The August Krogh principle applies to plants

In 1975, Hans Krebs published his paper: "The August Krogh Principle: For many problems there is an animal on which it can be most conveniently studied." Krebs quoted August Krogh (1929, p. 247) as follows:

> For a large number of problems there will be some animal of choice, or a few such animals, on which it can be conveniently studied. Many years ago when my teacher, Christian Bohr, was interested in the respiratory mechanisms of the lung and devised a method of studying the exchange through each lung separately, he found that a certain kind of tortoise possesses a trachea dividing into the main bronchi high up in the neck and we used to say as a laboratory joke that this animal had been created expressly for the study of respiration physiology. I have no doubt that there is quite a number of animals which are similarly 'created' for special physiology purposes, but I am afraid that most of them are unknown to the men for whom they are 'created' and we must apply to the zoölogists to find them and to lay our hands on them.

Based on Krogh's concept, Krebs asserted that there are organisms that, because of their anatomy or physiology, provide easy access to the mechanisms that underlie interesting and important physiological and biochemical problems. He named this principle after Krogh. Many biologists, including Gregor Mendel (1926), Albert Szent-Györgyi (1937), W. J. V. Osterhout (1958), and George Beadle (1977), whose experimental philosophies were resonant with those of Krebs and Krogh, conducted experiments on organisms that seem to have been "created for special physiology purposes" (Krogh 1929). Studies on such "convenient" organisms allow one to develop techniques and hypotheses that are applicable to other organisms. Krebs and his son John also cautioned that the diversity of nature has often resulted in variations of physiological mechanisms (Krebs and Krebs 1980), and extrapolation from a single example to a generalization may not always be warranted. Yet the successes in unraveling physiological mechanisms have almost always arisen from the innovative selection of an appropriate organismal species.

Krebs (1975) has called our attention to the concept that "ideas analogous to the Krogh principle have been widely accepted since time immemorial with reference to the plant world—namely, that for each illness the Creator had provided a special plant as a cure. 'The Complete Herbal' by Nicholas Culpeper, M.D.,...lists over 600 medicinal plants and uses as a motto the quotation from Ecclesiasticus 38,4 'The Lord has created medicines from the earth and a sensible man will not disparage them'" (Culpeper [1653] 1814 as cited in Krebs 1975, p. 225). However, this motto is no longer in vogue.

Recently, a trend has developed in plant biology in which research focuses on a single species, *Arabidopsis thaliana*. Although *Arabidopsis* may be the organism of choice for many genetic studies, due to its small genome, little repetitive DNA, lilliputian size, and rapid life cycle, some of the traits that make it an excellent organism for molecular genetic studies make it unsuitable for many physiological, biochemical, and biophysical studies. We are not overlooking the value of *Arabidopsis* for molecular genetic research; nevertheless, we want to emphasize that there are other plants whose anatomical, morphological, and developmental characteristics make them superior choices for studying many important questions in plant cell biology. Although targeted systems are also productive in animal physiology, imagine what our knowledge of neurophysiology and muscle physiology would be had scientists such as Alan Hodgkin, Hugh and Andrew Huxley, Szent-Györgyi, and Setsuro Ebashi been pressured to work on *Drosophila melanogaster* or *Caenorhabditis elegans*.

In this article, we present a brief history of plant cell biology to demonstrate the importance of conducting studies on a wide variety of taxa. We focus on the successful application of the August Krogh principle to various aspects of plant cell biology, emphasizing for each example the qualities of the organism that made it an appropriate choice.

by Randy Wayne and Mark P. Staves

Photosynthesis and respiration

Rapid progress in the understanding of photosynthesis began only after Otto Warburg (in 1919) decided to study this process in *Chlorella*, a single-celled alga, instead of in the whole plants or leaves used by his predecessors (Krebs 1981, Myers 1974). The switch to populations of small *Chlorella* cells allowed the development and use of rapid and sensitive techniques to measure oxygen evolution. Thus, Warburg measured gas exchange from photosynthesis per se, without complications of growth effects. From studies using his newly designed manometer, Warburg proposed that oxygen is liberated from the carbon dioxide, which is directly reduced to make carbohydrate by the light-activated chlorophyll. Cornelius van Niel (1941), stressing the importance of a comparative physiological approach using a diverse sample of microorganisms, suggested that although Warburg's measurements were impeccable his interpretation was wrong, and that in reality, the oxygen is liberated from water and the carbon dioxide must be fixed indirectly.

