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Module C **Growing Value**
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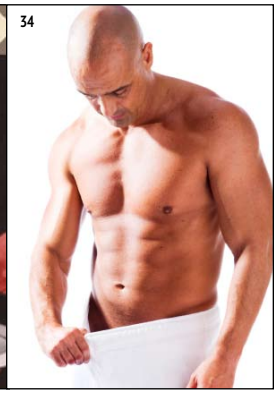

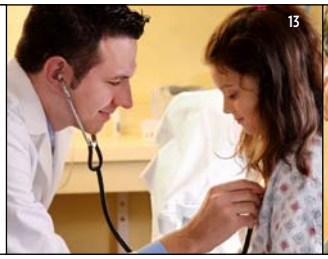

DEPARTMENTS

METRICS

NEWS

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COVER: Illustration by Josh Lockwood, November 2008

A New World Order

The recent market turmoil may have begun with the housing markets, but what we are witnessing is something far bigger than failed government policies, Wall Street's reckless speculation, and the banking industry's bad home loans. While the current crisis is unfortunate to say the least, the biotechnology industry will need to come to terms with the new world that is being forged in this financial crucible.

For two decades, biotechnology companies have enjoyed generally cheap and easy access to capital. That time is gone. Some will argue that we've been through this before. They say that this is just another cycle. They argue the financial players involved in biotechnology love this industry and will not go away. And they point to the acquisitions of Imclone and Genentech in the works, saying there's a potential $55 billion that's going to be freed up and redeployed within the sector. This view is frankly naïve.

What we are witnessing today is not a "this-too-will-pass" moment. The downturn in the stock market has gutted the values of biotechnology companies. We've seen the market caps of about 30 percent of the nearly 370 publicly traded life science companies tracked by Burrill & Company fall below $100 million. There are only 44 companies with a market cap of $1 billion or more. The total market value of the sector stood at $406 billion as of October 29. Of that, $347 billion belongs to those 44 companies. By and large, the biotechnology industry has been transformed into a micro cap sector.

This is not a cyclical downturn. This is a structural realignment of the capital markets. On the sell side, there will be fewer investment banks focused on researching and funding life science companies. The bankers who remain will not be looking to sell $50 million IPOs for privately held companies valued at $150 million. On the buy side, the hedge fund and mutual fund managers who have been active investors in the sector are not going to be interested in steering their millions into micro caps.

For venture capitalists, the business model has become troubled, too. Private companies may find some VCs still have deep pockets but short arms. There is no IPO market to speak of right now and little reason to think that will change significantly in the next year. With investment bankers looking at the biotech deals done in recent years and seeing that two-thirds of them are under water, venture investors realize there is no IPO exit strategy. And while Big Pharma has cash and continues to need products, there is little incentive for these companies today to race to make deals or pay up for assets. They know the capital markets will not finance these companies. They will wait for cash-hungry biotechs to grow desperate.

The economic problems are not limited to the United States. This is a global problem and one that will take time to resolve. We could be looking at a down cycle of 5 to 10 years. It's going to be tough for biotechs to raise money. The first thing companies that thought they were going to go out and raise $100 million should do is rip up their business plans and start over. They need to figure out how they are going to survive.

Companies will need to think not only about how they will generate revenues, but also how to monetize the assets they have. The United States may no longer be the market of choice. Economies across the world are suffering, but countries such as China, India, and Brazil still have emerging middle classes and are looking to build their life science sectors. Companies in these countries may see greater value in a given drug or technology and be willing to pay more to access products for specific markets. And when the capital markets return, it may be markets overseas that place the greatest value on companies here.

We are not writing biotech's obituary. In fact, these trying times will force companies to be more disciplined, strategic, and resourceful. They will also have to look farther afield for financing and potential partners. The industry has been and will be as creative in its survival as it has been in its product development. From this we will emerge an even stronger industry.

G. Steven Burrill

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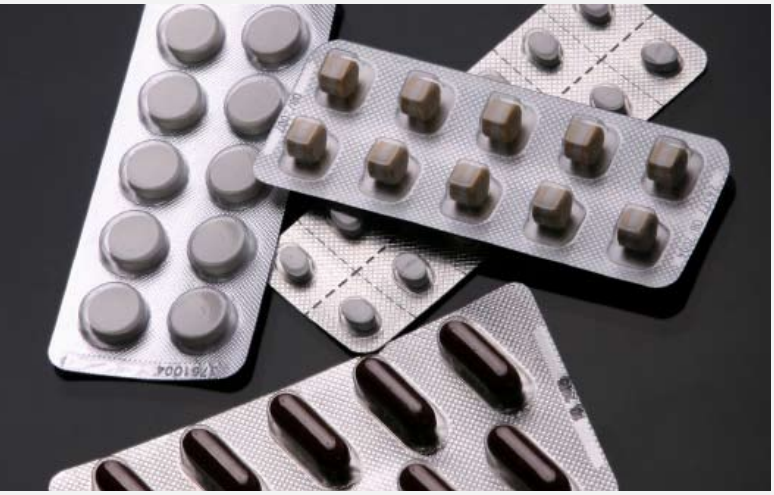
PHARMACEUTICALS

Free Drugs Have A Cost

Study finds samples end up costing uninsured patients more than generics.



Habit forming: Wake Forest researchers say free drug samples affect the prescribing practices of doctors to the economic detriment of their patients.

It may seem that it doesn't get any cheaper than free, but the more than $15-billion worth of prescription drugs doctors give away as samples each year could actually wind up costing uninsured patients more than if they just paid for the drugs. How Come? Free samples affect the prescribing habits of doctors, a new study finds.

Free drug samples have long been a subject of controversy among physicians. Some believe it provides an important source of free medication for uninsured patients, allowing them to try before they buy to see if the drugs are effective. Others, though, feel pharmaceutical companies use free drugs as a powerful marketing tool to get doctors to prescribe their newer and more expensive brand-name drugs. The skeptics see no role for free drugs in their practice for fear they would have undue influence on their prescribing habits.

Researchers at Wake Forest University Baptist Medical Center set about to see if the use of free samples could be doing more harm than good by increasing patient costs over the long run. The study, published in September issue of *Southern Medical Journal*, found that doctors who did not give out free samples were three times more likely to prescribe generic drugs than doctors who did give free samples to their patients. "The magnitude of that increased likelihood of giving out generic drugs did surprise us," says David Miller, lead researcher and internal medicine physician at Wake Forest Baptist.

The study looked at the prescribing habits of more than 70 physicians in a university-affiliated internal medicine practice in the months immediately before and after the closing of their drug sample closet. Miller and his colleagues tracked all of the prescriptions in four classes of chronic medications given to uninsured and Medicaid patients. They tracked nearly 2,000 prescriptions categorized as antihypertensives (blood pressure medications), oral diabetic agents, peptic ulcer and gastroesophageal reflux medications, and non-narcotic pain medications for the nine months leading up to and following the relocation of the practice. At that time, the drug sample closet was permanently closed due to a lack of suitable storage space in the new building.

Researchers found that, for uninsured patients, the percentage of medications prescribed as generics rose to 30 percent from 12 percent after the clinic closed its drug sample closet. For Medicaid patients, however, there was no significant change in generic prescribing.

Drug samples tend to be available for brand name drugs, which are often newer, more heavily advertised, and almost always much more expensive than generic drugs in the same class. "The theory is that drug companies hand out samples because it gets physicians in the habit of using a drug, and physicians, therefore, are more likely to prescribe that drug later," Miller says.

Many times, a patient will be given a sample of a drug to test tolerability and effectiveness. Often, when a physician gives a patient a sample, it is accompanied with a prescription to fill after the sample is gone, Miller says. Sometimes free samples are used by physicians to help patients who cannot afford medications. But the availability of drug samples is not always predictable. When patients return for refills, the samples they need may be missing from a practice, either because the drug representative didn't leave enough or stopped distributing them altogether. Patients who were started on brand name drugs

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in sample form, in such instances, are left paying the price when they have to fill a prescription.

Ken Johnson, senior vice president of the Pharmaceutical Research and Manufacturers of America, says free samples provide doctors valuable first-hand experience with new medicines and can help patients quickly find the best medicine for them. The Wake Forest study overlooks the fact that America's physicians prescribe medicines based on a wide range of factors, not simply receipt of samples, he says. "Clearly, free sample medicines lead to better treatment and improved quality of life for millions of Americans, regardless of their incomes," he says.

But Sidney Wolfe, director of Public Citizen's health research group and editor of the consumer web site Worstpills.org, says quantitative studies on drug sampling like the Wake Forest one are relatively new. The research provides mounting evidence on the downside of sampling, he says. "Having to spend extra hundreds or thousands of dollars a year because the doctor prescribed an expensive brand name drug instead of giving you an equally effective and safe generic drug is just not good for patients," he says.

—Daniel S. Levine

EDUCATION

Income Inequality

Study links the primary care doctor shortage to fact that other specialties pay a lot more.

The medical establishment generally agrees the improvement of primary care is a desirable goal, as it leads to lower infant mortality rates and lower death rates overall. In fact, an increase of one primary care physician is associated with a 5 to 10 percent decrease in deaths per 10,000 people, according to Dr. Barbara Starfield, a professor at Johns Hopkins Bloomberg School of Public Health who studies primary care's benefits. But despite the obvious value of primary care to society, the specialty seems to be shrinking rather than expanding. The reason? It pays a lot less than lucrative specialties, leading to a growing shortage of primary care doctors, a recent study finds.

