says that a vaccine based on the artificial cones, which resemble actual viral structures, might be more successful. At the very least, the new work opens up these kinds of possibilities. Says Trono: "Any single event in HIV's life cycle is a valid target for therapy."

Finding HIV's First Home

Like most scientific fields, AIDS research has its share of dogmas. One of these concerns the kinds of immune cells in which HIV can replicate. Researchers have long assumed that T lymphocytes—the virus's primary target—must be in an active state to produce progeny HIV; that is, they must be immunologically stimulated to divide and proliferate. But because T cells are not activated against HIV in the earliest stages of the infection, many researchers have suggested that other immune cells, such as macrophages or dendritic cells—which can be infected and produce virus even when they are not dividing—are the main producers of HIV early on. T lymphocytes, according to this widely held view, become primary targets only after the immune system has begun trying to beat the virus down.

But in one of the most debated talks in Lausanne, retrovirologist Ashley Haase of the University of Minnesota Medical School in Minneapolis presented evidence that T lymphocytes may in fact be the most important target of early infection. Even more surprising, Haase reported that unactivated T lymphocytes can produce virus, a finding that flies in the face of much current wisdom. If correct, these new results might have important implications for how HIV gains a foothold in infected people, as well as for therapeutic strategies.

Haase and his co-workers, including research associate Zhi-Qiang Zhang, inoculated rhesus macaques with a strain of SIV, the simian version of HIV, that is capable of infecting both T lymphocytes and macrophages, and then analyzed a wide variety of tissues to see which cells were producing virus. Using molecular probes for SIV RNA, the team found that T lymphocytes made up almost all of the virus-producing cells, even in the earliest days after infection. Moreover, most of these infected cells did not show signs of activation or cell division, usually signaled by the appearance of cell surface proteins such as HLA-DR, Ki67, and CyclinA. Haase and his co-workers then went back and looked at lymphoid tissue from HIV-positive patients, where most T lymphocytes in the body are found, and discovered that they, too, harbored large numbers of unactivated but virus-producing T lymphocytes.

The macaque results, in particular, show that "T lymphocytes and not macrophages or dendritic cells are the main targets at the very beginning of infection," says pathologist Paul Racz of the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. Haase told the meeting that these quiescent cells, which produce progeny HIV at a low rate and may be more resistant to anti-HIV therapies than activated cells, could be key vectors for spreading the virus to other unactivated lymphocytes during transmission of HIV and early infection. Moreover, these cells seem to differ from previously identified "reservoirs" of HIV infection: T lymphocytes that harbor latent viral DNA in their chromosomes but produce no virus until activated (*Science*, 14 November 1997, p. 1227).

All is not calm. Quiescent T lymphocytes may be targets for HIV in early infection.

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If so, some researchers say, current experimental attempts to "burn out" the latently infected reservoir cells by activating them so they will be destroyed when virus progeny burst out could backfire, because the virus might infect new populations of drug-resistant quiescent cells. "This may be telling us that instead of activating, we should be trying to shut down residual replication in these cells," says immunologist Giuseppe Pantaleo of the Vaudois Hospital Center in Lausanne.

As intriguing as these findings are, many researchers are treating them with caution. Brigitte Autran, an immunologist at the Pitié-Salpêtrière Hospital in Paris, told *Science* she was not yet convinced that Haase's HIV-producing cells are fully quiescent. Autran says that some of the markers Haase used to determine their activation state, such as the appearance of HLA-DR, can lag many hours behind activation. Similar concerns are expressed by molecular virologist Didier Trono at the University of Geneva, who says that T lymphocytes may not fall into simple categories of "quiescent" and "activated" but that there might be a gradient between these two states.

Although Haase's results need further confirmation, AIDS researchers will be following this story very closely. "This is really a major concern," says Pantaleo, especially if "these [quiescent] cells are the ones that are not responding very well to antiviral therapy."

