beam intensity, but this runs into the same difficulty.

By this summer, three groups in the United States had progressed to the point where they were reporting at conferences phase-sensitive reduction in noise. The Bell Labs group used sodium vapor to obtain four-wave mixing, as did an MIT team comprising Mari Maeda, Prem Kumar, and Shapiro, although the experiments differed in the way they brought the two outputs together. The third group, consisting of Levenson, Robert Shelby, and Stephen Perlmutter of IBM, used an optical fiber as the nonlinear medium in its four-wave mixing experiment. None of the three, however, could push the noise below the quantum fluctuations limit.

The Bell Labs group has now succeeded, although just barely, with a 7 percent noise reduction below the quantum fluctuations limit (*4*). In brief, calculations of Yurke (*5*) had shown that imbedding the nonlinear medium in an optical cavity with only one entry/exit port would enhance the squeezing. When a resonant frequency of the cavity nearly matches that of the pump, light passes many times through the medium, effectively increasing the interaction. At the same time, this allows operation at lower pump intensities and at a frequency not so close to that of the atomic resonance (the higher frequency line of the sodium D doublet), thereby reducing spontaneous emission noise.

Finally, having only one open port minimizes the loss of signal while it prevents entry of extra quantum fluctuation noise into the cavity. In quantum optics parlance, even if no light shines into an open port, the vacuum along with its fluctuations does, thereby introducing extra noise. And one port solves the problem of how to combine the two four-wave mixer output waves, since they both must exit through it.

In their experiment, the Bell Labs researchers first measured and optimized the amplification and deamplification of the quadrature amplitudes of the laser light that was injected into the four-wave mixer. Since the quantum noise amplitude was about 1000 times smaller than that of the injected light, it could not be seen in this measurement. To resolve squeezing effects, the investigators closed off the input beam to the mixer. In this way, the vacuum, which consists only of noise, became the input signal, and the squeezed noise spectrum was detectable.

The researchers used a nearly degenerate four-wave mixer rather than an exactly degenerate one; that is, the frequency of the signal beam was slightly different from that of the pump beams. However, the results are quantitatively in agreement with an updated version of the theory of Reid and Walls by John Klauder, Samuel McCall, and Yurke of Bell Labs.

To ever be useful, the amount of squeezing should be more like a factor of 10 than one-tenth. Should such a performance eventually be achieved, high-sensitivity interferometry could be the first beneficiary. The minimum phase difference measurable with conventional interferometers is proportional to $1/\sqrt{N}$, where N is the number of photons passing through the interferometer during the measurement. Ring laser gyroscopes now operate at this limit. Carlton Caves at the California Institute of Technology has calculated that, by feeding squeezed rather than coherent light into an interferometer with two input and two output ports, the minimum measurable phase difference would be proportional to $1/N$, if the photodetectors were 100 percent efficient (*5*). Since N is typically about 10^{12}, this represents a large improvement. More recently, Yurke, McCall, and Klauder have proposed an interferometer based on four-wave mixers rather than beam splitters that could achieve the same sensitivity with only coherent laser light and the ubiquitous vacuum as the inputs. Mixing of vacuum fluctuations with the laser light internally generates the squeezing that gives rise to the sensitivity. —**ARTHUR L. ROBINSON**

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Finding Biological Clocks in Fetuses

Researchers are finding that animal fetuses have functioning biological clocks and that the clocks are set by the mother

Newborn animals and humans do not immmediately express circadian rhythms. But, researchers began to ask, is it possible that the brain's pacemaker cells that ultimately direct circadian rhythms are working even before daily rhythms are apparent in such things as sleep-wake cycles and hormone outputs? And, if so, how early does an animal's biological clock start to work?

The answer seems to be that, in rats and squirrel monkeys at least, a biological clock is oscillating during fetal life, and the timing of the fetal clock is set to the light-dark cycles of the outside world by the mother. Immediately after birth, while the young animal's neural pathways are maturing, the mother continues to coordinate the biological clocks of her offspring. This raises the question of why biological clocks develop so early in life, whether these findings apply to humans, and what the biological significance of the finding might be.

Animals have an intrinsic biological clock with a cycle that is approximately 24 hours long, but is reset to an exact 24-hour day by the light cycle to which the animal is exposed. A number of investigators working over the past 13 years established that the pacemaker cells for a biological clock in mammals are located in the brain, in the suprachiasmatic nucleus, which is part of the hypothalamus. Nerve connections between the eye and the suprachiasmatic nucleus provide the pacemaker cells with information on light-dark cycles, which keeps the clock ticking correctly. This hypothalamic tract is independent of the pathways used for vision. And since it is not in place at birth in rats, neurobiologists thought that newborn animals could not have functioning biological clocks that are in tune with daily light-dark cycles.

Then, 9 years ago, Takeo Deguchi of the Tokyo Institute for Neurosciences reported the first hint that young rats have functioning circadian clocks before their retinohypothalamic pathways are in place and before they have daily hormonal and enzymatic rhythms or regular sleep-wake cycles. What he learned was

that the rhythm of the pineal enzyme *N*-acetyltransferase, which is manifest in 4-day-old rat pups, starts out in synchrony with the rhythm of the enzyme in the rat's mother, even when the pups are reared from birth in an environment free of light-dark cues. Thus, Deguchi concluded, the rat pups must have had a biological clock functioning before day 4 that was entrained by their mothers.