Offering an average salary of $185,740—the lowest of 13 key medical specialties—family medicine had just 42.1 percent of its residency positions filled by U.S. graduates of medical schools, says study author Dr. Mark Ebell, a professor at the University of Georgia. That was the lowest percentage of all residency positions. By contrast, with an average salary of more than $400,000, radiologists (88.7 percent) and orthopedic surgeons (93.8 percent) had the highest percentage of filled residency positions among U.S. graduates. "Certainly, the income disparity among the specialties has grown compared with what it was 20 years ago," says Ebell, who published his results in the September 10 issue of the *Journal of American Medicine*. "The primary care specialty is not an attractive lifestyle for many students." Primary care includes pediatrics, family medicine, and general internal medicine.

Ebell compared 2007 starting salaries for specialties with the percentage of medical school graduates choosing them and found a strong direct correlation between higher overall salary and higher residency fill rates with U.S. graduates. In the past decade, the number of U.S. graduates filling family practice residencies has fallen 50 percent, Ebell says. Both U.S. and foreign graduates of international medical schools have helped close the gap, making the total filled positions in family medicine residencies 88.3 percent. But that's still the lowest fill percentage, with orthopedic surgery and radiology residencies having 99.7 percent and 100 percent fill rates, respectively.

Salary disparity alone does not account for the decline, Ebell says. In the past 20 years, a med student's average debt has quadrupled to $140,000 from $35,000 he says, making the

The average family physician makes $185,740 versus more than $400,000 for the average radiologist.

higher salaries all the more attractive, or even necessary. Often, specialties such as anesthesiology are considered more prestigious than primary care, he says, and may offer better working hours. What's more, procedures and diagnostics performed by specialists receive higher insurance reimbursement rates than the type of medical decision-making required of primary care doctors. "We reimburse doing things to people and taking pictures of people more than we do talking to them and communicating to them effectively," Ebell says.

Better primary care is important for America, Starfield says. "Compared with other industrialized nations, the United States already has a surplus of specialists, but not of primary care physicians," she wrote in a 2005 article in *The Milk Quarterly*. "We believe that the health of the U.S. population will improve if this maldistribution is corrected."

As for Ebell, he sees several ways to try to reverse the problem. For starters, debt relief could be expanded to medical school graduates who decide to go into primary care. The reimbursement system could be reformed to better compensate the counseling and diagnosis skills required of primary care physicians, he says. Improving information technology might enable primary care doctors to get a better handle on the broader base of knowledge that is required than in other specialties. And medical schools could do a better job of mentoring students for primary care and identifying good candidates for the specialty, he says. "Too often, they are discouraged from being generalists and told 'you are too smart for that,'" Ebell says.

Medical school officials are aware of the primary care shortage, but with the aging population, they say there are growing shortages in other areas including oncology and cardiology. In 2006, the Association of American Medical Colleges instituted a plan to boost medical school enrollment by 30 percent by 2015, says Edward Salsberg, who is head of the association's Center for Workforce Studies. The association doesn't favor any mandates on specialty choice, he says, because "we really believe the marketplace is more important than the medical education system for providing incentives for specific medical careers."

Like Ebell, he also sees a need for more primary care mentors as well as reimbursement reform. But he also believes the primary care delivery system might continue its current trend whereby nurse practitioners and other non-physicians increasingly handle more routine care, whereas physicians take care of more complex and chronic conditions. "I think the long-term solution is really having the primary care doctor being the lead of a team and that would make the specialty more attractive and allow them to get higher reimbursement," Salsberg says. Making the specialty more appealing is a worthwhile goal: Starfield and other researchers estimate as many as 127,617 deaths in the United States could be averted each year just by adding 1 primary care physician per 10,000 population.

—Eric Wahlgren

NUTRITION

A Real Buzz Kill

Researchers call for warning labels on energy drinks.

Energy drinks can pack quite a punch, and that's the message they seek to convey with names such as "Full throttle," "Jolt," and "Adrenaline Rush." Often they catch the imagination of young people with edgy marketing, but the $5.4-billion market in the United States for these drinks has also caught the eyes of researchers at Johns Hopkins.

These scientists are concerned about their potential dangers to adolescents who may not be ready to handle the wallop some of the drinks pack. They're also worried about the way that these beverage companies are aggressively targeting young people. In fact, the researchers would like to see the U.S. Food and Drug Administration require something not usually found on drinks available to minors in grocery stores: warning labels.

The researchers acknowledge that caffeine is both ubiquitous and generally quite safe. Some 80 percent to 90 percent of Americans consume caffeine, they estimate, and it's not going to cause cancer, at least as far as they know. But problems can arise as a body's response to caffeine depends on how much the person is used to consuming it. Children 14 and younger

generally are not daily coffee drinkers, and if they chug an energy drink, they could be in for some trouble.

The potential problems fall under the heading of "caffeine intoxication," which can include such symptoms as increased heart rate, stomach aches, insomnia, anxiety, and nervousness. A caffeine-intoxicated person's face can become flush, the individual can lose fluid, and speech can began to ramble. And while it's extremely rare, it is possible to overdose on caffeine, like many other drugs, and die.

If that all sounds a bit extreme, consider that while some energy drinks contain modest amounts of caffeine, others are loaded with it. There's usually no way to tell the difference since many drink makers don't list caffeine content in their beverages. The researchers found a wide range in the caffeine content of these drinks, with those with the greatest amount containing 10 times the amount as those at the low end. A 20-ounce can of Fixx contains 500 milligrams of caffeine, while a 24-ounce can of Wired X 505 packs a 505-milligram punch of the stimulant. That compares to anywhere from 80 to 150 milligrams of caffeine in a 6-ounce cup of brewed coffee or about 14 times the 35 milligrams of caffeine a kid would get in a 12-ounce can of Coke.

Adding to the concern is the marketing of these beverages, some of which carry names suggestive of street drugs while others promise to help young drinkers feel good or enhance their performance. Chad Reissig, the study's lead author, says the companies are targeting children with a message that says they will feel great and perform better if they drink this can. "What this says is 'it's okay to use a substance for recreational effects,'" says Reissig, a fellow at Johns Hopkins University who published the study in the journal *Drug and Alcohol Dependence*. "'It's okay to use a substance for performance enhancing effects.' I don't think that's a very good message to be sending to kids."

Reissig and his colleagues would like the FDA to require labels similar to the ones the agency demands of over-the-counter caffeine pills. These labels state caffeine content and warn of side effects such as dizziness, irritability, nausea, and nervousness. What's more, they caution users not to exceed a given dose within a specific period of time.

The American Beverage Association, though, calls such warning labels "unnecessary," adding they would create a slippery slope. The trade group criticizes the report for not making a distinction between what the association describes as "mainstream" energy drinks with those produced by "novelty" companies. "It's unfortunate that the authors of this article would attempt to lump all energy drinks together in a rhetorical attack when the facts of their review clearly distinguishes the mainstream responsible players from novelty companies seeking attention and increased sales based solely on extreme names and caffeine content." It argues that a 16-ounce cup of coffee at a popular coffeehouse contains twice the 160 milligrams found in a comparable size mainstream energy drink.

But the researchers are not the first to call for more scrutiny. In fact, the Washington, D.C.-based consumer group Center for Science in the Public Interest petitioned the FDA in 1997 to require the labeling of foods and drinks with significant caffeine to list their caffeine content.

"We think because food products have now reached the levels of caffeine that you find in over-the-counter drugs, there's no reason food shouldn't have the same kind of warning label," says David Schardt, senior nutritionist with the center. When his organization contacted the agency at the end of last year to check on the status of the petition, he says the FDA responded it was still active and pending and that the agency has not reached any decision yet. He may want to put on another pot of coffee while he waits.

—Daniel S. Levine

Surge protectors: researchers want to see warning lables on energy drinks such as *Wired* because of their caffeine content.

HEALTHCARE

Sticker Shock

Health insurance premiums have doubled since 1999 and workers are shouldering more of the cost.

An overwhelming majority of Americans—eight in 10—believe the U.S. health system

needs to be fundamentally changed or entirely rebuilt, according to The Commonwealth Fund, a private organization devoted to improving healthcare. That sentiment is hardly a shocker, given that a separate report finds that premiums for employer-sponsored health insurance rose 5 percent this year, once again outstripping both inflation and wage increases.

But here's the finding that will have people reaching for their nitroglycerin pills: Since 1999, annual insurance premiums have actually doubled to $12,680 for family coverage, says the report from the Kaiser Family Foundation and the Health Research & Educational Trust, both independent healthcare policy and research organizations. In the same nine-year period, workers' wages rose only 34 percent, while general inflation increased 29 percent, says the report, which was published in *Health Affairs* in September. On average, workers are paying $3,354 a year out of pocket to cover their share of the cost for family coverage.