–MICHAEL BALTER

MATHEMATICS

From Solitaire, a Clue to the World of Prime Numbers

The strange sort of randomness seen in a simple version of solitaire may hold a key to proving a hypothesis about how primes are distributed

"I am convinced that God does not play dice," wrote Albert Einstein in a 1926 letter to physicist Max Born. With this now-famous quote, Einstein expressed his reservations about the emerging theory of quantum mechanics, which has randomness at its very core. But recent mathematical results might suggest that Einstein simply forgot to finish his sentence: "God does not play dice—He plays solitaire."

Solitaire is a subtler game than dice. Although the probability of winning at various dice games can be computed easily, no one knows the theoretical odds of winning at solitaire. "One of the embarrassments of our field," says Persi Diaconis, a probabilist at Stanford University, "is the fact that we cannot analyze the common game of solitaire." But a simpler version of solitaire has now been cracked, Diaconis announced at an October workshop on mathematics and the media at the Mathematical Sciences Research Institute in Berkeley, California. In work that is still being refereed, Percy Deift, a mathematician at New York University, along with Jinho Baik of New York University and Kurt Johansson of the Royal Institute of Technology in Stockholm, has proved that a deep similarity exists between a simple form of solitaire and a mathematical tool called random matrices, originally developed to understand the quantum behavior of large atoms.

The implications could go well beyond card games to some of the most puzzling patterns in mathematics. Other recent work suggests that the same random matrix key might unlock the most important problem in number theory: proving the Riemann hypothesis, which describes how prime numbers are distributed among other integers.

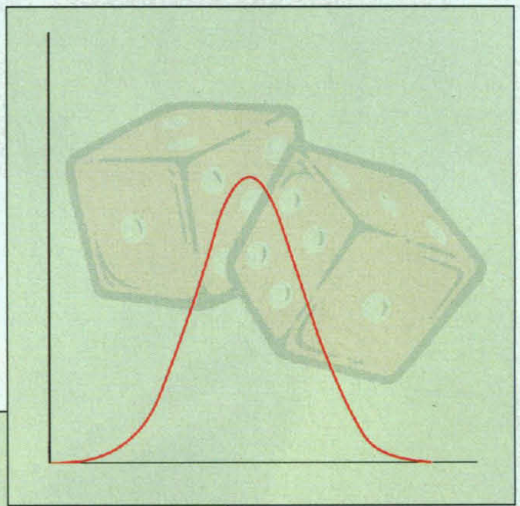
In the solitaire game that Deift and colleagues solved, the deck is shuffled and the player turns over the cards one at a time, placing each one on top of any higher ranking card that is already exposed. Sometimes there is only one possibility; sometimes the player has to choose among several piles. If no higher card is showing, he places the card in a new pile. The object of the game is to make as few piles as possible, and the group tackled the puzzle of just how many piles a perfect player can expect to make—a number that will depend only on the random order of the cards in the deck.

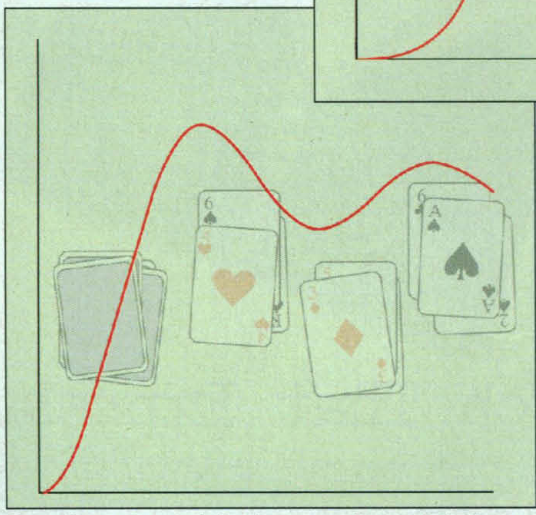
Mathematicians answer this sort of question with a probability distribution—a function that represents the likelihood of each possible outcome. In dice, the frequency with which you will get particular sums of spots in a large number of rolls forms a Gaussian distribution, or bell curve. But Deift has proved that solitaire is not like dice. In fact, the solitaire game has a probability distribution that Diaconis says is "so esoteric that even mathematicians roll their eyes at it." More precisely, it's the distribution of the largest eigenvalue of a certain class of random matrices, which are a mathematical tool familiar to quantum physicists.

