at The Scripps Research Institute in La Jolla, California, notes that Haber's results point to the most obvious candidates. "One wonders whether different cancers could be explained by mutations in human versions of some of the other half-dozen or so yeast checkpoint genes around," he says.

And because LFS patients with *p53* or *hCHK2* mutations are virtually indistinguishable, Haber thinks there may be a link between the two proteins. "The most fascinating possibility is that p53 is directly phosphorylated by chk2," Haber speculates. For cell cycle expert Stephen Elledge of Baylor College of Medicine in Houston, Texas, a direct path from DNA damage via chk2 to p53 "makes perfect sense." He notes that although yeast does not have a *p53* gene, the organism makes other proteins that, when phosphorylated by chk2, induce a cell cycle stop, much as p53 does.

Still to be worked out are the details of where chk2 fits into the checkpoint control program in human cells. But, says Thanos Halazonetis of the Wistar Institute in Philadelphia, whose as yet unpublished results support a direct chk2-p53 link, "the interesting thing is that genes mutated in cancer fall in a very small number of signaling pathways, and the p53 pathway—including chk2—is likely the most important one." **–MICHAEL HAGMANN**

DEFORMED FROGS

Link to Parasites Grows Stronger

PHILADELPHIA—As scientists labor to unmask the villain behind a rash of frog deformities across the United States, a suspicious character previously linked to this odd crime in California has now turned up in misshapen amphibians throughout the Northwest. The suspect—a parasitic flatworm, or trematode—has also been found in the Minnesota pond where the discovery of dozens of frogs with twisted, missing, or extra legs touched off a hunt for the perpetrator.

Abnormal growth. A worm caused the limb deformities in this lab-raised Western toad.

Linking trematodes to more crime scenes doesn't mean the case is closed—far from it. Abnormal frogs from some ponds still test negative for the parasite, sustaining the notion that chemicals or high doses of ultraviolet (UV) light might also be messing with frog development. "Without question there are other things that can cause [deformities]," says ecologist Pieter Johnson of Claremont McKenna College in Claremont, California, who described his team's trematode findings here last month at the annual meeting of the Society of Environmental Toxicology and Chemistry. But the circumstantial evidence suggesting that the worm is a major culprit has researchers worried that it is being nourished by a surfeit of nutrients, mainly chemicals in fertilizers, building up in U.S. watersheds.

Since students at a Minnesota middle school chanced upon misshapen northern leopard frogs on a field trip 4 years ago, deformities have been reported in more than 50 amphibian species in 44 states. Some scientists worry that the frogs are a "canary in a coal mine," the earliest victims of a developmental poison that may end up harming humans—too much UV light penetrating the thinning ozone layer, for example, or pollutants such as pesticides.

In a step toward unraveling this mystery, Johnson and his colleagues reported last spring that the trematode *Ribeiroia* burrows into tissue around the pelvic area, where a tadpole's limbs begin forming. There, the parasites encase themselves in cysts that may influence limb development by pushing cells around or by secreting hormonelike chemicals. Besides finding the parasites in Pacific tree frogs with extra or missing legs in northern California, the team infected tadpoles in the lab with the trematode, raised them to metamorphosis, and observed deformities mirroring those seen in the field (*Science*, 30 April, p. 802).

Wondering if frogs outside California are also falling victim to the dread worm, the researchers spent last summer crisscrossing six northwestern states in a van, collecting frogs, toads, and salamanders from 103 ponds, including 42 ponds where deformities were found in six species at rates ranging from 5% to 90%. The misshapen amphibians at 40 of 42 ponds had *Ribeiroia*, while those from normal ponds almost never had the parasite. A brief search in Minnesota also turned up the trematode—including at the Ney pond, where deformed frogs were first spotted, and another hot spot. Bolstering its fieldwork, the team has shown that trematodes can cause deformities in the lab in a more terrestrial amphibian: the Western toad (*Bufo boreas*), another denizen of the afflicted ponds. "The fact that they can induce [deformities in] another species gives [the theory] more breadth," says Andrew Blaustein, an ecologist at Oregon State University in Corvallis.

The findings do leave the chemical theory a leg or two to stand on. Although the northwestern waters tested free of pesticides, says Johnson, many of the ponds have a "long history of fertilizer input or cattle grazing." He speculates that such nutrients could be an accessory to the crime by spurring algal growth, which in turn would boost populations of *Ribeiroia*'s primary host, an aquatic snail. Others see a more direct role for chemicals. A group led by toxicologist Jim Burkhart of the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, has found that the water itself from the Ney pond and other sites can cause deformities in parasite-free African clawed frogs, a widely used lab species. "It's not either-or," says Burkhart. "There are factors in the water that contribute to malformations." He believes that mixtures of unidentified hormonelike chemicals in the water, as well as the trematodes, each can trigger deformities. And they may work in concert, Burkhart says: Chemicals could be predisposing the frogs to trematode infections by weakening their immune systems.

