SCI-TECH UPDATE

Drug industry told to stop gifts to doctors and healthcare professionals in the US

The government warned pharmaceutical companies that they must not offer any financial incentives to doctors, pharmacists, or other health care professionals to prescribe or recommend particular drugs, or to switch patients from one medicine to another. The government informed the industry that many practices commonly used in the marketing and sale of prescription drugs could run afoul of federal fraud and abuse laws. Specifically the government said that drug makers could not offer incentive payments or other tangible benefits to encourage or reward the prescribing or purchase of particular drugs by doctors, health plans or companies that manage drug benefits for employers and insurers.

The new standards, the first of their kind, were issued by the Department of Health and Human Services as guidance to the pharmaceutical industry. Aggressive marketing is common in the industry. For years, drug industry has treated doctors to free Broadway plays, weekend trips, expensive meals and other lavish perks. Many companies have rewarded middlemen, or pharmacy benefit managers, for putting their products on lists of recommended drugs, known as formularies. Some companies have also rewarded doctors and drugstores for switching patients from one medication to another.

Similarly, doctors in a position to influence prescribing drugs for large numbers of patients have been retained as advisers and consultants to drug manufacturers. While the new standards do not have the force of law, drug makers that flout them are more likely to be investigated and prosecuted for violations of federal fraud and kickback statutes. In today's environment of increased scrutiny of corporate conduct and increasingly large expenditures for prescription drugs, it is imperative for pharmaceutical manufacturers to establish and maintain effective compliance programs.

The public will have 60 days to comment on the standards. The government may revise them in the light of those comments. The government said it was concerned about the industry's marketing practices because they could improperly drive up costs for Medicare and Medicaid, the federal health programs for 75 million people who are elderly, disabled or poor. The federal government spends $400 billion on the two programs combined, and the cost is expected to double in 10 years. The new standards say switching arrangements, under which drug companies offer financial incentives to shift patients from one drug to another, are suspect under the anti-kickback statute.

Similar arrangements, under which companies pay drugstores or pharmacy benefit managers to contact patients or doctors to encourage them to change from one drug to another, are also suspect, the government said. It warned companies that they would run afoul of the law if they rewarded pharmacies and pharmacy benefit managers for moving market share from one product to another.

The inspector general said that payments to consultants, advisers and researchers pose a substantial risk of fraud and abuse if the payments exceed fair market value for the services rendered. The new guidelines say that drug makers can violate the kickback statute when they offer entertainment, recreation, travel, meals or similar benefits; when they sponsor educational conferences; and when they offer research grants, gifts, gratuities and other business courtesies to doctors, hospitals and other health care providers who influence the prescribing of drugs.

The standards also apply to financial incentives given to purchasing coalitions that buy drugs and medical devices for hospitals. The buying groups are sometimes paid by manufacturers whose products they are supposed to evaluate objectively. Every drug company should appoint a compliance officer, establish a hotline to receive complaints of fraud and
abuse and consider paying rewards to employees who report misconduct.

Under the new standards, companies are responsible not only for their own employees, but also for sales agents and contractors who engage in improper marketing and promotional activities on their behalf. In April the Pharmaceutical Research and Manufacturers of America, a trade group for brand-name drug companies, adopted a voluntary marketing code setting out what sales representatives may do in dealings with doctors and other health care professionals.

The code says, e.g., that a drug maker cannot give golf balls emblazoned with the company's name to doctors, because the product does not provide a benefit to patients. The compliance with the industry code was desirable, but it will not necessarily protect a manufacturer from prosecution or liability for illegal conduct. Employers and health plans hire pharmacy benefit managers to review and pay claims for prescription drugs, to help control costs and to coordinate care for patients.

Barrett Toan, chairman of Express Scripts, a pharmacy benefit manager in St Louis, said drug makers paid rebates to pharmacy benefit managers to make their products more attractive—to improve their position on the formulary, increasing the likelihood that their drugs will be prescribed, in preference to products made by other companies.

John M Rector, Senior Vice President of the National Community Pharmacists Association, said, that pharmacy benefit managers increasingly took payments from drug makers, with the result that patients were switched from a product that might be the best prescription drug for them to a more expensive brand-name product.

The new standards say that drug companies may be subject to civil and criminal penalties if they report inaccurate or incomplete data on the prices or sales of their products. The government uses such information to compute reimbursement under Medicare and Medicaid, and the inspector general said the reported prices should reflect any discounts or rebates offered to buyers.

When drug makers find credible evidence of violations of federal law or regulations, they should notify the government within 60 d, or sooner if beneficiaries could be harmed. In recent years the government has issued guidance to other segments of the health care industry on how to prevent fraud and abuse. Those guidelines were addressed to doctors, hospitals, nursing homes, laboratories, home care agencies and suppliers of medical equipment [Robert Pear, New York Times, 30 September 2002, www.nytimes.com].

PC makers hit speed bumps—being faster may not matter

Todd Schreiner, a Chicago business consultant, went to check out hot new PCs that could replace his three-year-old computer. He decided not to buy. It represents an unpleasant new reality for the personal computer industry. For decades it has relied on the certainty that customers have an unquenchable desire for speedier new machines. But computers have reached a point where for the most common home purposes—Web surfing, e-mail and word processing—they are already more than fast enough to suit a typical home user's needs.

He could not conceive of a situation with his software applications as of now where he would need a computer with a 2.4 gigahertz Pentium 4 processor. Therefore, he decided to make do with his three-year-old Dell PC, with a Pentium III chip only one-fifth as fast, and instead spent the money on more memory, a new digital camera and a CD-ROM burner to store his photos.

More than any other time in its 27-year history, the personal computer industry has found itself in a quandary, having to concoct new reasons to persuade the world's 500 million PC owners to replace their existing machines. And the problem goes beyond the computer makers themselves: no new computer generally means no new copy of Microsoft Windows sold, no upgrades to word processing or spreadsheet programs.

Computer and chip manufacturers have long used advances in speed as a central point to sell new computers. To be sure, such marketing will still appeal to people who edit video or process complex photographic images, e.g., or make calculations with large masses of data, or play video games on the PC. They still see big benefits when they upgrade to faster chips for such processor-intensive tasks.
But even some of them are having second thoughts. Norman H Nie, a political scientist at Stanford who has long thought of himself as a PC power user, was the co-inventor of a widely used and computer-power-hungry software program known as the Statistical Package for the Social Sciences. For more than three decades the software has taxed the power of first mainframes, then minicomputers and finally PCs. Nie has always acquired new, more powerful computers as they became available. But he was stunned not long ago to discover that his faster new computer did not improve the speed of his software. He predicted that for many people the upgrade cycle might be ending.

We are beginning to see a time where—except for the third world—the replacement cycle for computers looks like Detroit, where the desire for a new car every year yielded to a slower turnover, according to him.

That new attitude is shown clearly in a recent national opinion survey by Odyssey Ventures, a San Francisco market research firm. Among households with PCs, the intention to buy a new computer in the next six months has fallen to just 11 per cent from 21 per cent in early 2000 and the lowest level in five years. And half of PC owners now have home computers that are at least two years old—more than at any time since 1994, when Odyssey began keeping track. The pace of upgrades is crucial because, according to the Gartner market research organization, they account for 80 to 85 per cent of new computer sales. Probably a plateau has been touched according to Nicholas Donatiello (Jr), the Chief Executive of Odyssey. There are other digital needs in the home, and people may be spending money around the TV rather than the PC.

The computer industry’s boosters insist that growth has leveled off before and that slumps have been only temporary. Each time the PC business has appeared to run out of steam in the past it has been revived by a burst of software creativity—from the spreadsheet to video games to the Internet—that has attracted millions of first-time buyers followed by successive waves of upgraders.

The cycle has repeated itself so regularly over time that Intel, the company that pioneered the microprocessor chip that made the PC possible, has a name for the process—the digital spiral. At regular intervals, driven by the industrial process known as Moore’s Law, computers increase in power as new hardware emerges. And like clockwork, software is developed to take advantage of the new power. "Is there another spin of the software spiral in front of us to drive growth?" asked Paul S Otellini, Intel's President and Chief Operating Officer. But so far, innovative new software to spur big new sales has not materialized.

The industry’s slowing growth comes at a time when its rate of technology advancement has never been faster. At the end of 1999, most personal computers being sold were based on 500-600 MHz Intel Pentium III chips. By next fall—three years later—the typical performance will have shot up four times, on average, to above 2 GHz, according to industry analysts. The PC industry continues to hold out hope that a variety of new applications—ranging from increasingly complex video games to home video editing and new needs that will arise if the high-speed Internet finally takes hold—will come along and start a new cycle of growth.

But new computing markets appear increasingly to be moving away from the desktop PC. And many of the new applications that have held out hope for a new round of growth are now appearing as cheaper, specialized computer products. Techno-lust has gone elsewhere according to Richard A Shaffer, publisher of the ComputerLetter, a newsletter from Technologic Partners that covers the technology business, e g, video game players are being aggressively courted by seductive alternatives to the PC—most recently, from none other than Intel and Microsoft. The two companies that pioneered the personal computer have now come together to offer a powerful special purpose alternative, the Xbox game system, priced at 10-20 per cent of the cost of a desktop PC. Other PC applications such as Web browsing and e-mail may also be increasingly offered in less expensive, wireless consumer packages.

In fact, many others in the industry think it is possible that the next digital cycle, when it repeats itself, may not happen on desktop PCs but in some new device that looks nothing like a computer today. The transition away from the desktop PC is most apparent in the collapsing growth rate of the industry, which had for more than a decade been accustomed to double-digit expansion of sales each
That bubble burst along with the dot-com collapse in 2001. Amid the prolonged general economic downturn, sales of PCs in the US show no signs of reviving soon. Gartner estimates that the industry’s sales shrank last year by almost 5 per cent after growing by 10-27 per cent/y since 1990. This year promises to be just as bleak. Nevertheless, Gartner analysts estimate that one billion personal computers will be sold in the next six years. At the same time, the market researchers acknowledge that their projected 9 per cent annual growth rate will in the future be largely based on continued expansion of sales in the developing world.

The forecast for the US remains cloudy, and signs of consolidation in the PC industry are everywhere. Earlier this year, e.g., Hewlett-Packard and Compaq Computer, the top makers of personal computers behind No. 1 Dell Computer, merged largely in response to the slowing growth of the industry. So far the response of the personal computer industry to its worst decline in history has largely been one of denial.

The world is being turned upside down and that is not a happy thing for most PC companies according to David R Ditzel, the Founder and Chief Technology Officer of Transmeta, a maker of microprocessors for portable computers. Things are going to be tough for the traditional PC industry because they will not go back to the usual 20 per cent growth rates. Even personal computer industry veterans acknowledge the paucity of new ideas that currently troubles the computer industry.

As long as new PCs are just faster, cheaper, better than old PCs slow growth will be the result according to Robert Frankston, a co-inventor of the computer spreadsheet application.

Intel, as might be expected, sees the world in a different light. Although Otellini acknowledges that many applications do not benefit from greater speed—a 1.5 gigahertz Pentium 4 chip will play a DVD movie with no less fidelity than a 2.5 gigahertz chip—he points to the gains in applications like video editing, which will continue to improve significantly with each new generation of faster chips. He also says there are new categories of software that will continue to drive growth in the existing personal computer market: technologies like voice recognition, more sophisticated search tools, wireless networking and computer security.

Still, hints of such a shift abound. In the midst of a general computing and chip-making downturn, ARM Holdings, a British company that is the world’s largest designer of microprocessors for consumer devices like cellphones and personal digital assistants, is experiencing record growth. ARM chips are designed for the new world of computing away from the desktop PC. This year, there are 1.3 billion ARM microprocessors in cellphones, personal digital assistants and other consumer devices—for the first time exceeding the one billion personal computers that have been produced.

There is tremendous growth in all the little things that help life according to John Rayfield, ARM Vice President based in Los Gatos, Calif. Centralizing them all in one large computer makes no sense. [John Markoff, New York Times, 30 September 2002, www.nytimes.com].
New pastures for Linux wonder boys

They were the darlings of the Linux boom: Red Hat, VA Linux, LinuxCare, Caldera and TurboLinux. The first companies to see a real market for the free operating system, they helped sell the world on Linux, luxuriated in the warm embrace of a giddy financial community and then — one by one — they watched as their stock values dropped, their employee rosters thinned and their prospects dimmed.

So now that the Linux revolution is over, what do the revolutionaries do for an encore? After Art Tyde resigned last year from his open-source startup Linuxcare — which had just about collapsed under the weight of a management shake-up, a market downturn and a failed merger—he did what a lot of post-tech-boom ex-CEOs did: He gassed up his dune buggy, i.e., he got away from it all.

After briefly flirting with the idea of becoming a private investigator, Tyde — along with his Linuxcare co-founders David LeDuke and David Sifry—decided to jump back into the industry. He is now CEO of a Wi-Fi gateway software startup called Sputnik, which will soon release the first version of its product.

Tyde is not the only Penguin revolutionary in the process of reinventing himself. Last weekend in Raleigh, North Carolina, Red Hat founder Bob Young pulled back the curtain on the first in a yearlong series of Lulu Tech Circuses.

Young says the idea for Lulu—the circus and his new venture, Lulu Enterprises—occurred to him a year ago after he argued with journalists about whether the open-source story was over or just beginning. The implication of all of their questions was that once the bubble around the Linux phenomenon has burst whether a real job was necessary. In addition to staging technology shows that Young promises will be fun for regular people, Lulu Enterprises is developing a custom publishing arm that could, e.g., help university professors produce customized textbooks.

Another Red Hat founder who has recently landed a real job is former CTO Marc Ewing, who is now founder and publisher of a glossy $12.50/issue climbing magazine called Alpinist, set to launch in November.

After leaving Red Hat in January 2000, Ewing got back into climbing. The first thing was to get in shape again after several years of pizza and Coke excesses. It was apparent to him soon that something was missing from the climbing literature—a magazine that really communicated about climbing and being in the mountains. It may be easier to reinvent oneself after having made, like Ewing and Young, a boatload of cash, for the Fortune magazine recently pegged Ewing's net worth at $120 million.

For other Linux revolutionaries, the second act means a more buttoned-down job with an established company. Noted Linux kernel hacker, Ted Ts'o — a VA Linux alumnus who, along with a fair number of Linux startup refugees, now hangs his hat at IBM — says that as far as he is concerned, times are still good. According to him, it was only human that on occasion he felt wistful that he could not afford a house on Lake Tahoe, but on the whole he appeared incredibly grateful as he is paid quite well for his work (Robert McMullan. http://www.wired.com/news/technology/0,1282,55336,00.html and 0,1282,55336-2,00.html).

Reality check for web design

Kendra Mayfield, The power of the Web is in its universality. Access by everyone regardless of disability is an essential aspect. Tim Berners-Lee, inventor of the World Wide Web, recognized that universal access is a critical element of good design.

The Web's landscape has altered dramatically since its inception, when many websites completely ignored users with disabilities. Most project managers assumed that blind people could not use the Web anyway, therefore, they also could not use the specific website that was being developed according to Web usability guru Jakob Nielsen. The misunderstanding, has since been eradicated and most Internet managers now do know that they have to care about users with disabilities. Despite progress on this front, websites today are still three-times harder to use for users with disabilities than for other users.

In most projects, accessibility received low priority as project managers underestimate the number of people who are affected by such design problems. They think that they are losing just a handful of customers, whereas in hard numbers that matter, they may be turning away millions of customers, especially
among the senior citizens—a big and rich group that is getting more active online. Now, a new software product allows developers to check pages for compliance with usability guidelines as they code.

The software, LIFT-Nielsen Norman Group Edition (or LIFT NN/g), works with Macromedia Dreamweaver (4.0 or MX) on both Windows and Macintosh. It checks to ensure that websites are compliant with the World Wide Web Consortium's (w3c's) accessibility- and Section 508 guidelines.

The software makes it easier to be a Web designer and to remember the guidelines for users with disabilities. Instead of relying on having the designer remember every single guideline at every single step of website development, LIFT NN/g offloads the memory burden onto the computer, which is extremely alert and checks for a lot of details all the time without getting tired.

After conducting user tests and observing a range of users—including the blind or with impaired vision or with motor-skill challenges—and interacting with a variety of websites, the Nielsen Norman Group created guidelines. The software alerts developers of any possible violations of these guidelines. A fix wizard automatically repairs broken tables, images, scripts, cascading menus and other glitches. A JavaScript Analyzer avoids common errors. A monitor checks work as it is completed, so mistakes are fixed before they are perpetuated on multiple Web pages. Hundreds of pages can be processed in just a few minutes, saving precious hours—otherwise necessary for coding by hand—that can be spent on more useful or gainful activities, particularly on new ideas.

The benefit arises as the computer does not get tired; or fatigue setting in the way it happens to humans, thus, it will check every design detail for every single guideline with the same alertness and efficiency all the time. Also, the software has a simple link from any occurrence of a potential usability problem to the relevant research material that explains why it is an issue and what questions to consider when deciding whether to keep or fix the questionable design element. It is much faster than having to look up the answer in a book, and in fact it is a great example of the original promise of hypertext.

The software goes beyond merely focusing on accessibility to promote usability and improve the Web user experience for everyone. Mere technical accessibility is not enough to make a website easy to use according to Nielsen. The real question is whether users can get what they want from a website in a reasonable amount of time and whether the visit is pleasant for them. Users with disabilities are humans and need easy and simple user interfaces just like anybody else. Making websites more accessible can go beyond the benefits to people with disabilities in the views of Doug Bowman, Network Design Manager for Terra Lycos (Terra Lycos is Wired News' parent company). Accessibility measures also make good business sense.

The Web is just as much a public space as our downtown office buildings and suburban shopping malls. By not being aware of, or taking the time to implement, common Web accessibility measures and guidelines, the website producers—are essentially hiding the elevators, ramps, handrails and wide doors which welcome anyone into the virtual buildings and help them find their way or move from place to place. But while the software automates many core usability and accessibility solutions, humans must ultimately decide whether a design has a usability problem. As with all usability, it is based on the need to create desirable human interaction, so it is important not to take the human out of the design process.

The LIFT NN/g software works like Microsoft Word's grammar check, allowing designers to check fundamentals that are sometimes missed due to busy schedules and tight deadlines. But like grammar, usability does not always follow strict conventions. While it is helpful to know when a designer goes outside the normal, recommended practices, automated software could as well misguide someone with less experience in Web accessibility every suggestion is followed blindly or with insufficient experience.

