therapies aimed at blocking methylation of RARβ2 and other targets of the oncogenic protein. "The implications of the work range all the way from the basic to potential clinical applications," says Stephen Baylin of Johns Hopkins University School of Medicine in Baltimore, Maryland, whose own work focuses on gene methylation.

On the basic side, the discovery helps resolve a paradox concerning gene methylation in cancer cells. The genomes of cancer cells usually carry fewer methyl groups than normal, but particular genes—including several tumor suppressors whose loss or inactivation contributes to excessive cell growth—often have more than their share of the chemical additions. This presumably shuts down the genes' activity. "The big question is what targets methylation to [those] specific sites," says Peter Jones, a methylation expert at the University of Southern California in Los Angeles.

To address that question, Di Croce, Pelicci, and their colleagues turned to APL cells. They carry an oncogenic protein, named PML-RAR because it's the product of an abnormal gene formed by fusing two genes, one encoding the α form of the retinoic acid receptor (RAR) and the other encoding the so-called promyelocytic leukemia protein (PML). Normal RAR, when bound to retinoic acid, alters gene expression in immature white blood cells, causing them to mature and stop dividing. PML-RAR has the opposite effect: It blocks the development of immature white blood cells, which consequently grow out of control. The protein apparently does this by suppressing gene activity, and the Milan team wanted to find out whether it might do so by facilitating methylation of its target genes.

Several lines of evidence suggest that it does. For example, the researchers found that in immature white blood cells, PML-RAR binds to a DNA segment needed for the expression of one of its targets, the gene for the β form of the retinoic acid receptor (RARβ). And once the protein binds to the regulatory site, Pelicci says, "we see hypermethylation of this target promoter." This in turn silences the gene.

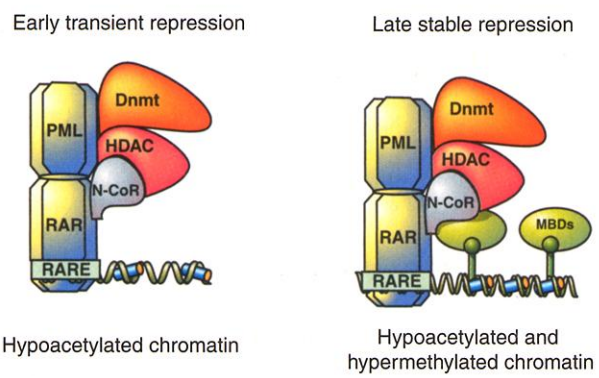
Further work indicated that PML-RAR triggers hypermethylation by drawing in two methylating enzymes. The enzymes bound to the RARβ promoter only when PML-RAR is present. "It's the first example in a human tumor where a genetic change [formation of the PML-RAR fusion gene] is setting up an epigenetic change," Baylin says.

What's more, that epigenetic change seems to be what holds the cells in the immature, dividing state seen in APL: Di Croce and his colleagues showed that once the epigenetic changes were established, the fusion protein was no longer necessary. They did this by setting up the experiments so that the PML-RAR gene was expressed in the white cell precursors only in the presence of zinc ions. If they turned off PML-RAR production after 48 hours by removing the zinc, the cells remained locked in their undeveloped condition.

Conversely, the team found, treatments known to return APL cells to a more normal behavior demethylate the RARβ gene and increase its activity. This can be done, for example, by treating the cells with both retinoic acid, which makes PML-RAR behave more like normal RAR, and the drug 5-Aza-dC, which removes methyl groups from DNA.

Although intrigued by the findings, some researchers want to see more evidence of PML-RAR's ability to recruit methylating enzymes to its target genes. "I would be more convinced if they had been able to show that for more than one gene," says Jean-Pierre Isse of the University of Texas Southwestern Medical Center in Dallas. "RARβ is methylated in a lot of cancers without PML-RAR."

Still, Baylin says, researchers interested in epigenetic events in cancer now have a new line of investigation to follow. He points out that many leukemias and lymphomas feature both fusion proteins and hypermethylated tumor suppressor genes. The question now is whether any of them work the same way that PML-RAR does in transforming cells to malignancy. **–JEAN MARX**



Gene lock-up. On binding to its target promoter, PML-RAR attracts an enzyme (HDAC) that removes acetyl groups from histone proteins and also enzymes (Dnmt) that add methyl groups to the DNA. The actions of these enzymes, together with the proteins (MBDs) attracted by the added methyl groups, eventually shut down the gene.