So far, it hasn't been shown that trematodes are killing off significant numbers of frogs—they have only been blamed for deformities—so they don't appear to play a role in the worldwide decline of amphibians, notes parasitologist Peter Daszak of the University of Georgia, Athens. But Blaustein has a prime murder suspect: He's found that even low concentrations of nitrates from fertilizers can directly kill larvae of several Western species in decline, including the Cascades frog, one of the species with deformities. "The message on the effects of fertilizers is important," Blaustein says. "Fertilizers are everywhere."

–JOCELYN KAISER

CIRCADIAN RHYTHMS

Possible Clock Messenger Identified

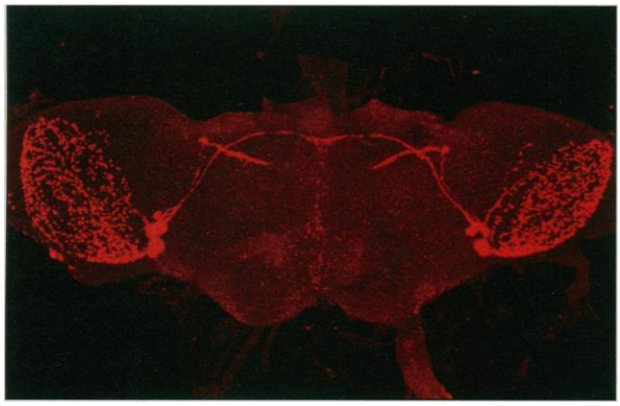
A clock is useless unless it has an output—hands, a digital display, or an alarm. The same goes for the 24-hour molecular "clock" that ticks in organisms from bacteria to humans. To impose its rhythm on behaviors such as activity, sleep, and feeding, the oscillating molecules that make up the clock must communicate, through some kind of outgoing signals, to the brain areas that drive those behaviors. Now researchers working in fruit flies have for the first time put their hands on a good candidate for such a messenger.

In this week's issue of *Cell*, a team led by Paul Taghert at Washington University in St. Louis and Jeff Hall at Brandeis University in Waltham, Massachusetts, reports evidence that a peptide called PDF is a key outgoing clock signal. The researchers have shown that

CREDIT: J. EMIL MORHARDT, CLAREMONT MCKENNA COLLEGE

flies in which the *pdf* gene has been inactivated have functional clocks but lose their rhythmic activity patterns under certain conditions, suggesting that a signal from the clock that affects activity is missing.

The finding builds on earlier hints, including one reported in *Cell* 2 weeks ago by Michael Young of The Rockefeller University in New York City and postdoc Justin Blau, who found that the clock genes regulate PDF production, as would be expected if it were an output signal from the clock. If PDF does turn out to be a bona fide output signal, says clock researcher Paul Hardin of the University of Houston, it will help researchers to "ultimately map out a pathway" from the clock to behaviors that it controls.



Rhythm centers. The red stain shows the distribution of the protein that gives rise to PDF in the fruit fly brain.

CREDIT (LEFT TO RIGHT): P. H. TAGHERT AND S. C. P. RENN; BEIJING UNIVERSITY

The first clues that PDF (for pigment-dispersing factor) might be involved with the clock came from its resemblance to a peptide called pigment-dispersing hormone, which drives a daily rhythm of color changes in some crustaceans. Rhythm researcher Charlotte Helfrich-Förster at the University of Tübingen in Germany provided further evidence for that idea in 1993 when she discovered that PDF is made in certain of the so-called lateral neurons of the fruit fly: clusters of neurons on each side of the fly's head where its clocks are housed. What's more, she showed in 1998 that those neurons make direct connections to the part of the fly brain that appears to control the fly's activity level, and that those connections are essential to maintain daily activity rhythms. That strongly suggested that something made by the lateral neurons acts as the messenger controlling clock activity. PDF was a good candidate, but researchers had not yet knocked out the gene to test that idea.

Then last December, Taghert and graduate student Susan Renn were studying neuropeptide expression and in their lab stocks found flies that were missing PDF. Further testing showed that the flies had a mutation in the *pdf* gene. To check out whether the mutation affects the flies' clocks, Renn and Taghert joined forces with clock researchers Hall, Michael Rosbash, and postdoc Jae Park, who were already studying *pdf* gene expression. The researchers found that the animals have working clocks; for example, in normal light-dark cycles, the flies became active in anticipation of darkness, a sure sign that their clocks were running. But in constant darkness, their activity rhythms gradually faded away over several days. Because PDF is apparently not part of the clock itself, the fading suggests that it contributes to the output signal that controls activity rhythms, says Taghert. It can't be the only signal, because flies still have activity rhythms under some conditions without it, he notes, but it seems to dominate under constant dark conditions.