The software is available at UsableNet for $549—and it could be quite prohibitive for some small websites. It is difficult to visualize smaller companies readily and willingly spending another $550 for the accessibility software when they really have not yet been educated on the benefits of making websites accessible. And some larger companies use other HTML editors besides Dreamweaver for designing and managing websites, which further complicates the matter.
The LIFT NN/g software is just one of the evaluation, repair and transform tools that can be used in conjunction with more complex websites serving environments used by large websites. Developers can also check the accessibility of their website free of charge using a tool commonly known as *bobby*, which checks for compliance with the basic W3C standards.

Large, dynamic database-driven sites often use complex scripts and serving environments to pull together content from multiple sources, then compile it into HTML. Website design may begin in an editor like Dreamweaver. But the final HTML churned out by a content management system may leave out some of the accessibility-checked code from Dreamweaver. Despite these drawbacks, software producers and designers agree that any improvement in accessibility for people with disabilities will also make it easier for other Internet users to navigate the Web. Over time, these tools become educational in nature. Repeated reminders of what could be done can eventually become ingrained and lead to common practice [http://www.wired.com/news/technology/0,1282,55190,00.html and 0,1282,55190-2,00.html].

### Lightning rods for nanoelectronics

Electrostatic discharges threaten to halt further shrinking and acceleration of electronic devices in the future. Walking on a new carpet can generate a 35,000 V discharge. One is not harmed as the amount of charge that flows is puny. Still, it is sufficient to destroy sensitive micro-electronic components. Research has come up with ways to prevent such damage. But smaller circuits are sensitive to electrostatic discharge (ESD). Can we continue to find new ways to prevent electrostatic damage and thereby maintain the pace of innovation?

People who like to tinker with their computers know that when they open up their machines, they should ground themselves—perhaps by touching the metal radiator panel or attaching a wire from their fingers to a metal fixture. The grounding diverts any built-up charge into another object. Microprocessors and other chips have built-in protection circuits, but for tomorrow’s equipment such precautions will be of even greater concern. ESD is not only an issue for finished products but also during their manufacture, from wafer fabrication to packaging to the assembly of complete systems. Each step has its own electrostatic hazards.

In general, electrostatics poses the greatest threat during manufacturing and handling to install the devices and is less of a concern once the components are safely ensconced inside machines such as the personal computer. Some protection methods explicitly rely such an assumption. The hazards start at the earliest stages of manufacture: even photolithographic masks, with entirely mechanical function and not electrical, are at risk. The chief danger to microelectronics is damage to the active elements caused by heating and by electrical breakdown of insulating layers. Magnetic disk drive heads, however, face their own unique problems, including magnetic effects of discharges and aerodynamic considerations.

ESD protection devices have been incorporated into microchips since the 1960s and have evolved over the decades according to technological necessity and corporate strategy. The main goal with each new generation of microelectronics is to perpetuate Moore's Law by building elements such as transistors that are smaller and faster. In the not too distant a future the industry will hit a wall that blocks further progress. The point where a smaller, faster transistor cannot be designed and built is the limit. There is also a second wall—even if the next transistor could be built but no way to protect it adequately against ESD. No one knows which wall is coming first.

**Thermal Runaway**—What causes electronics to fail when ESD occurs? The heat generated by the electric current of the discharge can melt the material. Internal temperatures from ESD events can exceed 1500 °C, above the melting points of aluminum, copper and silicon. Damage occurs even without melting. The properties of diodes and transistors are determined by the doping of the semiconductor—the carefully introduced impurity atoms, or dopants, produce regions with specific electronic properties. Excessive heating can allow dopants to migrate, changing or damaging the pattern essential for the device to function properly.

Processes known as electro-current constriction and thermal runaway concentrate heating in a hot spot—when one location of a semiconductor heats up significantly, its resistance falls, and more current...
flows through the hottest place, heating it even more leading to the damage. Geometry and design symmetry distributes current evenly through a device to forestall the onset of thermal runaway. The material's thermal conductivity, heat capacity and melting temperature all put together determine its ability to store the heat or diffuse it evenly.

Just as important as the sophisticated transistors of modern devices are the electrical connections between different elements. These include interconnect wires along the surface of the chip's semiconductor layers and vias that connect vertically from one layer to another. All these are reduced in size along with the rest of the device to improve the speed and computational power of high-performance semiconductor chips. For many years, aluminum was the metal of choice for interconnects, but it melts at a low 660 °C. Since 1997, after 10 y research, the microelectronics industry migrated to copper interconnects, mainly due to its superior electrical conductivity, enabling smaller and faster circuits. Its higher melting point, 1083 °C, is an additional benefit which gives interconnects higher tolerance to heating.

In contrast to the transition to copper, a generational change in insulating materials had a negative effect on sensitivity to ESD. These low-k materials form the insulating regions between metal lines in devices being rolled out in the marketplace. The low dielectric constant (k) of these materials reduces capacitance between the lines which reduces cross talk and increases the travel speed of high-frequency signals and short pulses. Unfortunately, low-k materials have lower thermal conductivity than silicon dioxide, the traditional insulator, or dielectric, so they are not as effective at dissipating energy from electrostatic events. It is compensated for by careful electrical design, wider interconnects or other techniques to reduce heating. The introduction of copper and low-k materials improved sturdiness against ESD. It helped bring about the transition to 1 GHz applications.

Transistors — The primary digital technology today is the MOSFET device, named after the metal-oxide semiconductor field-effect transistors that they contain. It consists of two doped regions, source and drain, separated by a region called the channel. An electrode, called the gate, sits above the channel, separated from it by a thin layer of silicon dioxide dielectric. The voltage applied to the gate controls how current flows in the channel between source and drain.

Such devices have entered the nanostructure age in recent generations. In August, e.g. Intel announced plans to manufacture chips with gates 50 nanometers long and gate oxides 1.2 nanometers thick—a mere five atomic layers. The thinner the dielectric, the lower the voltage needed to cause breakdown. Dielectric breakdown is caused not by heating but by the electrical carriers, electrons or holes, breaking molecular bonds and cutting a path through the insulator like a tiny bolt of lightning. The defects formed by oxide failure are known as pinholes. With very thin oxide layers, mere handling of microelectronic chips can produce pinholes in the gates.

The source and drain of a MOSFET are also sensitive, and ESD on those regions leads to MOSFET thermal breakdown. When the high voltage of the discharge arrives at the drain, say, it increases the electric field there. This strong field accelerates the current-carrying electrons, making them energetic enough to knock other electrons free. These secondary electrons (and corresponding holes) increase the current flow even more and are themselves accelerated enough to knock more electrons free, and so on. Called avalanche multiplication, this process causes current to flow from the transistor into the nearby substrate, which puts the transistor into an unstable "negative resistance" state, further exacerbating the situation. As the current increases, heating leads to the thermal runaway, or thermal breakdown, described earlier. Inclusion of ESD protection circuits on the chip is the chief technique to protect delicate transistors that diverts current from discharges away from the transistors toward the ground or power electrodes. Other circuits can then transfer the current from one power rail to another until it finds the ground potential.

In the 1960s and 1970s these ESD devices were generally silicon-controlled rectifiers, but 1980s and 1990s technology often used MOSFETs themselves—transistors to protect transistors. The ESD transistors are designed to be much sturdier than the transistors they protect, which is possible because they do not have to meet the same high-performance standards as the active transistors. Adding such circuits does, however, affect the microchip's performance, and
optimizing the design to minimize this impairment for each new microchip is a huge chore.

The silicon p-n diode is the favorite ESD device, which can handle larger discharges than a transistor ESD device of comparable size can, as the transistor is limited because it must send the current through its narrow channel and its gate must resist dielectric breakdown. The widely used CMOS (complementary metal-oxide silicon) technology has a natural p-n diode structure running from the MOSFET to the chip substrate, which can be adapted to function as the ESD device. Additional p-n diodes running down to the substrate are easy to incorporate, although optimization remains a problem.

Since about 1995, when circuit line widths shrunk to 250 nanometers and less, smart circuits known as ESD power clamps have been used to discharge the ESD current through the final stage, from the power rail to the ground. e.g., some power clamps use a simple frequency-dependent filter to discriminate an ESD pulse from normal signals. Others detect the excess voltage of the discharge. Once the device senses the pulse, a signal powered by the pulse turns on robust transistor circuits to discharge the current safely to the ground plane. Many years ago transistors did not respond fast enough to cope with the highest-frequency part of an ESD pulse, which can be as high as a GHz. Modern high-speed transistors no longer have that difficulty.

Today all microprocessors and many other devices, such as radio-frequency chips, use ESD protection circuits and power clamps. With each new generation of smaller circuitry, the task of designing these devices becomes harder because they, too, must be smaller while providing better protection and without disturbing the ever higher performance of the transistors they are protecting. The jury is still out on whether these techniques will suffice for future semiconductors.

Silicon-on-Insulator — In silicon-on-insulator technology, the ESD protection methods used in traditional MOSFETs face an obstacle. The technology promises higher speeds by reducing transistor capacitance (recall that capacitance slows down signals in the metal interconnects as well). In silicon-on-insulator devices the active circuit elements are in a thin silicon film that is separated from the rest of the chip substrate by a layer of insulator. The insulating film means that there is no natural diode structure available to divert ESD away from the sensitive electronics and down through the substrate. In the absence of vertical diodes, the only choice is to build lateral structures in the thin silicon film. In 1994, when research work began, some observers doubted that suitable ESD protection could be built for silicon-on-insulator technology. But by 2000 lateral p-n diodes running from the input signal lines to power rails were providing excellent ESD protection in IBM’s mainstream silicon-on-insulator microprocessors. This technique will continue to suffice for future ultrathin devices, in which the silicon layer may be as thin as 20 nm.

CMOS systems are well suited to digital applications, such as microprocessors, in part because they draw very little current in the 0, or off, state, and they conduct efficiently in the 1, or on, state. They are not so well suited to applications such as the high-speed communications that are increasingly a part of modern life, including cellular telephones, laptop computers and personal digital assistants connected to the Internet, whether by wires or wirelessly. This market will continue to grow rapidly in the next decade, and application speeds are increasing from 10 to 100 GHz, requiring faster, smaller circuits that will be inherently more sensitive to ESD. (A technology called radio-frequency CMOS works between 1 and 10 GHz but is not yet used beyond 10 GHz).

The technology that MOSFETs replaced, the bipolar transistor, is making a comeback for these types of applications through the use of new materials, in particular silicon germanium (SiGe) and gallium arsenide (GaAs). Bipolar transistors differ from field-effect transistors in that current flowing between two regions, called the emitter and the collector, is controlled by a small current entering an intervening region, called the base. A property of a semiconductor called the band gap determines how much it is like a conductor or an insulator. By engineering the band gap, one can build transistors that run 100 times as fast as in pure silicon. Transistor manufacturers control the band gap directly in the base of a SiGe transistor by adjusting the percentage of germanium. A transistor whose regions have different band gaps in this way is called a heterojunction bipolar transistor. (Herbert Kroemer was awarded the 2000 Nobel Prize in Physics for his early work on developing heterojunction transistors.) SiGe transistors are used
in high-speed oscilloscopes, cell phones, Global Positioning System (GPS) devices and high-speed communications.

One can combine the advantages of SiGe with those of CMOS by building SiGe transistors on top of a layer of standard silicon CMOS technology. ESD protection of these devices is very similar to that used for CMOS: diodes built from bipolar transistors in the SiGe divert current from the SiGe transistors, and the usual diodes and MOSFETs do the same for the CMOS components.

These techniques have worked well all the way out to 100 GHz, but what will happen beyond that speed? (Already IBM has demonstrated 200-GHz transistors in the laboratory and is manufacturing 120-GHz technology). At speeds of a few hundred GHz, we will probably have to start from scratch with a completely different form of ESD protection from that used now (see sidebar: Magneticians and Electrostatic)

Another heterojunction technology uses gallium arsenide, which has better electrical characteristics than silicon. Physicists employ extremely high quality GaAs to study the fractional quantum Hall effect and other esoteric phenomena. Commercially, GaAs shows up in the power amplifiers of mobile phones and the optical interconnects that join electronic circuits to fiber optics. It is widely utilized for space applications such as satellites and interplanetary probes.

Standard CMOS devices are difficult to make with GaAs. In silicon, insulating layers can be made out of silicon dioxide, but there is no comparable native oxide in GaAs. The lack of an oxide also stymies the use of the type of ESD protection that is used in silicon, silicon-on-insulator and SiGe technologies. Consequently, GaAs devices are more sensitive to ESD: few would survive contact by a person carrying as little as 1,000 volts, let alone the several thousands of volts easily generated just by walking on carpet.

Spark Gaps — ESD protection is of great concern for the space applications, in which charges build up on surfaces from sources such as the Van Allen belts near the earth and particles streaming from the sun. High-energy electrons can penetrate the interior and cause charge buildup on circuit boards deep inside. Developing adequate ESD protection for GaAs will be a challenge but is essential if future missions are to succeed.

Nearly a decade ago Karlheinz Bock, then at the University of Darmstadt in Germany, demonstrated a new type of protection for GaAs chips called field-emission devices or spark gaps. These are conical shapes etched into the GaAs, with an air gap between the cone's tip and another part of the device. A voltage from a discharge produces a very high electric field at the pointed tip, and sparking across the gap discharges the voltage. Field-emission devices have a number of advantages over diode- and transistor-based ESD protection: first, they have low capacitance and therefore minimal impact on the normal functioning of the device. More important, they can discharge high currents, and they can do so repeatedly. Field-emission devices will provide the level of ESD protection needed for GaAs power amplifiers and space applications once they make the transition out of the laboratory and into practical devices.

In years to come, traditional methods of ESD protection for semiconductors may not be acceptable with smaller, faster devices. Technologies other than GaAs might move to solutions such as spark gaps. Alternatively, designers might use new materials to make intrinsically sturdier transistors and rely on off-chip devices to prevent ESD pulses from reaching the nanocircuitry.

In 600 BC, when Thales of Miletus was exploring electrostatic charge, little did he dream that 26 centuries later, electric charge would be influencing the direction and reliability of technology and that we would still be struggling with electrostatics. Understanding how semiconductors, magnetic recording heads, photomasks and other nanostructures charge and discharge will continue to be a focus of research and development. Inventions and patents of ESD circuits will burgeon as technologies are scaled to smaller sizes and as new disciplines realize that electrostatics does matter [Sci Am, October 2002].
and a high fat content among them. But last April, scientists in Sweden added another drawback to the list. They announced that carbohydrate-rich foods that had been heated could contain elevated levels of acrylamide, a chemical known to cause cancer in rats at high doses. How the substance came to contaminate the foods was unclear, however. Now two papers published in *Nature* (October 2002) hint at its source.

During the cooking process, amino acids and sugars combine in what is known as the Maillard reaction. The new work shows that this reaction can sometimes produce acrylamide as well. Donald S Mottram of the University of Reading, England, and his colleagues combined the amino acid asparagine—which accounts for 40 per cent of the amino acid content of potatoes used to make chips—with glucose. They found that temperatures above 100 °C were sufficient to produce the substance and that temperatures above 185 °C prompted significant acrylamide formation. A second team, led by Richard T Stadler of the Nestle Research Center in Lausanne, Switzerland, reached a similar conclusion after testing the reactivity of 20 amino acids at elevated temperatures. Other plant-based foods such as cereals, wheat and rye flour are also rich in asparagine, the scientists note.

The effects of acrylamide on humans remain unclear, but it causes cancer in rats and fruitflies when ingested in concentrations 1000-times those found in the average diet. The World Health Organization has listed the substance as *probably carcinogenic to humans* and is organizing efforts to coordinate further research into its consequences. An understanding of how heat leads to acrylamide formation could also lead to methods of limiting its production, either through modifications to the Maillard reaction or by utilizing ingredients with lower asparagine content. Scientists feel that people should be more concerned with eating a healthy, balanced diet, which includes plenty of fruits and vegetables, rather than with what might be lurking in french fries and other such products [Sarah Graham, *Sci Am*, October 2002].

**Report calls for plan of sharing data to prevent terror**

A bipartisan report by some of the nation's leading information technology and national security experts recommends that the Bush administration develop a system to share intelligence gathered in the United States and abroad among local, state and federal agencies while developing guidelines to protect against abuses.

The 173-page report, which is scheduled to be released today, outlines a *road map* for establishing truly national, decentralized information systems that would both protect privacy and prevent terror. Toward that end, the report, *Protecting America's Freedom in an Information Age*, strongly endorses giving responsibility for analyzing such information not to the Federal Bureau of Investigation, but to a new domestic intelligence center inside President Bush's planned Department of Homeland Security. Legislation to create the department is mired in Congressional wrangling over such issues as whether labor laws should apply to the agency's employees.

The study also calls upon President Bush to devise new guidelines on what information federal agencies may and may not collect about individuals in the US and with whom, and under what circumstances, such data may be shared. Finally, it warns that while Washington must play a critical role in gathering and analyzing data aimed at preventing terror, state and local officials will inevitably provide much of the information needed to protect the nation. Information systems that exclude them, or prevent them from receiving and contributing to such federal data, are destined to fail, the study concludes.

Unless information provided by state and local officials, as well as the private sector, is shared with Washington, we may wind up getting all of the disadvantages of invasion of privacy with none of the national security gains, thus conclude the task force's co-chairmen, Zoe Baird, the President of the New York-based Markle Foundation, and James L Barksdale, a businessman and former chief executive of Netscape.

Although the Bush administration did not commission the report or formally participate on the 44-member panel that studied the issues for more than six months, senior administration officials who followed the group's work praised the effort. This
impressive group of people was definitely asking all the right questions, and have come up with some very reasonable first answers.

Several task force members are scheduled to meet today with Tom Ridge, the President’s Homeland Security Adviser, to discuss their findings. They have gotten people who normally do not talk to one another — privacy advocates and former intelligence and national security officials — to agree on some basic prescriptions for safeguarding civil liberties and protecting the US.

The study, sponsored by the Markle Foundation, was conducted with two influential research groups—the Brookings Institution and the Center for Strategic and International Studies — and with the Miller Center for Public Affairs at the University of Virginia. The center's president, Philip Zelikow, a former White House official who is close to Bush administration officials, is the task force's executive director.

The information and technology that could have prevented the 9/11 attacks already exists. Had such systems been in place, September 11, 2001 might have been the nation’s most important intelligence coup, instead of a day of national tragedy. The report says that while federal agencies are investing some $50 billion a year on information technology partly to prevent terrorism, almost none of this money is being spent to solve the problem of how to share this information and intelligence among those agencies. In this fiscal year’s $38 billion request for domestic security, e.g., the Bush administration has asked for only $200 million for information integration, and is having trouble getting even that.