Subsequently, James Bassham and Melvin Calvin (1962) took advantage of the convenient morphological and physiological properties of *Chlorella* to elucidate the chemical reactions involved in carbon fixation. In these experiments, *Chlorella* was supplied with $^{14}CO_2$ and killed after various periods of time. Paper chromatography of the radioactive carbon compounds allowed Calvin and Bassham to define the sequence of reactions involved in carbon fixation, which is now widely known as the Calvin cycle.

The study of carbon dioxide fixation was simplified by using *Chlorella* because it grows in water and all the inorganic substrates could be readily and uniformly supplied to each and every cell. By contrast, in nonaquatic plants the fixation of carbon dioxide by way of the Calvin cycle requires the uptake of carbon dioxide into the plant through open stomata, resulting in a concurrent loss of water. This consequence may be too costly for a water-stressed plant, and thus modifications of the Calvin cycle that are unnecessary for *Chlorella* have evolved in other plants (see, for example, Hatch 1992). Thus, variations in pathways require the study of diverse species from different environments. Such studies allow one to learn the limits of a generalization derived from a convenient organism.

Phytochemical studies of genera representing at least five families of plants provided the background necessary for understanding the pathways of respiration. This is because the elucidation of the Krebs cycle was accomplished by the addition of putative intermediates of respiration to minced pigeon muscle to see if they stimulated oxygen uptake (Szent-Györgyi 1937). These intermediates had been isolated previously from convenient plants in which they occur in high concentrations because they have a secondary function (Krebs 1981a). The names of the plants from which they were first isolated are enshrined in the names of the intermediates: citric acid from citrus fruits; aconitic acid from the monkshood (*Aconitum*); succinic acid from *succinum*, a fossil resin from an extinct pine; fumaric acid from the fumatory (*Fumaria*); and malic acid from the apple (*Malus*). Thus, a variety of plants and animals, each with its unique advantage, contributed to our understanding of respiration.

Biochemical mechanisms

Peter Mitchell (1966) proposed that respiration and photosynthesis produce ATP by transporting protons across an intact membrane. ATP synthesis occurs concomitantly with the flow of electrons along the electron transport chains in the inner mitochondrial membrane and thylakoids. The resulting unequal distribution of protons results in a proton motive force. According to Mitchell's chemiosmotic theory, the proton motive force possesses energy in the form of a chemical and/or electrical potential that can be used to synthesize ATP.

Using thylakoid membranes isolated from the mesophyll of spinach leaves, a soft tissue that allows the ready isolation of chloroplasts, André Jagendorf and Ernest Uribe (1966) provided experimental proof of Mitchell's hypothesis. In these experiments, Jagendorf and Uribe (1966) artificially induced a pH gradient across thylakoid membranes using permeant acids. These charged membranes could then synthesize ATP in the presence of its constituents, ADP and inorganic phosphate. Thylakoids were convenient material to test the chemiosmotic hypothesis for two reasons. First, the internal volume is large relative to that of submitochondrial particles, a feature that allowed a large buildup of protons per surface area of membrane. Second, the proton motive force is due almost exclusively to the chemical potential, which was easy to control experimentally, rather than to the electrical potential, whose manipulation had to await the introduction of the ionophore valinomycin, an antimicrobial agent isolated from *Streptomyces*.

The so-called pH jump experiments worked out in chloroplast membranes were later carried out on mitochondrial membranes, which are more difficult to manipulate (Thayer and Hinkle 1975). The experiments showed that mitochondria, too, synthesize ATP in response to the proton motive force during respiration, in a manner similar to that in chloroplasts. The Krogh principle can therefore be applied not just within kingdoms but also between kingdoms. Here is a case in which the best organism for testing the chemiosmotic theory was not an animal but a plant.