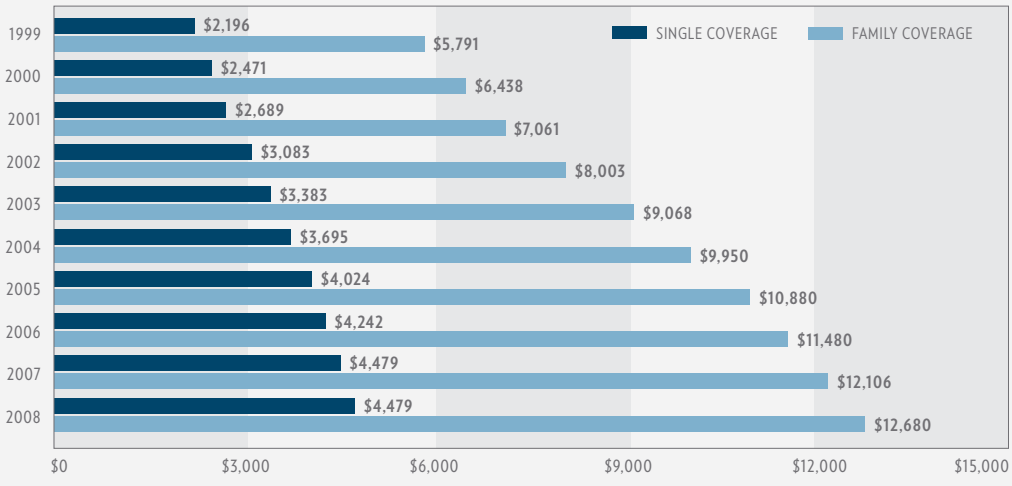
Unfortunately, there's more bad news in the report. Workers are shouldering more of the healthcare cost burden in other ways, the report says, with the number of workers with general plan deductibles of at least $1,000 rising to 18 percent from 12 percent of all covered workers over last year. In small businesses—those with 3 to 199 employees—the increase in employees with $1,000-plus deductibles was the sharpest, jumping to 35 percent of all covered workers in 2008 from 21 percent last year.

"Firms and insurers are really trying to figure out ways to prevent premiums from increasing at steeper levels and increasing deductibles is one way of doing that," says Bianca DiJulio, a senior policy analyst with the Kaiser Family Foundation in Washington, D.C. But higher deductibles do mean that workers are paying more out of their pocket before their full coverage kicks in. There is some care that people might not get" because of the higher deductibles, she says. The report was conducted between January and May and included 2,832 public and private firms with three or more employees.

Among other findings, the average annual premium for single coverage also rose about 5 percent to $4,704. Large firms remain the best places to work for comprehensive health insurance. Some 99 percent of large employers (200 or more workers) provide health benefits. By contrast, only 62 percent of small firms (3 to 199 workers) do, the report says.

Overall, the trends are particularly worrisome for low-wage workers, says Alwyn Cassil, a spokeswoman for the Center for Studying Health System Change, a nonpartisan policy research organization, also in Washington, D.C. "The reality is that lower-wage work-

AVERAGE ANNUAL PREMIUMS FOR SINGLE AND FAMILY COVERAGE, 1999–2008



SOURCE: KAISER/HRET SURVEY OF EMPLOYER-SPONSORED HEALTH BENEFITS, 1999-2008

ers are increasingly being priced out of the employer-sponsored insurance arena," says Cassil, who adds that firms with higher-wage workers tend to offer more comprehensive benefits as a retention tool. "The lower-wage workers either can't afford their premium contribution or they face higher deductibles and that can make the difference between going or not going to get care."

The percentage of an individual's paycheck devoted to healthcare has actually declined, says Cassil, from about 30 percent at its peak to 14 percent today, she says. But because wage growth has continued to slow, "ultimately you're paying for those healthcare benefits with lost wages," she says.

As for small businesses, they say the affordability of healthcare is among their top concerns. Todd Stottlemyer, president and CEO of the National Federation of Independent Businesses, said in a recent interview with the Kaiser Family Foundation that in the last 8 years, healthcare costs to small businesses have soared 129 percent. And on average, small businesses pay 20 percent more to provide healthcare than do large businesses because they don't benefit from the same leverage with insurance companies. "Annual increases in healthcare premiums consume a higher percentage of a business' payroll now more than ever, far outpacing wage increases," Stottlemyer said in a separate statement to the media earlier this year. "As a result, many small business owners face a tough decision: provide a raise to their employees or offer healthcare coverage."

It's obviously a difficult choice. Some 28 million of the nearly 45.7 million uninsured in America are small business owners, employees, or their dependents, Stottlemyer told the Kaiser Family Foundation. His small business association has called for numerous reforms, including increasing insurance competition and expanding a government safety net for the neediest. "If you fix healthcare for small businesses, you fix healthcare for America," he told the foundation. With small businesses making up about 50 percent of the non-farm private sector workforce, it's likely they'll figure into any reform if President-Elect Barack Obama makes good on his pledge to tackle the healthcare mess.

—Eric Wahlgren

BEHAVIOR

Men Behaving Badly

Study finds that higher levels of testosterone fuel appetite for financial risk among males.

As the recent financial meltdown began to accelerate, lawmakers and pundits quickly sought to assign blame. They could not, however, reach a consensus on whether it was the fault of greedy Wall Street bankers, fat cat CEOs, predatory lenders, deregulating congressional reps, or poor people who bought houses they should have known they couldn't afford. In their rush to identify the guilty parties, they may have overlooked one culprit: testosterone.

A study from researchers at Harvard University and the Stockholm School of Economics examined the role the manly hormone plays in risk-taking among men. And while it may not explain how we found ourselves in the current economic mess, the researchers say they did find higher levels of testosterone are correlated with greater financial risk-taking behavior. The findings, they say, also help to shed light on the evolutionary function and biological origins of risk-taking.

The research, published online in the journal *Evolution and Human Behavior* in September, may help to explain the biological foundation of why some people are more inclined towards risk-taking than others. "The traditional economic view has been that people act out of rational choice," says Anna Dreber, a visiting researcher at the Program in Evolutionary Dynamics at Harvard University who co-led the study with Coren Apicella, a doctoral candidate at Harvard's Department of Anthropology. "Here we show it might not be that thought through. If testosterone is explaining some of the behavior, maybe we shouldn't focus only on rationality, but some of these other underlying

Risky business: researchers at Harvard University found that men with higher levels of testosterone took greater chances with money in a betting game.

behaviors to understand why we are making the decisions we are making."

Previous studies have shown that on average, men are more likely than women to take risks. The researchers theorize that these differences could be explained by the role of testosterone. Another recent study also demonstrates that stock market traders experienced greater profits on days their testosterone was above its median level.

However, this is the first study to directly examine the relationship between testosterone and financial risk-taking. In the study, the researchers took saliva samples from 98 men ranging in age from 18 to 23. The samples were obtained prior to the subjects participating in an investment game. The researchers also assessed facial masculinity, which is associated with testosterone levels at puberty.

Then they gave each of the participants $250 and asked them to choose an amount between $0 and $250 to invest. The participants kept the money that was not invested. A coin toss determined the investment's outcome. If the participant lost the coin toss, the money allocated to the investment was lost. However, if the coin toss was won, the participant would receive 2.5 times the amount of their investment. At the end of the study, the researchers used a lottery to select one person to receive the cash amount of their investment, which created a financial incentive for the participants.

The researchers found that a man whose testosterone levels were more than one standard deviation above the mean invested 12 percent more than the average man into the risky investment. A man with a facial masculinity score of one standard deviation higher than the mean invested 6 percent more than the average man.

So does the study explain the recent financial crisis? The researchers say no. "This is purely a study of association," says Apicella. "It's too early to say there is causality. We need to get at this relationship to tease out if testosterone is modulating risk."

The study represents a smart approach by taking a behavior and connecting it to a physiology, says Dan Ariely, author of the book *Predictibly Irrational: The Hidden Forces That Shape Our Decisions* and a professor of behaviorial economics at Duke University. He says it points in a promising direction. "The question is, what is causing what? Is the risk causing testosterone, or is the testosterone causing risk? Are they both being caused by something else? That's not something we know from the study. But nevertheless, the fact that there are some important relationships between those things it does tell us something about individual differences."

Previous studies have documented a winner-loser effect on testosterone levels. For instance, it has been shows that members of sports teams and their fans both experience increases in testosterone levels when their teams win and a drop in testosterone levels when their teams lose. Next up: Dreber, who is also a doctoral candidate at the Stockholm School of Economics, and Apicella want to look at whether or not financial wins and losses actually influence testosterone levels, and whether these changes can predict how risky someone might act in the future.

—Daniel S. Levine

SAFETY

A Dose Of Common Sense

A husband-and-wife team thinks its low-tech system will reduce medication mistakes.

Last year, a nurse at a Los Angeles hospital accidentally gave the twins of actor Dennis Quaid and his wife 1,000 times the appropriate dosage of the blood thinner heparin. Now the target of a lawsuit, the overdose allegedly occurred in part because the vials containing 10,000 units per milliliter of heparin looked a lot like those with the 10-units-per-milliliter concentration. The boy and girl have since recovered, but the incident spotlighted a grim statistic: nearly 15,000 people die annually in the United States due to medication errors, with some 66 percent of the cases involving infants and children.

