tighter, one is likely to hear "baba" or the familiar "dada." Merely by leaving the nasal port open, "mama" or "nana" may be produced, or if the voice is alternately suppressed, "papa" and "tata." It is through such maneuvers that infants, guided by little or no ambient learning, are able to achieve a small repertoire of speech-like sounds.

The ontogenetic implications are clear. The earliest speech-like behaviors of infants are sufficiently like those of competent speakers to do linguistic service, especially when the linguistic community and (on their own initiative) the parents present infants with equivalent constructions such as, mama, papa, dada, bye-bye, pee-pee. With no more to learn than a few associations between sound and meaning, infants can move seamlessly from babble into speech, and this is exactly what they do (*6*).

The open-close movements of the mouth described by MacNeilage and Davis in babbling infants are tenacious. Premature birth, focal lesions in the brain, or mental impairment rarely suppress them or conspicuously distort their action. Significant delays in their onset, however, may point to previously undiagnosed deafness or other problems in the neural circuitry responsible for language and cognition (*7, 8*).

Following an earlier finding by Stoel-Gammon (*9*), MacNeilage and Davis observe that as infants make sounds, places of oral constriction tend to overflow their consonantal banks—that is, lingual (tongue) consonants such as /t/ and /k/ pull adjacent vowels to the front or back of the mouth, respectively; labial (lip) consonants such as /p/ leave vowels more neutrally positioned (see the figure). But the matter doesn't end there, for the investigators track these patterns directly into the structure of established languages, thereby reconstructing the phonetic behaviors of previous generations of speakers. One thus appreciates new dimensions to the sympathetic relationship that exists between phonology and physiology.

Some years ago, I pointed to an "anterior-to-posterior progression" in the utterances of children and the vocabularies of English and French (*5*). Lip-to-tongue words like "pat" and "mad" surpassed reverse-order items like "tap" and "dam." MacNeilage and Davis now report that this labial-coronal (lip-tongue front) effect occurs in several other languages for which relevant statistics have become available. They reasonably suggest a biomechanical cause, although more investigation is obviously needed.

There are several challenges ahead. In the past, evolutionary theorists have needed to explain the fact that all languages, save the signed systems of the deaf, are spoken. Now they must also explain the emergence of mandibular oscillations. But these problems may be connected. Elsewhere, I have suggested that the vocal modality of language may be linked to two factors that emerge from research on nonhuman primates: an association between status and volubility at the social level, and the open-close movements associated with tongue- and lip-smacking at the physical level (*10*).

Ontogeneticists have some new responsibilities, too, for any comprehensive account of the development of spoken language will have to explain the emergence of oscillatory activity and its specific connections to speech. Relevant evidence currently includes the fact that jaw openings and closings may be carried out silently (*11*) and that audible and repetitious movements of the hand, typically the right hand, frequently begin within a few weeks of the onset of babbling (*7, 12*).

If the substance of speech influences its form, as the new work indicates, additional phonostatistical analyses may provide more information about the motor bases of speech and the structure of established languages. In parallel with such research, a variety of behavioral studies could, in principle, tell us how the sequences of sound movements selected for linguistic use in earlier times benefit modern users of language, either in their social communication or in moments of private cognition.

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PERSPECTIVES: CIRCADIAN RHYTHMS

Marking Time for a Kingdom

Michael W. Young

Our sleep-wake cycles, and many other behavioral and physiological rhythms, are controlled by endogenous, 24-hour (circadian) clocks. Over the last 30 years genetic screens have been systematically applied to the dissection of circadian clocks in *Cyanobacteria*, the fungus *Neurospora*, and the fruit fly *Drosophila melanogaster*, but only recently has circadian genetics been applied to mammals (*1*). In a major breakthrough for time-conscious mammals, Takahashi, Lowrey, and their colleagues (*2*) describe the identification of a crucial circadian gene in hamsters on page 483 of this issue. The *tau* mutation, accidentally discovered in a shipment of Syrian hamsters, reduces the period length of the hamster's circadian rhythm from 24 to 20 hours. The investigators show that the *tau* locus, encoding casein kinase Iε, is a homolog of the *Drosophila* circadian gene, *double-time*. It is astonishing that genetic screens are identifying the same molecular determinants of time in creatures as different as mammals and fruit flies.