Ashton Carter, a professor at the Kennedy School of Government at Harvard University and a former defense official, said the group’s endorsement of presidential guidelines for safeguarding privacy was based on the standards developed by the National Security Agency, which monitors telephone and electronic communications overseas. The agency has a good history of discipline about monitoring conversations of Americans abroad.

The report argues strongly for automated, interactive information systems that include data collected by the private sector and tips from local and state agencies, which the study calls the real front lines of homeland security. The FBI has 11,500 agents, but there are more than 50-times as many state and local law enforcement officers. Whereas the FBI has some 100 analysts working on domestic counterterrorism intelligence, the Los Angeles Police Department alone has 40 such analysts, and New York’s counterterrorism effort is larger still.

The US will make a mistake if it creates an old-fashioned centralized mainframe supercomputer architecture rather than a network of personal computers. Treading carefully in one of the most sensitive policy areas, particularly for conservative Republicans, the task force avoids recommending the creation of a standalone domestic collection agency — such as Britain’s MI-5 — or placing that responsibility under the FBI. The case for fundamental separation of criminal investigation and domestic counter-intelligence is strong according to the report [Judith Miller, New York Times, 07 October 2002, www.nytimes.com].

Smallpox vaccine backed for public in the US

The nation’s top public health officials favored offering smallpox vaccine to the public, even in absence of a bioterror attack, but only after up to 10 million health care workers are immunized and after a vaccine is licensed for general use, which is not likely until 2004. It was the first time the federal officials have said that the public should have access to the vaccine, which carries significant risk of serious side effects. But the final decision rests with President Bush and it was still under review.

The health officials, including Julie L Gerberding, Director of the Centers for Disease Control and Prevention, outlined a strategy that could go far beyond what they were considering just a few months ago, when they were talking about offering the vaccine to 500,000 health care workers facing the greatest risk of handling a smallpox case. Right now the thinking is in favor of making the vaccine available to the general public after adequate immunization of health care professionals.

The officials were not recommending that Americans take the vaccine, but rather that they have the option of weighing the risks and benefits for themselves. No one believes that it should be made available to the general public right now. At a news conference, officials also announced that one million
doses of smallpox vaccine will be provided to the military.

The recommendations were presented to President Bush by the Secretary of Health and Human Services, Tommy G Thompson. There are still a number of issues that need to be addressed before any final decision is made. The government halted routine vaccinations in 1972 as the disease was being eradicated from the world. But the terrorism attacks last year and the possibility that Iraq or other hostile nations might have the virus have caused health officials to consider a new battle against the disease.

Last week, officials gave guidelines to the states on how to be prepared possibly to vaccinate the entire country in the event a case of smallpox appears. Today's briefing focused entirely on vaccinations before such a case occurs. There is still the environment where there is no imminent threat. But there are countries with weapons of mass destruction that probably include smallpox.

Smallpox vaccine, made from a live virus related to the one that causes smallpox, is considered the most dangerous immunization. The government owns all American stocks of smallpox vaccine, and because none are licensed now, all are classified as investigational. When the vaccine was used, life-threatening complications occurred in 15 per million among those who received their first smallpox vaccination, and the number included about one to two deaths.

The rates would be lower among those who were re-vaccinated, but by how much is not known. The vaccine can also cause many non-life-threatening complications such as blindness. A large number of people, 30-50 million, might be disqualified from getting the vaccine as their immune systems have been weakened by cancer, AIDS or other diseases, or because they have two common skin conditions, eczema and atopic dermatitis, which increase the risk of complications.

These comments were meant to be a background briefing on various aspects of smallpox. The participants often had to clarify confusion created by such remarks. Much of the confusion centered on which people would get vaccinated.

One option, the health officials said, is a plan whereby vaccinations would expand to a growing number of health and emergency workers. Under one plan, health officials would start by offering vaccinations to about 500,000 workers who would be most at risk of encountering any smallpox cases in hospitals. Another option would be to consider expanding the 500,000 vaccinations to all the nation's estimated 10 million health care and emergency workers according to Jerome M Hauer, Assistant Secretary of Health and Human Services and Director of the Department's Office of Public Health Preparedness.

After that, and following licensing of what health officials hope will be a safer smallpox vaccine, they would offer it to the public. After the briefing, officials outlined how their thinking evolved since June, when a panel of outside experts recommended against vaccinating all Americans. The panel (the Advisory Committee on Immunization Practices) rejected a proposal to offer smallpox vaccinations to the general public. It recommended limiting vaccinations to health care and emergency workers who were likely to be first responders to a bioterror attack and estimated 15,000 people would be inoculated.

The recommendation is that a phased approach be used, starting with 500,000 and then moving in steps to 10 million. And if necessary, the 10 million could be given the vaccine in one step.

Absent a smallpox attack, or the imminent threat of one, the vaccine's benefits do not outweigh its risks for the general public. But it recognizes that individual citizens feel that if they understand the risks and benefits of the vaccine, they may choose to have it. Yet another administration official, Vice President Dick Cheney favors a mass vaccination approach, while President Bush favors a more moderate approach [Lawrence K Altman & Sheryl Gay Stolberg, New York Times, 05 October 2002, www.nytimes.com].

Trials halted on a gene therapy

Officials in the United States and France had suspended four gene therapy experiments as the treatment, which cured a 3-year-old boy of a fatal immune deficiency, may have given him an illness similar to leukemia. It was not clear to the scientists conducting the research whether the boy, who was
treated as an infant in France, was made sick by the therapy. But officials at the Food and Drug Administration said they suspected that the experiment, which until now had been hailed as the only unequivocal gene therapy success, was responsible.

It is not definitive, but the preliminary data have leads to the suspicion that it is not a coincidence according to Philip Noguchi, the Agency official who oversees gene therapy research.

The experiments—one in France, three in the US—were suspended in early September. The news was not made public until today to give the researchers time to notify the families of 14 children enrolled in the trials. It is yet another major setback for the fledgling field of gene therapy, which involves using viruses to introduce healthy genes into cells. The field is still reeling from the death of Jesse Gelsinger, 18, who lost his life three years ago while undergoing gene therapy at the University of Pennsylvania.

Scientists have long theorized that retroviruses, which were used in the suspended experiments, could trigger cancer. The risk was that the virus, which integrates itself into the patient's DNA, would lodge in or near a cancer-causing gene. But researchers said they had never seen this before, either in animals or humans, even though hundreds of people have received retroviruses in gene therapy experiments for a number of diseases. Experts said it was too soon to tell whether other children treated for immune deficiency were at risk.

This has been a spectacularly successful endeavor up to this point according to Savio Woo, former President of the American Society of Gene Therapy. This is a new enemy that has been discovered. Its theoretical possibility was known, but it has never been seen before. The suspended trials sought to cure severe combined immune deficiency, a disorder that leaves infants without working immune systems. Abbreviated as SCID, but commonly called "bubble boy disease," it is extremely rare and is fatal in the first year of life if left untreated.

In the most severe form, the disease affects boys who have faulty X-chromosomes. The only treatment is bone marrow transplant. But the transplants fail in 40 per cent of all children who lack a perfect donor match, so scientists looked to gene therapy as an alternative. In April 2000, Alain Fischer and his colleagues at the Necker Children's Hospital in Paris announced that they had used gene therapy to successfully insert corrective genes into the bone marrow stem cells of three babies with X-linked SCID. Coming on the heels of Gelsinger's death, Fischer's study was hailed as long-sought proof that gene therapy could work.

Fischer went on to treat six more babies and a teenager, who survived because he had a partial immune deficiency. Up until now, all these patients, more than three and a half years after treatment, are doing well according to him and all had close to normal immune functions.

But last spring one of the boys showed elevated levels of a particular type of white blood cell, called T-lymphocyte, though he had no symptoms. Subsequently, the boy developed chickenpox. By August he had a significant increase in the white cell counts, as well as an enlarged spleen, anemia and a drop in platelets. When scientists examined the child's cells, they could see that the genetic material of the retrovirus had inserted into a particular gene on the 11th chromosome that controls the proliferation of cells. However, it was not yet convincing that the gene therapy was entirely to blame.

Other factors, including the chickenpox infection and a family history of cancer, could also be at work. But W French Anderson, Professor at the University of Southern California who was among the first scientists to use gene therapy to treat SCID, said the gene therapy was likely responsible. It was known that it would happen sooner or later. Even if it turns out that gene therapy causes the disease, gene therapy might still be used to treat SCID because the illness was so devastating.

The child does not have leukemia per se. There is no name for his proliferation of cells because scientists have never seen it before, so Fischer is calling it lymphoproliferation. The boy is being treated with chemotherapy and is responding. But the abnormal cells have not disappeared.

The food and drug agency immediately put a clinical hold on three trials in the US, two at Children's Hospital in Los Angeles and one at the National Institutes of Health in Bethesda, Md. The NIH study, and one of the Los Angeles studies, have yet to enroll any patients.
The other Los Angeles study is being run by Donald Kohn, President-elect of the American Society of Gene Therapy. The four children Kohn and his collaborators have treated all have a form of SCID that is not the X-linked type. Kohn said the FDA was correct in suspending his research. The clinical hold is the only ethical and responsible course of action until more answers are available.

The FDA will convene a meeting of outside experts next week to discuss the trials. Other SCID trials had been going on in England and Germany. The German studies have been suspended, but the British research is continuing.

Daniel Federman, Professor of Medicine at Harvard Medical School who was chairman of the panel, said the panel was especially concerned about financial conflicts of interest in research. He spoke of a "hodgepodge of protections" that was so haphazard it was impossible to catalog how many Americans were enrolled in research experiments, and how many had been harmed by them.

At the present time, a lot of people are trying to do a good job, and almost certainly are according to Federman. They are trying to raise the level of the system as a whole.

Gelsinger's father, Paul, who has become an advocate for patient protection and reviewed the study in advance of its publication, applauded the work. He always felt like what happened to Jesse blew the lid off the can of worms of medical research. The system needs to be looked at, and it needs to be unraveled. This study goes a long way toward doing that [Sheryl Gay Stolberg, New York Times, 04 October 2002, www.nytimes.com].

An economic plan proposal

Although other news has been drowned out by the cry of possible war, something ominous is happening on the economic front. It may not be dramatic, but worse than expected numbers are trickling in. Let us review where we are and what should be done. The key point is that it is not your father's recession — it is your grandfather's recession, i.e., it is not just the standard postwar recession, engineered by the Federal Reserve to fight inflation, that can be easily reversed when the Fed loosens its reins. It is indeed a classic over-investment slump, of a kind that was normal before World War II. Such slumps have always been hard to fight simply by cutting interest rates.

There is no question that the Fed's rapid rate reductions last year helped avert a much bigger slump. But a hard look at monetary policy suggests that the Fed has not done enough — and possibly cannot do enough. Although the Fed funds rate, the usual measure of monetary policy, is at its lowest level in generations, the real Fed funds rate — the interest rate minus the inflation rate, which is what matters for investment decisions — is actually about the same as it was at the bottom of the last recession, in the early 1990s, because inflation is considerably lower.

And the drop in the Fed funds rate engineered by Alan Greenspan & Company, though faster than that in the last recession, has so far been considerably smaller; last time it fell by 6.75 points, this time it fell by only 4.75. Even if the Fed funds rate falls all the way to zero, that will be a smaller interest rate reduction than the last time around. If you think the excesses of the 1990s were larger than those of the 1980s, that the economy needs more stimulus to pull itself out, then it seems likely that the Fed has not done enough, and quite possible that even going all the way to zero still will not be enough.

The overhang of excess capacity, especially in telecommunications, will be worked off only slowly. It is all too possible the sluggish economy may as well extend itself into 2004, or worse, may even be beyond. The Fed should cut rates further — it may not be enough, but it will help.

What are other avenues available? There is a need of a sensible plan for fiscal stimulus — one that encourages spending now, to bridge the gap until business investment revives. Some of the elements of such a plan are obvious, and were described by Jeff Madrick in yesterday's Times [Ailing economy needs a remedy from Bush, New York Times, 03 October 2002]. (i) Extend unemployment benefits, which are considerably less generous now than in the last recession; this will do double duty, helping some of the neediest while putting money into the hands of people who are likely to spend it. (ii) Provide aid to the states, which are in increasingly desperate fiscal straits. This will also do double duty, preventing harsh
cuts in public services, with medical care for the poor the most likely target, at the same time that it boosts demand.

If these elements do not add up to a large enough sum — and $100 billion (or 1 per cent of the GDP) over the next year is a good target — why not have another rebate, this time going to everyone who pays payroll taxes? And how will we pay for all of this? Cancel tax cuts scheduled for the future. The economy needs stimulus now; it does not need tax cuts for the very affluent five years from now. This is not rocket science. It is straightforward textbook economics, applied to the actual situation [Paul Krugman, New York Times, 04 October 2002, www.nytimes.com].

Proofreading the human genome — a firm compiles extensive list of genetic variations

A biotech startup in Mountain View has produced the first comprehensive map of the genetic differences that help explain why humans vary in health, appearance and even behavior.

The human genome is a string of 3 billion nucleotides, four nucleotides to be precise, and each represented by a chemical letter — A, T, C or G, that spell out every inherited trait. Although the letters of all our genomes are virtually identical, here and there nature gets a letter different or wrong. These genetic misspellings — SNPs, or single nucleotide polymorphisms — are used to diagnose ailments and design better drugs, that has become one of biotech's Holy Grails.

Perlegen Sciences was founded two years ago to use new DNA scanning tools to read each and every letter in 50 different genomes, and then to compare each of these genomes, letter by letter, with the reference copy as released by the Human Genome Project. Perlegen has spent more than $ 50 million on the chemistry, instruments, computers and brain power needed to pull off the hellish job of proofreading.

Yet there was only a muted celebration a few weeks ago, when Perlegen's scientists decided they had found the last of the 1,717,015 SNPs that biotech firms have been seeking since the human genome was sequenced in 2000.

Two simple reasons explain Perlegen's restraint. Although the company claims to have found just about every SNP in creation, the scientific community has no proof. Perlegen will not publish its SNP map. Instead it will try to recoup its investment by helping drug firms use these subtle genetic variations to determine why some people react badly to medicines — or get sick in the first place.

That brings up another flaw in Perlegen's SNP map. Although Cox, a respected geneticist and former Stanford Professor, would may that Perlegen has located all the common genetic misspellings; he freely admits that he does not yet know which of the 1,717,015 SNPs are important in what diseases.

Despite these uncertainties, it is clear that Perlegen is in a competitive race to profile the genome at the individual level. In the coming issue of Wired Magazine, e.g. David Duncan will describe having his own SNP profile performed by a biotech firm in San Diego.

Let us look at how Perlegen proofread the genome.

Perlegen is a spin-off of Affymetrix, the Santa Clara firm that popularized a new DNA analysis technique called the DNA chip. The Affymetrix chips are slices of glass about the size of a lab slide. Their surfaces are studded with millions of short lengths of DNA. These DNA strands act like smart Velcro, binding only to matching genetic sequences in unknown DNA samples. In lab settings, scientists drop unknown DNA onto an array, slosh it around for a while, and then stick the array into an instrument that uses a laser to pinpoint matches.

Perlegen pushed the technology by creating larger DNA arrays. Each Perlegen array is 5 inches square and contains about 60 million genetic hooks. Perlegen designed these large arrays — 220 of them — to proofread specific stretches of the genome.

With these specialized arrays in hand, Perlegen faced its next task. The genome is 3 billion chemical letters repeated in an endless string. Perlegen cut the unbroken string into short lengths, and these slices had to correspond to the hooks on the 220 different arrays. This took some fancy chemistry. This is the part that Cox never thought would work. But the young people in the lab proved him wrong.
Armed with the 220 arrays, and the chemistry to chop out specific portions of the genome and direct them to the proper arrays, Perlegen then obtained 50 genomes, from diverse backgrounds, from the National Institutes of Health. The actual work of scanning 50 different genomes, and comparing them letter-by-letter with the Human Genome Project's master copy, is yet another example of how advances in computing are allowing biologists to solve genetic puzzles.

The task could not have even been attempted just four years ago, as the computing power was not available. Now, with the SNP map stored in its computer banks, Perlegen faces the more challenging task of correlating these genetic spelling errors with physical or behavioral anomalies.

In theory, Cox knows how Perlegen's technology can be used to explore whether SNPs are involved in diabetes, for instance. Take DNA samples from 500 people with diabetes, mix them all together, and look for SNP patterns. Then do the same for 500 people without diabetes, and compare the two sets of patterns.

Now Perlegen has to convince big drug and biotech firms that using its SNP map will guide them to better drugs, with fewer side effects, in less time. Cox has been in biotech long enough to know that capitalizing on technical advances is always easier said than done.

Custom Sequencing — While Perlegen was making its map, David Ewing Duncan was having his own DNA analyzed by Sequenom, a San Diego firm that is linking thousands of known SNPs to probable health outcomes. This was the first time a healthy human has ever been screened for the full gamut of genetic-disease markers according to Duncan. As he explains so well, at present SNP science is a mixed blessing. It can spot a genetic variant that seems associated with a disease. But we simply do not know enough to couple that diagnosis with a probability of getting sick. As Sequenom's chief scientist tells Duncan, using SNPs to diagnose ailments is a little like predicting weather.

In interviews with genetic counselors he lays out the current rules of that profession — no one should be screened for a condition that is untreatable, and test results should never bewilder patients. But Duncan suggests SNP vendors may ignore these prime directives in their need to turn a profit. It is a prescient observation. Just last week, e.g., the New York Times reported that a Florida firm is offering to chart people's racial backgrounds based on SNP analysis. The company says the $290 test could help people prove eligibility for race-based college admissions or government entitlements, or simply satisfy curiosities.

Using SNP maps to zero in on genetic ills — The human genome is a string of 3 billion chemical letters and most genomes are 99.99 per cent alike. But each contains a small per centage of differences called SNPs, or single nucleotide polymorphisms. Scientists believe that many conditions have roots in these subtle genetic differences.

Scanning for SNPs — Scientists at Perlegen, obtained 50 different genomes, and used DNA analysis techniques to scan each of them. They then compared each genome, letter by letter, with the Human Genome Project's master genome file to look for differences.

