Metabolic Control of Timing

Photoperiodic and rhythmic responses in plants and animals depend on control of metabolism by light.

Sterling B. Hendricks

To pretend that I understand the migration of the Canada goose would be a gross canard! It is now widely known that the flight V high in the autumn sky, the symbol of a season, is initiated by a change in the length of the nights and is one of the many displays of photoperiodic response in animals, but the mechanism of the time sense for navigation is still obscure.

The flowering of the colorful poinsettia in the Christmas season is another display of photoperiodism. The poinsettia blooms in response to long nights. In New Zealand, where Christmas comes in midsummer, the Christmas symbol is the brilliant pohutukawa tree, *Metrosideros tomentosa,* a plant that flowers in response to short nights and thus is in bloom in those latitudes in December.

Thousands of other examples of photoperiodism could be given (*1–3*). By means of timing responses, animals and plants adapt to variation in their surroundings; continuity of species is assured, through dormancy and through emergence of the young at a season or a time of day that is favorable for survival.

Photoperiodism implies a time-measuring system. But by what mechanism do animals and plants measure the season and the day? We know that plants distinguish between light and dark through the reversible reaction of a pigment and the action of this pigment on a substrate. But as yet we know little about the metabolic controls that manifest themselves in rhythmic activity. To understand them better we study both ends of the timing system—the final display and the hormonal requirements for initiation.

Timing in Animals

First, let us consider some of the manifestations of timing, such as the activity pattern of animals (*1–4*). Figure 1 is a record of the activity of a white-toed deer mouse, *Peromyscus,* kept in continuous darkness. The mouse was supplied with adequate food and water and given free access to a running wheel. Each narrow strip across the chart shows the pattern for a day, as observed by Kenneth Rawson of Swarthmore College (*5*). The mouse was active for about 4 hours each day during the 25 days of the study. The period of activity began every 22 hours and 50 minutes. That is, in continuous darkness, the period of the activity pattern was 22 hours and 50 minutes. If an interval of light (say, 12 hours) was introduced each day, the period of the activity pattern became exactly 24 hours and was phased, or set, by the time at which the last light interruption ended. When the mouse was returned to continuous darkness, the 22 hour 50 minute rhythmic period was resumed; again, the pattern was phased from the end of the last period of illumination. Other species of mice and other small mammals that do not hibernate surely follow a similar rhythmic period as they scurry in the darkness of their runways under the snow.

The same general pattern has been extensively observed in other animals, and reference should be made to the many studies on mammals and insects made by Colin Pittendrigh of Princeton University. Among insects, the cockroach has been closely studied; it displays a regular activity pattern on a running wheel when kept in continuous darkness. Each cockroach has an activity pattern with a characteristic period; for one, this may be 22 hours 10 minutes; for another, 23 hours 18 minutes. The period, which is constant for an individual cockroach to within as little as 2 minutes, is about a day—that is, the pattern is circadian. It is in the region of 20 to 28 hours for all animals and plants. In the regular sequence of day and night, however, the period for the cockroach is strictly 24 hours. The endogenous activity is entrained by the environment in much the same manner as it is in the deer mouse.

From these examples one might conclude that only the higher animals show the rhythmic behavior. However, among unicellular forms the red marine armored dinoflagellate *Gonyaulax polyhedra,* studied by S. W. Hastings and Beatrice Sweeney (*6*), which emits light when it is disturbed, and which is so often evident as a luminosity in the surf, emits this light in accordance with a rhythmic circadian pattern (Fig. 2). *Gonyaulax,* accustomed to the slowly changing temperature of the ocean, shows another feature indicative of rhythmic response: the periods of light emission change only slightly with changing temperature. The responses are usually independent of temperature over a range of about 10 degrees Celsius in poikilothermic animals and plants living at the temperature of their surroundings. This degree of variability, in a teleological sense, is adequate for most of their needs.

One way of finding the metabolic controls is to study the effect of light and its absence. Nightfall, or the end of a period of illumination, often sets the phase of a response. Light, in contrast to other stimuli, can reach a point deep within a cell without producing effects along its path of entry. Absorption of light is a single act, the excitation of an electron from a normal to a higher level in a molecule of a particular compound. Light can do only one thing in a complete organism, despite the complexities of the final display. The photoreaction is often the first, or an early, step in a reaction sequence, and thus it defines a starting point. It immediately gives information about the pigment involved, and knowledge of photochemistry may serve as a guide to possible associated reactions.

Timing and photocontrol are both illustrated in the reproduction of a marine polyp, the coelenterate *Hydractinia echinata,* which is about the lowest of the higher animals. In this polyp, two layers of cells enclose a thin layer of nervous jelly. Sexual cells

---

The author is chief scientist at the U.S. Department of Agriculture's Mineral Nutrition Laboratory, Beltsville, Md. This article is adapted from an address delivered 26 December 1962 at the Philadelphia meeting of the AAAS.

develop in the outer layer of cells. The animals grow in unisexual colonies on the captive shell housings of hermit crabs. The eggs and sperm develop to a definite stage, then remain at that stage until sunrise. Under the stimulus of light, development is resumed, and release into the surrounding water takes place 60 to 80 minutes later. The gregariousness and pugnacity of the crab insures that oppositely sexed colonies of *H. echinata* will be brought into close proximity for fertilization.