In *Drosophila*, seven genes appear to interact together in clock-like feedback loops in a bewildering array of cell types inside and outside the nervous system (*3*). The fly clockworks are approaching genetic saturation: New mutations tend to map to old genes, suggesting that the most important elements of the fly's circadian clock have already been identified. But what do these fly genes tell us about circadian rhythms in other organisms? Recently, molecular biology has hinted that there is a single toolbox of clock parts carried by the entire animal kingdom. Homologs of the fly clock genes *period*, *timeless*, *clock*, *cycle*, *double-time*, *vrille*, and *cryptochrome* have been isolated from fish, frogs, mice, and humans; for some of these genes, further testing in vertebrates supports their involvement in circadian rhythmicity. But, the acid test is genetic screening. For example, in the absence of preconceptions, what would independently surface in mammalian clockworks if we were to ask for a list of its most important parts?

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The *tau* mutation, the first to be isolated because of effects on a mammal's circadian rhythm, was described by Ralph and Menaker in 1988 (*4*). Animals homozygous for the *tau* mutation produce striking short-period, 20-hour rhythms of sleep-wake behavior. The mutation also has fascinating effects on photoperiodism (the ability to measure changes in day versus night length, and to trigger programmed responses such as hibernation, migration, even fertility), confirming in a very direct way the essential role of circadian clocks in seasonal timing (*5*). Hamster eyes rhythmically produce melatonin in a 24-hour cycle; when eyes from *tau* hamster mutants are explanted and cultured in vitro they produce melatonin in a shorter 20-hour cycle (*6*). Neural transplants between *tau* mutants and wild-type hamsters have clarified the importance of the suprachiasmatic nucleus, a part of the hypothalamus long believed to regulate mammalian circadian behavior. Transplanting the suprachiasmatic nucleus from *tau* hamsters to wild-type recipients transferred short-period behavior (*7*). In addition, neurons derived from the *tau* suprachiasmatic nucleus are electrically active in culture with a 20-hour rhythm (*8*). The *tau* hamster has yielded a wealth of observations, but the molecular identity of this mutation has been buried for more than 12 years.

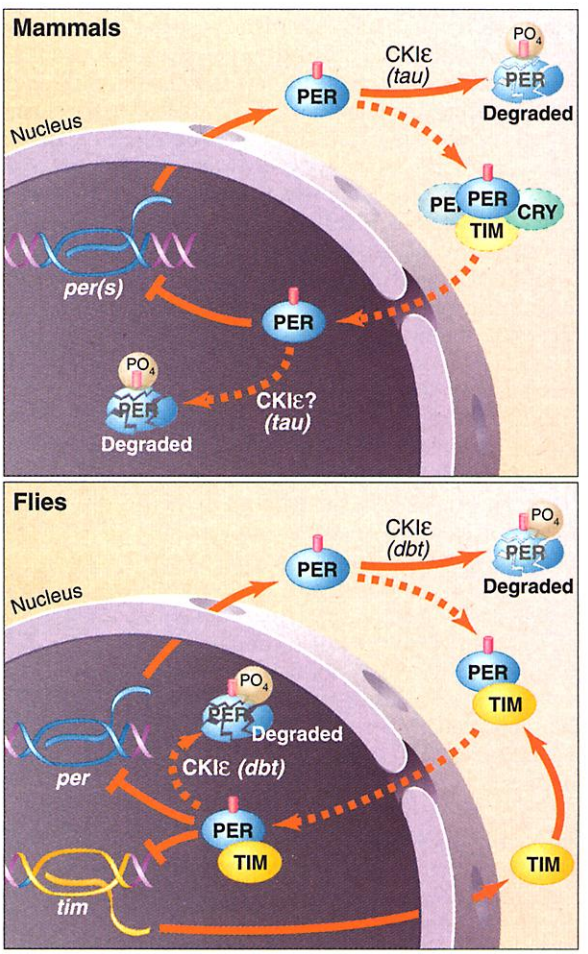
At the time that the *tau* mutation was discovered, very little was known about the molecular biology of circadian clocks. Only the *period* gene of *Drosophila* had been characterized at the molecular level, and its sequence completely failed to suggest its biochemical function. No clock gene from *Neurospora* had been cloned, and clock mutations had not yet been recovered in *Cyanobacteria*. Nevertheless, there was optimistic speculation by some that *period*, *tau*, and the most significant *Neurospora* clock gene, *frequency*, might somehow be related.

In 1995, Takahashi's laboratory discovered the first mouse circadian mutant, *Clock* (animals homozygous for this mutation showed complete arrhythmia in their circadian rhythms). Two years later his group cloned *Clock* and showed that it encoded a transcription factor. Mutations in a fly homolog were soon recovered in genetic screens of *Drosophila* (*1*, *3*). CLOCK and a second protein, CYCLE, were found to activate transcription of *period* (*per*) in mammals, and *per* and *timeless* (*tim*) in flies (see the figure). At the time of the *Clock* discovery, PER and TIM proteins were already known to collaborate in the regulation of their own expression in *Drosophila*, assembling in PER-TIM complexes that permitted nuclear translocation and inactivation of *per* and *tim* transcription in a cycling negative feedback loop (see the figure) (*1*, *3*). Thus, the first mammalian clock mutation to be linked to a molecular function was also represented in the central clockworks of the fly.