Using SNPs in research — With SNP maps like Perlegen's, scientists can now compare the genomes of sick and healthy people, and look for correlations between SNPs and sicknesses [Tom Abate, http://www.sfgate.com/cgi-bin/article.cgi?chronicle/archive/2002/10/07/BUI86760.DTL].

Codebusters crack encryption key

Andy Patrizio. It took four years, 331,000 participants and a difficult legal case, but the relentless efforts of Distributed.net and its supporters have finally broken a 64-bit encryption key developed by RSA Data Securities.

When Distributed.net set up shop in 1997 to test various forms of encryption by essentially breaking through them, the organizers figured it could take 100 y to uncover the RC5-64 sequence due to limited computer power and the fact that so many people would have to participate in the effort. Still, they forged ahead.

They were confident that the rate would improve and that Moore's Law would help cut down on that time according to David "Nugget" McNett, President of Distributed.net. Not to mention a $10,000 reward
put up by RSA. (Ultimately, $6,000 went to Distributed.net to cover its operational costs, participants voted to give another $2,000 to the Free Software Foundation and the winner took home the remaining two thousand.)

There was so much data to analyze for the project that when the key was eventually found in mid-September, McNett and his crew of participants around the world initially overlooked the winning entry — The unknown message is: Some things are better left unread.

The man who discovered the secret message used a 450-MHz Pentium II to find the solution. A resident of Tokyo, Japan, he has asked to remain anonymous.

With so much time and hardware needed to process the keyspace, it would seem that 64-bit encryption is secure. McNett is not convinced. It is safe for any secret that is not still a secret in two years. People with secrets to keep should factor in not only the importance of the secret but the timeliness. While the accomplishment of breaking the 64-bit encryption standard is noteworthy, there are even greater challenges ahead for Distributed.net.

Next up is breaking through RC5-72, RSA's next highest encryption key. RSA also has a 128-bit key, but trying to break a key that long is practically impossible because there are so many combinations of keys to consider. Major advances are needed in keyrate processing before that would be even approachable.

Along with SETI@Home, Distributed.net was one of the earliest distributed computing projects — so-called because it split up a massive computing problem into small, manageable pieces solved by a large number of volunteers running programs on their individual computers.

The nonprofit organization, based in Austin, Texas, relies on contributors to provide both servers and bandwidth. It shares office space with United Devices, a commercial operation that runs a distributed computing project geared toward finding cancer treatments.

During the past two years, the quest to break RC5-64 has endured its share of intrigue. At one point, a laptop owned by one of the project's participants was stolen. Fortunately, the thief did not realize that a program was running in the background on the computer he had swiped. When he connected the machine to the Internet, it reconnected the laptop to the Distributed.net servers, and the organization was able to track down the thief using his IP address [http://www.wired.com/news/technology/0,1282,55584,00.html].

Internet topology — and tackling AIDS

It is less random than people thought. A few questions are simultaneously so baffling and so significant as: “what is the structure of the Internet?” Baffling, because the thing has grown without any planning or central organisation. Significant, because knowing how the routing computers that are the net's physical embodiment are interconnected is vital if it is to be used properly. At the latest count, there were 228,265 of these routers around the world. They direct the packets of data that make up Internet traffic.

Any effort to map the Internet is necessarily incomplete and out of date the moment it appears. Instead, Albert-Laszlo Barabasi and his colleagues at the University of Notre Dame, in Indiana, treat the net as though it were a natural phenomenon. What scientists generally do with a natural phenomenon that they do not understand is to build a model of it. Dr Barabasi's latest paper on the matter, just published in the Proc National Acad Sci, presents a general framework for improving the accuracy of Internet models.

Until 1999, randomly generated graphs with routers represented by points, and the links between them by lines, was the standard modeling tool. But it turns out that such random graphs are a poor approximation as they miss two important features: (i) Links in the net are preferentially attached, i.e., a router with many links to it is likely to attract still more links, and another router that does not have a link, will not attract any, and (ii) The Internet has more clusters of connected points than random graphs do. These two properties give the Internet a topology that is scale-free — in other words, small bits of it, when suitably magnified, resemble the whole.

Barabasi noticed in 1999 that the World Wide Web (the most visible bit of the Internet) was scale-free. His observation touched off a flurry of research,
and others pointed out that the Internet as a whole was scale-free, too. It has several implications. On the one hand, scale-free topology is resistant to random failures—one reason the Internet, despite the lack of artifice in its design, has proved so reliable. On the other hand, because there are disproportionately many hubs (as well-connected routers are known), the net is particularly susceptible to deliberate attacks on those hubs, and cyberterrorists generally attempt such attacks.

The goal is to create models that are statistically indistinguishable from the real Internet. When and if that is achieved, the models should have predictive, as well as descriptive, powers.

Already, understanding the net’s scale-free structure has led to new results. For example, it had long been thought that the best way to curb the spread of a computer virus was to change the software of machines on the net so that they were less easily infected. Studies using random graphs had shown that changing the software on more machines had a cumulative effect. It is not true in a scale-free setting where most software changes make no difference to the rate at which a virus spreads (although they obviously protect the machines in question). However, treating a relatively small number of hubs in a scale-free system can stamp viruses out completely.

That observation may have implications beyond the virtual world. Research has also shown that the network of human sexual partners seems to be scale-free. In other words, some people have all the luck, while others have none. So stopping the spread of a disease such as AIDS may be a comparatively simple matter of getting treatment to the right people—a strange but real corollary to a piece of research on cyberspace [http://www.economist.com/science/displayStory.cfm?story_id=1365118].

**On scientific fakery and the systems to catch it**

In some ways, the pivotal figure in the research misconduct case at Bell Labs was not J Hendrik Schön, the scientist fired last month for fabricating and manipulating data, but Bertram Batlogg, the man who hired him in 1998.

An investigatory panel cleared Batlogg, and all other co-authors, of knowledge of the deception. But without Batlogg’s imprimatur, the remarkable findings in superconductivity and organic electronics, now discredited, would have been scrutinized more skeptically and sooner.

Schön in 1998 was unknown, a newly minted Ph D from the University of Konstanz in Germany. Batlogg was prominent for work on high-temperature superconductors and had a reputation of being smart and meticulous. The idea behind Schön’s experiments—using strong electric fields to alter the electronic behavior of organic crystals—came from Batlogg.

He has done excellent and reputable work in the past according to Robert B Laughlin, a Stanford Professor who won the Nobel Prize in Physics in 1998. Therefore, most people felt it was unthinkable that the work could not be true. He put his personal stamp of approval on these experiments.

Fraud cases this year at Bell Laboratories and Lawrence Berkeley National Laboratory have led to re-examinations of the scientific process, raising questions about the frequency of scientific fraud and how to keep it in check. Above all, the cases have forced scientists to examine a standard feature of modern science, collaboration. What are the roles and responsibilities of co-authors? How much should scientists rely on trust?

Like the Bell Labs scandal, the Lawrence Berkeley case, in which the laboratory was forced to retract its claim of synthesizing the heaviest atom ever, has been attributed to the fakery of a single scientist.

Those fooled included not only the co-authors, but also the bosses at Bell Labs and Lawrence Berkeley, the prestigious journals that published the work and the physicists who read the papers and believed them.

In each instance, scientists point out that the process worked, ultimately, in exposing the fabrications. They also concede that they wish it had worked more quickly.

Known cases of research misconduct—defined as making up data, changing the data or the results to misrepresent the experiments, or copying other scientists’ work—are rare.

In the last decade, there have been about 50 cases of misconduct among basic science research
sponsored by the National Science Foundation and 137 cases of misconduct among biological and medical research financed by the National Institutes of Health. The foundation finances about 20,000 projects a year, and the institutes finance twice as many.

There is also a nagging worry that many other cases of scientific dishonesty are not caught and that someone less ambitious in scope — Schön's claims were groundbreaking, and, if true, Nobel Prize-worthy—may achieve a quietly successful career. One in four respondents to a poll in 1991 by Science said they had personally encountered fabrication, falsification or theft of research in the prior 10 y.

After the scandals, Bell Labs has reminded researchers of its scientific honor code and strengthened its internal reviews. Journals, which do not generally make researchers submit underlying data, are considering measures like asking for additional data.

The two cases have spurred the American Physical Society to work on an addition to its ethics guidelines that spells out to what degree scientists need to vouch for the work of their collaborators. James Tsang, an IBM scientist who is chairman of the Society's public affairs panel, said the proposed guidelines would strike a middle ground between collaborators' being narrowly responsible for their own contributions and being responsible for the work of all their co-authors. All authors have some responsibility.

After the first papers were published, Batlogg gave many talks promoting the results. Many scientists are upset that when the misconduct allegations arose publicly in May, he quickly distanced himself.

In a more conciliatory tone, Batlogg wrote in an e-mail statement last month: "As co-author, I acknowledge a responsibility to ensure the validity of data in publications. If, I have recently given an impression to the contrary, it is most unfortunate and does not reflect my real intentions."

He has also sent apologetic e-mail messages to colleagues over the last few weeks, acknowledging, that by virtue of being a senior author, he lent considerable credibility to the work. Schön declined to comment.

The Bell Labs investigation, led by Malcolm R Beasley, Professor, Applied Physics at Stanford, raised the question of whether Batlogg, who left Bell Labs in September 2000 to become a professor of physics at the Swiss Federal Institute of Technology in Zurich, had fulfilled his professional responsibility in examining Schön's reported findings. In its report, the panel asked, rhetorically, should Batlogg have insisted on an exceptional degree of validation of data in anticipation of the scrutiny that a senior scientist knows such extraordinary results would surely receive?

Arthur P Ramirez of Los Alamos National Laboratory, once a postdoctoral researcher for Batlogg, said he asked for raw data files from his postdoctoral candidates, not to look for fakery but to make sure that he was familiar with the experiments. With one exception, Batlogg, it turned out, did not witness any of the disputed experiments, and he did not directly analyze the original data. Colleagues say that is unusual for Batlogg. In fact, they add, he is known for uncovering overlooked nuggets.

Once exposed, Schön's fabrications appear obvious and clumsy. A graph published in November 2000 said it showed how soccer-ball-shaped molecules of carbon known as buckyballs transformed into superconductors, their electrical resistance suddenly vanishing at low temperatures.

But the curves were impossibly smooth. It was clear that these were not real data; they were generated using mathematical functions, and only four of the 117 data points might be real data according to the panel.

The co-authors, Batlogg and Christian Kloc, also of Bell Labs, did not notice. Had they spotted the fabricated data, scientists around the world would have been spared considerable time and effort trying to reproduce the experiments. In the inquiry, Schön admitted to the fabrication, but said it was based on actual experimental observations.

According to the panel co-authors represent the first line of defense against misconduct. When that defense fails, as in this case, it emphatically raises the question of whether the community has a right to expect more from co-authors.

But the involvement of co-authors can vary wildly. Because Kloc is a chemist, not a physicist, the panel decided, it would be unreasonable to expect him
to notice data misrepresentations that were so long missed by even experts in the field.

The panel was much more critical of Batlogg. He was a continent away from many of the experiments, which were conducted not at the lab in Murray Hill, NJ, but in Germany, at the laboratory of Ernst Bucher, his graduate adviser at Konstanz.

The panel wrote that it agreed that Bertram Batlogg took appropriate action once explicit concerns had been brought to his attention beginning in the summer of 2001. The report, however, does not detail the concerns or the actions Batlogg took behind the scenes. But it also wondered whether he should have openly questioned integrity of the data after scientists began to raise serious doubts.

Laughlin of Stanford said that at a symposium in October in Santa Fe, Batlogg gave a talk that was very aggressive and bold, as though we were on track and there was nothing amiss at all. Laughlin said he later told Batlogg that no one believed the experiments and that they needed to be reproduced outside Bell Labs, to which Batlogg replied that he was shocked.

Laughlin said he did not believe Batlogg. By that time he knew there was a problem and did not reveal it. I do not believe he did not know.

Horst L Störmer, Physics Professor at Columbia University, who shared the 1998 Nobel with Laughlin, saw the exchange and came to the opposite conclusion. Bertram was extraordinarily upset about it. He had not suspected misconduct at the time and he did not believe that Batlogg knew of any data problems. In this regard Bertram is integrity itself.

Despite raising the questions about his professional responsibility, the panel said it would make no judgment, particularly in the absence of a broader consensus on the nature of the responsibilities of participants in collaborative research endeavors.

Batlogg insisted that he had asked probing questions and that Schön had provided answers that appeared to make sense. He learnt that the control measures he followed in this case were not adequate to prevent or uncover the scientific misconduct that occurred. Too much trust was placed in the collaborator.

Batlogg declined to specify the questions he had asked and the answers Schön had provided or how he had missed the fabricated data in the superconducting buckyball graph. Batlogg said he had given that information to the panel.

Robert C Dynes, the Chancellor, University of California at San Diego, who once headed chemical physics research at Bell Labs, said he found the equivocal conclusions of the committee appropriate. According to him, the committee carefully, and maybe appropriately, left that as an issue for the community to decide. One has to trust collaborators. On the other hand, collaborations occur when you sit and argue over the data. Every collaborator has a responsibility that they are comfortable with what is said in the papers. [Kenneth Chang, New York Times, 15 October 2002, www.nytimes.com].

Judge voids rules on pharmaceutical tests on children in the US

Robert Pear, A federal judge has struck down rules that required drug companies to test their products in children. The rules were intended to give doctors and parents more information about the drugs' safety and the proper dosage.

The pediatric rule exceeds the FDA's statutory authority and is, therefore, invalid according to the Judge Henry H Kennedy (Jr) of the Federal District Court here. The Judge Kennedy said in the ruling that the food and drug agency was overreaching, just as when it tried to regulate tobacco products. In both cases the agency's rules were inconsistent with the statutory framework established by Congress.

The Clinton administration proposed the drug rules in 1997 and issued them in final form in 1998. The Bush administration said in March 2002 that it planned to suspend the rules, but reversed itself a month later after an outcry from pediatricians and some members of Congress.

Hillary Rodham Clinton, who championed the rules during the Clinton White House years, is now the chief Senate sponsor of a bill to write the testing requirements into law. The bill, approved in August by a Senate committee, has not reached the Senate floor.

Most drugs prescribed for children have been tested only in adults, with an assumption that the drugs' effects in children would be very similar. But,
the FDA argued in issuing the rules that correct pediatric dosing could not necessarily be extrapolated from adult dosing information. And the agency said that children often received inappropriate doses, or they get older, less effective medicines.

Lawrence Bachorik, a spokesman for the drug agency said that they were disappointed that the court struck down the pediatric rule that was vigorously enforced throughout the litigation. The agency has not yet decided whether to appeal the decision.

The plaintiffs who challenged the rule are conservative or libertarian organizations: the Association of American Physicians and Surgeons, the Competitive Enterprise Institute and Consumer Alert. Its Executive Director, Jane M Orient, said that it was inappropriate to use kids as guinea pigs. The regulations would have made drugs scarcer and more expensive in the long run, by adding to the risk and the expense of drug development.

Drug companies initially objected to the rules, but learned to live with them. Judge Kennedy said the rules were incompatible with two laws that encourage, but do not mandate, the study of prescription drugs in children: the FDA Modernization Act of 1997 and the Best Pharmaceuticals for Children Act, signed in January by President Bush.

In those laws, Congress created financial incentives for drug companies to test their products in children. By contrast the judge observed that the FDA have adopted a command-and-control approach. Under the statutes, if a company voluntarily does pediatric studies of a new drug, the product may be shielded from competition for six additional months. Such market exclusivity can produce hundreds of millions of dollars in revenue for the manufacturer.

The basic problem is that the rules required drug companies to study the effects of their products in children, even when the companies did not label or market the drugs for use by children. After a drug is approved for one purpose, doctors often prescribe it for other purposes. Under the rules, the government could have ordered drug companies to develop pediatric formulations of some adult medicines. Young children often have difficulty swallowing pills, tablets and capsules, so companies could have been required to devise liquid, chewable or injectable forms. The government could have obtained court injunctions to enforce the rules. Violators could have been held in contempt and fined.

Mrs. Clinton said the court's rejection of the rules underscores the need for immediate Congressional action to impose similar requirements. One of the Republican co-sponsors of the bill, Senator Susan Collins of Maine, said that it was even more important now that this legislation is passed to give FDA statutory authority to mandate that drug companies do research on pediatric drugs.

Philip D Walson, a spokesman for the American Academy of Pediatrics, said that in the absence of clinical data, a doctor had to make an educated guess about how much of a drug to prescribe for children. Youngsters generally need smaller doses, he said, but for some drugs, they require adult doses, or even more.

A child of 6 can metabolize some drugs more rapidly than a person age 36 or 60. And some organs like the liver work better in young children than in middle-age or elderly patients.

The court did not assess the merits of the rules as health policy. The pediatric rule may well be a better policy tool than the one enacted by Congress according to Judge Kennedy. It might reflect the most thoughtful, reasoned, balanced solution to a vexing public health problem. The issue here is not the rule's wisdom. The issue is the rule's statutory authority that the court finds lacking.

But Mark Isaac, Vice-President of the Elizabeth Glaser Pediatric AIDS Foundation, said that if the court decision was allowed, it would be a devastating blow to children's health [New York Times, 19 October 2002, www.nytimes.com].

Stop the patent process madness

Watch your step: If you have ever exercised your cat by having it chase the reflected spot of a laser pointer, you and kitty may be in violation of a bona fide US patent. Just take a look at the patent (the US Patent No. 5,443,036, Method of exercising a cat, USPTO, 1995) to be shocked.

Welcome to the wacky, wild, out-of-control world of IP. Most network geeks translate IP as Internet Protocol, as in TCP/IP, but to those in
uniform it is Intellectual Property—as in pay through the nose. Intellectual property these days covers everything from the shape of Mickey Mouse's ears to the format of Web image files to patterns of DNA. Copyrights, patents, trademarks, all these and more fall under IP's wide and expanding umbrella.

IP controversies are finding their way out of the back of the business section and onto the front page. While recent Supreme Court arguments against the never-ending barrage of copyright extensions seem unlikely to sway the current stable of Supremes, the fact that the case even got there shows that IP disputes have gone prime time in a big way.

Meanwhile, trademark battles tangle the Net domain-name world into knots, with new top-level domain extensions filling up with protective registrations that will never really be used, but exist solely to make sure nobody else can get their hands on them.

Another aspect of the IP stranglehold, the infamous Digital Millennium Copyright Act, has chilled security researchers with the prospect of hard time in the state pen. Business methods and software patents have become a cesspool of attempts to control what many observers feel to be routine and obvious procedures. Amazon obtained a patent for the concept of a one-click Web purchase, while British Telecom unsuccessfully claimed in court that the very concept of Web links violated one of their old patents.

