention of Norwegian friends on campus. However, he was just as happy to join in the laughter when the joke was on him, a condition that we didn't hesitate to try to achieve as frequently as possible.

Folke was an active person and a man of rather tall and athletic frame. In his youth, he had played soccer and a Scandinavian game similar to ice hockey. In college, he became interested in track and enjoyed considerable success as a runner. At the age of 24, he ran the 1500 meters for Sweden in the 1932 Olympics, finishing sixth. (In later years, he would claim he should have won because he had beaten the winning time in trials. Nevertheless, he felt it was probably best that he had not achieved an Olympic medal; otherwise, he might have become a ''track bum''). Perhaps also revealing is a story he told of how, as a recent emigrant to the U.S., one of the questions he had missed on the Cal Tech entrance exam was ''Who is Babe Ruth?'' Although he hadn't known the answer at the time, he thought this was ''a good question, considering the number of bookworms who applied for admission''. He always retained his interest in track and other athletics, and he became a close follower of the football fortunes of the University of Wisconsin and the Green Bay Packers. His recreational interests also included regular poker sessions with a select group of university friends.

Folke, on occasion, could be an intimidating presence, and it was always with some trepidation that a young graduate student or postdoc approached his office to report a disappointing result or some experiment gone awry. On these occasions, he would listen carefully, with one hand on his chin, now and again commenting, ''Is that so!'' Finally, at the end of the recital, the head would cock to one side, the reading glasses would come down on the nose, and for one long unnerving moment the intense blue eyes would peer at you over the frames. Then, more often than not, a soft chuckle would emerge, and he would lean back in his chair and offer some ambiguously reassuring comment, a

favorite being ''Results always seem to follow the principle of maximum human unhappiness.''

The Skoog laboratory at Wisconsin was a site of continuous intellectual traffic. Most of the leading figures in plant physiology visited the lab at one time or another. They were always brought to the morning or afternoon coffeebreaks to meet and talk informally with students, technicians, and postdocs. Coffeebreaks were social occasions that included the personnel associated with the laboratories of Eldon Newcomb, Gerald Gerloff, and Paul Allen, as well as Skoog's group. The Skoog group itself, usually consisting of a dozen or so people, had a distinctly international flavor, with students and postdoctoral associates from around the world. Weekly laboratory meetings of the group involved both original research and literature presentations. The goal was always to thoroughly dissect what had been done and to find the flaws. These sessions could be punishing experiences for the unprepared, but we all quickly learned to prepare, and the training in critical evaluation of the literature and our own experiments was invaluable. Folke was seldom one of the more aggressive participants in these exchanges, but his standards shaped and informed the discussions. It was a demanding, exciting, and lively environment in which to work and acquire a graduate education.

Throughout his years at Wisconsin, Folke was sustained by the quiet strength and affection of his wife, Birgit. Dealing with the sometimes raucous group of students, friends, and associates that surrounded him could not always have been easy, and the patience and good humor with which she dealt with this large and unconventional extended family (and its somewhat eccentric head) were admirable. Their daughter, Karin, occupied a special place in both their lives, and in later years, Folke took considerable interest and pride in the emerging intellects of his grandchildren.

The strength of Folke's intellect and character, his special foibles, and the vitality of his personality will always be remembered by his friends and associates. It is difficult to adequately capture these qualities on paper. For those interested, some sense of the person may perhaps be best gleaned from his own words as he talked about his career in a published interview conducted late in his retirement (Skoog 1994). He was a remarkable person as well as an exceptional scientist, and I feel fortunate to have known him. He enriched the lives of the many people who came under his influence, and his passing leaves the world a poorer place for all of us.

Appendix

Chronological List of Publications

Yost DM, Anderson TF, Skoog F. 1933. The free energy of formation of IBr in CCl_4 solution. J Am Chem Soc 55:552–555.

Thimann KV, Skoog F. 1933. The inhibiting action of the growth substance on bud development. Proc Natl Acad Sci USA 19:714–716.

Thimann KV, Skoog F. 1934. On the inhibition of bud development and other functions of growth substance in *Vicia faba*. Proc R Soc Lond B Biol Sci 114:317–339.

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Skoog F, Goo-Chow C. 1939. Experiments on vegetative propagation of pineapple. II. A study of the inhibition and development of lateral buds. Pineapple Producers Cooperative Association Private Journal.

Skoog F, Goo-Chow C. 1939. Experiments on vegetative propagation of pineapple. III. Production and distribution of auxin in the pineapple plant. Pineapple Producers Cooperative Association Private Journal.

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Skoog F, Hopkins M. 1945. Biotin and growth factor for *Memnoniella echinata* Australia #2. OQMG Reports.

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Sievers RF, Lawton AH, Skoog F, Neal PA, von Oettingen WF. 1945. A medical study of the effect on the TNT on workers in a bomb and shell loading plant. US Public Health Service Bulletin No 291, p 1–84.

Skoog F. 1946. Food Yeast Production and Utilization in Germany. IQMG TSFET. Technical Report, US Department of Commerce Publication.

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