photolyases, which are DNA repair enzymes, and homologous proteins which are not photolyases and were first shown to be blue light photoreceptors in *Arabidopsis*. The latter are called cryptochromes, and it is now known that they function as circadian photoreceptors in plants and flies. In mammals, cryptochromes appear to be essential for free-running clock function, and their identity as photoreceptors remains to be proven. Expression of the cryptochromes cycles in both flies and mammals; in mammals this may be explained by their role in clock activity, but in flies it is of unknown significance. Interestingly, cryptochromes, like the clock genes, are expressed in many mammalian body tissues that, to date, are not associated with clock function.

Output signals. How the circadian clock conveys time-of-day information to the rest of the organism and produces rhythmic molecular, behavioral, and physiological outputs is a big unknown. At a molecular level, it is believed that clock genes affect output through transcriptional regulation. Thus, when PER-TIM enter the nucleus to regulate their own transcription, they presumably also regulate downstream genes that are targets of CLK/CYC. Genes that cycle under control of the clock have, in fact, been identified in several organisms, but the links between these genes and the clock or between these genes and the overt rhythm are yet to be determined.

The most direct link between clock genes and a known clock output comes from analysis of the gene encoding vasopressin, a peptide whose levels cycle in the suprachiasmatic nucleus. Suprachiasmatic nucleus vasopressin acts locally to regulate neuronal activity and is also released to other brain regions. A recent study showed that the vasopressin gene is transcriptionally regulated by the CLK, BMAL1, PER, and TIM proteins in a manner analogous to that described above for *per* and *tim*; that is, an E-box in the vasopressin promoter mediates transcriptional activation by CLK-BMAL1, and this activation is inhibited by PER-TIM. While these studies were conducted in a cell culture system, CLK-dependence of vasopressin cycling is supported by the observation that vasopressin does not cycle in CLK/CLK mutant mice.

The area of clock output is clearly going to be the focus of intense research for many years. It is likely that these studies will have relevance not only for chronobiology but also for a general understanding of physiological processes, such as sleep and hormone action, which happen to be controlled by the clock. *See* MIGRATORY BEHAVIOR; REPRODUCTIVE BEHAVIOR.

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Biological oxidation

A biochemical reaction involving the transfer of a negatively charged electron from one organic compound to another organic compound or to oxygen. When a compound loses an electron, or is oxidized, another compound gains the electron, or is reduced. Oxidation-reduction (redox) reactions represent the main source of biological energy. Redox reactions occur simultaneously, and one does not occur without the other. The principal sources of reductants for animals are the numerous breakdown products of the major foodstuffs: carbohydrates, fats, and proteins. Energy release from these substances occurs in a stepwise series of hydrogen and electron transfers to molecular oxygen. *See* OXIDATION-REDUCTION.

Biological oxidation-reduction reactions. There are four prevalent varieties of biological redox reactions.

Direct transfer of electron. In one type of redox reaction, an electron is transferred directly from a donor to an acceptor [reaction (1)]. In this process, an elec-

$$\text{Cytochrome } c\,(Fe^{3+}) + \text{cytochrome } b\,(Fe^{2+}) \rightarrow \text{cytochrome } c\,(Fe^{2+}) + \text{cytochrome } b\,(Fe^{3+}) \quad (1)$$

tron is removed from the ferrous iron (Fe^{2+}) of a protein called cytochrome *b* and is transferred to the ferric iron (Fe^{3+}) of cytochrome *c*. Cytochrome *c* is the oxidizing agent, or oxidant, and cytochrome *b* is the reducing agent, or reductant. The cytochromes are a family of heme proteins; the heme group is an iron-porphyrin system similar to that found in hemoglobin, the protein that gives red blood cells their color. *See* CYTOCHROME.

Electrons transferred with protons. In a second type of redox reaction, electrons are transferred with protons in a process formally equivalent to the transfer of a hydrogen atom, which is made up of two positively charged protons and two negatively charged electrons ($2H^+ + 2e^-$). The enzyme pyruvate dehydrogenase functions in this fashion. This enzyme complex contains tightly bound flavin adenine dinucleotide (FAD). Pyruvate dehydrogenase mediates reaction (2).

$$\text{Pyruvate} + \text{coenzyme A} + \text{pyruvate dehydrogenase-FAD} \rightarrow \text{acetyl-coenzyme A} + \text{carbon dioxide} + \text{pyruvate dehydrogenase-FADH}_2 \quad (2)$$

Coenzyme A (for acylation) functions in the transfer of acyl [R—C(═O)—] groups, and pyruvate is a breakdown product of glucose. In reaction (2), pyruvate donates the equivalent of a hydrogen molecule to FAD, the oxidizing agent. *See* COENZYME; ENZYME.