When hydra are placed in light of different wavelengths (*7*) after a period of darkness and exposed to constant energy at the various wavelengths, they respond as shown in Fig. 3. The sketched curve gives the energy at various wavelengths which results in release of half the gametes. Maximum effectiveness is found in the violet part of the spectrum at 4150 angstroms, where adsorption of a few quanta per cell produces a detectable effect. The absorbing pigment, to judge from the several wavelengths of the action maxima, seems to be a porphyrin; it is probably a coproporphyrin. Porphyrins can be formed by degradation of several compounds of great biological significance, including myoglobin, hemoglobin, and chlorophyll. They are very effective as sensitizers of photochemical oxidations by molecular oxygen, and they lead to the breaking of cell walls in disorders involving light sensitivity which are fatal to sheep (for example, Klamath weed toxicity) and, rarely, to man (*8*).

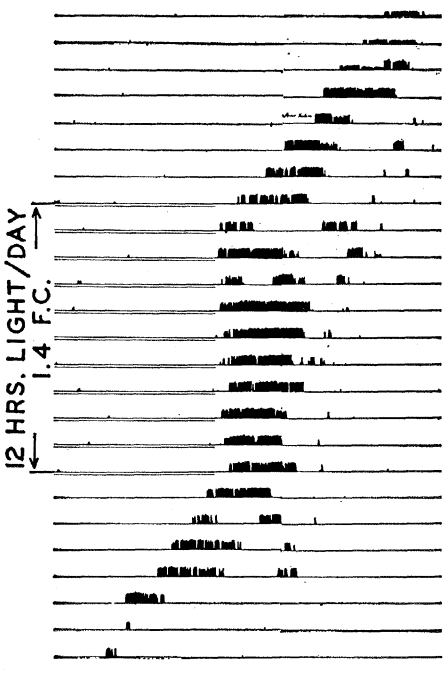


Fig. 1. Twenty-five day record of running activity of a female *Peromyscus* (the record runs from top to bottom). The rhythmic onset of activity in constant darkness has a period of 22 hours 50 minutes. The activity is entrained by periods of light. [After K. S. Rawson (*5*)]

The hydra illustrates an initiating function of light. Gamete release an hour after illumination begins results from four factors dependent on time: preparation in light (8 + hours); darkness (6 + hours); light (1 second); and a period of development (60 to 80 minutes). The time course is readily entrained in the ordinary 24-hour day in a way not essentially different from the entraining of egg-laying by a hen, which is phased by nightfall of the penultimate day.

Timing of Flowering

A pronounced feature of plant growth is strong seasonal dependency, but daily rhythms are also evident. The seasonal effects partially depend upon temperatures, but some actions are independent of temperature. Reproduction through flowering is controlled by the length of the night. The dependence of flowering on night length is illustrated by soybeans and chrysanthemums, which require the long nights of autumn, and by wheat and snapdragons, which require the short nights of early summer. Plants of either group can be made to flower by controlling the length of the night; in some plants, one night of suitable length is adequate to bring about flowering.

When soybeans are grown under conditions of 8 hours of light and 16 hours of darkness, they soon flower. If the routine 16-hour periods of darkness are interrupted by a moderately intense light for a few seconds, flowering is suppressed. The fact that the dark period is required for flowering and the fact that its effects can be suppressed by a small amount of light are both significant. They imply reception of light by a pigment in the plant. The pigment, being a substance instead of a necessarily tenuous concept, becomes the center of the problem.

Study of the flowering response at various wavelengths has shown that the pigment is blue (*9*)—that is, it absorbs red light—but it occurs in such minute quantities that it is not visible in the leaves of the plant. Eventually the flower-promoting effect of the absorption of red light is reversed by radiation at wavelengths near the red limit of vision. The reversibility opens the way to study the nature of the molecular changes.

A feature of the timing pattern is now evident. The reversibility stems from the fact that the pigment exists in two forms which are interchanged by light. One form is unstable relative to the other, and in darkness it can change toward the less stable form, which turns out to be the red-absorbing pigment (*Pr*). This reversion has a rate, and the timing in flowering is in part determined by the rate. The reversible reaction can be written as follows:

$$Pr \underset{\substack{\text{far-red light}\\ \text{or darkness}}}{\overset{\text{red light}}{\rightleftarrows}} Pfr$$

where *Pr* is red-absorbing pigment and *Pfr* is far-red absorbing pigment. Flowering of the soybean is controlled by the far-red-absorbing form of the pigment, which is the predominant form in sunlight. In fact, to promote flowering, the night must be long enough not only for far-red-absorbing pigment to be reduced to a low level through reversion to the red-absorbing form but also for this low level to be maintained for some hours. The pigment not only reverts to the red-absorbing form but also acts in another reaction as a catalyst or enzyme. The rates of both reactions increase with temperature, so the resultant action is temperature-compensated (Fig. 4). Reversion of far-red-absorbing to red-absorbing pigment in soybean, petunia, chrysanthemum, and