It is this disturbing fact that prompted Dr. Tracy Dallman, an Indianapolis anesthesiologist, and her product-developer husband Brent Dallman to begin designing a system to curb drug-dispensing errors in 2006. Their work has resulted in the Drug Index Safety System, which has

built-in safety features developed to thwart the kind of accidents that befell the Quaid children. "I think the accident would have been avoided" with this system, says Doug Diedrich, a business development executive with DiedrichHarmon, the marketing firm hired to represent it.

The system seeks to avoid drug stocking and dispensing errors in several ways. Today, drug vials are often packed loose in hospital trays with other drugs that are differentiated only by label and bar code. In this system, each drug vial would instead be fitted with its own unique plastic extension, allowing drug names and labels, including any warnings, to be printed in more readable type. The extensions would be particular to the drug type and dosage—and would also have room for an RFID chip for better tracking. A vial containing 10,000 units per milliliter of heparin might have a plastic extension or "key" in the form of a swoop, say, while a vial with the 10 units-per-milliliter dose might have a triangular key.

What's unique to the system is that the drug docking station would only accept the drug with the matching key, assuring that only the right medication and dose goes into the right spot. "It prevents humans from putting a square head in a round hole," says Cathi Harmon, also a business development executive with DiedrichHarmon. "It's kind of like at the gas station where the pump allows you to only put diesel fuel in a diesel tank." That concept is called "forced function," and the system's proponents believe it would keep humans from putting the wrong drugs in the wrong docking station. The system allows for more than 10,000 distinctly shaped keys, they say.

Adding another layer of safety, the system is designed so that a drug storage drawer or shelf will only accept the docking station carrying the dose and drug assigned to that location. "This is a solution that is already prototyped, designed, and engineered," says Harmon. "It can be easily put into any hospital system and is easy to understand."

Harmon and Diedrich are now looking to sell the Drug Index Safety System, which has patent protection in 128 countries including the United States, to a company that could roll it out on a broad scale. They believe the system would be of interest to a drug packaging or healthcare services firm that would encourage drug companies to adopt the system. The pair says the system would add only pennies per vial to the cost of drugs—an increase they say would be worth it because of what they say are the safety benefits.

COURTESY OF DIEDRICHHARMON

Dr. Sanjaya Kumar, CEO of Quantros, a provider of healthcare safety software and services, says system proponents may face challenges when it comes to integrating it into existing practices in hospitals and other healthcare settings. "You will be asking end users to do something new," Kumar says. "How feasible will it be for them to take an extra step outside of what they have been following? What is the return on investment? How effective will it be vis-à-vis comparable systems?"

As for medication errors expert J. Lyle Bootman, dean of the University of Arizona's College of Pharmacy, he says these types of systems are a "good step in the right direction." The Drug Index Safety System would reduce the types of errors that occur when the wrong drug is put on the wrong shelf or the wrong vial is picked up by a nurse, he says. But, he adds, there are many kinds of medication errors, including errors of omission, the use of drugs that have expired, and the wrong rate of drug administration. The system "will prevent certain types of medication errors," he says, but "it is certainly not the majority."

Bootman says he's in favor of institutions appointing a chief medication officer to implement systems to reduce drug errors. Too often, he says, the responsibility for the problem is dispersed, ensuring that it is never properly addressed. Sounds like the Drug Index Safety System is just the sort of offering a medication error czar would want to evaluate.

—Eric Wahlgren

The right spot: The Drug Index Safety System seeks to reduce medication errors by attaching to drug vials special keys that ensure the right medication and dose are stocked in the correct place.

Mojo Working

The sex lives of septuagenarians are heating up these days despite their age, according to a recent Swedish study. The study, one of the first to look at the function rather than dysfunction in elder sex, found that the number 70-year-old men and women having sex increased over a 30-year period. In 2001, some 68 percent of married men surveyed reported doing the deed, compared to 52 percent when the survey began in 1971. During the same period, the number of married women reporting sex rose to 56 percent from 38 percent. The researchers from the University of Gothenburg in Sweden studied four representative population samples of 70-year-olds in Sweden who were interviewed in 1971-1972, 1976-1977, 1992-1993, and 2000-2001. More than 1,500 people in all were included in the study, which was published in July online in *BMJ.com*.

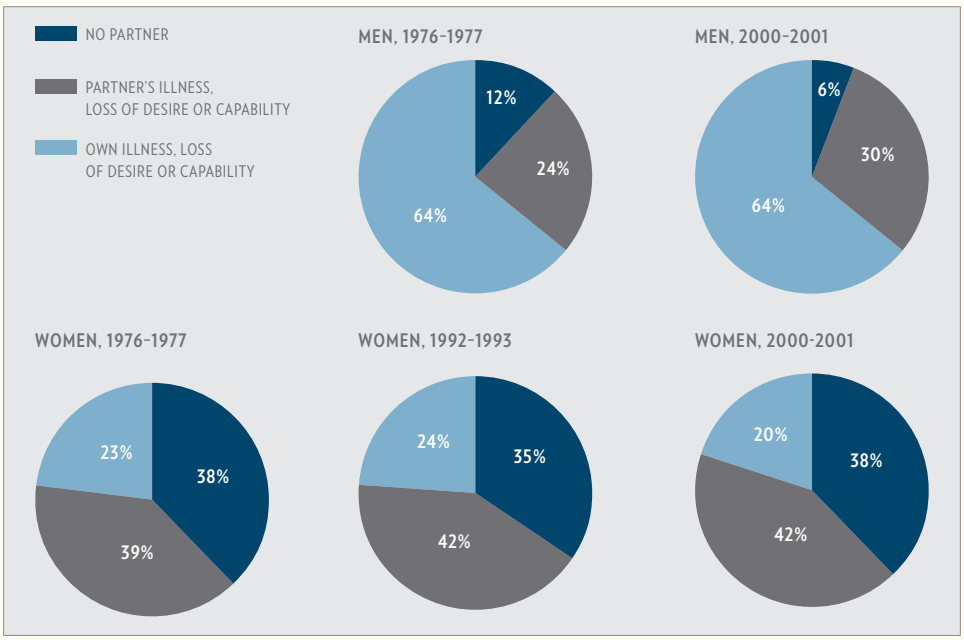
Among the other findings, unmarried men reporting having sex rose to 54 percent from 30 percent, and unmarried women to 12 percent from 0.8 percent. In addition, the number of women reporting high sexual satisfaction increased. More women reported having an orgasm during sex and fewer reported never having had an orgasm. Both men and women blame men when sexual intercourse stops between them. The researchers say their study shows that most elderly people consider sexual activity and associated feelings a natural part of later life.

The trend in Sweden appears to be the case in the United States as well. A separate study, published in August 2007 in the New England Journal of Medicine, found a majority of adults aged 57 to 85 remain sexually active, as defined as having sex with at least one partner within the past 12 months. However, the study involving more than 3,000 people in the United States did find that sexual activity declined with age, and that the decline was more closely linked to health than age.

—Daniel S. Levine

HANGING UP THEIR SPURS

Reason for cessation of sexual intercourse reported at age 70. Values are number who answered question of total number examined.



SOURCE: SECULAR TRENDS IN SELF-REPORTED SEXUAL ACTIVITY AND SATISFACTION IN SWEDISH 70-YEAR-OLDS: CROSS SECTIONAL SURVEY OF FOUR POPULATIONS, 1971-2001. BMJ 2008;337:A279 DOI:10.1136/BMJ.A279

HAPPY CUSTOMERS

Sexual satisfaction and function among sexually active 70-year-olds from Gothenburg, Sweden, examined in 1971-2, 1976-7, 1992-3, and 2000-1.

VARIABLE	MEN		WOMEN		
TIMEFRAME	1976-1977	2000-2001	1976-1977	1992-1993	2000
High Satisfaction	58%	71%	41%	48%	62%
Low or no satisfaction	2%	8%	39%	15%	10%
Erectile dysfunction	18%	8%	-	-	-
Ejaculation dysfunction	5%	12%	-	-	-
Premature ejaculation	4%	4%	-	-	-
Always or usually orgasm	-	-	59%	54%	83%
Never had orgasm	-	-	41%	25%	6%

SOURCE: SECULAR TRENDS IN SELF-REPORTED SEXUAL ACTIVITY AND SATISFACTION IN SWEDISH 70-YEAR-OLDS: CROSS SECTIONAL SURVEY OF FOUR POPULATIONS, 1971-2001, BMJ 2008;337:A279 DOI:10.1136/BMJ.A279

GRAY MATTERS

Self-reported sexual behavior and attitudes in four samples of 70-year-olds from Gothenburg, Sweden examined in 1971-1972, 1976-1977, 1992-1993, and 2000-2001.