Drosophila's molecular clock oscillates in synchrony with day-night cycles because one of the two negative regulators, TIM, is degraded in response to light. This reaction requires the activity of the photoreceptor CRYPTOCHROME (CRY) (*3*). But sustained oscillation in the absence of an environmental light cue requires a kinase, DOUBLE-TIME (DBT), which controls the phosphorylation and stability of PER. In the absence of the DBT kinase, PER proteins overaccumulate, and constitutive feedback brings the clock to rest (*9*, *10*).

The new work by Lowrey *et al.* (*2*) reveals the connection between the gene encoding DBT (*dbt*) and *tau*. Attempts to clone *tau* have been complicated by the absence of a genetic map in the hamster. The investigators overcame this substantial obstacle by identifying DNA polymorphisms that would segregate with *tau* in crosses involving a second wild-type hamster strain. A syntenic (comparable) region of human chromosome 22 was found to contain the *casein kinase Iε* gene, the homolog of *dbt*. The kinase gene was then mapped to chromosome 15 in the mouse, which also shows synteny with the hamster *tau* interval. The researchers found that the *tau* hamster has a point mutation in the gene encoding casein kinase Iε, which results in the substitution of cysteine for a conserved arginine. They then showed that normal casein kinase Iε binds and phosphorylates mammalian PER, whereas *tau* kinase is defective in PER phosphorylation assays.

As Lowrey and co-workers were unraveling the identity of *tau*, members of Virshup's laboratory were testing human casein kinase Iε in cultured cells coexpressing mammalian PER (*11*). They too found evidence that the kinase binds to PER and phosphorylates it, and made the intriguing discovery that the subcellular localization of at least one mouse PER protein (mPer1) depended on the kinase. Apparently, when the kinase phosphorylates mPer1 it some-



Tempus fugit. In mammals (**top**), the *tau* gene encodes a constitutively produced casein kinase Iε (CKIε) (*2*) that appears to phosphorylate PER, masking its nuclear localization signal (pink) (*11*) and promoting its retention in the cytoplasm and its degradation (*12*). Levels of *per* mRNA (blue ribbon) oscillate with a 24-hour rhythm, such that peak rates of PER synthesis—and possibly its association with CRY, TIM, or other forms of PER—may periodically favor hypophosphorylation of PER, its nuclear translocation, and repression of *per* transcription. In flies (**bottom**), *double-time* (*dbt*), the fly homolog of *tau*, which encodes a CKIε (DBT), promotes phosphorylation of PER and its retention and degradation in the cytoplasm (*9*, *10*). PER-TIM heterodimers do not appear to be modified by DBT, allowing periodic nuclear translocation of PER-TIM and repression of *per* and *tim* gene transcription (*9*, *10*). Phosphorylation may affect the PER nuclear localization signal in flies (as in mammals). After TIM degradation, PER is phosphorylated and removed from the nucleus by the activity of DBT, a step that might also occur in mammals.

how masks the nuclear localization signal ensuring that mPer1 is retained in the cytoplasm (see the figure) (*11*). But in the absence of casein kinase Iε, mPer1 moves to the nucleus where it represses transcription of *per* genes (*11*). In another recent study, Keesler *et al.* (*12*) link phosphorylation of human PER to a decrease in its stability. The results so resemble those obtained with DBT in *Drosophila*—where binding of TIM periodically shields PER from phosphorylation, retention in the cytoplasm, and degradation (*9*, *10*)—that we might expect casein kinase Iε to play a central role in timekeeping everywhere in the animal world (see the figure).

The most recent common ancestor of insects and mammals is thought to have lived more than 550 million years ago, and, not surprisingly, differences have been recognized in the unfolding clockworks of mammals and flies. In mammals, CRYs are transcriptional regulators of the clock but may not be the key players in photoreception that they are in the fly (*1*, *3*, *13–15*). The TIM and CLOCK proteins appear to be involved in mammalian and fly clocks, yet circadian cycling of the expression of both genes may be limited to *Drosophila*. Although TIM and PER heterodimerize in *Drosophila*, and CRY and PER associate in mammals, only direct interactions between TIM and CRY may be conserved among all animals (*1*, *3*, *13*). Yet easily overshadowing the differences is a compelling conservation of each of the known clock genes. With the cloning of *tau* the supply of mammalian clock mutants has been exhausted for the moment, but there is little doubt that many of the critical elements of animal clocks have been identified. A rudimentary clockworks, now known to us, is surely marking time throughout the animal kingdom.