THE GONYAULAX CLOCK

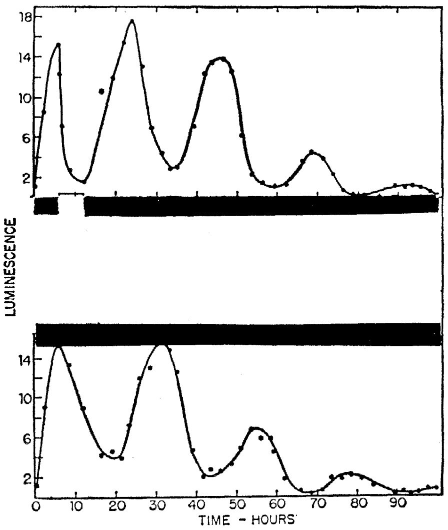
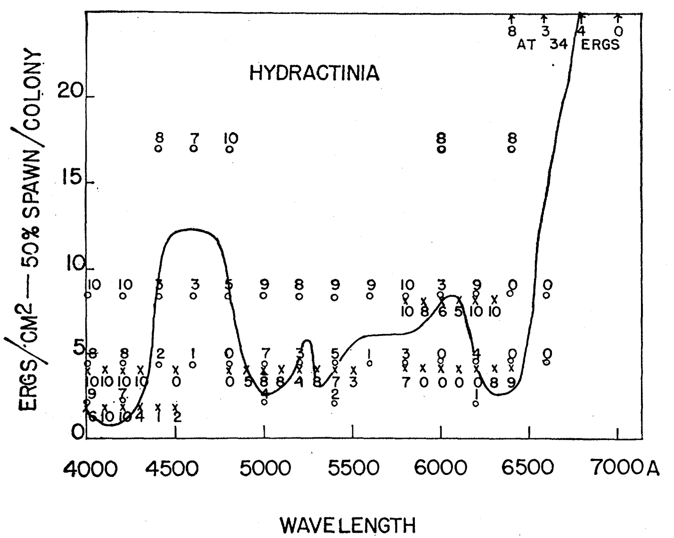


Fig. 2. Rhythmic luminescence of *Gonyaulax polyhedra* in continuous darkness (lower curve). A shift in phase induced by exposure to light for 6 hours (illumination, 1400 lu/ft^2) is shown by the upper curve. [After J. W. Hastings and B. M. Sweeney (*28*)]



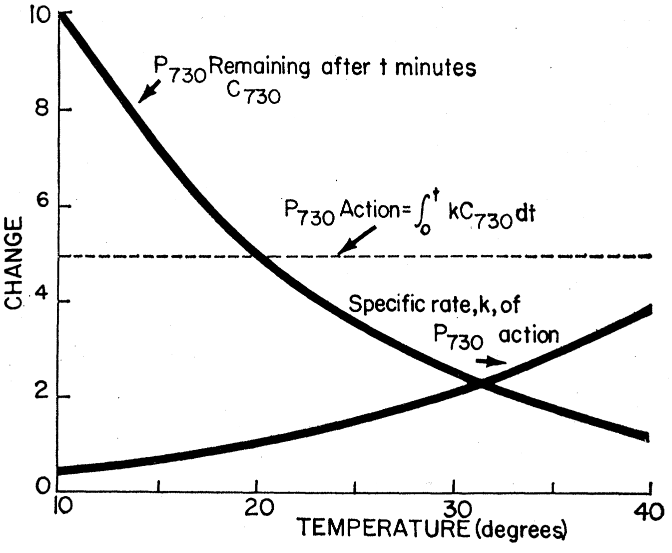


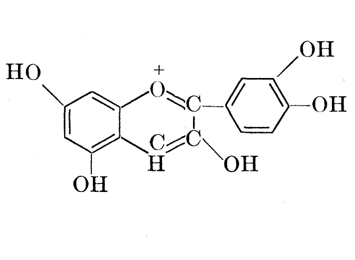
Fig. 3 (left). Dependence of gamete release of the hydrozoan *Hydractinia echinata* on the wavelength and energy of exciting light. [Jenner, Paris, Hendricks, and Borthwick (*7*)] Fig. 4 (right). Invariance, with change in temperature, of control of flowering by phytochrome.

snapdragon is shown by the effects of intermittent lighting on flowering (Fig. 5). Toward the end of the night and on into the following day the synthesized stimulus moves from the leaf to the cells where flowering is induced. If the night is interrupted with just a little red light, the far-red-absorbing pigment produced suppresses the increasing reaction toward flowering. There are more words than real compounds in an explanation of this kind; an objective of the physiologist is to change the words describing a general plan to specific reactions.

Part of the daily timing pattern, which, when repeated, constitutes seasonal control of flowering, can be summarized as follows: a daily light period for photosynthesis (8 to 15 hours); use of photosynthetic reserves and decay of far-red-absorbing to red-absorbing pigment (1 hour); darkness, with continued use of reserves at a slowing rate, with a very low level of far-red-absorbing pigment (remainder of the 24-hour period). Some students of the subject, in particular Erwin Bünning of the University of Tübingen (*10*), note that the patterns of photoperiodic responses are formally similar in plants and animals, and this similarity, they suggest, arises from basic dependence upon a characteristic rhythm. In this sense, sheep and soybeans respond reproductively to long nights, while chickens and wheat respond to short nights. Metabolism in plants undergoes profound change at nightfall, from dominant photosynthesis to utilization of reserves. This is an ideal condition for the generation of rhythmic variation of many reaction sequences, but whatever their nature, far-red-absorbing pigment is the controlling factor for flowering, a kind of master factor with strong control that is readily asserted among other variations.