It is time to stop these time-wasting, costly shenanigans. Even when courts ultimately rule a particular IP claim invalid, the real winners in these battles, as usual, are the lawyers, who rake in the fees either way. A commercial running on CNN is explicit on this score, promoting a law firm skilled at high-stakes patent litigation.

IP madness not only wastes money directly, but also blows time and opportunity, which ultimately costs all consumers dearly. Ethical inventors, innovators and entrepreneurs, both corporations and individuals, must pore through patent databases and unceasingly look back over their shoulders, scanning endlessly for stealth patents that might blow up like hidden time bombs.

There is constant concern that an overworked patent examiner has already granted some simple, obvious process or procedure a ridiculous patent that would never stand up to serious scrutiny, but that the beneficiary will still appear like an evil genie, demanding a king's ransom, an expensive court battle or both.

The negative effect on innovation is real. Inventions or products that are abandoned stillborn out of patent fears never have an opportunity to work their magic or change the status quo. They are like ghosts of machines and ideas that we shall never know. This is precisely the result that those who manipulate the world of IP have in mind, and so far they seem to be pretty much winning the day.

Abraham Lincoln said that patents added the fuel of interest to the fire of genius, by promoting the creation of new and useful inventions. He did not say that patent laws, or by extension intellectual property laws in general, were created to be cash cows solely for the gain of those with sufficient resources to play the system and intimidate any challengers into inaction.

We need to take a hard look at the fundamental ways in which IP laws have been perverted from their original purpose as creativity enhancers, into sordid money machines in this country and around the world. Courts cannot be depended upon to consistently handle these cases in an appropriately balanced manner given current IP laws, so efforts to improve those laws would seem the best bet. The recently introduced Digital Media Consumers Rights Act is a start.

This may seem like a formidable battle—and it is. But intellectual property laws were created to promote the public interest, and it's time that we all truly benefit from them. That is, assuming nobody already has a patent on this idea.

The author, Lauren Weinstein, is the co-founder of People for Internet Responsibility (PFIR), the creator and moderator of the Privacy Forum, and an outspoken commentator on technology and society [Lauren Weinstein, wired.com, 21 October 2002].

Milky-way's supermassive black hole

The discovery of a star orbiting the center of the Milky-way galaxy provides compelling evidence that a supermassive black hole lurks there, according to a new study. Previous research had pointed to the
presence of a supermassive black hole at the center of our galaxy, but the observations could still be explained by other theories. Now findings published in the journal Nature all but rule out those alternate theories, scientists say.

Using ten years of high-resolution images collected by telescopes around the world, a team of astronomers led by Rainer Schödel of the Max Planck Institute for Extraterrestrial Physics in Germany tracked a star as it moved around the astrophysical object known as Sagittarius A (SgrA*) at our galaxy's core. The star, dubbed S2 came closest to SgrA* last spring, when it was 17 light-hours (or three times the distance from the sun to Pluto) away from SgrA*, which acts as a compact source of radio waves. S2 completes its orbit in 15.2 y and travels nearly 200 times as fast as the Earth moves around the sun, the researchers found. We are now able to demonstrate with certainty that SgrA* is indeed the location of the central dark mass known to exist according to Schödel. Even more important, the new data have shrunk by a factor of several thousand the volume within which those several million solar masses are contained. According to the most recent model calculations the black hole's mass is roughly 2.6 million times that of the sun.

According to the report, the new results eliminate the possibility that a compact cluster of neutron stars, a stellar-size black hole or low mass stars could be responsible for the radio waves emanating from SgrA*. In theory, SgrA* could be a hypothetical star comprised of elementary particles known as bosons. And even if such a boson star is in principle possible, it would rapidly collapse into a supermassive black hole anyhow [Sarah Graham, scientificamerican.com, 17 October 2002].

Lemon juice is HIV-killing spermicide

Laboratory tests show that lemon juice is a potent destroyer of both HIV and sperm, Australian researchers say. If planned tests in primates and people are successful, lemon juice could be ideal for women without easy access to safe barrier contraceptives, such as condoms, says the team at Melbourne University, led by Roger Short.

But experts in anti-AIDS medications warn that the safety of using the juice internally and its efficacy in people are as yet unknown. Short says a solution of 10 per cent lemon juice produced a 1000-fold reduction in HIV activity in a lab sample. And half a teaspoon of the juice wiped out two teaspoons of sperm in 30 s. The high acidity of the juice is responsible for killing HIV and sperm.

The great advantage of lemon or lime juice as an anti-viral contraceptive is that the fruit can be grown very cheaply in the developing world, says Short. Women might use the juice by inserting a soaked piece of sponge or cotton wool before intercourse, he says. Women researchers in Short's lab said using the juice caused no pain.

This method of contraception was widespread in the Mediterranean before the advent of modern methods, such as the Pill. Julian Meldrum of the London-based National AIDS Manual says: The basic principle that acids such as lemon juice can inactivate both sperm and HIV has been known for some years. Although lemon juice was used historically as a contraceptive, however the degree of damage done directly to the vagina and the interior of the cervix and uterus, and indirectly, on the makeup of microbes in the vagina is not known.

More work is needed to verify if women really could rely on lemon juice to protect themselves against pregnancy and HIV in the human body without side effects. The team is now planning experiments involving macaque monkeys in Indonesia [Emma Young, newsscientist.com, 10 October 2002].

Free software hurts the US

An attack on the software license behind the Linux operating system has stirred up a free software controversy in Washington. Earlier this week, three
members of the House of Representatives, Adam Smith, Ron Kind, and Jim Davis, sent a note to 74 Democrats in Congress attacking Linux’s GNU General Public License (GPL) as a threat to America’s innovation and security.

The note urged members to support a letter written by Reps. Tom Davis and Jim Turner to Richard Clarke, who heads the board in charge of hammering out the US cybersecurity policy. Davis and Turner’s letter asks that the plan explicitly reject licenses that would prevent or discourage commercial adoption of promising cybersecurity technologies developed through federal R&D.

There is only one problem: Tom Davis and Jim Turner say their letter has absolutely nothing to do with open source or the GPL. The Davis letter requests that the status quo be maintained, so that we can maintain interest in federal R&D. Smith, whose largest political contributor is Microsoft, has come under fire for his involvement in the controversy. But he is reported to be motivated by a desire to foster innovation. The Microsoft’s hand driving technology policy has been denied.

The GPL’s creators disagree. The rhetoric is almost word for word what Microsoft has been saying for 19 months according to Bradley Kuhn, executive director of the Free Software Foundation. But how is it that that kind of rhetoric should end up in a congressperson’s letter?

It is speculated that some members of Congress may have signed the anti-GPL note without fully realizing what they were doing. They were probably hastened into something that most of them would now recognize as not being that well advised.

Created after September 11 attacks last year, Clarke’s Critical Infrastructure Protection Board recently released a draft of its plan to secure America’s technology infrastructure. The draft plan makes no mention of the GPL, and only one mention of Linux. In a section of recommendations for home and small-business users, it advises that Windows, Macintosh and Linux users regularly update their operating systems.

In their note, Smith, Kind and Jim Davis asked for the cybersecurity plan to be modified to reject the GPL. ‘And while Davis and Turner’s letter urges drafters of the plan to explicitly reject licenses that would discourage commercial adoption of technology, representatives from both congressmen’s offices declined to say what licenses should be rejected.

Computer security expert Gene Spafford said Congress should look beyond the free software license if it wants to encourage companies to adopt federally developed technology. Why do we also reject any software patents and copyrights that could discourage the adoption and use of software developed under federal funds? Spafford asked.

Open-source advocates say this controversy is just one of the opening salvos in what they expect will become a major struggle to define the role of open-source and GPL software in the federal government.


**RBI wants banks to step into project financing**

The days of PIs may well be over. Can banks step into the shoes of these long-term lenders? RBI is exploring the possibility of banks, largely confined to short-term exposures, being able to participate in project finance. Deposits account for a large chunk of banks’ funds. However, depositors can withdraw these deposits *on demand*. This prevents banks from locking their funds in long-term loans.

Now an RBI internal group has recommended certain backstop arrangements that will help banks to take up project finance. It could primarily be in the form of *take-out* finance — a bank which is funding a long-gestation project transfers the outstanding of such funding to the books of another institution on a pre-determined basis.

A bank may deploy a slice of its demand deposits for the first few years of the project, after which another agency takes it over. In other words, a bank may withdraw from the project if it faces an asset-liability mismatch.

Take-out finance has been introduced for infrastructure projects, even though it is yet to take off in a significant way. The RBI has suggested specific changes in investment valuation norms, which will
make it more beneficial for banks to buy debt paper floated to finance large projects.

A backstop structure is a facility that banks may use to do project finance. The other option is for banks to directly raise long-term funds, say through bonds, and deploy the money to finance projects. The RBI group has not tackled this issue. As of now, there is no restriction on banks to float bonds.

These bonds (known as Tier-II bonds or subordinated debt) usually come at a cost exceeding the average cost of funds. The method is primarily used to improve capital adequacy ratio. Under the norms, Tier II capital — includes preference shares and investment fluctuation reserve — cannot exceed Tier-I capital (i.e., equity and free reserves). Understandably, banks abstain from raising such debt beyond a certain level.

The industry feels that RBI and the government will address the scope of banks to raise long-term funds. The international experience is that even with short-term funds banks are active up to seven-year maturity exposures. However, this is more because of the depth of the bond market in advanced economies and the various structured products available [newsletter.indiatimes.com, 25 October 2002].

First light for attophysics

Owing to the invention of an attosecond (as) X-ray source, physicists measure directly the decay of an electron cloud in a core-excited atom for the first time. Physicists in Germany and Austria have performed the first experiments with an attosecond (as, 10^{-18}s) light source. The ultrashort pulses allowed Markus Drescher and colleagues at the University of Bielefeld to investigate the rearrangement of an electron cloud around a krypton atom using pump-probe spectroscopy [Nature, 419 (2002) 805].

In the experiment, the X-ray pulse first ejects an electron out of an orbit close to the atom's nucleus. The Bielefeld team measured the time it took this vacancy to refill by carefully controlling the time delay between the X-ray pump and subsequent probe laser pulses.

This has not previously been feasible, as the decay processes in the electron cloud take just a few femtoseconds — and the fastest laser sources have similar pulse durations. However, the attosecond source recently developed by Ferenc Krausz and colleagues at the Vienna University of Technology (see related story) has opened up new possibilities for probing ultrafast atomic phenomena.

It is rather essential that the exciting X-ray pulse is much shorter than the decay process being investigated to achieve good temporal resolution according to Drescher. The pump pulse must be in the X-ray region because the pulse duration is fundamentally limited by its wavelength. The limit for visible pulses, given by the light oscillation period, is about 2.5 fs. For the X-ray source used in the experiment, the fundamental limit has been pushed to 40 as.

He told Optics.org that the next aim was to measure sub-femtosecond phenomena, such as ionization processes including two or more competing reaction pathways.

Commenting on the work in Nature, Brookhaven National Laboratory scientist Louis DiMauro likened the attosecond source to the shutter speed of a camera — but one which is fast enough to take a snapshot of electrons tumbling between energy levels close to the atom's nucleus.

There are few papers that announce the beginning of a new era, but this paper falls into that category according to DiMauro. With these experiments, we are entering a new realm of hyperfast measurement — the age of attophysics has begun (The author is technology editor of Opto and Laser Europe magazine). [Michael Hatcher, http://optics.org/articles/news/8/10/25/1].

Flying blind

The world is changing faster than our ability to measure it. Nobody knows anything. It is the one constant in Hollywood, immortalized in William Goldman's Adventures in the Screen Trade. Tinseltown may have more formulas than face-lifts, but nobody can confidently predict whether a picture will be Basic Instinct or Showgirls. Making movies is a crapshoot: differences invisible to investors and executives alike are enough to produce genius — or a total dog.
The titans of the silicon age continue to calculate the pace and direction of technological change, at fast and furious Internet speeds. But nobody knows what works. A century ago, business forecasting and economic policymaking were in roughly the same situation. Nobody knew anything quantitative, nobody knew anything reliable. This void called forth a response: Bureaus of Labor Statistics and Economic Analysis were born, along with think tanks and national income accountants. Their data collection and analysis efforts made available manufacturing surveys, productivity estimates, and consumer price index reports, the statistics that to this day define an economy. And, for a while, it kind of worked.

But then came the information age—Past industrial revolutions—steel, e.g. or the coming of mass production to the automobile—had seen explosions of technology that drove prices of key commodities (train rails, the Model T) down by 5-10 per cent/year for one, two, or three decades. The price of computation, according to Yale’s Bill Nordhaus, has dropped 42 per cent/year over 60 years—a trillion-fold fall since 1940.

Today’s technological revolution has so far lasted 2-6 times as long as the previous revolutions. It is between five and ten times as fast. And it is a larger share of the economy. It changes what people do in their work, where it is done, and even what economic activity is. The problem: One is not sure how. Spare a thought for Alan Greenspan—negotiating a soft landing is even harder when one does not know where the statistical ground is.

Suppose one needs to know the volume of Internet traffic. A company like Telegeography will provide beautiful information graphics and statistics on capacity. The University of Minnesota’s Andrew Odlyzko will say that Internet traffic each year is 1.75 times as much as it had been the year before, and that data traffic will become a larger share of telecommunications than voice traffic sometime in the next several years. But what one really wants to know is not the capacity but its use. And the difference between 70 and 150 per cent annual growth (let alone the 16-fold increase claimed by ex-WorldCom executives) is the difference between prosperity and bankruptcy for multibillion-dollar companies [see After the Gold Rush, pp. 194].

Say one wants to know the size of the Web. Netcraft will tell you about the 35 million Web servers it can find, and explain that after growing from 1-35 million in the previous 5 years the number has fallen in the past two months. Netcraft cannot tell, however, whether a Web server is a shared slice of a single computer, or 20 different computers networked together. And Netcraft cannot also tell how busy those Web servers are.

Just four years ago, it mattered less that nobody knew anything. Tech growth was faster than anybody could handle, and the right strategy was to throw as many resources into the sector as one could. But now the first phase of explosive growth is over, and a great deal hinges on being able to form a coherent picture of what high technology will be like five or ten years down the road. One does neither want to invest too much and create the equivalent of the fiber glut elsewhere in the economy, nor want to invest too little and fail to grasp the opportunities.

What one tries to know is not the capacity, but its use — One may try to tease out a partial picture of what is happening by combining individual pieces of information and extrapolating. It turns out the most reliable pieces are not those about quantities, but prices. Intel and AMD are confident that for this decade at least they will continue to deliver double the microprocessor power at the same cost every two years. Disk drive manufacturers: double the storage every 15 months. Memory manufacturers: double the memory every 18 months. As telecommunications companies flame out, go bankrupt, and get recapitalized, the price of intermediate (not last-mile) connectivity will fall rapidly and reliably, too.

It is known very well how fast the information-processing and information-producing capabilities are growing. However, how they will be used is not known, and how valuable those uses will turn out to be, and how rapidly they will diffuse are also not known. Like talking pictures or the railroad before it, the Internet changes everything. If only one could understand how [J Bradford DeLong (www.j-bradford-delong.net), wirednews, issue10.11, November 2002].
Powerful collider—goal of physicists worldwide

As Stanford Linear Accelerator Center enters its fifth decade, it is helping to shape a revolutionary new way of doing particle physics. The laboratory, which stretches for more than two miles through the foothills above Menlo Park, is known for its discovery of some of the fundamental building blocks of matter—discoveries that led to three Nobel prizes.

Now it is helping to launch a project whose size, scope and international flavor are unlike anything before. It involves:

- A machine 20 miles long and 100 feet below ground.
- Thousands of scientists using it to carry out experiments.
- The possibility of operating the machine from thousands of miles away—perhaps passing the baton from continent to continent, with Europe running it for one shift per day, North America the next and Asia the third.
- Collisions between some of nature’s most fundamental particles that are 10-times more energetic than ever achieved. In the debris from those collisions, researchers hope to gain new insights into what makes the universe tick.

The project is known as the International Linear Collider, a new atom-smashing center that would help take SLAC’s work to the next level. Scientists hope it will shed light on some burning questions in physics: Why do particles have mass? Does the universe have more than four dimensions? What is dark matter, the mysterious stuff that appears to predominate over the ordinary matter seen all around?

The collider is the next step, the next tool, needed to answer the question, *What is the world made of at the most fundamental level?* according to Persis Drell, Director of Research at SLAC.

Still a dream—At this point, the collider is still a dream. Its design and site have not been chosen, although possible locations have been scouted in the Central Valley of California, Illinois and near Hamburg, Germany.

But the dream may be nearing reality, as researchers from dozens of countries rush to work out the remaining bugs in the technology and persuade their governments to chip in money toward building it. The cost is estimated, very roughly, at $6-$8 billion.

It is a grass-roots effort according to Maury Tigner of Cornell University, Chairman of an International Steering Committee that is overseeing the project. The interested scientists in each of the regions have organized themselves spontaneously to look at the scientific and technical challenges.

Particle physics has long been one of the most collaborative sciences as the equipment needed to smash particles together and discover their secrets has grown so big, expensive and technically challenging that no single country can do it alone. It is not unusual for hundreds of scientists to work on a single experiment, e.g., one current project at SLAC involves 556 scientists, half of them from outside the US.

But the International Linear Collider takes things to a new level. Rather than originating in a single country or region, it sprang up spontaneously among scientists in North America, Europe and Japan. All decided that the collider was the top priority project for the next two decades. The concept has been under study at SLAC for 20 y. The lab was home to the world’s only full-scale linear collider, which ran from 1988 to 1998; when it shut down, SLAC moved on to other projects.

To get the full benefit from the new linear collider, construction would have to start within two or three years. This would allow the collider to work in tandem with another large particle accelerator, the Large Hadron Collider, that is scheduled to open near Geneva in 2007. Like tag-team wrestlers, the two machines would jointly pry more information out of the world of subatomic particles than either could alone.

One of the two top competing designs for the collider is being developed at SLAC in collaboration with a Japanese laboratory. The other is being drawn up by an international collaboration led by the German Electron Synchrotron in Hamburg, which is known by its German acronym, DESY.

Flagship laboratory—Early this year, a high-level panel that advises the US Department of Energy said the US should make the new linear collider its top priority in particle physics. It recommended that the government mount a campaign to have the machine built here. While it could be remotely operated, allowing scientists from all over the world
to fully participate, there are distinct advantages to having it close by, the panel said.