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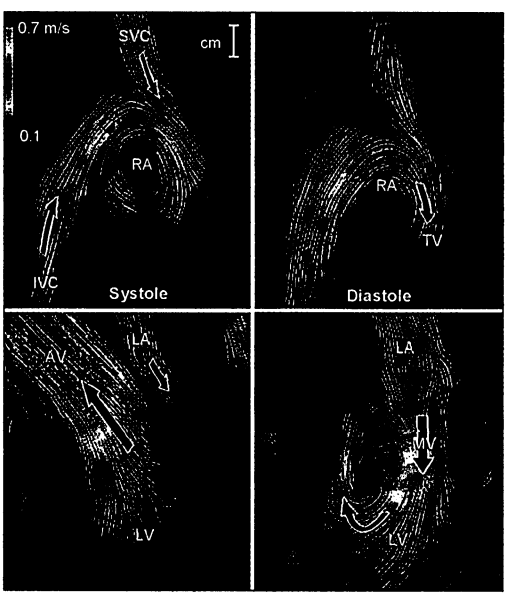
NOTA BENE: PHYSIOLOGY

Contortions of the Heart

The mammalian heart is an odd-looking organ, with four different-sized muscular chambers (two atria on top and two ventricles beneath) and a spectacular array of curving blood vessels that loop around each other in a contorted plumbing system. In a recent report, Kilner *et al.* (*1*) reveal that blood does not flow in a smooth, continuous stream but rather adopts asymmetric swirling patterns as it moves through the chambers of the heart. These whirlpools of blood may seem to be the antithesis of a well-heeled plumbing system, but the investigators argue that they are in fact beneficial, aiding the heart as its contractions increase during exercise.

The heartbeat has two principal phases: systole (contraction) and diastole (relaxation). In systole, the muscular walls of the ventricles contract, squeezing blood from the left ventricle into the aorta and from the right ventricle into the pulmonary artery. Meanwhile, the atrial walls relax and blood flows from the pulmonary veins into the left atrium and from the superior and inferior caval veins into the right atrium. In diastole, the walls of the ventricles relax (those of the atria contract), the tricuspid and mitral valves open, and blood flows from the right atrium into the right ventricle and from the left atrium into the left ventricle.

With the help of a noninvasive imaging technique, magnetic resonance phase-velocity mapping, Kilner *et al.* investigated changes in blood flow during the diastole and systole of successive heartbeats in healthy human volunteers at rest. They found that blood flow was asymmetric and that the streaming patterns that developed during diastole and systole were characteristic for each chamber. For example, as the ventricles contract, blood streaming into the expanding right atrium (RA) from the superior and inferior caval veins (SVC; IVC) does not collide but rather adopts a forward rotating, swirling motion that redirects flow toward the tricuspid valve (TV) (see figure, top left). The ventricles then relax and the blood moves leftward out of its clockwise rotation (away from the viewer) and through the tricuspid valve (top right). As the left ventricle (LV) contracts, blood is ejected into the aorta (bottom left) through the aortic valve (AV); then, as the left ventricle relaxes, blood streams into it from the left atrium through the mitral valve (MV), setting up a whirlpool below the valves' flexible leaflets (bottom right).



But why has the mammalian heart evolved such a sophisticated pattern of blood flow? Earlier work by Kilner's group using echocardiography to look at heart blood flow in exercising volunteers yields a possible answer. As the heart rate speeds up to at least double its normal rate during vigorous exercise, the contractions of the ventricles and atria alternate rapidly. The authors propose that asymmetries in blood flow conserve energy (by minimizing energy-consuming collisions between opposing streams of blood) and help to redirect blood movement, enabling its smooth passage to the next destination. They propose that, with exertion, the whirlpools of ventricular blood are hurtled in a slingshot motion along the sinuous curves of the blood vessels, minimizing disruption to the flow. Indirect evidence that the contorted curves of the vertebrate heart may be associated with dynamic efficiency comes from studying invertebrates such as the snail (not known for its virtuosity on the race track), which has a simple, linear two-chambered heart (with not a curve in sight). The researchers hope to test their hypothesis with a more advanced magnetic resonance system that should provide the rapid imaging necessary to follow the dynamics of heart blood flow in exercising volunteers.

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