Metabolic Controls

The change of the pigment and the substrates on which it acts are essential factors in the timing scheme, and from our knowledge of these changes we may learn what far-red-absorbing pigment does in a molecular sense. The pigment is readily seen to be an enzyme, or the catalyst for a limited reaction in plant development. The exact reaction is still unknown, but such phenomena as the photo-induced reddening of the apple, red cabbage, and many seedlings, which require far-red-absorbing pigment for formation of color, indicate that the control point is an acyl formation or a function of coenzyme A. The biochemical control is in the region of pyruvate utilization and apparently is determined by a reaction involving coenzyme A. The red color of these objects is caused by glycosides of anthocyanins, the general formulas of which are similar to the formula of cyanidin:



The phloroglucinol ring, at left, is formed by some type of condensation of acetyl coenzyme A molecules (*11*), and acetate utilization, followed with carbon-14 tracers, is influenced by light (*12*) schematically:

$$3\ \mathrm{CH_3CO-S-Co\,A} \xrightarrow{\mathrm{H_2O}} \mathrm{C_6H_3(OH)_3} + 3\ \mathrm{Co\,A\,SH}$$

High effectiveness in the control of growth requires substances that act on major controlling compounds, forming a kind of bottleneck. Coenzyme A and nicotinamide adenine dinucleotide (NAD) are the likely compounds. More than 80 percent of the carbon in a living system must have been in combination with coenzyme A at some stage of passage from initial to final products. Coenzyme A is essential for the formation and degradation of fats, carbohydrates, and proteins entering a reaction network with interlinkings and feedbacks, as indicated schematically in Fig. 6 (*13*). Nicotinamide adenine dinucleotide and its reduced form, $NADH_2$, shuffle back and forth between oxidizing and reducing reactions. The turnover of NAD can be rate-limiting in the network.

There are other metabolic controls in animals. Rapid oscillations in systems such as those which must operate in nerve transmission, muscular action, and vision, depend upon salt transfer with relatively slow re-establishment of the initial state. Controls of the type involved in the circadian timing systems are possibly of four types: (i) control point regulation; (ii) end-product action

Fig. 5. Change in the flowering of petunia resulting from reversion of phytochrome from far-red-absorbing pigment to red-absorbing pigment. Controls grown on a schedule of 16-hour nights are shown at right. Growing conditions for the other plants were as follows: plants at far left, 4 hours of low-intensity incandescent light after 6 hours of darkness; plants second from left, 15-minute cycles for 4 hours with 1.5 minutes of light per cycle; plants third from left, 30-minute cycles with 3.0 minutes of light per cycle.

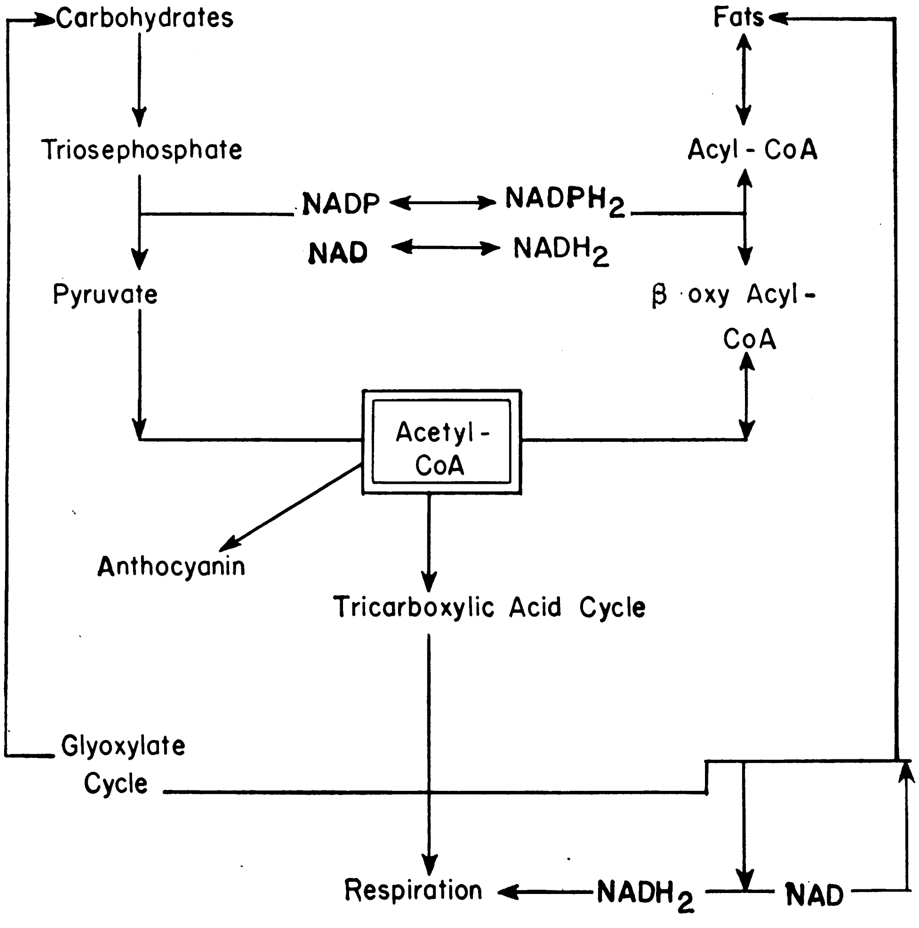


Fig. 6. Part of the reaction network in metabolic regulation mediated by acetyl coenzyme A and phosphopyridine nucleotides. The action of phytochrome in the timing of flowering is probably within this metabolic network.