The project would give the US a flagship international laboratory for fundamental physics and ensure the US leadership in one of the forefront scientific activities of the 21st century according to the panel. If history is any guide, the cutting-edge technology developed for the collider would eventually trickle down to industry, generating significant economic returns on the initial investment. The World Wide Web, for instance, was born at a particle accelerator near Geneva, and the first Web site in the US was at SLAC.

The cost—The panel estimated that if the collider were built here, the US would bear about two-thirds of the cost, part of which would have to come from cutting other physics projects.

If it is built somewhere else, the panel said, the US should participate as fully as possible, necessitating a 10 per cent increase in the budget for particle physics research. However, the country faces stiff competition from Germany, which in some respects is much farther along.

Both SLAC and the German laboratory have built small-scale versions of their machines for testing. But the German laboratory has mapped out a path for its machine, which would run north from Hamburg, and has started to talk to local officials along the route about getting approval to construct it. It has submitted a formal proposal to the German government, and last week issued a detailed description of how the project could be organized.

In this connection timeliness is absolutely important according to Albrecht Wagner, Director-General of DESY. The site in the end will be decided by the politicians. What he has has been telling the politicians is that, of course, it is a good thing to have it in Germany, but he would participate with DESY wherever the machine is built.

The SLAC team, meanwhile, has been scouting potential sites near the Fermi National Accelerator Laboratory in Illinois and along the western edge of the Central Valley in California. Two possibilities: between Tracy and Merced along Interstate 5, and north of Woodland.

Early strategy stages—David Burke, Director of the linear collider study at SLAC, said the search for a site is in a very early stage. One possible strategy would be to put the collider in one of the thin, narrow strips already defined by power transmission lines or aqueducts. It might simplify the process of getting approvals while giving the collider ready access to water and power. When fully operating, it is expected to use about 200 MW of power—enough to run 150,000 homes.

Jonathan Dorfan, the Director of SLAC, said the next linear collider is just one of several projects the lab is counting on to carry it into the next decades. But it is a critical part of the laboratory’s future; no matter which design is chosen or where the collider is built, he expects SLAC to be intimately involved in its design, building and operation [Glenda Chui, gchui@sjmercury.com, (408) 920-5453]

Moon-based solar power on Earth

The key to a prosperous world is clean, safe, low-cost electrical energy, according to University of Houston physicist David Criswell. And his idea for how to get it is literally out of this world.

For more than 20 y, Criswell has been formulating plans and justification for building bases on moon to collect solar energy and beam it through space for use by electricity-hungry Earthlings.

Prosperity for everyone on Earth requires a sustainable source of electricity. The World Energy Council, a global multi-energy organization that promotes the sustainable supply and use of energy for the greatest benefit of all agrees with it. The WEC’s primary message is that affordable modern energy services for everyone—including the two billion people who have no access to commercial energy—are a key to sustainable development and peace throughout the world.

Criswell estimates that by 2050 A D, a prosperous population of 10 billion would require about 20 TW power, or about 3-5 times the amount of commercial power currently produced.

The moon receives more than 13,000 terawatts of solar power, and harnessing just one per cent could satisfy Earth’s power needs. The challenge is to build a commercial system that can extract a tiny portion of the immense solar power available and deliver it to consumers on earth at a reasonable price.
The first priority is to make people realize that the lunar power system may be the only option for sustainable global prosperity on Earth. Criswell contributed a chapter to a new book, *Innovative Solutions for CO₂ Stabilization* (July, 2002), which addresses major aspects of sustainability and global commercial power.

Criswell's lunar-based system to supply solar power to Earth, is based on building large banks of solar cells on the moon to collect sunlight and send it back to receivers on Earth via a microwave beam. Solar cells gather sunlight and convert it into usable electricity. The microwave energy collected on Earth is then converted to electricity that can be fed into the local electric grid.

Such a system could easily supply the 20 terawatts or more of electricity required by 10 billion people according to Criswell. The system is environmentally friendly, safe to humans, and reliable since it is not affected by clouds or rain, either on the Earth or the moon as the latter has no weather.

The moon continuously receives sunlight, except once a year for about three hours during a full lunar eclipse, when stored energy could be used to maintain power on Earth.

The system could be built on moon from lunar materials and operated there and Earth using existing technologies, which would greatly reduce the cost of the operation. He estimates that a lunar solar power system could begin delivering commercial power about 10 y after program start-up.

Technology under development at UH increases the options for successfully building a lunar power base. UH researchers at the Texas Center for Superconductivity and Advanced Materials (TcSAM) are developing nanotechnology techniques that could transform the lunar soil into solar cells.

The raw materials needed to make solar cells are present in the moon's regolith according to Alex. Freundlich, Professor of Physics, who has examined lunar material to determine whether it contains the necessary ingredients for making solar cells. He, along with Charles Horton, Alex Ignatiev, Director of TcSAM, and a team of NASA-JSC and industry scientists also have used *simulated* moon soil to determine how to go about manufacturing the solar cell devices on the moon.

The plan is to use an autonomous lunar rover to move across the moon's surface, to melt the regolith into a very thin film of glass and then to deposit thin film solar cells on that lunar glass substrate. An array of such lunar solar cells could be used as a giant solar energy converter generating electricity.

Criswell began thinking about lunar-based power systems more than 20 y ago when he was an administrator at the Lunar Science Institute, now the Lunar and Planetary Institute. For about seven years at the institute, Criswell was responsible for reviewing nearly 3,400 NASA proposals for lunar science projects. He got to know the peer-review process and learned about all aspects of lunar science.

For the past 10 y, Criswell has been Director of UH's Institute for Space Systems Operations, which receives funding from the state for space-related research projects conducted by faculty and students at UH and UH-Clear Lake in conjunction with NASA-Johnson Space Center (http://isso.uh.edu). For further information contact: Amanda Siegfried, 713/743-8192 (office), 713/605-1757 (pager), asiegfried@uh.edu [http://www.globaltechnoscan.com/17thOct-23°Oct 02/solar_power.htm].

**Breakthrough mass spectrometry technology for a better proteome analysis in days**

A scientist at the Pacific Northwest National Laboratory saw his 15-y *big gamble* pay off in record-breaking results in proteome analysis using a new high-throughput method of mass spectrometry.

*D. radiodurans* is of interest because of its potential to degrade radioactive materials, its ability to withstand high levels of radiation and its impressive DNA repair capabilities. The Guinness Book of World Records calls it "the world's toughest bacterium".
The new instrumentation, a high-throughput technology that uses very high-pressure capillary liquid chromatography (LC) combined with a unique form of Fourier transform ion cyclotron resonance (FTICR) mass spectrometry was conceived by Battelle Fellow and Chief Scientist Dick Smith. The breakthrough technology enabled Smith's research team collaborate with Deinococcus radiodurans experts from Louisiana State University, Baton Rouge, and the Uniformed Services University of the Health Sciences, Bethesda, to identify more than 61 per cent of the predicted proteome (more than 1900 of the almost 3200 proteins predicted) of D. radiodurans, a radiation-resistant bacterium. These results represent the broadest coverage of any organism to date.

A proteome is the collection of proteins that make up a cell (or organism) under a specific set of conditions at a specific time. Studying the amount of each protein present at any time has become more important as scientists attempt to learn which proteins are involved in important cellular functions. DOE's Microbial Genome Program, an element of the Genomes to Life Program, provided the genomic information for various microorganisms, including D. radiodurans, and developed ways to predict the set of possible proteins, which hold the key to why and how these microbes carry out different functions.

They were able to see more proteins, especially those that existed in small quantities as evident from a recent study [Proc Natl Acad Sci, 20 August 2002] as their coverage was unprecedented. With this, they provide biologists with protein-level information they never had access to before.

Before Smith's team developed the high-throughput method of mass spectrometry, it took scientists 2-3 y to analyze a proteome with much less accuracy and depth than the recently completed analysis of D. radiodurans. With the high-throughput instrumentation and systems, Smith's team can now complete 5-6 such analyses of proteins of a proteome in a day with sensitivities 100 times greater than other methods.

Paradigm shift—The dramatic improvements in the high-throughput instrumentation and system over the old methods are a direct result of Smith's taking an entirely different research path to the innovative design.

Smith, the principal investigator and leader of a multidisciplinary team of researchers, has been aiming at doing it for about 20 y. He is supported through the Office of Science's user facility at PNNL—the William R Wiley Environmental Molecular Sciences Laboratory (EMSL). Years ago a lot of choices were made that were big gambles when they designed and selected the kinds of instruments they would develop for the EMSL.

Smith based his vision on using mass spectrometry to make biological measurements, when the conventional method had been (and still is in most laboratories) separations using two-dimensional gels to analyze a proteome. The two-dimensional gels are much less expensive than the present instrumentation, but suffer from limitations in protein coverage and the ability to detect low-level proteins. While the conventional approach can detect many of the more abundant proteins, an extremely time-consuming second stage of analysis called tandem mass spectrometry (MS/MS) is required for the identification of each protein.

When Smith began his research, mass spectrometry had never been used for making the kinds of biological measurements made today because there was no way to transport protein ions into a very high vacuum required for mass spectrometry. The ions were too large.

Smith's team solved the problem in 1985 by using electrospray ionization, a technique that ultimately would allow almost any protein to be studied using mass spectrometry. The electrospray ionization interface coupled separations (capillary electrophoresis in their initial work) with mass spectrometry to open the door for ultra-sensitive studies of biological mixtures. With the mass spectrometer interface problem solved, the team channeled their efforts into developing a better spectrometer. The new ionization method combined with further development of the then fledgling FTICR technology would allow biological systems to be studied in unprecedented detail.

The conventional approach requires something 10-50 times as many analyses to get the wanted information according to Smith. With the high quality of the FTICR, this extra step (tandem mass spectrometry) could be eliminated. Thus, we can not only study the proteome for an organism much faster.
but also with a much smaller protein sample—often a very important consideration in biological measurements." Added to this, Smith's new approach enables researchers to see most or all of the proteome—something that has been missing until now, regardless of the effort applied.

In addition to speeding up the process, Smith and team have recently invented a process called DREAMS (Dynamic Range Enhancement Applied to Mass Spectrometry) as a way to detect low-level proteins much more effectively. Low-level proteins can be important for cell signaling in key cellular functions and other important biological processes. DREAMS functions as a part of the FTICR instrumentation and allows researchers to extend the range between the most abundant and least abundant protein that will be detectable, thus allowing the mass spectrometer to look more deeply into the proteome.

What is now created is like the Model T of this technology that is a long way to go. But the Model T was a paradigm shift for modern travel in its day according to Smith. Now, it is a different era—one can study many different organisms and make many, many more measurements of the proteomes of those organisms than one ever could have before, and that is where interesting things can be learnt.

For example, to identify proteins involved in various functions like DNA repair, Lipton and team exposed *D. radiodurans* to several stresses and environments: heat shock; cold shock; exposure to chemicals that damage DNA such as trichloroethylene; exposure to ionizing radiation; and starvation. They were able to identify many proteins previously only hypothesized to exist on the basis of DNA information and also proteins that seemed to have little function. New proteins that became active only during a specific condition also were identified, as were proteins that appeared to exist all the time.

Making the measurement just once is not enough. It is necessary to make hundreds of measurements for an organism and to see how it responds to different changes. Essentially, all changes in a person are reflected by changes to the proteome. By making sets of such measurements one may learn about the role of each protein part of the proteome. If applied to the human proteome, which is a much bigger problem than the microbes currently being studied, such measurements can provide a molecular level understanding of diseases and a basis for much better and faster drug development, for example.

**Next steps**—It is really a significant breakthrough and according to Smith, who is the first to point out that the analyses they have made of the proteome of *D radiodurans* is just the first step in a long-term goal.

The next step is already underway—Smith's team has developed a prototype high-throughput version of the instrumentation that is automated and more robust. Scientists have previously considered FTICR to be difficult to use, said Smith. In response, the PNNL team developed a user-friendlier, automated version of the FTICR.

To build this system, they started with a 9.4 tesla FTICR system manufactured by Massachusetts-based Bruker Daltonics Inc. Then, they modified about half the system using technology developed at PNNL, including the electrospray ionization, an ion funnel technology, and DREAMS. The result is a reliable and powerful automated system.

The payoffs are potentially mind-boggling. The idea is not just to just understand *D. radiodurans*, but apply the technology to a range of important biological problems.

In the near future this will involve studies that center on microbes of interest to the DOE. It also has the potential to be applied to understanding human response to drugs—the detailed molecular changes...
that occur, for example, in cancer progression—and essentially almost every area of biomedical and health-related research. Proteome studies can also reveal the important proteins involved with a specific disease and the roles they play. Pharmaceutical laboratories developing new drugs may be able to design drugs to target these specific proteins.

This is an area where the rational laboratories really have a role to play. Right now the technology is just too expensive for others to develop, and the data production rate and its management is too large and too complex for most organizations to manage and use effectively. Additionally, the technology is still in its infancy, and as powerful as it is already, it will benefit from a series of advances planned to implement over the next few years.


A clearer view of crystal growing

As technology progresses toward ever finer microelectronic structures, the wavelength of the ultraviolet radiation used to depict them has to be shortened. The emerging generation of photolithographic processes works at 157 nanometers—a wavelength at which glass and even quartz glass are not transparent enough. The preferred material here is extremely pure low-defect, single-crystal calcium fluoride (mineralogically: fluorite or fluor spar).

In the form of lenses or prisms, it can concentrate and deflect UV at down to about 130 nm. Its refractive behavior should be as uniform as possible, so as not to lessen the quality of chip structures.

Anyone who has ever tried to grow large, perfect crystals from aqueous salt solutions foresees: The difficulties multiply when one flawless mono crystal has to be bred from the molten substance at temperatures of over 1400 °C. To determine the ideal process conditions and optimize the production plant, the Device Technology Department of the Fraunhofer Institute for Integrated Circuits IIS developed the computer program CrySVU. With the help of this program, since 1998, the Institute’s industrial partner Schott Lithotec has advanced to become the world’s leading manufacturer of calcium fluoride crystals.

“The crucial factor is to know the temperature distribution during the crystal growth process,” emphasizes Georg Müller, who heads the crystallography laboratory. “As in glassmaking, the molten mass has to cool down in a controlled manner, to prevent areas of thermal tension. Like streaks or reams in glass, such defects reduce optical quality.” In order to obtain a better understanding of the interactions between process conditions and material properties, the team built a crystal-growing apparatus which they used to investigate such factors as the effect of temperature distribution on the final quality of the single crystal.

This experimental work enabled them to produce an improved computational model, which provides results that deviate by only one per cent from the experimental data. Müller explains why: “The old standard model used an inaccurate description of heat transfer by infrared radiation inside the calcium fluoride. The improved model now delivers more precise information: It is even capable of predicting the form of the phase boundary between the melt and the growing solid crystal, which is a highly influential factor on crystal quality.” The impressive reward for their efforts is a completely transparent, colorless crystal cylinder, measuring 15 cm across and in length.

For further information: Prof. Georg Müller, Phone: +49 91 31 / 7 61-3 44, Fax +49 91 31 / 7 61-3 12; and Jochen Friedrich, Phone +49 91 31 / 7 61-3 44. Fraunhofer-Institut für Integrierte Schaltungen IIS-B, Bereich Baulelementetechnologie, Schottkistraße 10, 91058 Erlangen, Germany [http://www.globaltechnoscan.com/17thOct-23rdOct02/crystal_growing.htm].

New light on advanced materials

A unique, compact furnace combined with high-energy X-rays is giving researchers at Ames Laboratory the unprecedented ability to directly record the chemical and structural changes of complex
materials at high temperatures under real processing conditions.

This information is crucial to understanding and controlling the composition and microstructure of new materials. It previously took months or years to collect such data through the laborious process of heating, quenching, and then analyzing numerous samples. But the Ames Lab researchers can now gather the data in just a few days while getting a more detailed picture of what happens to a material's crystal structure as it heats and cools.

The new system is ideal for complex materials such as structural ceramics, superconducting wires and nanostructured materials. The insights gained through the Ames Lab system may speed the development of new materials for use in fields such as aerospace engineering, electrical distribution systems and microelectronics.

The furnace uses an analytical technique known as X-ray diffraction in which an X-ray beam is focused on a small sample of material. The beam is diffracted by the crystal structure of each material, producing a unique pattern of concentric circles, called Debye rings. By capturing images of the changes in the ring pattern as the material is heated and cooled, scientists gain a better fundamental understanding of what happens to the material's crystal structure at various temperatures.

In 1997, Kramer began working with senior materials scientist Bill McCallum, senior physicist Alan Goldman, assistant metallurgist Kevin Dennis and then-Ames Lab graduate student Larry Margulies on a design for a compact, portable furnace that would enable them to rotate samples during an experiment. They also wanted to be able to subject the samples to a variety of environments, such as inert or oxidizing atmospheres, encountered in processing conditions.

What emerged was a scaled-down version of the standard laboratory tube furnace, measuring about 18 in long and 6 in diam and capable of heating samples to 1,500 C (2,732 F). The furnace has an indirect, magnetic coupling system that connects to a motor shaft, which rotates the sample.

Samples are held at the end of a long tube and aligned with a 3 mm opening in the side of the furnace. The X-ray beam enters through the opening and the diffracted rays emerge through a slot in the case.

Kramer says the new system is an improvement over current high-temperature X-ray diffraction systems, in which samples rest on a flat plate. This does not allow the sample to be rotated and sometimes causes the liquid and solid phases of the material to draw apart. Also, the flat-plate systems don't always heat the sample uniformly, producing large temperature variations in the material that make it difficult to correlate the temperatures with changes in the crystal structure.

The excellent control over furnace means that one can select an exact temperature setting for measurement and know that the whole sample is at that temperature. And with the confined geometry, one can melt things and know that the liquid and solid are not separating.

In addition to the scientists who developed the furnace, the device has been used by Ames Lab scientists Doug Finnemore and Dan Sordelet as well as researchers at DOE's Brookhaven National Laboratory. The experiments are conducted at off-site facilities where high-energy X-rays of between 35-100 kV are available. Most of the experiments take place at the Advanced Photon Source at the Department of Energy's Argonne National Laboratory near Chicago and the Cornell High Energy Synchrotron Source in New York.

At Argonne's APS facility, the furnace has now found a home on a sector reserved for the Midwest Universities Collaborative Access Team, which is operated by Ames Lab and Iowa State University.