CREDITS: (TOP TO BOTTOM) ADAPTED FROM L. DI CROCE *ET AL.*; AP PHOTO

ScienceScope

Nuclear Shutdown Operations at a research nuclear reactor in the Netherlands were set to shut down this week after Dutch and European authorities expressed concerned about its safety. The High Flux Reactor (HFR) in Petten, owned by the European Union's Joint Research Centre, will remain closed pending a review by outside experts.

The 40-year-old reactor is used for energy-related research and makes more than half of all medical isotopes used in Europe. The apparent growth of a tiny, 18-year-old crack in the reactor vessel plus allegations by an operator of unsafe practices triggered the shutdown.

NRG, the company that operates HFR, claims the reactor is safe and says the whistleblower acted as part of a long-running labor conflict. Although he agrees that the crack is harmless, Dutch environment minister Jan Pronk last weekend said he wants experts to examine the lab's "safety culture."

Water Warning The National Academy of Sciences has waded into a battle over water policy in Northern California and Oregon with a report criticizing the judgment of federal fisheries biologists.

Last year, the U.S. Fish and Wildlife Service and National Marine Fisheries Service recommended water restrictions to protect two endangered species of suckerfish in Upper Klamath Lake and a downstream species of Coho salmon. The recommendations came in the middle of a regional drought and touched off angry protests by farmers and calls for an independent review of the move.

The committee's report, issued this week, found no clear connection between water levels and conditions that promote algal blooms and other problems that degrade water quality and can kill fish. At the same time, the committee said there was no evidence to support an alternative plan from the Bureau of Reclamation to release more water than normal to farmers.

Glen Spain, a fisheries expert with the Institute for Fisheries Resources in Eugene, Oregon, says the academy's conclusions put federal biologists in "a difficult box." The report suggests they shouldn't raise or lower Klamath Lake water levels, Spain says, although current levels contributed to the fish's plight. The agencies must come up with a new plan by 1 April to protect the fish during the upcoming growing season.

they would likely gain control over the movement of electrons and photons within individual wires, setting the stage for integrating devices right into the wires themselves—a development that could further shrink electronic circuits.

The three groups hit on the same solution. One team, led by Charles Lieber of Harvard University, reports its results this week in *Nature*. The other two—one led by Peidong Yang of the University of California, Berkeley, and a second led by Lars Samuelson of Lund University in Sweden—report their results in the February issue of *Nano Letters*.

To pull off the feat, all three groups tweaked the method for making single-composition nanowires. In each case they started with tiny gold particles—each just tens of nanometers across—which they placed on a surface inside a vacuum chamber. They then used either lasers or chemical methods to vaporize the semiconductors that were to make up the first segment of the wire. The semiconductor vapor condensed around the gold particle and began to crystallize out between the gold particle and the surface in a tiny cylinder that eventually raised the particle off the surface. To change the composition of the next bit of wire, the researchers simply fed the chamber a different precursor semiconductor, which was deposited between the gold particle and the previous semiconductor. Together the three teams showed that the process works for several of the most important types of semiconductors, including silicon, silicon-germanium, gallium arsenide, gallium phosphide, indium arsenide, and indium phosphide.

The striped wires could prove handy in molecular electronics, the effort to fabricate computer chips by assembling individual molecules into complex circuits. Striped nanowires are likely to make that assembly easier because they can create transistors and other devices within current-carrying wires, says Mark Gukiksen, a Harvard graduate student and first author on the *Nature* paper. Yang adds that striped nanowires should do wonders as well for thermoelectrics, materials that can use electricity to pump heat. Thermoelectrics are layered materials whose efficiency is expected to rise as their size gets smaller, a property Yang's team is now testing. Finally, Samuelson believes that the technique can be used to grow wires composed of numerous electron-trapping quantum dots. Because these dots are the basis for many quantum-computing schemes, striped nanowires could propel research in this area as well. With so many possible applications, Samuelson says, "it might quickly become a very crowded field."