on input into a reaction series; (iii) desuppression of enzyme synthesis at the level of the gene; and (iv) multiple hormone action in a series, with eventual feedback on the initial reaction. The first type is illustrated by the foregoing example of plant photoperiodism and is discussed by H. A. Krebs and J. M. Lowenstein (*14*) in connection with general metabolic control.

End-product action, the second type of control, was treated at length in the symposium on metabolic control held at Cold Spring Harbor in 1961 (*3*). It is illustrated by histidine synthesis, as observed by H. S. Moyer of Harvard University and B. N. Ames of the National Institutes of Health and their associates. When the amino acid histidine is present at a moderately high level meeting the requirements of protein synthesis, its rate of formation and use are balanced through a series of reactions. If histidine begins to accumulate because the rate of use is low, its production is controlled by back action that lowers the rate of a reaction crucial to its formation. This lowering may be through suppression of the action of essential enzymes or through suppression of the formation of the enzymes catalyzing the particular controlling reaction. It could take place in a man, a cockroach, or a gonyaulax. An equally striking example is the feedback inhibition of the formation of aspartokinase in *Escherichia coli,* observed by E. R. Stadtman and G. N. Cohen and their co-workers (*15*). The amino acids lysine and threonine are both derived in several steps from aspartic acid. Both, as their concentrations rise, inhibit utilization of aspartic acid. But they act on different aspartokinases, distinguished by the type of back inhibition as noncompetitive for lysine and competitive for threonine, and by their degrees of heat stability.

Rhythms

A scheme of rhythmic action is now apparent. A period of time is involved —the period between an initial and a final reaction. The final compound acts, or feeds back, to reduce the initial rate, but the reduction is effective only after a lapse of time equivalent to the average of the total time required for the series of reactions, from the initial to the final. Hence, the product increases for a time, drawing upon pools of intermediates even after exerting its controls, and

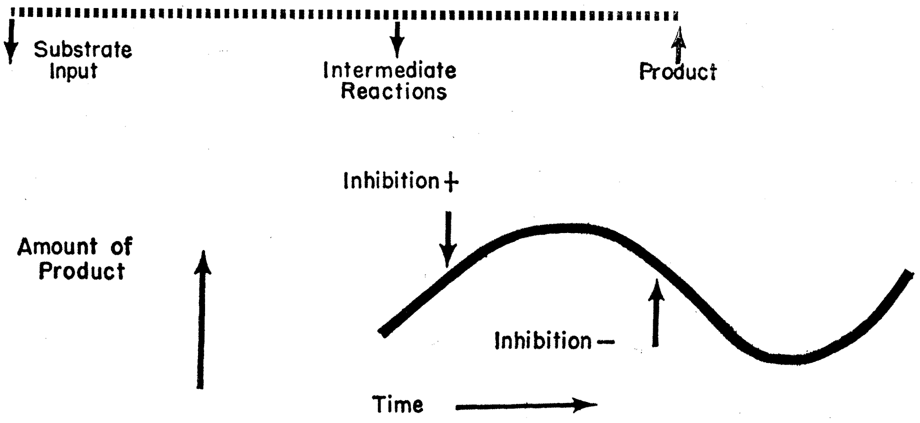


Fig. 7. A general pattern for regulation and rhythmic change.

then starts to decrease toward the steady level. As it decreases the initial rates again decrease, but the pools of intermediates must be filled. The system overshoots again, and the amount of the product oscillates back and forth. If the effective time for the reaction series is on the order of 12 hours, a complete oscillation takes approximately 24 hours, as shown diagrammatically in Fig. 7.

This, in fact, is the scheme formulated by Pittendrigh and Bruce (*16*) to account for the circadian rhythms of animal activity and used by them to account for many features of phase control. Their language is in terms of oscillator control (what some biologists call the brass brain), but it can readily be translated into chemical terms, with oscillating products and specific controls still to be identified.

Control through hormone action is another of the possibilities. A principal element of timing surely must lie here, arising from the action, in succession, of one endocrine system upon another —that is, from a time-consuming series of actions of the same pattern as the intermediate steps of histidine synthesis and of aspartic acid utilization. Many activities in man are responsive to pituitary action, with feedback from the final target organ—the gonad, for example—to the hypothalamus, neural secretion from which acts on the pituitary. Insects, however, are better experimental subjects than man.