If PDF is such an output signal, it must be controlled by the clock. And that appears to be so. In their *Cell* paper, Blau and Young described the discovery of a new clock gene, *vrille*, and reported that both *vrille* and another clock gene, *clock*, regulate PDF: *clock* controls the expression of the *pdf* gene in the lateral neurons, and *vrille* controls the accumulation of the PDF peptide. Surprisingly, PDF production remains level throughout the day, but it might be released rhythmically from the lateral neurons, which would explain its rhythmic effects on activity.

The data also suggest another possible function for PDF, as a signal that helps to synchronize the pair of fruit fly clocks. If the two clocks in the lateral neurons were to get out of time with each other, the fly's rhythms would disintegrate into chaos. Normally light should synchronize the clocks, but in constant darkness, they could drift apart without a backup. In that case they could show a gradual loss of rhythmicity similar to what happened in the PDF mutants kept in the dark. Helfrich-Förster found that some of the PDF-containing lateral neurons crossed to the other side of the brain, where they could act as a backup synchronizer.

Right now researchers can't tell whether PDF exerts its effects on activity patterns directly, by synchronizing the clocks, or both. Researchers might be able to resolve that issue by selectively destroying the lateral neurons that cross to the other side of the brain, but not the ones that project to the activity-controlling area. And if they could find the receptor through which PDF exerts its effects, they should be able to identify the neurons that respond to it. That would enable them to confirm that it controls daily activity rhythms

ScienceScope

Unsanctioned The U.S. government is scaling back sanctions imposed on 51 Indian research labs and industries after the country conducted nuclear weapons tests in May 1998. The organizations weren't allowed to receive U.S. exports, and their scientists were effectively barred from visiting U.S. labs.

The change, announced 16 December, follows a congressional directive to pare down a sanctions list of 204 Indian institutions to those "that make material contributions to weapons of mass destruction and missile programs." Indian officials see it as an effort by the Clinton Administration to nudge their country toward signing the Comprehensive Test Ban Treaty, which the U.S. Senate rejected this fall.

Both Indian and U.S. scientists are happy with the move, which will take a few months to put into effect. "It will be wonderful to have [Indian scientists] back on the team," says David Cutts, a Brown University physicist who is part of an international group upgrading one of the main particle detectors at Fermilab's Tevatron accelerator (*Science*, 21 May, p. 1259). Indian scientists built and shipped a piece for the detector but have been unable to travel to Fermilab to install it.

Double Duty Xu Zhihong, a 57-year-old plant biologist, has been named president of Beijing University. In an unusual move, Xu will also retain his position as a vice president of the Chinese Academy of Sciences (CAS) in a bid to cement links between the government and university research sectors. He succeeds physicist Chen Jai'er, who will become chair of China's funding agency for basic research, the National Natural Science Foundation.

Xu, who has spent most of his career at CAS's Shanghai Institute of Botanical Physiology, says his goals are to improve the quality of university teaching and encourage cross-disciplinary research. Researchers applaud Xu's appointment and see his dual role as a way to strengthen the sometimes tenuous relationship between CAS and universities. "Unfortunately, the two systems do not cooperate enough," says Zou Chenglu, a biophysicist at CAS's Beijing Institute of Biophysics and a CAS member.

Contributors: Mark Muro, Jeffrey Mervis, Pallava Bagla, Li Hui

and perhaps find other clock-controlled behaviors as well, says Rob Jackson of Tufts University College of Medicine in Boston. Indeed, even though it is not yet certain that PDF really is the clock's output signal, the flurry of speculation about its possible roles has begun. –MARCIA BARINAGA

HUMAN GENETICS

mtDNA Shows Signs of Paternal Influence

Women have struggled to gain equality in society, but biologists have long thought that females wield absolute power in a sphere far from the public eye: in the mitochondria, cellular organelles whose DNA is thought to pass intact from mother to child with no paternal influence. On page 2524, however, a study by

Mighty mitochondria. Human sperm mitochondria (yellow line) can gain entry to eggs.

Philip Awadalla of the University of Edinburgh and Adam Eyre-Walker and John Maynard Smith of the University of Sussex in Brighton, U.K., finds signs of mixing between maternal and paternal mitochondrial DNA (mtDNA) in humans and chimpanzees. Because biologists have used mtDNA as a tool to trace human ancestry and relationships, the finding has implications for everything from the identification of bodies to the existence of a "mitochondrial Eve" 200,000 years ago.

The study "is pretty compelling and I can't think of good alternative explanations," says Richard Hudson, a population geneticist at the University of Chicago. Anthropologists agree that if the study holds up, it could trigger a major shake-up in their field. "There is a cottage industry of making gene trees in anthropology and then interpreting them," says Henry Harpending, an anthropologist at the University of Utah, Salt Lake City. "This paper will invalidate most of that."