Plants and animals both store energy in the form of stable polymers, known as foodstuffs. Starch is the foodstuff typically stored in plants. It is usually hydrolyzed to glucose, which is the typical substrate oxidized during respiration. However, not all plants store starch, and thus alternative pathways of combustion must exist. In the 1960s (see, for example, Breidenbach and Beevers 1967), Harry Beevers began investigating the oxidation of fatty acids in lipid-storing seeds, particularly in castor bean seeds (see review by Beevers 1982). He found that the peroxisomes (glyoxysomes) in the endosperm cells convert fatty acids to succinic acid by way of β-oxidation and the glyoxylate cycle. Succinic acid can then enter the Krebs cycle and either be oxidized for energy or converted to water-soluble, translocatable carbohydrates. This dramatic progress could not have occurred had Beevers used most other plant species. Beevers's original research provided the conceptual and experimental framework for Lazarow and de Duve (1976), who later showed that the peroxisomes in liver are also capable of oxidizing fatty acids into carbohydrate and thus can regulate the level of lipids in the blood. Again, work on a "convenient" plant led to the understanding of vital processes in both plants and animals.

The field of polymer science arose from Hermann Staudinger's (1961) interest in botany. Plants are an abundant source of simple structural and storage polymers. In the

1920s and 1930s it was believed that organic molecules with molecular weights larger than 5000 did not exist and the so-called macromolecules were probably artifactual isomorphous mixtures of identical subunits. Staudinger and his colleagues (see review by Staudinger 1961), working with synthetic and natural polymers, including starch isolated from potato, cellulose isolated from cotton fibers, and natural rubber isolated from rubber plants, were able to formulate the concept of macromolecules, determine their structures, and prove their existence. Had Staudinger's interest been in zoology rather than botany, would he have come up with the notion of polymers?

Genetics and cytology

The field of genetics was founded by Gregor Mendel (1926), who wrote, "The value and utility of any experiment are determined by the fitness of the material to the purpose for which it is used, and thus in the case before us it cannot be immaterial what plants are subjected to experiment and in what manner such experiments are conducted" (p. 314) Using peas, with their well-known and readily observable variations in morphology, Mendel was able to elucidate the basic genetic concepts of dominance and recessiveness. Mendel also established the mathematical description used today for the assortment of independent traits.

The genetic material is associated with the nucleus (de Vries 1910), an organelle that can be difficult to visualize in live material. However, Robert Brown (1833), a pioneer in cytology, discovered the nucleus while he was observing the epidermal cells of the Orchideae, in which the nuclei are clearly visible in a light microscope. At this time the relationship between genetics and cytology had not yet melded. Corn was the first organism that enabled geneticists to examine the relationship between the chromosomes in the nucleus and phenotype. Corn is uniquely suited to this type of genetic study: Each of its ten chromosomes is easily identifiable by its length and the location of its centromeres, certain genes on the chromosomes can be localized by their linkage to specific chromomeres and other morphological features, and corn has easily observable phenotypes (e.g., color and texture of the kernels), the appearance of which are correlated with readily identifiable features of the chromosomes. Thus Barbara McClintock and her associates were able to use corn to demonstrate that genes controlling certain phenotypes are located at specific sites on specific chromosomes (Creighton and McClintock 1931, McClintock 1930). Later, McClintock's understanding of the development of phenotypic variation in corn allowed her to predict the existence of movable elements that control the expression of some genes (McClintock 1950). This prediction was borne out in corn and later in other plants, as well as in bacteria and animals. The importance of transposable elements for the regulation of gene function in plants and animals as well as interest spurred by their potential role in the development of cancer earned McClintock the Nobel prize in 1983.

The role of the nucleus in controlling cytoplasmic differentiation has been most elegantly demonstrated in experiments using the giant alga *Acetabularia*, the nucleus of whose cells can easily be removed and replaced with the nucleus of another cell (Hämmerling 1963). These algae are uniquely suited for nuclear transplantation studies because of their large cells and the position of their single nuclei. These studies revealed the role of the cytoplasm and the nucleus in cell differentiation. When a cell of one species had its nucleus replaced by that of a related species, the cell differentiated a reproductive structure, known as the cap, that was identical to that formed by the species from which the nucleus was derived.