Cockroaches and other insects show, as I mentioned previously, the striking circadian rhythmic patterns of activity in continuous darkness, phased by a preceding illumination. Janet Harker of Cambridge University (*17*) has followed the hormonal pattern of change in cockroaches: The legs of a cockroach that displayed rhythmic behavior were removed to prevent mobility, and the cockroach was joined through parabiosis to another cockroach that did not display such behavior. The first cockroach determined the activity in darkness. It is evident that the pattern is under control of a transmissible substance.

General consideration of the endocrine system of an insect is perhaps desirable at this point, before we proceed to a discussion of other experiments. The ocelli are simple eyes, blocking of which by opaque covering prevents the phasing of activity by light; they, rather than the multiple eye, are the perceptive organ. A stimulus through the ocelli activates medial and lateral neurosecretory cells of the brain, which discharge a hormone along the nerve axons to the corpus cardiacum, which lies just above the esophagus. This hormone is said to be cholesterol by M. Kobayashi and his co-workers at the Silk Culture Experiment Station in Tokyo (*18*). Whatever it is, it is stored in the corpus cardiacum and acts eventually on the corpus allatum.

The stimulated corpus allatum, in turn, secretes a hormone (or hormones) which functions to increase the rate of respiration and the associated activity. Janet Harker, by severing a small nerve between the corpus allatum and the subesophageal ganglion, lessened the activity of the cockroach and noted an accumulation of particles in the severed nerve. She concluded that the timing mechanism has two parts, one depending on the neurosecretory cells of the brain and the other associated with the corpus allatum in its activation of the subesophageal ganglion. The feature of the timing scheme not yet understood is the nature of the feedback and its place of action. The final display is the activity of the cockroach.

A seasonal response of insects illustrates (*19*) desuppressor action on enzyme synthesis at the level of the gene, but this may be only the display part of a timing pattern. This response is metamorphosis. The change is sometimes accompanied by a period of quiescence, or diapause, which is dependent on the season. The metamorphosis is controlled by another endocrine organ, the prothoracic gland, through the mediation of its secretion, the hormone ecdyosyn.

In the last 2 years Ulrich Clever of the Max-Planck Institute for Biology in Tübingen (*19*) has been observing the action of ecdyosyn on the giant chromosomes in the salivary gland of the pupae of a midge, *Chironomus tentans*, which swarms at sunset (*4*). He finds that the administration of ecdyosyn causes a puff to appear within 20 minutes at position 15C on the first chromosome and at position 2B on the fourth chromosome. The puffs are now considered to indicate the activation of a particular gene for the production of messenger RNA, which acts through a ribosome to produce a particular enzyme. In other words, ecdyosyn, a hormone, acts as a desuppressor of a gene to produce an enzyme and finally a system of enzymes necessary for the transformation of a pupa to an adult.

There are aspects of biological timing, interesting and important in themselves, about which I have not said much. I now turn to them, not with the intention of describing their many features but rather to examine what they add to our understanding of the mechanism. These aspects are (i) evidence of timing in man, and (ii) nagivation, particularly of birds. Each of these is a clean-cut area of experimentation, and such investigation is being actively pursued today, albeit not without divergence of opinions (*2*). In all such experiments it is difficult to separate patterns of behavior from "noise," or confusing background.

Timing in Man

Rhythmic and time-dependent activities surely occur in man, but not in such extreme form as in many creatures of the wild. Franz Halberg of the University of Minnesota (*20*), who created the word *circadian* several years ago, gives various examples. Among them are (i) variation in the number of eosin-staining cells of the blood; (ii) variation in the frequency of mitotic division in epidermal tissue; and (iii) variation in body temperature.

The number of eosin-staining cells and the number of mitotic divisions undergo a several-fold change from a maximum near midnight to a minimum during the daylight hours. A major question is: Are these variations endogenous or are they induced by variation of the surroundings? Halberg supported the view that the three changes are endogenous by noting that they persist through periods of electroshock.

The importance of the study of man to our understanding of timing lies primarily in our considerable, though still very incomplete, knowledge of his endocrine systems—of the nature of the hormones and the means by which hormonal function is controlled. The endocrine systems of mammals and birds are enough alike to permit extension of findings from one species to another.

Navigation

Migration and navigation of birds, bees, and butterflies have long excited interest. A connection between the feeding patterns of bees and timing systems was first made in the period around 1912 by the Swiss physician August Forel (*21*) and the German von Buttel-Reepen (*22*). An immense amount of biological knowledge, the result of patient observation, ingenious experimentation, and objective testing of theory, is to be found in the work of von Frisch on the "dance of the bees," and of Gustav Kramer on celestial orientation of migrating birds (*23*). The definitive papers appeared about 1952, but the work extends over the period from 1952 until Kramer's untimely death in 1959. Von Frisch's work on the communication of bees is, of course, a classic of our day, and I am taking some liberties in extracting one point from it for consideration in connection with Kramer's observations. This is von Frisch's statement that both the bees and the birds use an internal timing system and observations on the azimuthal position of the sun to establish direction. Azimuth is the angle between a fixed line on the earth's surface and the projection of the sun's direction on the surface. The azimuth angle swept by the sun in a fixed time varies with the time of day and the latitude. A bee on a nectar-collecting expedition fixes the position of the hive relative to the sun. A captive bird, with its seasonal requirements for migrating met, flutters along in its direction of migration regardless of the time of day if it can make an observation on the sun, or perhaps on a constellation if it is a night migrator (*2*). Not only the bird but the migrating fish and monarch butterfly orient with respect to the sun in the direction of migration.