Before an experiment begins, the furnace must be aligned with the X-ray beam—a painstaking process because the beam itself is about 1 mm wide and 0.5 mm high. "That is the hard part," Kramer says. "The first time we did this, it took us three days to align the furnace to the beam and then another hour or two to align the sample to the beam itself. But we've gotten the process down well enough now that it only takes us about a half a day to line it up and minutes to put the sample in."

The researchers have also found that shuttering the beam, rather than using a continuous ray, enables them to take better sequential images from the diffracted rays. The reactions are monitored with a time resolution of less than 2 s, fast enough to make a virtual movie of images that capture the material's structural transformation during temperature-driven processing.
Kramer adds that colleagues at Argonne and the European Synchrotron Research Facilities have asked about having Ames Lab build similar furnaces for them. He notes that the Ames Lab group is also willing to let other researchers use the furnace. For more information contact: Matt Kramer, (515) 294-0276, mj.kramer@ameslab.gov [Susan Dieterle, http://www.globaltechnoscan.com/17thOct-23rdOct02/advanced_materials.htm].

Bran filters chlorinated hydrocarbons and arsenic out of waste water

Researchers of Fraunhofer IGB together with GUTec mbH have succeeded in filtering carcinogenic substances out of industrial waste water with bio-adsorbers using bran. Compounds of arsenic and hexachlorocyclohexane (HCHs) previously occurred above all in the production of pesticides. Pesticides containing HCHs have been prohibited in Germany since the 1980s. Arsenic is still used in the semiconductor and glass industries and pollutes water and the soil in many places. Since HCHs and arsenic are carcinogenic substances and can cause organ damage, very strict limit values apply to their presence in water, soil and the air. Water leaking from dumps and old production sites often greatly exceeds these limit values. Producers therefore cannot dispose of waste water containing HCH or arsenic without pretreatment.

In collaboration with GUTec mbH, the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) has developed a mobile HCH and arsenic treatment system for a large chemicals company. It combines an electrochemical process with bio-adsorbers made from chemically modified bran. “You can get bran from grain mills for a few Euros per metric hundredweight. We modify it chemically and use its hydrophobic properties, so that it can bind the toxic substances”, reports Dr. Manfred Kühn of Fraunhofer IGB.

With the aid of the newly developed system, arsenic can be bound almost completely, apart from 0.004 mg/L, and hexachlorocyclohexane can be bound apart from 0.13 μg/L. Thus, we can reduce the concentration far below the statutory limit values of these pollutants for disposing waste water. In order to use the bio-adsorber a number of times, it is possible to desorb the arsenic and the hexachlorocyclohexane. However, disposal by means of combustion or composting is more economical.

The system is highly flexible as far as the process is concerned: At 2.5 m long, 1.3 m wide and 2 m high, it can be used at different locations. It can be operated continuously fully automatically as well as in batch mode.

The arsenic and HCH treatment plant is already being operated by our client on a semi-industrial scale. Additional systems with bio-adsorbers that originate from the collaboration between Fraunhofer IGB and GUTec mbH have for several years been used successfully to remove heavy metals such as copper, lead, cadmium, zinc and chrome.

For further information contact: Henrike Henschen, Fraunhofer Institut für Grenzflächen- und Biowerfahrenstechnik IGB, info@igb.fhg.de, +49/711/790-4031 [http://www.globaltechnoscan.com/17thOct-23rdOct02/bran_filters.htm].

Stanford researchers sharply cut risks of gene therapy

Researchers at Stanford University Medical Center have devised a new gene therapy technique that appears to eliminate one of the major health risks linked to gene therapy. The technique [Nature Biotechnol, 15 October 2002] overcomes the need for viral vectors that have plagued gene therapy trials, while retaining the ability to insert therapeutic DNA into specific sites in the chromosomes. The approach provides an alternative that did not exist before.

The goal of gene therapy is to insert a healthy copy of a gene into a cell where it can take over for a faulty version. If the therapeutic DNA does not integrate into the human chromosome, it produces its protein for a short time before being turned off or broken down within the cell. For a long-term cure, the gene has to wedge itself into a chromosome where it remains indefinitely integrated, getting passed on when the cell divides.

Current gene therapy approaches that cause genes to integrate use a viral vector to sneak the therapeutic DNA into the host cell. However, the
DNA inserts itself into the chromosome at random positions. In one recent French gene therapy trial, the randomly inserted DNA apparently activated a neighboring oncogene, causing a patient to develop leukemia. That sort of puts another cloud over the existing gene therapy trials.

Calos' technique avoids the pitfalls of other gene therapy approaches by integrating DNA without using viral vectors, inserting the DNA at known locations. This new technique can also handle genes that are too large to fit into a viral package, such as the gene for Duchenne's muscular dystrophy.

In developing this new approach, Calos used a mechanism used by a bacteria-infecting virus (called a bacteriophage) to integrate its genes into bacteria. The bacteriophage makes a protein called integrase that inserts the viral genes into a specific DNA sequence on the bacteria chromosome. It turns out that humans also have a version of that DNA sequence. When the researchers insert a copy of the therapeutic gene and a gene coding for integrase into a human cell, the integrase inserts the gene within the human sequence.

Within a week, mice that received this injection made 12-times more Factor IX than their littermates that received the injection without the integrase. Further experiments confirmed that the Factor IX gene had successfully integrated into the mouse DNA.

Although the mouse genome contains at least 53 potential integration sites, Calos and her team found the Factor IX gene in only two locations, with one location by far the more common. She said that for each tissue there may be a particular site that is the most likely insertion point. Her group is testing the technique in different tissue types to ensure that no human integration site is near a potential oncogene.

Calos is also modifying the integrase so it targets specific integration sites that her team knows are safe. The enzyme has been mutated and evolved by them so it will prefer one place over another. Her approach should be effective for treating diseases in several different human organs including skin, retina, blood, muscle and lung. She hopes to start human trials for the technique in a fatal childhood skin disease called recessive dystrophic epidermolysis bullosa, which she has already treated in mice. If that trial shows that it is safe then that will open the door for trials in other diseases as well. She has collaborations underway testing the technique for use in Duchenne's muscular dystrophy and cystic fibrosis, among others.

For more information contact: Amy Adams, amyadams@stanford.edu, 650-723-3900, Stanford University Medical Center [http://www.globalechnoscan.org/17thOct-23rdOct02/gene_therapy.htm].

Use computer WIT to win structural genome race

With all of the known data and unknown variables involved in genome research, the computer is rapidly becoming a critical tool in linking a gene's structure to its function, and eventually putting that information to work aiding human life. Computer scientists have developed new bioinformatics tools that are available on the Internet. A relatively new science, bioinformatics uses computers to develop models of genes and proteins and their functions.

Five years ago everything was done by the experts according to Natalia Maltsev, leader of the Computational Biology Group in Argonne's Mathematics and Computer Science Division. Now there is a need to use automated programs because of the vast amount of genetic data out there to answer such questions as What are the functions of the genes encoded by the particular genomes? and What roles do genes play in the network of biochemical reactions that support the cell?

Argonne computer scientists developed a database system on the World Wide Web for researchers to compare their findings with detailed analyses of 39 sequenced genomes. Called WIT2, it is available at wit.mcs.anl.gov/ WIT2. The site has 3000-5000 visitors daily and about 20000 regular research users.

Argonne scientists are following up by creating the next generation of bioinformatics tools, WIT3. A prototype is on the Web and in partial use. WIT3 will be an interactive database on the Internet that stores
genomic and metabolic information to assist scientists in interpreting newly sequenced genomes. The database will be automated to speed the process of retrieving data and constructing models. WIT3 will eventually store all available sequenced genomes and 3230 functional metabolic diagrams.

A scientist using either WIT system can build his or her own model of an organism’s life processes. This model will predict how the organism derives energy from its environment, how it transports nutrients into its cells and how it builds its components. A researcher can also take a genetic sequence from an organism and compare it with sequences of other organisms in the database to find out how one organism evolved into others.

*Hosting enzyme and metabolic pathways*—Argonne hosts the public server of the Enzymes and Metabolic Pathways (EMP) database, the world’s largest publicly available database on the biochemistry of life. These data are available for public use via WIT.

Computer scientists plan to link WIT3 with laboratories to help biologists verify computer predictions of gene functions. Bioinformatics can significantly reduce the amount of effort in the wet lab, e.g., wet lab biologists can use the findings to help decide which enzymes to explore in detail. It can help them determine which enzymes are most interesting and why.

Maltsev and her group create static or theoretical models of an organism’s biochemistry in a process called *metabolic reconstruction*. They then try to determine how an organism’s genes are related to its metabolic pathways. The ultimate goal is to better understand how the organism works and how it can be changed.

When a particular gene or pathway stumps researchers, they look for similarities between the unknown gene and other genes in the database whose structures and functions are known. Everything in biology is reverse engineering, according to Maltsev. You are taking something that you do not know and comparing it with something known. And that is how you eventually discover the function of the gene. Argonne computational biologists have analyzed the whooping cough bacterium, *Bordetella pertussis*, and the diphtheria bacterium, *Corynebacterium diphtheriae*.

*Targets for antibiotics*—Maltsev’s group is working with the Structural Genomics Group in Argonne’s Biosciences Division to locate potential targets for antibiotics. By studying the genetic sequence, the Computational Biology Group identifies what genes and metabolic pathways are unique to pathogenic organisms. By attacking those unique structures, the antibiotic will not hurt the human host. The Structural Genomics group then uses protein crystallography to determine the three-dimensional structure of the proteins.

In addition to working with the Structural Genomics Group, computer scientists are collaborating with the Molecular Evolution Laboratory at the University of Chicago and Pacific Northwest National Laboratory.

For more information contact: Evelyn Brown (630/252-5510 or eabrown@anl.gov) at Argonne [http://www.globaltechnoscan.com/17thOct-23rdOct02/genome.htm].

**Electrons defeat anthrax**

Perhaps, bioterrorists will not be able to spread lethal bacteria of anthrax in envelopes all over the world. Siberian biologists and physicists have thought up how to adapt electron accelerator that is usually used for sterilizing medical equipment for decontamination of letters. To optimize the power of the accelerator they calculated how many bacteria could get into a human body when touching the letter infected and how many bacteria should be destroyed to avoid the tragedy.

For their experiment the scientists chose two bacteria species that form almost ineradicable spores. Both species were genetically close to anthrax. One of them is a harmless inhabitant of soils whereas the other causes a disease in insects. Its spores in the mixture with the powdered mineral kaolin can be used as insecticide. When imitating the probable actions of mail terrorists the scientists made 60 paper packets with the sides of 50 and 25 mm and poured a quarter of a gram of sterile kaolin. Then several drops of suspension, which contained 10 million spores per one milliliter, were added into each packet and intensively mixed with kaolin. Then the packets were dried at 70 °C and put into envelopes.
The samples were treated with an electron beam from the industrial electron accelerator. The doses applied were varied from 1 to 400 kGy. To find out the effect from a particular dose the powder with the bacteria was dissolved in distilled water and placed in culture medium. It turned out that the dose of 10 kGy killed a lot of spores. The scientists could not find any live microbes after treating the samples with the dose of 20 kGy and the dose of 400 kGy even made the paper destroy. It became fragile.

When you touch the powder about 50 mg of kaolin may remain on your fingers. However, the skin is better protected against penetrating the infection inside in comparison with the lungs. How much kaolin with the spores can a person breathe in? To find it out the researchers tore the envelopes open, placed the powder on a platter and collected the air polluted with a pump with a filter at a height of 30 cm above the platter for a minute. The operation was repeated three times and then the quantity of kaolin on the filter was determined chemically. According to the data obtained a person can breathe in 1-2 thousandth of a milligram of the powder.

Based on the results and the calculations, the scientists recommend irradiating the correspondence with a dose of about 50 kGy. However, to reduce the probability of infection from one letter to one case per million the dose of 22 kGy proved to be quite sufficient. The electron accelerator, which is produced at the Budker Institute of Nuclear Physics (Novosibirsk), can be used for this purpose. The accelerator weighs about ten tons and can be placed on the area of about 50 sq m. To protect the staff from radiation the accelerator is isolated with concrete layer of one and a half meter.

Electron accelerator can sterilize relatively thin objects. That is why the letters should be placed in one layer. According to the calculations the rate of sorting will remain within the norm if the number of staff doubles or the process of sorting is automated. The sterilization of parcels seems to be more complicated task. Only dangerous sources of gamma radiation are able to solve it. However, the biologists doubt that terrorists will start using parcels for their subversive activity and believe that electron accelerator can eliminate the problem of mail terrorism sufficiently.

For further information contact: Andrey Kudryavtsev, Budker Institute of Nuclear Physics, Siberian Division, Russian Academy of Sciences, pr. akademika Lavrent’eva 11, Novosibirsk, 630090 Russia, phone: +7 (383 2) 39 47 60, e-mail: A.M.Kudryavtsev@inp.nsk.su; Institute of Limnology, Siberian Division, Russian Academy of Sciences, ul. Lermontova 281, Irkutsk, 664033 Russia, e-mail: info@lin.irk.ru [http://www.globaltechno scan.com/17thOct-23rdOct02/anthrax.htm].

Bloodworm’s way with copper likely to provide paradigm for new materials

Researchers report [Science, 11 October 2002] the first detection of a living organism that makes a copper-containing mineral structure as part of its skeleton. The finding is remarkable because the amount of copper detected in the jaw tip of the marine bloodworm would normally be toxic to an organism. They determined that copper also occurs in non-mineral form in the bloodworm jaw where it may act as a structural element in cross-linking long chains of fibrous proteins. According to the authors, the marriage of protein with copper mineral as well as with bound copper ions is an intriguing conceptper se but may also serve as a design prototype for new materials that need to be hard, lightweight, and durable.

In addition, they found the non-mineral form of copper on the surface of the jaw canal through which venom is injected. That copper may be acting as a catalyst that activates venom being discharged by the worm into its prey.

The authors include University of California Biology Professor Herbert Waite and Chemistry and Materials Professor Galen Stucky. First author Helga Lichtenegger, who was trained in Austria as a physicist, approached Waite and Stucky about working with them on a research project. Waite dipped into a repository of promising projects, which he calls hisorphans, and suggested Glyceridaibranchiata—better known to fishermen as the common bloodworm, favorite bait for certain kinds of fish, according to Waite.

Back in 1980 two British investigators reported high levels of copper [up to 13 per cent by weight] and zinc in the jaws or fangs of two rather common
species of polychaete worms according to Waite, who studies mussels and fibers mussels make to attach themselves to stones in inter-tidal basins. The mussel fibers consist largely of proteins, but one per cent of their mass is metallic—copper, zinc, or iron. He has been trying to understand the role of these transition metals in those fibers. It is discovered that if the metals are leached out the structure weakens.

Because of Waite's long-standing interest in metals in mussel fibers, he had earmarked the 1980 report on the copper and zinc in blood-and clamworms as intriguing. Funding sources, however, failed to share Waite's enthusiasm for the worms. Supported by the Austrian Science Fund (Fonds zur Foerderung der wissenschaftlichen Forschung, FWF), Lichtenegger joined Waite and Stucky as a postdoctoral fellow at UCSB to study the worms despite the absence of specific funding for the project. They did not have enough preliminary information to justify independent funding for the project. It just seemed an interesting orphan.

Orphan though the genesis be, the progeny of the research are not. In addition to providing a possible paradigm for a new material system, other possible applications include, for instance, drug delivery. This research is an example of biomimetics, whereby an organism's biomolecular strategies for adaptation are studied and then employed to make new materials and devices. The paper focuses on the first step of determining and understanding the organism's biomolecular structures and raises even more tantalizing questions about them than it answers.

A skilled x-ray scattering specialist, Lichtenegger and another postdoc in Stucky's group in the UCSB Department of Chemistry and Biochemistry, Michael Bartl (also an author on the published paper), employed a full arsenal of high resolution imaging techniques to study the worms.

The thing that galvanized our attention was Helga's detection of copper biomineral at the bloodworm's jaw tip according to Waite. The 1980 findings gave no indication that the copper was associated with a mineral. As the authors state at the outset of the paper, Biomineralization is a major strategy for tissue hardening and manifests an astonishing diversity of bioceramic structures with exquisite microarchitectures that have specially adapted physical properties.

The bloodworm (10-15 in long) comes equipped with a proboscis not ordinarily visible. The proboscis is hydrostatically ejected—i.e., water pressure is used to extend it fast the way a paper noisemaker unfurls when blown. At the end of the fleshy red-pink proboscis are four black jaws that resemble in shape the thorns on a rose bush. The jaws at the end of the proboscis grab and bite prey the way four-pronged devices at the end of long poles are used to grasp and to pluck products from the high shelves of a grocery store. In contrast to the clamworm, the bloodworm's jaws are hollow, like syringes, and are used to conduct venom into the prey.

The researchers found that the jaw tip exhibits the ordered crystalline structure of the copper-based biomineral atacamite, Cu$_2$(OH)$_2$Cl, the first discovered instance of a copper biomineral in a living organism.

Though copper is needed in trace amounts for enzymatic processes, in greater quantities it is toxic. The research leaves raises questions. How does the worm collect all this copper and concentrate it in a safe form until it is invested in these jaws? What kind of biochemical pathways has this organism evolved to prevent copper toxicity, and what kind of protein carriers are there that bring it to the site of mineralization?

The bloodworm lives in the gravel of marine sediments and smells out its prey. The worm is going to miss its prey several times that means that its jaws are being abraded by gravel. So they need to be made of more robust material than the jaws of the clamworm, which is a scavenger and lives by grabbing things that have died.

The researchers found that the bloodworm's unmineralized copper as well as the copper biomineral is concentrated in the first half millimeter of the jaw. They discovered that the copper biomineral is organized in nanostructured fibers (about 50 nm diam) within a protein matrix, and that the fiber orientation within the tip is roughly parallel to its outer shape, according to the paper entitled High abrasion resistance with sparse mineralization: copper biomineral in worm jaws.

Through a complex procedure called nanoindentation (performed by the author Thomas Schöberl of the Erich Schmid Institute for Materials Science, Leoben, Austria), the researchers mapped...
hardness (H) and stiffness (E) with composition in the bloodworm jaw. They then determined that both hardness and stiffness increased with increasing mineral content.