VARIABLE	MEN			WOMEN			
TIMEFRAME	1971-1972	1976-1977	2000-2001	1971-1972	1976-1977	1992-1993	2000-2001
Positive attitude towards sexuality in old age	82%	80%	97%	65%	63%	89%	94%
Married or cohabiting	83%	80%	96%	70%	60%	88%	93%
Not married	77%	83%	97%	61%	65%	89%	96%
Sexuality a positive factor in life	-	26%	95%	-	5%	54%	78%
Sexual intercourse during past year	47%	48%	66%	12%	18%	35%	34%
Married or cohabiting	52%	53%	68%	38%	37%	54%	56%
Not married	30%	30%	54%	1%	4%	11%	12%
Sexual intercourse once weekly or more among sexually active	10%	27%	31%	9%	18%	20%	26%
Sexual debut before age 20 (median age at sexual debut)	52% (19.35%)	56 % (18.7%)	77% (17.7%)	19%	28%	49%	64%
Sexual intercourse before marriage	83%	88%	88%	48%	74%	75%	88%
Sexually inexeperienced	1%	0%	0%	11%	7%	0.4%	0.4%

SOURCE: SECULAR TRENDS IN SELF REPORTED SEXUAL ACTIVITY AND SATISFACTION IN SWEDISH 70 YEAR OLDS: CROSS SECTIONAL SURVEY OF FOUR POPULATIONS, 1971-2001, BMJ 2008;337:A279 DOI:10.1136/BMJ.A279

Playing Defense

Vaccines are no longer the boondocks of the pharmaceutical world. Global sales were up 38 percent in 2007 to $16.3 billion, thanks in part to the introduction of Merck's Gardasil for cervical cancer, according to research group Kalorama Information. Kalorama forecasts vaccine sales could grow at a compound annual rate of 13.1 percent to $36 billion in 2013, outstripping the growth rate of pharmaceuticals overall. Growth of vaccines will be fueled by new product introductions and rising usage in all regions, says Kalorama.

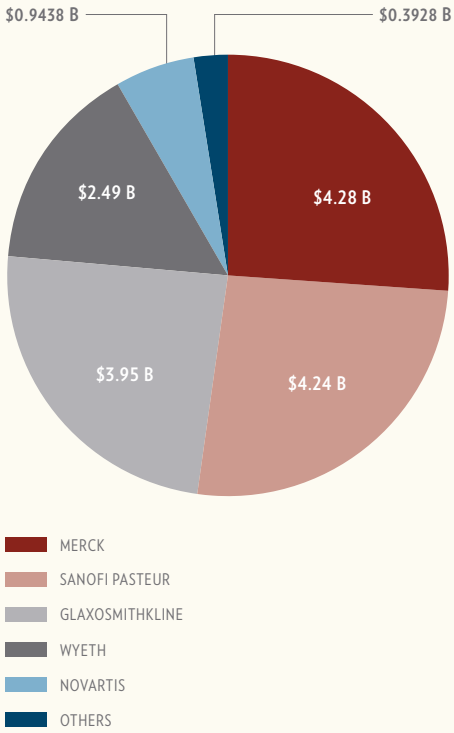
Immunization now averts more than 2.5 million deaths every year in all age groups from diptheria, tentanus, pertussis (whooping cough), and measles, says the World Health Organization, citing 2006 figures. But an equal number of deaths—many in Africa and South East Asia—result because of continuing lack of coverage from diseases preventable by vaccines, the WHO says. That said, there have been considerable increases in coverage, even in a relatively short period. Global coverage of infants with three doses of hepatitis B vaccine, for example, rose to 60 percent in 2006, from 3 percent in 1992. The Western Pacific region leads the world in vaccine coverage at 92 percent, followed by the Americas and Europe, with 90 percent immunization coverage.

Within the United States, flu immunization coverage in 2006 doubled to 69 percent of people 75 and older from 34.2 percent in 1989. As for the human papillomavirus (HPV), which can lead to cervical cancer, some 25.1 percent of adolescent women received the HPV4 vaccine against four strains of the virus in 2007, the first year that the Centers for Disease Control began tracking its use.

—Eric Wahlgren

SHARE OF WORLD VACCINE MARKET

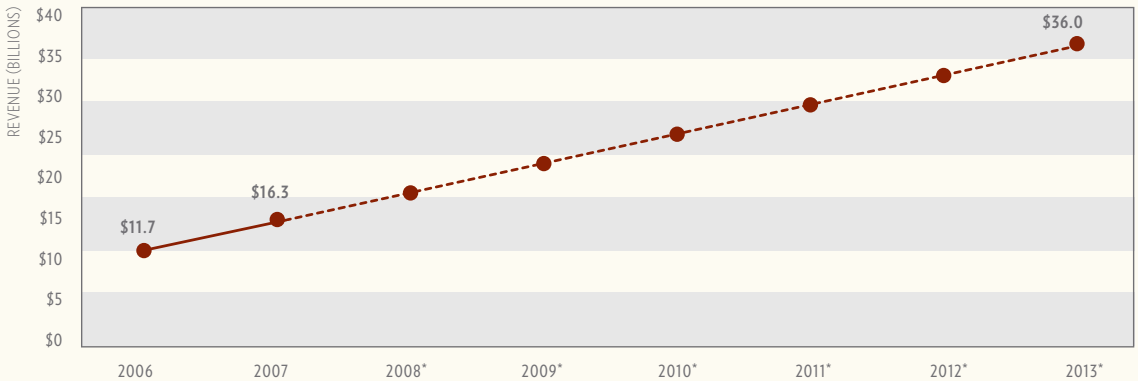
Merck leads 2007's $16.3-billion market, thanks in part to sales of Gardasil for the HPV virus.



SOURCE : KALORAMA INFORMATION

WORLD VACCINE MARKET

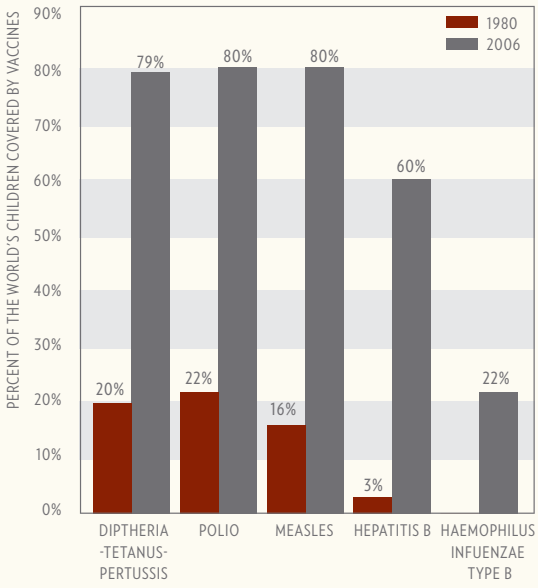
Sales, which hit $16.3 billion in 2007, are seen growing at a compound annual rate of 13.1 percent through 2013.



SOURCE: KALORAMA INFORMATION, *PROJECTED

GLOBAL COVERAGE

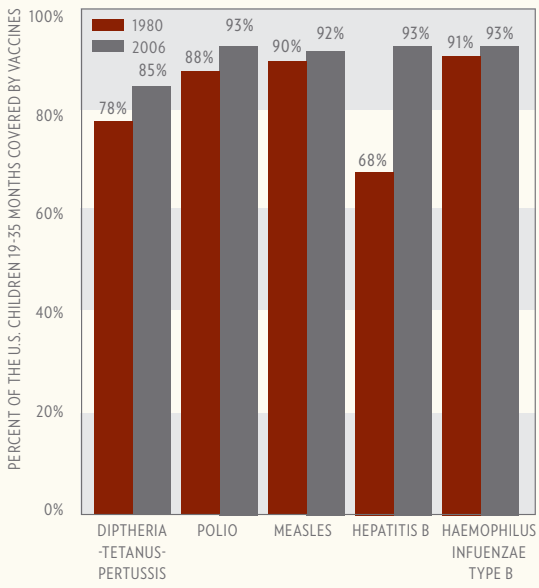
Dek: Percent of the world's children covered by vaccines has increased dramatically for certain immunizations.



SOURCE: WORLD HEALTH ORGANIZATION, UNICEF. HEPATITIS FIGURES BEGIN WITH YEAR 1992 AND REFER TO COVERAGE OF INFANTS WITH THREE DOSES OF THE VACCINE. MEASLES REFERS TO COVERAGE OF CHILDREN WITH ONE DOSE BY THEIR SECOND BIRTHDAY. POLIO REFERS TO INFANTS WITH THREE DOSES OF THE VACCINE, AND DPT COVERAGE IS FOR CHILDREN. THERE ARE NO 1980 FIGURES FOR HIB VACCINE.

U.S. COVERAGE

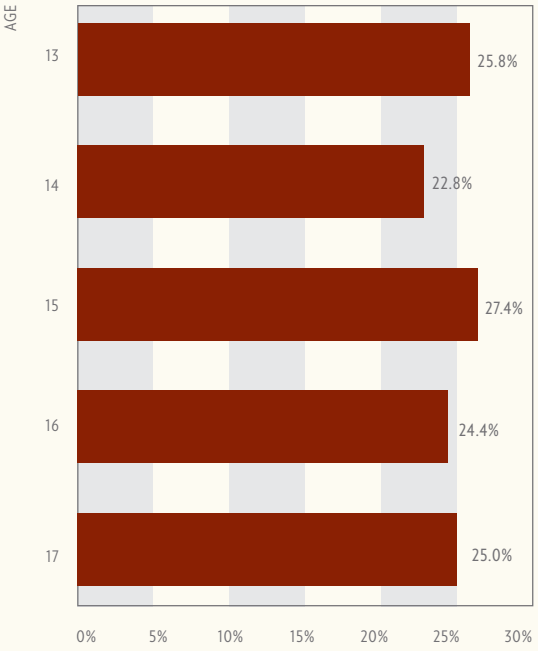
Percent of the U.S. children 19-35 months covered by vaccines has increased for every disease type between 1995 and 2006.