Yet not everyone is ready to grant a role to fathers in mtDNA inheritance just yet. Hudson and others caution that the new result "changes our view dramatically enough that we have to continue to think of other ways to explain it." Fathers contributing mtDNA to their offspring "implies several different novel and important biological phenomena that no one's ever seen before," such as contact between maternal and paternal mtDNA, adds Neil Risch, a human geneticist at Stanford University School of Medicine.

Researchers have assumed that mtDNA passes only through the mother, in part because experiments have shown that eggs destroy sperm after fertilization, and that mitochondrial traits, including a variety of inherited disorders, seem to come only from mothers. But some mtDNA sequences didn't fit neatly into a tree of maternal descent (*Science*, 5 March, p. 1435), so the scientists decided to look for signs of mixing between paternal and maternal mtDNA.

Such mixing—the usual fate of DNA in the cell nucleus—is called recombination, and it takes place when a piece of a DNA strand from one parent crosses over and pairs up with a strand from the other parent. The process generates a novel DNA molecule with features donated by each parent.

To probe whether recombination occurs in the mitochondrial genome, the team analyzed DNA variations. DNA in different individuals varies at many positions, so each new mutation arises on a distinctive genetic background. Unless the DNA can reshuffle itself, the new mutation will stick with the variations already on the same chromosome as it is passed on. But recombination, which mixes up pieces of the DNA, should gradually destroy such nonrandom linkages between DNA variations. The farther apart two sites lie on the chromosomes, the faster recombination can eliminate the linkage. Thus, if recombination is operating, specific variations are less likely to be found together if they are far apart on the chromosome than if they are neighbors.

Using mtDNA from humans and chimpanzees, the researchers tallied how often specific mutations at different sites tended to occur together; they also noted the distance between the mutation sites. In four out of five human data sets and one chimp set, nonrandom mutations at distant sites were less likely to be linked than nearby mutations—implying recombination between maternal and paternal DNA, says Eyre-Walker.

Such recombination could be a blow for researchers who have used mtDNA to trace human evolutionary history and migrations. They have assumed that the mtDNA descends only through the mother, so they could draw a single evolutionary tree of maternal descent—all the way back to an African "mitochondrial Eve," for example. But "with recombination there is no single tree," notes Harpending. Instead, different parts of the molecule have different histories. Thus, "there's not one woman to whom we can trace our mitochondria," says Eyre-Walker.

What's more, over time, recombination mixes up genomes so that they become more homogeneous. That "makes even distantly related people look more similar to each other," says Eyre-Walker, and causes past events to seem more recent than they really are. Our last common female ancestor, for example, would be older than the mtDNA implies. But not every mtDNA study would be invalidated by recombination, Eyre-Walker notes. "The major impact will be on the timing of those events and our basic understanding of mtDNA evolution," he says.

Even so, many researchers aren't ready to accept these data as ironclad evidence of recombination. Other genetic processes might create a similar pattern, says evolutionary biologist Rebecca Cann of the University of Hawaii, Manoa. Some researchers have proposed models in which one mutation is more likely to occur close to another. "It's not yet clear whether there aren't explanations other than recombination," agrees Vincent Macaulay, a mathematical geneticist at the University of Oxford.

Skeptics and supporters alike note that how recombination could be happening remains a mystery. Recombination requires physical contact between egg and sperm mtDNA, for example, and it's not clear when or how these molecules touch. In any case, it's possible to square previous observations of mtDNA inheritance with "a little bit of paternal leakage," adds Jody Hey, an evolutionary geneticist at Rutgers University in Piscataway, New Jersey. Just how much leakage might take place is a critical question in practical as well as research uses of mtDNA, such as identifying human remains. "If the sequences are identical, the chances are very good that that's the woman's son or daughter," says Eyre-Walker. "If you get a one-base-pair mismatch, do you say 'This is not your child?'" –EVELYN STRAUSS

PLANETARY SCIENCE

Galileo Catches Lava Fountain on Io

SAN FRANCISCO—Astronomers are galvanized by a new image of what may be a curtain of lava spewing above a volcano on Jupiter's moon Io. The picture, snapped by the Galileo spacecraft during its daredevil dive past Io on Thanksgiving and released last week at a meeting of the American Geophysical Union, also reveals a complex, jagged cliff arcing near the volcano—further evidence of the moon's geologic turmoil.

Planetary scientists have long known that Io is the most volcanically active body in the solar system, thanks to constant gravitational tugs from Jupiter and its other moons that churn Io's interior. Galileo had previously revealed surface flows within vast volcanic

CREDIT: PETER SUTOVSKY