A matrix is nothing more than a square table of numbers. Each entry in the table might, for example, show the probability that a photon of wavelength i will emerge from an atom when it absorbs a photon at wavelength j. Often, matrices can be resolved into a "spectrum" of numbers, called characteristic values or eigenvalues—and indeed physicists calculate the spectra of simple atoms from matrices like these. In the physical example, the eigenvalues correspond, roughly speaking, to excited states that the atom "likes" to be in.

For large atoms, such calculations are hopelessly difficult. But by choosing the matrix at random from a family that has certain symmetry properties, physicists can reproduce the distribution of spectral lines statistically, even if the lines do not exactly match those of the true atom. The approach, first proposed by the Nobel Prize–winning physicist Eugene Wigner, "was an immensely revolutionary thought," says Deift. "It says there is no mechanism—or that the mechanism is irrelevant. The only thing that matters is the symmetry of the matrices and the probability distribution."

Random matrices, naturally enough, have random eigenvalues. But theirs is a very peculiar sort of randomness: The eigenvalues seem to push each other away, as if they were electrically charged atoms in a long tube. Thus they end up spaced at fairly regular intervals on a number line, in a curious limbo between complete regularity and complete randomness. Deift and colleagues have confirmed that the same kind of randomness governs the number of piles in the solitaire game.





Spaced out. Sums of dice in many rolls form a bell-curve distribution (*top*). Eigenvalues of random matrices collect into piles whose even spacing controls the number of piles in a solitaire game (*above*).

SOURCE (BOTTOM): M. RUBINSTEIN

Number theorists, who ordinarily study prime numbers rather than card games, are excited by the solitaire work because the same spacing law seems inherent in their most famous unsolved problem—the Riemann ζ function. The ζ function is part of a remarkable formula, discovered by the German mathematician Bernhard Riemann in 1859, that precisely describes how prime numbers are distributed among the other integers. According to Riemann's formula, the density of primes decreases gradually, with a lot of small fluctuations, as their size get larger. The size and wavelength of the fluctuations are controlled by the "zeros of the ζ function": in other words, by the numbers x and y that solve the equation $\zeta(x + y\sqrt{-1}) = 0$. Riemann believed, but couldn't prove, that in every solution, x (which controls the size of the fluctuations) equals $\frac{1}{2}$.

Investigators have used computers to crank out millions of solutions, and so far all of them have queued up on the critical line $x = \frac{1}{2}$. But no one has been able to prove that all the unknown ones fall on that line as well, which would make it possible to predict the full distribution of primes. "The Riemann ζ function is a leftover from the last century," says Peter Sarnak, a number theorist at Princeton University. "It is the last elementary function we don't understand."

Computer calculations by Andrew Odlyzko of AT&T Labs Research in Florham Park, New Jersey, have shown a suggestive pattern, however: The y values in Riemann's equation satisfy exactly the same spacing law that eigenvalues of random matrices do. This suggests that the combinations $x + y\sqrt{-1}$ are, in fact, eigenvalues of some random matrix. At the October workshop, Sarnak suggested a way to exploit this connection. According to Sarnak, the ζ function is only one of a "zoo" of related functions, called L-functions. He and his Princeton colleague Nicholas Katz were able to match one of the tamer sets of L-functions in this zoo with a family of random matrices, whose eigenvalues are known to lie on the critical line. (Their work is set to appear later this year as a book published by the American Mathematical Society.) If this process could be repeated for the set of L-functions that includes the Riemann ζ function—a big "if"—then the Riemann hypothesis would follow. Sarnak and other number theorists think the methods developed by Deift and colleagues might hold clues to how this could be done.

These hints that random matrices may hold the key to proving the Riemann hypothesis are adding to what Sarnak describes as a sense of "euphoria" among number theorists these days, which began with Andrew Wiles's proof of Fermat's Last Theorem. "You have the feeling that, if he can do that, then we can do this problem!" Sarnak says.

–DANA MACKENZIE

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