The question as to why the bloodworm selects copper for its jaws is very puzzling; most other organisms mineralize with calcium phosphate/calcium carbonate. And in all those other calcium-based biting, chewing, fighting structures, the mineral to protein ratio is more like 10 to 1. That is also true for enamel (the biting surface of teeth) and for the tips of serpent fangs. Most other organisms make bioceramics in which a gossamer protein scaffold is mineralized with ordered arrays of inorganic components with certain geometries such that the combination provides for wear resistance. But this worm turns that paradigm on its head. It makes a structure that is 10 parts protein and one part mineral and exploits that structure for wear resistance. If you want to make something hard, how do you do it with a preponderance of protein? The worm appears to do it by adding copper!

UCSB Materials Professor Frank Zok helped to clarify the cleverness of that strategy exhibited by the bloodworm by suggesting a more mathematically complex understanding of wear resistance than the team had been employing. Relying just on hardness and stiffness values had led the team to conclude that the copper biomineral does not compare favorably with other bioceramics. Schöerl, however, had noticed that the hardness to stiffness ratio in bloodworm jaws was higher than in other known mineralized tissue. Zok suggested that this was indicative of a high abrasion resistance, commonly understood as equal to hardness to the three halves divided by stiffness $[H^{3/2}/E]$. 

With the worm it is that quotient that is revealing rather than individual hardness and stiffness measurements. So when you look at that quotient, the wear resistance value is very close to the best materials we can make. But high values for H and E also correlate with the presence of copper, even where the copper is not in mineral form. Lichtenegger's analysis of the distribution of copper in the bloodworm jaw suggested that about half the copper was in a biomineral form and half in the form of copper aggregates. That finding particularly interested Waite.

The proteins in invertebrate jaws and particularly in the jaw tips are not complicated. They have generally just two types of amino acids, glycine and histidine. These two amino acids probably repeat in a precise chainlike sequence. In this respect it is one of Nature's closest analogues to synthetic polymer molecules. It is expected that the copper cation in the bloodworm jaw plays a role in the cross-linking of these amino acid chains.

So the copper contributes two ways — in mineral form and in cross-linking — to make the jaw material strong and tough. Finally, the authors raise the possibility that copper may mediate the activation of venom during injection.

Storing venom in non-toxic form that is being catalytically activated as it passes through this syringe may afford us a model for delivering an unstable chemical by activating a stable form of it as part of the parting shot. Among the applications he envisions is a system for delivery of unstable drugs—those with a short shelf life. We may be able to synthesize the drug in a precursor form and have that last important step done as part of delivery.

Stucky, who is an expert on the molecular assembly of organic and inorganic species into three-dimensional, hierarchically patterned materials and whose research group has extensively studied marine organism biomineralization, is a participant in the California NanoSystems Institute (CNSI). Waite is a participant in UCSB's Marine Science Institute (MSI).

For further information contact: Jacquelyn Savani, jsavani@engineering.ucsb.edu, 805-893-4301, University of California [Santa Barbara, http://www.globaltechnoscan.com/17thOct-23rdOct02/bloodworm.htm].

Global warming increases disease risk

Increase in temperature does not create environmental problems, but a new report from Andrew Dobson of Princeton University shows global warming could make one sick also. A rise in infectious disease outbreaks among plants and animals across the globe associated with changing weather patterns could soon spread to humans.
Climate change is disrupting natural ecosystems as it has made life easier for infectious diseases. The accumulation of evidence has made humans extremely worried. The diseases are shared with some of these species. The risk for humans is going up.

Researchers analyzed disease epidemics among plants and animals on land and in the oceans. Then they looked at ways that changes in temperature or climate could influence these trends and what that may mean for humans.

Researchers documented examples of disease-carrying bacteria, viruses, and fungi that develop more rapidly under warm conditions. As the temperatures rise, these disease carriers may spread to new areas and have potentially dangerous effects on the native ecosystems, wildlife, and even humans.

According to Richard Otsfeld from the Institute of Ecosystem Studies in Millbrook, New York, this is neither just a question of coral bleaching for a few marine ecologists nor just a question of malaria for a few health officials — the number of similar increases in disease incidence is astonishing.

Cold winter months normally act as a safeguard against the growth of dangerous viruses and bacteria by killing them off each season. But as global warming makes winters shorter and summers larger, these organisms can grow unstratified for longer periods.

According to Dobson, global warming may have the most dramatic effect on diseases that are spread by insects, such as malaria. As the temperatures rise, the insects that carry these diseases in the tropics that spreads across larger areas.

Although tropical regions have a greater variety of species that can keep these insects in check, other regions do not — slowing the diseases to spread more easily [http://content.health.msn.com].

Polymerization reactions using pressure and laser light

Chemical reactions can be induced at high pressure. Many reactions can also be induced by photosynthesis. Roberto Bini and coworkers at the University of Florence and the European Laboratory for the non-linear spectroscopy in Italy, have worked out a method that takes the advantage of both phenomena. Bini’s group has been using FTIR spectroscopy to monitor the behaviour of unsaturated compounds under pressure in a diamond anvil cell.

The researchers observe that butadiene dimerizes for several days at 0.7 gp, primarily producing vinylcyclohexane via cycloaddition. But when the pressurized sample is irradiated with a 488-nm laser beam, dimerization is completely inhibited and highly stereoregular trans-polybutadiene is formed in quantitative yield.

Generally, butadiene polymerization is a high temperature catalytic process that results in a mix of both trans- and cis-isomers.

In the new experiment, Bini believes that the pressure forces the molecules to align and that the laser light selectively directs them into a specific electronic state that leads to the polymer. Increase in the light energy allows faster reactions at lower pressures, potentially leading to practical green chemistry “without the use of solvents, catalysts, and radical initiators” [Chem Eng News, 80 (11) 2002 p. 34; also see Science, 295 (2002) p. 2058].

Noble gases bond to uranium

Laster Andrews and Binyong Liang at the University of Virginia found that CuO-formed from the reaction of laser-ablated uranium so forms with carbon monoxide in a frozen noble-gas matrix-exhibits very different stretching frequencies in solid argon than in a solid neon. Argon, krypton, and xenon interact with the uranium atom in the molecule CuO, forming the first noble gas-actinide complexes, according to spectroscopic studies and supercomputer simulations.

According to the researchers, when they use a matrix of 1 per cent argon in neon the results suggest that a distinct complex is formed between CuO and argon atoms.

Bruce E Bursten at Ohio State University and Jun Si, now at Pacific Northwest National Laboratory, performed relativistic density functional calculations that predict that one or several argon atoms can form a single CuO molecule.
Further experiments and calculations together provide “strong evidence for direct bonds” between argon, krypton, or xenon atoms and CuO [Chem Eng News, 80 (a) (2002) p.35; also see Science, February 28 (2002), Science Express, http://www.sciencemag.org/scienceexpress/recent.shtml].

Automated machine for uniform surface finishing of moulds

Mecshot has successfully engineered and supplied machines for uniform surface finishing of glass mould to achieve surface finish within close range of +/- 0.5 Ra in single operation.

The machine consists of large blast chamber fitted with doors for easy access with pitless Pneumatic Recovery System as well as high level of internal illumination. The enclosure has a white, reflective inner surface to enhance the operator’s visibility. The vision glass is made from toughened safety glass.

The machine incorporates automated workcar with rotary table for ‘in’ and ‘out’ of moulds from the enclosure. Oscillating arms mounted with multiblast nozzles for covering with complete job, profile/surface. The motion of oscillating norms is synchronized with rotary table rpm for consistent surface finish.

Such heavy-duty machines can operate 24 h/d, 7 d a week. The inside walls and turntable are lined with UHMW material and all gun holder, gun rods, gun arms and tooling are made of hardened steel for long service life.

The machine is also featured with PLC and electronic panel view of operational sequence parameters selection and fault findings.

The components are cleaned by automatic air purging after blasting. High efficiency Reversejet Filter Elements Cartridge Type Dust Collectors ensures that air exhausted is maintained at high level of cleanliness.

For further information, contact:
Mecshot Blasting Equipments Pvt Ltd, E-279, MIA, Phase II, Basni, Jodhpur 342 005, TF: 91-291-740609, FAX: 91-291-742409 Website: www.mecshot.com, E-mail: mecshot@vsnl.com

Surface finish gage speeds up crankshaft measurements

Adcole Corporation of Marlborough, Massachusetts USA has developed a new, fully automatic surface finish gage for crankshafts, camshafts, and transmission shafts that features a 6 min average cycle time for crankshafts and provides a report of measured results on-screen or in plots.

The Adcole Model 1000 Surface Finish Gage features three variable reluctance pickups, each having 5µm diamond stylus that can measure roughness parameters such as Ra, Rp, Tp, and RsK on main and rod journals as well as thrust faces. This manually loaded, fully automatic gage utilizes Windows NT® software friendly graphics and may be stored and used in SPC programs.

Capable of scanning 2,000 points/mm, the Adcole Model 1000 surface finish gage measures the entire length of a journal in one scan and reports the results in 5.6 mm evaluation lengths which are industry-standard. Incorporating proven machine designs of other Adcole camshaft and crankshaft gages, this present gage accommodates shafts up to 91.5 cm L.

The Adcole Model 1000 surface finish gage is priced at $165,000. (USD) up, depending upon specific customer requirements.

For more information contact:
Adcole Corporation, J. Brooks Reece, Vice President, 669 Forest St. Marlborough, MA 01752 USA, (508) 485-9100 FAX (508) 481-6142.
E-mail: breece@adcole.com, www.adcole.com

3-D features within photogenic crystals

Paul V Brown et al. at the University of Illinois, Urbana-Champaign have developed a new technique which can shape 3-D patterns within photonic band-gap materials. Such embedded features, which can serve as wave guides or optical cavities, most often are fashioned by painstakingly building photonic crystal layer by layer.

Researchers instead use a laser scanning confocal microscope for multiphoton polymerization of a photoactive acrylate monomer within a colloidal crystal, composed of uniform silica spheres.
According to Brawn, by carefully moving, complex 3-D patterns can be created. Unlike layer-by-layer techniques, one can move through the crystal in any direction. The unreacted monomer is then removed, leaving the transparent polymer scrape nestled among the silica spheres.

The researchers suggested that for most applications the remaining interstitial spaces in the colloidal template should be filled with a high-dielectric constant material \[\text{Chem Eng News, 80 (8) (2002) p. 32; also see: Adv Mater, 14 (2002) p. 271}\].

Metal patterns from polymer composites

Joseph W Perry et al. at the University of Arizona have developed a new patterning technique with which metal nanoparticles can be directed to grow into lines and 3-D structures. The method could find use in fabricating 3-D electronic, optical, and electrochemical devices. They designed polymer nano-composites containing ligand-coated metal nanoparticles, a metal salt, and a photoreducing dye.

Single-or-two-photon excitation of the dye with a laser induces it to transfer an electron to a metal ion, which adds onto a seed nanoparticle. The "laser writing" results in continuous silver, copper, or gold microstructures. Alternatively the researchers shaped patterns by using electron-beam irradiation of thin films containing a metal salt and a dye attached to metal nanoparticle.

The nanocomposites are photochemically stable and still photoactive after months of storage without special precautions, suggesting that they might be used optical data storage \[\text{Chem Eng News, 80(7) (2002) p. 46; also see: Adv Mater, 14 (2002) p. 194}\].

Diesel exhaust linked to cancer

Diesel exhaust from — buses, big rigs, bulldozers — as already known is quite harmful, shows the EPA's first study to link diesel exhaust fumes with lung cancer.

Long-term inhalation exposure is likely to pose a lung cancer hazard to humans, as well as damage the lung, otherwise depending on exposure, as per the statement from the EPA's National Centre for Environmental Assessment.

Short-term exposure may cause irritation and exposure may also cause worsening of allergies and asthma symptoms. The report is based on data from diesel engines built prior to the mid-1990s.

It corroborates findings in the State of California and other institutions that diesel exhaust is a health hazard and that it needs to be cleaned up, according to Frank O'Donnell, executive director of the Clean Air Trust, WebMD.

Cleaner diesel engines are likely to be available shortly. However, one of the biggest diesel engine manufacturers — Caterpillar — is lobbying to block tougher standards imposed on diesel engines.

In fact, those "cleaner fuel and engine standards" — adopted during the Clinton administration — will be made tougher in next 8 y. It would prevent more than 8,300 premature deaths and of other health damage per year. Therefore, it is a very important standard that will be maintained.

Some oil companies have also fought for the tougher standards and lost in Court. The fuel standard is absolutely critical because without the cleaner fuel the emission controls do not work.

The fuel is filthy, full of sulphur, which in itself becomes a contaminant when it is burned, similar to coal burning out of an electric plant. Hence, it is very crucial to clean up these engines and fuel as well.

An even bigger issue: off-road vehicles with diesel engines — construction equipment, bulldozers, tractors, etc. wherever there are building highways. It is not unregulated, but is subject to very minimal standards.

Recently, state and local regulators made a study that diesel fuel and off-road equipment are even bigger problems than the diesel truck problem alone.

Currently, truck fuel contains 500 ppm of sulphur. Under the new standards, by mid-2006, that will drop to 15. But for off-road construction equipment the standards today are 3,000 ppm.
To fix the problem the Bush administration has proposed an "emissions trading plan" that worries environmentalists like O'Donnell. Thus, diesel engine makers will be able to trade emission-reduction credits instead of producing cleaner trucks and buses.

The US is very much concerned with this, mainly because it is thought that it may not lead to the strongest controls thought to be possible [and] would not lead to the best outcome for the environment. It will not promote the development of technology and will lead people to search for the least-cost approach [http://content.health.msn.com].

Parents confused about specifics of vaccines

Most of the parents recognize the importance of having their children immunized, and are confused and anxious about the details, according to a new survey done by GlaxoSmith-Kline and others. Created by a collaboration of several nursing associations and supported in part by GlaxoSmith-Kline the survey asked parents about their attitudes, behaviors, and knowledge of immunizations.

Immunizations in the US have been proven to the most effective tool for protecting children and eradicating some infectious diseases. But 80 per cent of the roughly 1,000 surveyed parents did not know how many vaccines their children needed. Currently, infants receive 20 or more injections in the first 2 y of life to protect them from 11 serious diseases including tetanus, whooping cough, chickenpox, and polio. Combination vaccines are used to protect against multiple diseases such as measles, mumps, and rubella.

Other findings in the survey, conducted during July 2002, include:

- Eighty-three per cent of parents do not know how many immunizations a child should receive during the first two years of life.
- More than half could not identify vaccine-preventable diseases such as polio or hepatitis B.
- Eighty-four per cent of parents said that they were sympathetic towards pain suffered by children who receive the vaccine, and four out of five parents found it difficult to watch.

One thousand phone interviews were conducted. The survey was 97 per cent correct.

Parents have developed an idea that everyone needs exercise, even infants and toddlers.

According to the pediatric experts, parents who use strollers, playpens, cars and infant seats for hours at a time, are most likely delaying their child's physical and mental development.

Developing bodies and brains

Regular exercise causes the kind of development that may be critical for health in later life. Infancy and the toddler years are the time that the brain is developing pathways and connections to the muscles.

Children who do less exercise may miss out on the chance to make the strong kinds of brain-muscle connections that make physical activity easier and more enjoyable. As the child grows and matures, it is that physical competence that makes exercise more likely to become a life-long habit.

And that is important for all kids, not only for those who may become athletes.

In a two-year study of obese 8-to 12-y-olds from 90 families, increased activity and reduced television viewing resulted in significant weight loss.

What the guidelines recommend

The NASPE's Active Start guidelines are divided into two groups of activity levels — one for infants and another for toddlers.

Here are some of the suggestions for infants:

- Infants should be placed in settings that encourage physical activity and do not restrict movement for longer periods.
Parents and caretakers should be aware of the importance of physical activity and encourage the child’s movement skills.

For toddlers, according to NASPE basic movement skills such as running, jumping, throwing, and kicking are definitely influenced by the environment they grow up in. For instance a child who does not have access to stairs may be delayed in stair climbing and a child who is discouraged from bouncing and chasing balls may lag in hand-eye-coordination.

Here are some of the suggestions for toddlers:

- Toddlers should do at least 30 min daily of structured physical activity.
- Preschoolers need at least 60 min.
- Both toddlers and preschoolers should not be restrained for more than 60 min at a time in car seats or strollers, except when sleeping [http://content/health.msn.com].

A soft drink from waste dairy whey developed

The waste material of dairy products specially whey liquid which is obtained during the manufacture of cheese and paneer, produces foul smell if kept for some time. A process has been developed to obtain cheap and healthy drink from whey. This non-carbonated drink called, acido-whey is fermented with selected strain, sweetened, and mixed with essence to make it a flavoured drink. It has therapeutic value for gastric problems and can also be used as an ideal dehydration liquid for dehydration patients.

Whey is liquidous product, separated from the solids in the process of preparation of paneer and cheese. The separated whey contains 6 to 7 per cent of total solids comprising approx. 70 per cent of lactose, 0.9 per cent of protein and trace amount of water soluble vitamins, minerals, and fat. So far the whey separated from the cheese or paneer is considered to be a waste product.

The National Dairy Research Institute, Karnal has developed a process to prepare a palatable soft beverage, utilizing whey which has so far been considered as waste material. This beverage unlike the other carbonated beverages, which are not of much use is precious drink from health point of view.

Some of the important advantages of this beverage are:

(i) It has a good nutritional value;
(ii) It has therapeutic values namely: (a) Protection against gastro-intestinal disorders and (b) Bio-availability of vitamins;
(iii) It has three months of self-life under refrigeration;
(iv) It is economical, compared to other known and available beverages or carbonated drinks.

It is already sold on commercial basis by National Dairy Research Institute, Karnal. The shelf life of the acido-whey is two months at 4°C. The process is economical for those dairy industries which are engaged in processing fluid milk and manufacturing paneer and cheese simultaneously.

The product costs Rs 25 lakhs and the plant and machinery costs Rs 15 lakh only [Invent Intell, 37 (No. 5) (2002) p. 267].

Milk adulteration test kit developed

'Synthetic milk' which is adulterated with chemically synthesized milky liquid has become hazardous and a major concern for the dairy industry. Synthetic milk is prepared by emulsifying vegetable oils with appropriate amount of detergents, urea, caustic soda, sugar, salt, etc. are dissolved in water and blended with the natural milk supply in varying proportions. Several tests are employed by the dairy industry to check this adulteration.

A simple biophysical method called Milk Adulteration Test (MAT) has been developed in which the sample is subjected to centrifugation followed by microscopic examination for detection of micro coagulation of milk proteins and detection of non-milk (emulsified oil).

MAT is highly sensitive and specific for detection of synthetic milk adulteration in milk.