Seasonal displays of this kind, even the most intriguing ones, are manifestations of timing. Associated with the orientation are the seasonal requirements for migration, which are known to depend upon the length of the night. These seasonal requirements, in an endocrine sense, are being studied by Albert Wolfson of Northwestern University (*24*) and Donald Farner of Washington State University and their associates. In studying the endocrine requirements they are working near the beginning of the timing system rather than at its end—the final display, the act of migrating.

Their studies depend upon observations on the hypothalamic-pituitary region of the endocrine system of the bird. Neurosecretory cells in the hypothalamus are active in the bird that is preparing for migration. These cells are near the ends of fibers leading to the pituitary. If lesions are produced in the hypothalamus in the region of the neurosecretory cells, or if the fibers are injured, the seasonal displays are suppressed.

Wolfson early found a pronounced deposition of fat in migrating birds. It seems reasonable to suppose this to be the source of the required energy. You may recall something about fat deposition in man, about its endocrine dependence, final control over the thyroid gland lying with the hormones from the pituitary.

The pathway of timing in the bird may possibly include (i) phasing by the absence of a stimulus from the eye or optic nerve as night comes; (ii) neurosecretory activity in the hypothalamus; (iii) activation of the neural lobe of the pituitary; (iv) hormonal secretion from the pituitary; (v) action on other endocrine organs, leading to metabolic control, with feedback on either the hypothalamus or the pituitary; and (vi) final activation of particular reactions, such as fat deposition, leading to seasonal displays.

Precision in timing is perhaps the most striking feature of seasonal and daily variations in plants and animals. An example of a simple rhythmic system is the synchronous division of unicellular cultures—of algae or bacteria, for instance—resulting initially from manipulation of the food supply, with final release of many cells to active growth at the same time (*25*). This system is a kind of race track, with the runners, starting together, bunching on each turn and spreading out only after many laps. A synchrony of this type, while not exact, and surely not as persistent as rhythmic activity in animals, can be maintained for hundreds of cycles by elimination of the fast and the slow.

The periodical cicada or 17-year locust, *Magicicada septendecim*, illustrates the synchrony by the persistence of cyclic increases in abundance with 17-year periods. These cycles are known to persist for specific broods for hundreds of years. Adults emerge, however, throughout the period and are particularly noticeable in the year that precedes or the year that follows the peak year. The spread, if undisturbed, is enough to wash out the cycle in a few turns. But birds and other predators control the aberrant individuals and thus narrow the peak to a single year for a given brood.

Conclusion

It is a significant fact of rhythmic activity that each individual has a characteristic circadian period distinctly different from the period of other individuals. The multicellular organization of higher creatures and the multifunctional compartments of single cells have a correlative dependence or interaction that forces the parts into synchrony. The aberrant period of activity is eliminated by the functioning of the whole organism, much as the precocious cicada is eliminated in its environment. Each individual ends up with a unique period, save in gregarious groups of unicellular forms where interaction of individuals is a preliminary of eventual organization or a measure of awareness of neighbors.

In concluding, it seems appropriate to quote two sentences, written more than 2½ centuries apart. One is from an article by Niels Bohr, published in 1961 (*26*): "On the grounds of classical physics, the very question of maintaining a high degree of order of such complicated systems presents serious difficulty." The other, written by John Woodward (*27*), who succeeded in finding the material supplies of plant life where van Helmont and Robert Boyle had failed, appeared in 1699. "There is," Woodward says, "a procedure in every part of nature that is perfectly regular and geometrical if we can but find it out." Timing systems and mechanisms are clearly examples of complexity and examples of regularity as well. The regularities become increasingly apparent as we pursue our investigations and extend our efforts to "find them out."