The bread mold *Neurospora*, due to its simple nutritional requirements, provided an ideal system to learn that the genes in the nucleus control cellular function by coding for enzymes (Beadle 1977). In these experiments, George Beadle and Edward Tatum found mutants that require a given vitamin because they are unable to synthesize it (Beadle and Tatum 1941). Crosses between such mutants and the wild type revealed that the deficiency in one step of the biochemical pathway that led to the synthesis of a given vitamin was the result of a single gene mutation. As a result of this work, Beadle and Tatum demonstrated that genes code for enzymes.

Development

Although the distinct morphologies of cells are typically directed by the genetic material they inherit, they sometimes develop a pattern by cuing in to environmental factors. In such cases, a meager environmental signal is amplified into a sizable and irreversible one. This process, known as cell polarization, was initially studied by Lionel Jaffe (1979) in the fertilized eggs of the brown alga *Fucus*. Jaffe chose *Fucus* because the polarization process of its egg could be conveniently studied. For example, the egg of *Fucus*, unlike that of most other organisms, is readily accessible because it is not surrounded by an ovule or ovary. Moreover, the polarization process, which begins after fertilization, does not become irreversible for almost ten hours, after which the fertilized egg differentiates and divides into a thallial cell and a rhizoidal cell. Jaffe's studies of isolated eggs showed that each fucoid egg drives an ionic current through itself. The site of current entry predicts which end is likely to develop into a rhizoid and thus establishes its initial polarity. Moreover, blockage of the ionic currents, particularly the current carried by calcium ions, prevents polarization.

Subsequent work on such diverse species as the frog *Xenopus*, the moth *Cecropia*, and the medaka fish *Oryzias* showed that self-driven ionic currents are a widespread mechanism for establishing polarity in eggs. Asymmetrical ion currents also are involved in the regeneration of limbs and the directed growth of neurons. Again, finding a suitable species made it possible to discover the basic mechanisms of polarity.

Differentiation typically (but not always; Turgeon 1975) follows cell division. Studies of the morphological and biochemical changes involved in the cell cycle have been greatly facilitated by the introduction of tobacco BY-2 cells (Nagata et al. 1992). With these rapidly growing, easily synchronized cells it is even possible to collect enough phragmoplasts to do biochemistry and microscopy on this dynamic and ephemeral structure, which is involved in cell division (Shibaoka 1992).

Similar headway in the study of the contribution of microtubules to the mechanism of mitosis was made as a consequence of the introduction of flattened, transparent preparations of *Haemanthus* endosperm cells, with their leviathan chromosomes (Inoué and Bajer 1961, Inoué and Ritter 1975), and diatoms, with their so-called primitive spindles (Pickett-Heaps 1991). These studies revealed the dynamic behavior of microtubules that occurs during chromosome segregation in living cells.

The study of membrane biology, a central theme in developmental biology, was launched by the use of characean internodal cells (Osterhout 1958). The large size of these algal cells made it possible for Collander and Bärlund (1933) to measure the uptake of various chemicals into single cells. Their results allowed them to propose that the plasma membrane must be essentially lipid in nature, but that some small pores must be present to account for the anomalous permeability of small polar molecules like water. The fact that the pores in the plasma membrane change their conductance during an action potential was also first demonstrated in characean cells, even before it was observed in neurons (Wayne 1994). The first action potentials in single cells were observed in the characean alga *Nitella* by Cole and Curtis (1938).

Hungarian peppers and vitamin C

Sometimes important breakthroughs come from unexpected places (Szent-Györgyi 1972, 1974). Szent-Györgyi was interested in studying Addison's disease, which causes a browning of the human adrenal gland. His work was "led by the conviction that there can be no real difference in the fundamental chemical mechanisms of plants and animals" (Szent-Györgyi 1937, p. 67) and that "[w]e are but all young buds of the same old tree of life, expressions of the same fundamental principles appearing under different disguises" (Szent-Györgyi 1937, p. 67). Szent-Györgyi (1937) began working on potatoes as a simple system because they turn brown after wounding. He identified two groups of plants that produce different types of disinfecting compound in response to wounding. One group, which includes potatoes, apples, and bananas, releases polyphenoloxidase when bruised. The released polyphenoloxidase produces o-quinols, which have antibacterial activity and also oxidize proteins, causing the wounded area to turn brown. The other group, which includes cabbages and lemons, does not brown on injury. Its members have a different bactericidal mechanism: they contain high levels of peroxidase activity, and the resulting peroxides oxidize other compounds and thus sterilize the wound.