SOURCE: CENTERS FOR DISEASE CONTROL. DPT IS FOR 4 DOSES OR MORE. POLIO IS THREE DOSES OR MORE AS ARE HIB AND HEPATITIS B.

CERVICAL CANCER VACCINE

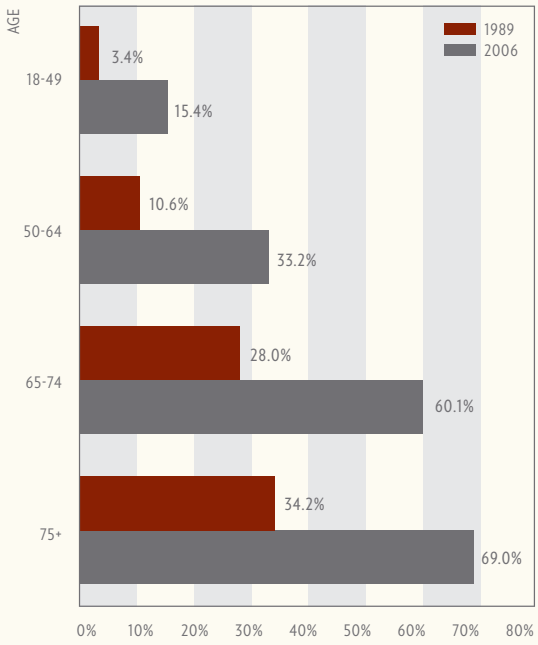
In 2007, some 25.1 percent of adolescent girls received the new HPV4 vaccine against four strains of human papillomavirus.



SOURCE: CENTERS FOR DISEASE CONTROL

INFLUENZA VACCINE COVERAGE

Flu immunizations among U.S. adults 18 and over has increased dramatically in the last 17 years.



SOURCE: CENTERS FOR DISEASE CONTROL

Stormy Weather

The Burrill Biotech Select Index, a price-weighted index tracking 20 of biotech's blue-chip companies, finished October down 10 percent. In comparison, the Dow fell 14 percent and the NASDAQ took a 17 percent hit. The performance of the indices reveals the true magnitude of the effect that the market perturbations had on the valuations of biotech companies in the various sub-sectors of the industry. They also reflect the realities that investors still have faith in the blue-chip biotechs but are staying well away from the more risky emerging biotech companies, with the stock values of the mid-cap and small cap biotechs taking a pounding.

As for biotech IPOs, 2008 is shaping up to be one of biotech's worst in history, with only one completed as of early November. Except for venture capital deals, which have remained at a steady state for the past three quarters, generating about $1 billion each quarter, all other forms of financing have fallen, compared to the first quarter of 2008 and comparative 2007 figures.

Collectively U.S. biotech financings, both for public and private firms, raised $2.5 billion in the third quarter, bringing the year-to-date total to almost $8.2 billion. The industry is on pace to generate about $10 billion in the year.

—Peter Winter

BIOTECH INDICES

Index	12/31/07	10/31/08	% change Month	% change Year	% change Year
Burrill Biotech Select	331.52	297.38	-10.41%	-10.30%	-10.30%
Burrill Large-Cap Biotech	437.71	384.97	-12.00%	-12.05%	-12.05%
Burrill Mid-Cap Biotech	201.89	144.63	-19.17%	-28.36%	-28.36%
Burrill Small-Cap Biotech	137.6	83.51	-24.28%	-39.31%	-39.31%
Burrill Genomics	104.29	64	-24.70%	-38.63%	-38.63%
Burrill Diagnostics	159.43	139.75	-18.46%	-12.34%	-12.34%
Burrill Nutra-ceuticals	593.04	402.44	-20.12%	-32.14%	-32.14%
NASDAQ	2652.28	1720.95	-17.35%	-35.11%	-35.11%
DJIA	13264.82	9325.01	-14.06%	-29.70%	-29.70%
Amex Biotech	786.5	674.34	-13.99%	-14.26%	-14.26%
Amex Pharma	338.52	269.99	-7.69%	-20.24%	-20.24%

SOURCE: BURRILL & COMPANY

US BIOTECH FINANCINGS ($M)

	2005	2006	2007	2008 Q1	2008 Q2	**2008 Q3**	**TOTAL**
PUBLIC							
IPO	$819	$920	$2,041	$6	$0	**$0**	**$6**
Follow-ons	$4,194	$5,766	$6,311	$701	$312	**$693**	**$1,706**
PIPEs	$2,376	$2,027	$1,618	$370	$203	**$308**	**$881**
Debt	$5,565	$13,978	$6,749	$1,622	$360	**$408**	**$2,390**
PRIVATE							
VC	$3,518	$4,236	$4,425	$837	$1,007	**$1,085**	**$2,929**
Other	$1,114	$425	$611	$20	$226	**$20**	**$266**
Total	$17,586	$27,352	$21,775	$3,556	$2,108	**$2,514**	**$8,178**
PARTNERING	**$17,268**	**$19,796**	**$22,365**	**$3,091**	**$4,141**	**$2,962**	**$10,194**
TOTAL	**$34,854**	**$47,148**	**$44,140**	**$6,647**	**$6,249**	**$5,476**	**$18,372**

SOURCE: BURRILL & COMPANY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Bike Messengers

People with cancer raise awareness of the disease in "Breakaway Miles" that take place during the annual Amgen Tour of California, the country's premier cycling event.

Story by Eric Wahlgren, Images courtesy of Amgen

Got your back: Brandi Newquist *(left)* and her support team including Amgen's Joe Miletich *(front, right)* ride a Breakaway Mile in Santa Clarita, California in February some six months before cancer would overtake her.

The grueling Amgen Tour of California cycling race covers some 650 miles across some of the Golden State's toughest terrain. But the most demanding mile is perhaps cycled by non-racers on urban straightaways. An hour before the professional racers stream across the finish line of key stages in the Tour, cancer survivors and their "support teams" ride what's called a "Breakaway Mile" to raise awareness of the disease and of the free services available to patients. Although these rides are ceremonial, the reception these cyclists get is anything but. Cow bells clang raucously. An ESPN television crew follows their progress. And super-sized video screens broadcast the event to the cheering crowds lining the route.

One of the Breakaway Mile riders during the last Tour in February was Brandi Newquist, whose battle for survival began with a breast cancer diagnosis in 2003. Two months after her ride, the Valencia, California resident was diagnosed with brain cancer and the disease later spread to her liver. Cancer finally claimed her life in August, her husband Bobby Newquist says. For Brandi, who liked to ride a mountain bike and take spin classes, the Breakaway Mile was an emotional tribute to her courage and strength, he says. "Hearing everyone ringing the bells made you feel like a professional ath-

lete," says Newquist, who rode on Brandi's support team along with her oncologist, friends, and Amgen's Joe Miletich, senior vice president, research and development. "That was something you didn't get when we walked into a chemotherapy room."

Before cancer overtook her, Brandi did all she could to raise awareness of the disease, taking part in three clinical trials and volunteering as an organizer with a fundraising event organized by the American Cancer Society, Newquist says. Brandi saw the Breakaway Mile as a chance to honor people who helped her along the way, he adds. "They all played a part in trying to get her to feel better and to deal with the disease on a daily basis," Newquist says. "That experience for her was exhilarating. She was so overwhelmed by the generosity of everyone."

Just as professional cycling teams have support staff including coaches, mechanics, and doctors who help them win, Breakaway Mile participants ask some 10 individuals including oncologists, spouses, and friends who have helped them battle cancer to ride along with them. "Once a person hears the words 'you have cancer,' they don't hear anything else," says Kathryn West, Amgen's oncology advocacy director. "You do need people who are advocating for you and supporting you. That makes a difference in people's outcomes."

Rain, rain, go away: Riders and spectators gather at the hospitality tents in Pasadena, California.

Biotech giant Amgen officially announced its sponsorship of the eight-day Tour of California, perhaps the largest pro cycling race in the United States, in 2005. It was unusual for a company like Thousand Oaks, California-based Amgen to sponsor a sporting event, says Amgen spokeswoman Mary Klem, as such events usually receive backing from consumer products companies seeking opportunities to market their products. Amgen medicines aren't sold directly to patients, but rather are prescribed by doctors for serious illnesses. Amgen viewed the sponsorship as an opportunity to help educate people about biotechnology and raise awareness of the services available to people with cancer. As a complementary component of the Tour, the Breakaway from Cancer initiative, of which the Breakaway Mile event is a part, was born. The initiative also helps support free programs offered by The Wellness Community and

(bottom) Team effort: Brandi Newquist *(fifth from the left)* and Amgen's Joe Miletich *(to Newquist's right)* along with other members of her support team.

the National Coalition for Cancer Survivorship, two national cancer support organizations.