References and Notes

1. Many activity patterns of rhythmic change and examples of metabolic controls are described in two recent volumes of *Cold Spring Harbor Symposia on Quantitative Biology* (see *2, 3*).
2. *Cold Spring Harbor Symp. Quant. Biol.* **15 (1960)** (1961).
3. *Ibid.* **16 (1961)** (1962).
4. Introductions to the extensive literature are E. Bünning, *Die Physiologische Uhr* (Springer, Berlin, 1958); D. S. Farner, *Ann. Rev. Physiol.* **2**, 71 (1961); and H. M. Webb and F. A. Brown, Jr., *Physiol. Revs.* **39**, 127 (1959); popular accounts are F. A. Brown, Jr., "Biological Clocks," *Am. Inst. Biol. Sci. Pam. No. 2* (1962), and, with particular reference to bird migration, W. Delvingt and J. Leclercq, *Endeavor* **22**, 27 (1963).
5. K. S. Rawson, in *Photoperiodism*, R. B. Withrow, Ed. (American Association for the Advancement of Science, Washington, D.C., 1959), pp. 791–800.
6. S. W. Hastings and B. Sweeney, in *Cold Spring Harbor Symp. Quant. Biol.* **15 (1960)** (1961).
7. C. A. Jenner, O. H. Paris, S. B. Hendricks, H. A. Borthwick, *Proc. Intern. Congr. Photobiol., 1st, Amsterdam* (1954), pp. 75–77.
8. H. F. Blum, *Photodynamic Action and Diseases Caused by Light* (Reinhold, New York, 1941).
9. H. A. Borthwick and S. B. Hendricks, *Science* **132**, 1223 (1960).
10. E. Bünning, in *Cold Spring Harbor Symp. Quant. Biol.* **15 (1960)** (1961).
11. J. W. Watkins, E. W. Underhill, A. C. Neish, *Can. J. Biochem. Physiol.* **35**, 229 (1957).
12. H. Grisebach, *Proc. Intern. Congr. Biochem., 4th, Vienna, 1958* (1959), vol. 2.
13. F. Lynen and K. Decker, *Ergeb. Physiol. Biol. Chem. Exptl. Pharmakol.* **49**, 327 (1957).
14. H. A. Krebs and L. M. Lowenstein, in *Metabolic Pathways*, D. M. Greenberg, Ed. (Academic Press, New York, 1960), vol. 1, p. 129.
15. E. R. Stadtman *et al.*, *Cold Spring Harbor Symp. Quant. Biol.* **16 (1961)** (1962).
16. C. S. Pittendrigh and V. G. Bruce, *ibid.* **15 (1960)** (1961).
17. J. Harker, *ibid.*
18. J. Kirimura, M. Saito, M. Kobayashi, *Nature* **195**, 729 (1962).
19. U. Clever, *Chromosoma* **12**, 607 (1961).
20. F. Halberg, in *Cold Spring Harbor Symp. Quant. Biol.* **15 (1960)** (1961).
21. A. Forel, *Das Sinnesleben der Insekten* (Reinhardt, Munich, 1910).
22. H. V. von Buttel-Reepen, *Leben und Wesen der Bienen* (Vieweg, Brunswick, 1915).
23. G. Kramer, in *Cold Spring Harbor Symp. Quant. Biol.* **15 (1960)** (1961).
24. A. Wolfson, *ibid.*
25. E. Hase, Y. Morimura, S. Mihara, H. Tamiya, *Arch. Mikrobiol.* **32**, 87 (1958); T. Iwamura, E. Hase, Y. Morimura, H. Tamiya, *Studies Tokugawa Inst.* **7, (1954)**, No. 3 (1955).
26. N. Bohr, in *Symposium on Light and Life*, W. D. McElroy and H. B. Glass, Eds. (Johns Hopkins Press, Baltimore, 1961), p. 2.
27. J. Woodward, *Phil. Trans. Roy. Soc. London* **21**, 173 (1699).
28. J. W. Hastings and B. M. Sweeney, in *Photoperiodism*, R. B. Withrow, Ed. (American Association for the Advancement of Science, Washington, D.C., 1959), pp. 567–584.

News and Comment

National Academy: Public Policy Group, Headed by Kistiakowsky, Seems Bound for Important Role

Without fanfare, a 15-man group of scientists, conveniently referred to as "Kisty's Committee," is cautiously but surely moving toward a major role in relations between the federal government and the scientific community.

"Kisty" is George B. Kistiakowsky, Harvard chemist, White House science adviser under President Eisenhower, and a key scientific adviser to the Kennedy administration. As one of the elder statesmen of science and government, Kistiakowsky has for years radiated considerable influence, but now, as chairman of the National Academy of Sciences' recently established Committee on Science and Public Policy, he is engaged in a venture that may be one of the most significant things to happen in the science-government area in a long time.

The committee, which was formally established last February after a year's operation on an *ad hoc* basis, is yet to bring its role into clear focus, but it appears that this is going to be along the lines of critic, guide, and illuminator in the increasingly complex and troubled interdependence of science and government. This is a role from which the Academy has heretofore shied away, usually leaning on the argument that its chartered role as a nongovernmental adviser to government was one of waiting until its advice was asked, not of venturing on its own initiative into areas of controversy. There was nothing, of course, to prevent such self-initiated ventures, and occasionally they did take place, but usually against the feeling on the part of Academy members that mixing in public affairs would be detrimental to the Academy's image as the prestigious apex of American science.

Such feelings at first greeted the establishment of Kistiakowsky's committee, but, by and large, the response in and out of the Academy has been enthusiastic, for as the bond between science and government becomes thicker each year, it has become apparent that the scientific community has done little to equip itself for protecting its own interests in this relationship. Concern over this led Detlov W. Bronk to promote the establishment of the Science and Public Policy Committee in his final year as Academy president, and it has led his successor, Frederick Seitz, to look upon the committee as one of the Academy's most significant activities.

This is not to suggest that the Academy is setting itself up as the advocate of the nongovernmental scientist. The relationship between science and government is now too intertwined for any useful distinction to be made. (This is perhaps best symbolized by the presence of both Kistiakowsky and Seitz on the President's Science Advisory Committee.) But while recognizing that this intertwining exists and will continue, the Acadamy is now setting forth to bring some much-needed diversity—at least of an organizational sort—into the high councils of science and government. It might be argued that it isn't going to make much difference, since the multiple-hat-wearing in these councils will simply mean, in effect, that the committee members will be writing reports to themselves. But Kistiakowsky