Szent-Györgyi (1937) noticed that when he assayed for peroxidase activity in cabbage, the reaction had a lag time of one second, whereas when he assayed the purified enzyme, he observed no lag. Szent-Györgyi then isolated from normal adrenal glands a carbohydrate that caused a delay in the peroxidation reaction in cabbage. Although Szent-Györgyi knew it was a carbohydrate, he was ignorant of its function; therefore, he wanted to name it ignose. The editor of *Biochemical Journal*, Arthur Harden, would not allow him to call it that, and also turned down his alternative suggestion of God-nose. It was then named hexuronic acid (Moss 1989). The addition of this newly isolated compound to the polyphenoloxidase-containing plants prevented them from browning on wounding. This finding suggested to Szent-Györgyi that normal adrenal glands might have high concentrations of hexuronic acid that prevent browning. They did. Although hexuronic acid turned out to be irrelevant to Addison's disease, the small sample of hexuronic acid isolated from adrenal glands prevented scurvy in guinea pigs and thus was found to be vitamin C. Because of its anti*scorbutic* activity, the name of hexuronic acid was later changed to ascorbic acid (Szent-Györgyi and Haworth 1933).

At that time, vitamin C could not be purified in large quantities from any plant tested due to the presence of many chemically similar compounds. Thus, it had to be isolated at great expense from adrenal glands. The expense became prohibitive, and in the summer of 1932 further work on vitamin C came to a standstill. One day when Szent-Györgyi's wife was serving Hungarian red peppers (*Capsicum annuum*) for dinner, Szent-Györgyi noticed that these peppers avoided the browning reaction. In his excitement, he ignored his invited guest and escaped to the lab (cited by Moss 1988). That night he discovered that Hungarian pepper, or paprika, unlike all other plants tested, was high in ascorbic acid. A few weeks later he obtained kilograms of material from this convenient organism, allowing for a complete analysis and subsequent industrial synthesis. Szent-Györgyi received the Nobel prize in 1937, in part for his discovery of vitamin C.

An appeal to the plant biology community

All of these examples show that an appreciation of the diversity of nature has led to great advances in biology. What a barrier to progress it would have been had these scientists been limited by granting agencies that favored any one species. There is now a conservative trend in the plant biology community to focus research on a single plant, *A. thaliana*. Has interest in *Arabidopsis* arisen from a grassroots movement? Or was it managed from the top, by administrators in the agencies that fund basic research in plant biology? Although *Arabidopsis* may be the organism of choice for genetic studies, many of the traits that make it an excellent organism for this type of research make it highly unfavorable for many physiological, biochemical, and biophysical studies. We would therefore like to introduce a corollary to the August Krogh principle: No single organism (or technique) exists that can provide easy access to the diversity of hidden mechanisms that underlie all interesting and important physiological and biochemical problems.

Our reservations regarding the habitual use of *Arabidopsis* for addressing any given mystery in plant biology stems from our belief that the problem, and not the organism, should be selected first. After that, it is important to choose the appropriate organism(s) and technique(s) that offer useful characteristics for solving the problem. The current epistemology in the plant biology community favors the reverse approach. We call on that community to recognize the splendid array of species in the "treasure-house of nature" (Pringle 1966), whether they are in the test tube, under a cover slip, on our dinner plate, in the garden, or in the rain forest.

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Note added in proof: While this article was in press, two other articles appeared that have similar messages, one by Howard Gest (1995) and one by Jessica Bolker (1995).

Randy Wayne is an associate professor and Mark Staves is a research associate in the Section of Plant Biology at Cornell University, Ithaca, NY 14853. Their teaching interests revolve around plant cell biology, and they are currently collaborating on a textbook on that subject. Their research interests, supported by the US National Aeronautics and Space Administration, focus on understanding the mechanism of gravity sensing in living cells.