As it happens, Amgen was no stranger to cycling events, having been a sponsor of The Arthritis Foundation's California Coast Classic Bicycle Tour, which raises more than $1 million annually in the fight against arthritis. But Amgen's sponsorship of the Tour initially raised some eyebrows because the company makes recombinant versions of the hormone erythropoietin or EPO, which boosts production of the oxygen carrying red blood cells. Although the drugs are used to treat anemia in chemotherapy patients and patients with chronic kidney disease, the so-called EPO drugs have become the pro cycling world's most abused performance-enhancing drugs and are banned by the Tour de France, the Olympics, and other sporting events, including the Tour of California. At the time of the sponsorship announcement on November 5, 2005, Amgen said the company's involvement would help it combat the inappropriate use of its drugs and educate athletes about the potential dangers of misuse. Kristen Davis, another Amgen spokeswoman, says the sponsorship gives the company "an opportunity to talk about the appropriate uses of our medicine."

When the Tour of California takes place February 14-22, there will be four Breakaway Mile segments featuring local cancer survivors. Among the support-team riders will likely be Amgen's Miletich, who has already participated in two previous years. The event is inspiring, he says, giving patients a chance to feel good about where they are in their lives. The "survivors battle so hard and so long and they never get a chance to actually display how proud they are of what they have accomplished," Miletich says. "When is a cancer patient ever treated like a hero? They are in front of thousands of people getting applause."

Miletich says the ability to participate has been important for him and other scientists because "it reinforces that the work you do might mean something to somebody some day," he says. Miletich says that after his rides, he has shared the survivors' stories with other Amgen scientists, engineers, and employees. "They all understand this mission and they would all

(top) Strong finish: Racers near the finish line of a Tour of California stage in San Luis Obispo, California.

Winner for a day: George Hincapie crosses the finish line first in stage 7 of the Tour in Pasadena, California, but he does not win the overall race.

rather do this instead of something that is not quite as impactful," he says. "But when they actually hear the stories, you see they are visibly affected."

Although survival rates are improving, cancer remains the third biggest killer worldwide after heart disease and infectious disease, responsible for 12.6 percent of all deaths, according to the World Health Organization. The Breakaway Mile helps remind the public that there is still a long road ahead, survivors say.

"It was one of the best experiences of my life," says Bob Hammer, a 40-year-old testicular cancer survivor, who cycled a Breakaway Mile in Santa Rosa, California in 2006. "Personally, it just felt great to be out there and representing the fight against cancer in that way."

For his support team, Hammer, a father of two who lives in Danville, California, picked 10 buddies who helped him get through his long struggle that began with his diagnosis in 1999. "To have the support from your friends is huge," says Hammer, a marketing executive who spends his free time organizing an annual Have a Ball Foundation golf fundraiser for cancer. "A lot of times, they don't know what to say, but the fact that they are there or calling means so much at the end of the day."

George Hincapie, a professional cyclist and Tour de France veteran, has taken part in the Breakaway from Cancer initiative since it began, helping to raise money through a charity ride and other activities. "Nearly everyone is touched by cancer, including my family, and it's important for those affected to realize they don't have to face the illness alone," says Hincapie. Indeed, Hincapie should know. He assisted a high-profile cancer survivor—Lance Armstrong—in all of his Tour de France victories. TJOLS

The Amgen Tour of California and the Breakaway Miles will take place February 14-22.
Visit www.amgentourofcalifornia.com and www.breakawayfromcancer.com for more information.

Job well done: Cancer survivors Justin Baldwin *(on the white cruiser)* and his wife Deborah Baldwin *(directly behind him)* finish their Breakaway Mile in San Luis Obispo, California.

With a little help from my friends: Cancer survivor Bob Hammer *(front, left)* picked buddies who had helped him get through his struggle with the disease to accompany him on a Breakaway Mile in Santa Rosa, California..

Pedal power: The Amgen Tour of California covers some 650 miles across some of the Golden State's toughest terrain.


QUICK STEP

Super Size Me

Even when their penises are of a normal size, men will go to great lengths to go to great lengths.

By Daniel S. Levine

Feeling small: men are bad judges of how their genitals compare to other men's and often think they are smaller than average when their penises are of a normal size.

In one of the commercials for the "natural male enhancement" pill Enzyte, Smiling Bob, a happy guy with the carved-in-stone smile across his dopey face, dons a Santa suit for an office holiday party. The ad, chock full of double entendres like all the Smiling Bob spots, features a voiceover that tells viewers that "Bob's got the one thing every lady likes" now that he is taking Enzyte. As the women line up to sit on the "chubby Santa's lap," the announcer reports that "with things heating up on the ol' North Pole," it looks like "there's no mistaking this Santa for an elf anymore."

The not-so-subtle television ads for Enzyte were nothing compared to the claims the company had once run in the backs of men's magazines and on its website. According to a lawsuit, when Berkeley Premium Nutraceuticals (formerly LifeKey) launched the product in 2001, it claimed the product would add "one to three inches to your size" and it boasted a 98.3 percent success rate. The company also claimed that Enzyte users experienced, on average, a 24 percent increase in erection size, and that over an eight-month program, users' erectile chambers, as well as their penis, would enlarge up to 41 percent.

Bob may be forever smiling, but Berkeley's founder and CEO Steve Warshak is not. Warshak, who once ran a company that sold billboard space for ice rinks and soccer fields, had bigger ambitions. Taken with the success of Viagra, he commissioned a New Jersey company to formulate a concoction of vitamins and herbal ingredients with reputed libidinous powers and dubbed it "Enzyte." Though he was on his way to building a nutraceutical empire, he has fallen on hard times. In 2004, he projected the company would reach $240 million in sales for Enzyte and a variety of other herbal products touted to do such things as fight aging, manage weight, and spice up life in the bedroom.

But his fortunes turned. Following a complaint with the Federal Trade Commission, two class action lawsuits, and a federal criminal prosecution, a federal court found him guilty of 12 counts of mail fraud, three counts of bank fraud, and 73 counts of money laundering. Warshak was sentenced to 25 years in prison and ordered, along with Berkeley and other defendants, to forfeit more than $500 million in assets. Several others involved with Berkeley were sentenced to shorter sentences including Warshak's 75-year-old mother. The Forest Park, Ohio-based company filed for Chapter 11 bankruptcy protection in September, although Enzyte ads were still running in October.

"The fact that it's been able to be sold with no credible evidence shows how little consumers are protected with fraud of this kind and how ineffective government regulation of these

dietary supplements are" says David Schardt, senior nutritionist with the consumer watchdog group the Center for Science in the Public Interest, which filed a complaint over Enzyte with the Federal Trade Commission. "Enzyte was in one respect no different than a lot of other products. The companies make claims that they do not substantiate and are not required to substantiate really. The Food and Drug Administration does not challenge these companies as long as they don't make a claim about disease."

While Enzyte may be unusual in both its success and failure, it is not alone. In fact, rather than representing a crackdown on purveyors such as Berkeley, Warshak's legal problems resulted from his financial shenanigans rather than outrageous claims made for his products, Schardt notes. Though no one tracks the market for so-called "male enhancement," the case shines light on how big a business penis enlargement has become and how vulnerable men are to marketers who exploit the insecurities they have about their own bodies.

> People are insecure. They are looking for a short cut. They are looking for a panacea. They are looking for the enlarged penis at the end of the rainbow, as it were. They'll try anything.
>
> —*Corey Nahman, Publisher, Internet Drug News*

Berkeley is by no means the only company targeting these men. One lawsuit against Berkeley noted that there were some 50 penis enlargement products sold as herbal dietary supplements with "impossible medical claims" designed to prey on men's anxiety over the size of their penises and their desire to be something more than they are. And it's not just pills. Like any medical condition, it appears there are pharmaceutical, medical device, surgical, and natural approaches, or so marketers would have you think. Whether it's pills, exercises, traction devices, penis pumps, fat injections, weights, or surgery, men are willing to go to great pains (sometime quite literally), to tug, stretch, pull, pump, suck, stab, or cut their way to a greatness that would make women swoon and lesser men weep. When it comes to their penises, it seems most men want to be residents of Lake Woebegone where everyone is above average.

But the quest often ends in disappointment. "There is no pill that can actually change the shape of your penis," says Corey Nahman, a registered pharmacist and publisher of *Internet Drug News* (www.coreynahman.com), which had sought to debunk Enzyte through an analysis of its ingredients. "It's like looking for the pill that makes your arm grow or nose grow. It would be the best-selling pill in the world. People are insecure. They are looking for a short cut. They are looking for a panacea. They are looking for the enlarged penis at the end of the rainbow, as it were. They'll try anything."

Though women often get criticized for being obsessed with issues of body image, it seems men may be no better. In fact, one 2000 study found that 43 percent of men were dissatisfied with their own appearance. Other research shows men are just as prone to body dysmorphic disorder as women. Men's concerns include such worries about scarred skin, thinned hair, overgrown noses, and undergrown muscles.

But among those worries, fears that the genitals don't stack up are a common area of focus. One problem is that men tend to be poor judges of themselves when it comes to their dangling manhood. Men who have a normal-sized penis (between 5.5 and 6.2 inches in length erect and 4.7 to 5.1 inches in girth) tend to believe they don't measure up. A research review published in the urology journal *BJU International* in 2007 reported that men not only worry more about penis size than women (women are more interested in girth than length). Sufferers of "small penis syndrome," a term used to describe men who are overly anxious about the size of their genitals, is also much more common in men with normal-sized penises than those with a micropenis (an erect penis of 2.7 inches or less). Micropenis results from inadequate exposure to testosterone in utero.