Transfer of hydride ion. In a third type of redox reaction, a hydride ion ($H:^+$) is transferred; the hydride ion consists of a proton and two electrons and bears a negative charge. This is illustrated in the final portion of the pyruvate dehydrogenase reaction (3) where the hydride ion is transferred from

$$\text{Pyruvate dehydrogenase-FADH}_2 + \text{NAD}^+ \rightarrow \text{pyruvate dehydrogenase-FAD} + \text{NADH} + \text{H}^+ \quad (3)$$

tightly bound $FADH_2$ to nicotinamide adenine dinucleotide (NAD^+). NAD^+ functions as the oxidizing agent. FAD is alternately reduced by pyruvate and reoxidized by NAD^+. In order for such reactions to continue, the reduced coenzyme (NADH) has to be reoxidized by another substance. NAD^+ and nicotinamide dinucleotide phosphate ($NADP^+$) are derivatives of the vitamin niacin. Some enzymes use NAD^+ as oxidant, others use $NADP^+$, and still others can use either NAD^+ or $NADP^+$. *See* NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD^+); NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE ($NADP^+$).

Electron transfer via direct reaction with oxygen. In a fourth type of oxidation-reduction, molecular oxygen (O_2) reacts directly with the reductant. This can be a monooxygenase or a dioxygenase process. In a monooxygenase reaction, one atom of O_2 is reduced to H_2O and the other is incorporated in the product [reaction (4)]. Phenylalanine, an amino acid, is

$$\text{Phenylalanine} + \text{tetrahydrobiopterin} + \text{O}_2 \rightarrow \text{tyrosine} + \text{H}_2\text{O} + \text{dihydrobiopterin} \quad (4)$$

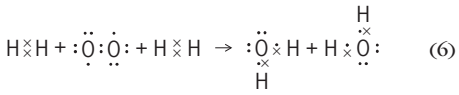
oxidized to tyrosine, an amino acid that contains a hydroxyl group. The reaction is catalyzed by phenylalanine hydroxylase.

In a dioxygenase reaction, both atoms of molecular oxygen can be incorporated into an organic molecule [reaction (5)]. Both atoms of oxygen occur

$$\text{Homogentisate} + \text{O}_2 \rightarrow \text{4-maleylacetoacetate} \quad (5)$$

in 4-maleylacetoacetate. Homogentisate is a breakdown product of the amino acids phenylalanine and tyrosine.

Molecular oxygen exhibits two properties that make it a good oxidant. First, oxygen is very electronegative (second only to fluorine) and tends to attract electrons to it. Second, oxygen is electron-deficient. Each oxygen atom in the molecule lacks a complete octet of electrons. When oxygen reacts with two molecules of hydrogen, two molecules of water form, and the oxygen in water has a complete octet of electrons [reaction (6)], which is a more



(6)

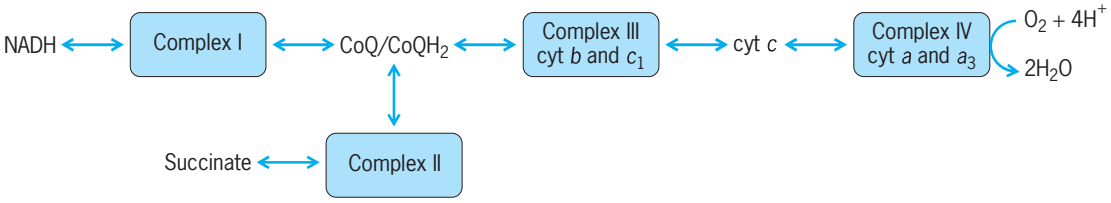
stable condition. (The electrons in molecular oxygen are represented by the dots, and the electrons in molecular hydrogen are represented by x's.)

Oxidative phosphorylation. Oxidative phosphorylation is responsible for most of the adenosine triphosphate (ATP) generated in animals, plants, and many bacteria. The transfer of electrons from NADH or $FADH_2$ to oxygen sustains the synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate (P_i) by oxidative phosphorylation. Oxidative phosphorylation requires an electron transport chain in a membrane, O_2, and an ATP synthase. *See* ADENOSINE TRIPHOSPHATE (ATP).

Mitochondrial electron transport. The components of the electron transport chain are found in the inner mitochondrial membrane of animal and plant cells. The electron transport chain consists of four independent protein complexes (I, II, III, and IV). Coenzyme Q and cytochrome *c* transport electrons between the complexes. The transfer of electrons from reductant to oxidant is energetically favorable.

NADH, which is generated by pyruvate dehydrogenase [reaction (3)] and many other processes, donates its electrons to complex I (see **illus.**). Electrons are transferred from complex I to coenzyme Q to produce coenzyme QH_2. The flavin dehydrogenases, such as succinate dehydrogenase (complex II), transport electrons to coenzyme Q. (Succinate dehydrogenase is one of the enzymes of the Krebs tricarboxylic acid cycle.) Coenzyme QH_2, in turn, donates its electrons to complex III. Cytochrome *c* carries an electron from complex III to complex IV, or cytochrome oxidase. The cytochrome oxidase reaction of complex IV accounts for more than 95% of all oxygen consumed by humans. *See* CITRIC ACID CYCLE; MITOCHONDRIA.