–ROBERT F. SERVICE

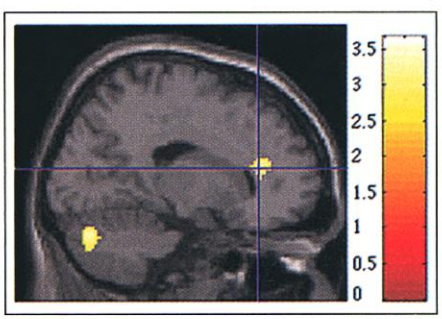
CREDIT: (TOP) P. PETROVIC *ET AL.*

NEUROSCIENCE

Drugs and Placebos Look Alike in the Brain

Researchers in Sweden and Finland say they have finally shown what scientists have long suspected: that a placebo activates the same brain circuits as painkilling drugs. This first brain imaging study of placebo analgesia, reported online this week by *Science* (www.sciencexpress.org), graphically illustrates the principle that higher brain functions help control how humans perceive pain, say the researchers, headed by neuroscientist Predrag Petrovic of Stockholm's Karolinska Institute.

Psychoneurologist Pierre Rainville of the University of Montreal describes the finding as "really great news." There is already considerable evidence that placebos harness the same endogenous painkilling circuits as do opioid drugs. But the evidence is all indirect, drawn primarily from studies showing that compounds that block opioid action also block a placebo's analgesic effect. "For at least 5 years we've been waiting for a good functional imaging study of placebo effects," says Rainville.



Painless. This is your brain on placebos.

To provide such images, Petrovic and his colleagues used positron emission tomography to scan the brains of nine men while a 48°C metal surface was pressed to the backs of their hands. The team compared brain responses after subjects were given intravenous injections—by a doctor in a white coat—of either an opioid painkiller or a placebo.

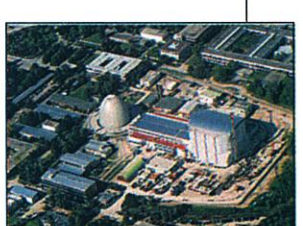
Both the genuine analgesic and the placebo led to increased blood flow in areas of the brain known to be rich in opioid receptors: the brainstem and the rostral anterior cingulate cortex (ACC), which exchanges information with a network of brain regions, including the orbitofrontal cortex, a relatively sophisticated part of the brain known to process emotions. Furthermore, those people who responded most to the placebo—according to their ratings on a scale of 0 to 100 of how much it reduced their pain—also showed more rostral ACC activation from the drug. This,

ScienceScope

Exodus, Chapter 7 Marvin Cassman, director of the National Institute of General Medical Sciences (NIGMS) in Bethesda, Maryland, announced this week that he is heading to California in May to head up a new state-funded quantitative biology institute. Cassman is the seventh top administrator to leave the National Institutes of Health (NIH) in the past 2 years, including former NIH director Harold Varmus. One vacancy has been filled: Andrew C. von Eschenbach, formerly of the M. D. Anderson Cancer Center in Houston, took the oath as director of the National Cancer Institute on 4 February.

At NIGMS, Cassman says, he favored a "complex systems" approach that applied engineering, computational science, physics, and other quantitative disciplines to basic biology. Now he intends to implement this strategy as head of "QB3," a quantitative biology consortium that includes University of California (UC) schools in San Francisco, Berkeley, and Santa Cruz. Lab construction will begin soon at UCSF's Mission Bay campus; the budget has not been set.

Delayed Again The long-awaited operation of a nuclear research reactor in Garching, outside Munich, has again been delayed, this time because of safety concerns in the wake of the 11 September attacks. The federal environment ministry says that FRM-II, which is also a neutron source, needs to develop rules for dealing with accidents and a better plan for the disposal of its spent fuel, highly enriched uranium, to prevent its use in a bomb. The delay comes amid the finalization of plans by Germany's red-green government to phase out nuclear energy production.



FRM-II was completed in August 2000, and Germany's radiation protection agency gave it a thumbs-up in December for experimental operation. The Bavarian government, which has to gain the approval of federal authorities, said it would submit a revised application by May, and federal officials have promised a speedy review.

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