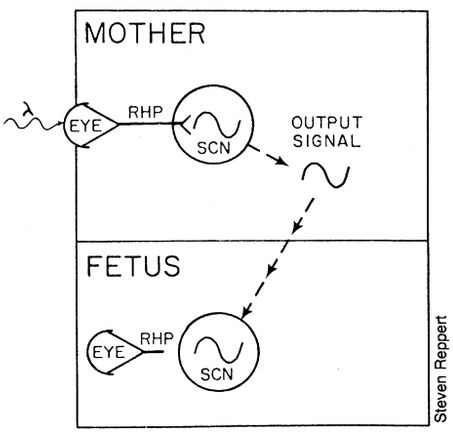
Deguchi's work stimulated Steven Reppert and his colleague William Schwartz of Massachusetts General Hospital to ask just when it is that the biological clock starts to function. As a probe to monitor the biological clock, they used the deoxyglucose method of Louis Sokoloff of the National Institute of Mental Health. Deoxyglucose is a glucose analog that is taken up by the brain but not completely metabolized and can serve as a marker of cell metabolic activity. Its use in the study of circadian rhythms is established. For instance, in 1977, it was used in studies by Schwartz, who was then at the NIMH, and Harold Gainer of the National Institute of Child Health and Human Development when they learned that there is a unique circadian rhythm of metabolic activity in the rat suprachiasmatic nucleus. The cells are active in the day and inactive at night.

So, to study the origin of circadian rhythms in developing animals, Reppert and Schwartz injected pregnant rats with deoxyglucose at different times of day. The isotope passes through the placenta and is taken up by the fetal brains as well as the brain of the mother, so Reppert and Schwartz could get information on both the mothers and the fetuses at the same time.

What they found was that a circadian rhythm of metabolic activity is established in the pacemaker cells of the fetal suprachiasmatic nucleus as early as 3 days before birth—rats have a 22-day gestation period—which is shortly after these cells of the rat hypothalamus are formed. The circadian rhythm seems to be there shortly after the cells that produce it are in place.

Then, through various manipulations of the mothers and fetuses, Reppert and Schwartz learned that, as Reppert puts it, "the fetus always knows what time of day it is relative to the outside world." And the fetus seems to get this information indirectly from the mother and not directly from light passing through the mother's abdomen. To test this, the two investigators gave the fetuses a choice—they could select the mother's clock time or the time of the light-dark cycle in the outside world. They blinded the mother rats early in pregnancy and then reversed the external light-dark cycle. The circadian rhythms of blinded rats would remain as they were at the time they were blinded. Given this choice, the rat fetuses shared their mothers' intrinsic day-night cycles. "The animals were out of phase with the rest of the world but were beautifully in phase with their mother's clock time," Reppert says.

The two researchers have extended their work to the squirrel monkey and find, once again, that circadian rhythms become established in fetal life and that the fetus's clock matches that of the mother. Reppert and others also have found that, at least in rodents, the mother somehow maintains the timing of the biological clock of her pups—if pups are cross-fostered to a mother with a different circadian rhythm, their rhythms start to drift toward that of the foster mother. The maternal influence on the rat pups' biological clocks starts to wane after the first week of life.



Steven Reppert

Setting the fetal clock

Light signals are conveyed to the mother's suprachiasmatic nucleus (SCN) by her retinohypothalamic projection (RHP). Then a signal passes to the fetus, setting the fetal clock.

One obvious question is, what is the nature of the signal that passes between the mother and her offspring both before and just after birth? So far, investigators know only what it is *not*. Reppert, for example, thought at once of melatonin, a pineal hormone whose production is greatly influenced by environmental light conditions and is passed to the fetus across the placenta. But when he removed the mother rat's pineal gland, the fetal clock was unaffected. In fact, Reppert and Schwartz have found they can remove the mother's adrenal gland, pituitary, thyroid, parathyroid, or ovaries and still have no effect on the fetal rhythm. But they and others, including Fred C. Davis of the University of Virginia, find that if they remove the mother's suprachiasmatic nucleus early in pregnancy, thus destroying her circadian rhythms, the fetal clocks continue to work but no longer know what time it is relative to the outside world.

Another question about the fetal clocks is, what is their significance? "We've speculated that the fetal clocks may be involved in the initiation of birth," says Reppert. "The mother may provide the fetus with time-of-day information, and the fetus may in turn use that information in order to initiate birth." Rats and other nocturnal species tend to give birth in the daytime. There is some evidence that humans are more likely to give birth at night, Reppert adds. In the case of the rats, the daytime births make sense because the rat mothers can then forage for food the night after the pups are born. Most higher primates, including humans, are diurnal.

Although it is not at all clear how fetuses might initiate birth, it is known that, in sheep, the fetal adrenal gland is involved in starting labor. And the adrenal is ultimately controlled by the hypothalamus, which might provide a way for the pacemaker cells in the hypothalamus to control the timing of birth, Reppert speculates.

All the work on fetal biological clocks has involved laboratory animals. So far, no one has any idea whether human fetuses have active biological clocks, but Reppert suspects they do. For instance, the finding that squirrel monkey fetuses have functioning clocks makes it more likely that humans do. But the development of the human neurological pathways that set the time of the clocks are still poorly understood. "We don't have any idea when the human circadian system first responds to light," says Reppert. "Humans do have a suprachiasmatic nucleus that is functioning by the 28th week of gestation and a retinal pathway like that in rats and monkeys probably exists. But we don't know when the retinal pathway is functional in humans."

If a biological clock is functioning in the fetuses and newborns of humans, then, Reppert notes, "One has to think about conditions in which abnormal circadian communications can occur." In particular, he remarks, it may be more important than is now appreciated for hospitals to try and maintain some semblance of day-night alternation in lighting in newborn nurseries and intensive care units.—**GINA KOLATA**

Additional Reading

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