Proton translocation in oxidative and photosynthetic phosphorylation. The chemiosmotic theory proposed by Peter Mitchell in 1961 provides the conceptual framework for understanding the mechanism of oxidative phosphorylation. The redox reactions of electron transport provide energy for the translocation of protons (H^+) from the inside (matrix) of the mitochondria to the space between its inner and outer membranes. Electron transport generates and maintains an electrochemical proton concentration difference across the inner membrane. An analogous



Overview of the mitochondrial electron transport chain.

situation occurs in aerobic bacteria, in which protons are translocated from the interior to the exterior of the cell membrane. The protons return into mitochondrial matrix, or bacterial cells, through a membrane-bound ATP synthase, and this energetically downhill process drives the energetically uphill conversion of ADP and P_i to ATP. Photophosphorylation in photosynthetic cells occurs by an analogous mechanism, except that light provides the energy to generate reductants for an electron transport chain. *See* PHOTOSYNTHESIS.

Reactive oxygen species. The reaction of oxygen with a single electron results in the formation of the superoxide anion radical [reaction (7)]. Superoxide

$$O_2 + e^- \rightarrow O_2^- \quad (7)$$

formation can occur by the spontaneous (nonenzymatic) reaction of oxygen with ferrous ion or reactive oxidation-reduction intermediates. Superoxide is a reactive substance that can cause the modification of cellular proteins, nucleic acids, and lipids in membranes, and is therefore toxic.

Superoxide dismutase is the enzyme that catalyzes the conversion of two superoxide anions and two protons to oxygen and hydrogen peroxide [reaction (8)]. Superoxide dismutase plays a pivotal role in protecting cells against oxygen toxicity.

$$2O_2^- + 2H^+ \rightarrow O_2 + H_2O_2 \quad (8)$$

Hydrogen peroxide is a reactive substance that can modify cellular macromolecules, and it is toxic. Hydrogen peroxide is converted to oxygen and water in a process mediated by the enzyme catalase [reaction (9)].

$$H_2O_2 \rightarrow H_2O + {}^1/_2O_2 \quad (9)$$

A third toxic oxygen derivative is the hydroxyl free radical. The hydroxyl free radical is more reactive and toxic than superoxide and peroxide. The hydroxyl free radical (denoted by the dot) can be formed through a nonenzymatic reaction of hydrogen peroxide with ferrous iron [reaction (10)]. The

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^- + OH^\bullet \quad (10)$$

hydroxyl free radical is also formed by the reaction of superoxide with hydrogen peroxide [reaction (11)].

$$H_2O_2 + O_2^- \rightarrow O_2 + OH^- + OH^\bullet \quad (11)$$

In addition, the hydroxyl free radical can be formed by the radiolysis of water produced by cosmic rays, x-rays, and other energetic electromagnetic radiation. The hydroxyl free radical reacts with and modifies cellular macromolecules. A widespread enzyme, glutathione peroxidase, mediates the destruction of hydroxyl free radicals [reaction (12)]. Glutathione

$$2OH^\bullet + 2GSH \rightarrow 2H_2O + GSSG \quad (12)$$

(GSH) is a peptide consisting of three amino acid residues, and its —SH group is the reductant. Moreover, a hydroxyl free radical can be destroyed by its reaction with ascorbate (vitamin C), β-carotene (vitamin A), or vitamin E. These actions may play a role in the beneficial and protective antioxidant effects of these vitamins. *See* ANTIOXIDANT.

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Biological productivity

The amount and rate of production which occur in a given ecosystem over a given time period. It may apply to a single organism, a population, or entire communities and ecosystems. Productivity can be expressed in terms of dry matter produced per area per time (net production), or in terms of energy produced per area per time (gross production = respiration + heat losses + net production). In aquatic systems, productivity is often measured in volume instead of area. *See* BIOMASS.

Ecologists distinguish between primary productivity (by autotrophs) and secondary productivity (by heterotrophs). Plants have the ability to use the energy from sunlight to convert carbon dioxide and water into glucose and oxygen, producing biomass through photosynthesis. Primary productivity of a community is the rate at which biomass is produced per unit area by plants, expressed in either units of energy [joules/(m^2)(day)] or dry organic matter [kg/(m^2)(year)]. The following definitions are useful in calculating production: Gross primary production (GPP) is the total energy fixed by photosynthesis per unit time. Net primary production (NPP) is the gross production minus losses due to plant respiration per unit time, and it represents the actual new biomass that is available for consumption by heterotrophic organisms. Secondary production is the rate of production of biomass by heterotrophs (animals, microorganisms), which feed on plant products or other heterotrophs. *See* PHOTOSYNTHESIS.

Productivity is not spread evenly across the planet. For instance, although oceans cover two-thirds of Earth's surface, they account for only one-third of the Earth's productivity: it is estimated that the global terrestrial primary productivity is approximately 120×10^9 tons of dry weight per year, while the sea primary productivity is estimated at approximately 60×10^9 tons per year. Furthermore, the factors that limit productivity in the ocean differ from those limiting productivity on land, producing differences in geographic patterns of productivity in the two systems. In terrestrial ecosystems, productivity shows a latitudinal trend, with highest productivity in the tropics and decreasing progressively toward the Poles; but in the ocean there is no latitudinal trend, and the highest values of net primary production are found along coastal regions.