"I think many men are worse than many women," says Kevan Wylie, a specialist in sexual medicine at the Porterbrook Clinic in Sheffield, United Kingdom, who co-authored the *BJU International* study. Men's anxiety about their penises represents a form of body dysmorphic disorder, he adds. In part, he blames that on conservative social policy that keeps men badly informed about issues of sex and a society where nudity is more frowned upon than in European countries, giving American men scant opportunities to assess their manhood. "Sex education isn't the flavor of the month in the U.S. or the U.K. In Scandinavia, there's excellent sex educa-

No longer smiling: Enzyte's iconic pitchman Bob keeps smiling, but not so for the male enhancement pill's maker. A federal court found Berkeley Premium Pharmaceutical's CEO and founder Steve Warshak guilty of 12 counts of mail fraud, three counts of bank fraud, and 73 counts of money laundering and ordered him, other defendants and the company to forfeit more than $500 million in assets.

Hung like a god: A statue of Priapus, *(right)* a fertility deity from Greek mythology, who doubled as a protector of male genitalia.

tion, and they are not as hung up about it."

In fact, a 2005 study in the journal *Urology* that examined 92 men complaining of having a small penis size found that 71.7 percent complained of having a short penis in the flaccid state while 28.3 percent grumbled of having a short penis in both the flaccid and the erect state. Study author Rany Shamloul, at the time a doctor in the Department of Andrology and Sexology at Cairo University Hospital in Egypt, reported that when these men were asked about what was the normal size of a penis, 94 percent overestimated the normal length, while the rest said they had no idea at all.

Even men who are not that obsessed about the size of their penises may feel insecure about their size, according to Debby Herbenick, sexual health educator at the Kinsey Institute and a research scientist in the Department of Applied Health Science at Indiana University. Questions about penis size have always been among the most common ones she has had to field, says Herbenick, who hosts the Institute's *Kinsey Confidential* podcast. And that's by no means a recent phenomenon. Even Dr. Alfred Kinsey's letters from men in the 1940s include inquiries from men about what constitutes a normal-sized penis.

Problem is, companies appear to be preying on men's unrealistic expectations. Herbenick tells of one email from a college student who considered buying penis enhancement pills over the Internet through a website and wanted to know if the treatment would work. When Herbenick viewed the site, she was stunned to see it told potential customers that the average penis size is 7.5 inches, even though in fact it is between 5 and 6 inches. Though she explained this to the student and assured him he was normal in length, he said he didn't want to be average. He wanted to be an "A plus student, not a C student," she recalls the student telling her.

"A lot of men have said to me that they have been made more anxious about this because all they have to go on is messages they hear about size, which make them feel inadequate and they don't have any reason to believe that its wrong because the only thing they see is porn," says Herbenick. "When guys really see the data, most of them over time will come around and be okay with their bodies—not all of them. It's not an overnight thing because there's still a lot of unlearning that happens, but it really seems to be an informational issue to me for most men."

The desire to trade in a Yugo for a Cadillac is by no means limited to modern men in advanced industrial societies. Men worldwide have strived to enhance the size of their penis, including the

Topinama of Brazil, who encourage poisonous snakes to bite their penises to enlarge them for six months at a time, report the researcher Wylie, along with his colleague Ian Eardley. Other practices? Indian Sadhus use weights to increase the length of their penis. Dayak men in Borneo pierce the glans of their penis and insert items into the holes to stimulate their partner. Today, there are many places on the Internet that even promote "jelqing," an ancient Middle Eastern technique for so-called penis exercises that proponents say helps increase blood flow to the penis and allows the penis to build strength of the penile chambers and muscular texture.

But many researchers believe the bombardment of messages ranging from high school dick jokes to magazine ads and infomercials promoting so-called male enhancement products aren't helping. Then there's the reality that the only time men tend to get a good look at another man's genitals is by watching porn featuring larger than life stars. All of this does fuel a skewed view.

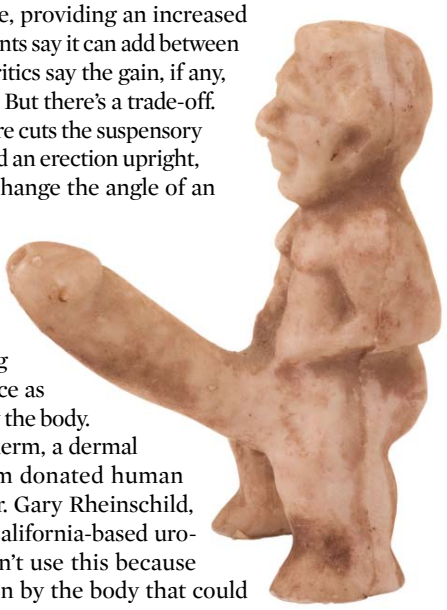
Despite the fact that expectations are rarely met, experts said some penis enlargement methods have success, albeit limited and temporary. And more drastic approaches, they add, can lead to permanent enlargement, although not without risks. Though like pills, researchers interviewed for this article said they are not aware of any clinical evidence that such exercises have any long term effect on the size of the penis. Suction devices, which temporarily increase blood flow by pumping out the air of a chamber in which the penis is placed, are short lived.

There is some evidence that traction devices, which anchor themselves at the base of the penis and stretch it out by grabbing under the head, can actually increase the flaccid size of the penis, say researchers. What evidence there is, however, is poorly documented to support their use, says Wylie. These devices are worn for hours at a time over several months. They are a sleeker and more high-tech approach to an older practice of tying weights to under the head of the penis.

At one website, traction kits retail for between $200 and $500. Men who go this route, though, can overdo it. One urologist described a patient who had come to see him because of a loss of sensation from using weights—20 pounds worth—over a prolonged time, which the doctor described as "utterly ridiculous." This technique can also pool blood in the head of the penis and cause discoloration. Weights and traction devices are also used in conjunction with phalloplasty, surgical penis enhancement. Doctors will recommend the use of weights and traction devices over a year or two following surgery to get the full benefit of the procedure.

> A lot of men have said to me that they have been made more anxious about this because all they have to go on is messages they hear about size, which make them feel inadequate and they don't have any reason to believe that its wrong because the only thing they see is porn.
>
> *—Debby Herbenick, Sexual Health Educator, Kinsey Institute*

Surgical procedures include means for both increasing the length and the girth of the penis. The surgery is not without risks and botched procedures can result in loss of sensation, loss of function, infection, and disfigurement. The cost of penis enlargement surgery varies, but can run around $15,000. The procedure for lengthening the penis doesn't actual increase the length of the penis. Instead, cutting two sets of ligaments—suspensory and fundiform ligaments—that attach the penis shaft to the pubic bone allows part of the penis that is within the body to hang outside, providing an increased appearance. Proponents say it can add between 1 and 2 inches, but critics say the gain, if any, is in the flaccid state. But there's a trade-off. Because the procedure cuts the suspensory ligaments, which hold an erection upright, the procedure will change the angle of an erection.



To increase the thickness of a penis doctors sometimes inject fat, which can lead to a disfiguring corkscrew appearance as the fat is absorbed by the body. Others will use alloderm, a dermal matrix derived from donated human cadaver skin. But Dr. Gary Rheinschild, an Anaheim Hills, California-based urological surgeon, won't use this because of potential rejection by the body that could

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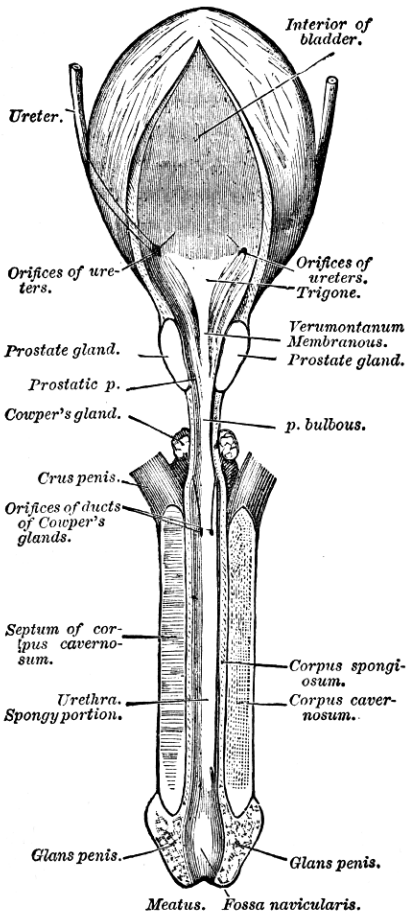


No. 230. — Interior Penal Structure.

lead to what he called an "unaesthetic" penis. Instead, he uses grafts taken from the patient's lower back and buttocks.

Rheinschild, who says he has performed more than 5,000 phalloplasty procedures, has had to perform many reconstructions on other surgeons' patients who underwent phallosplasty procedures that went awry. He blames this in part on plastic surgeons and general surgeons doing these procedures without an adequate understanding of the unique problems affecting male genitalia. He also says good health and healthy habits before and after surgery are critical to a successful outcome.

"Surgery doesn't always work," Rheinschild says. "It depends on the problems the patient may have as far as health is concerned—how well they take care of themselves and whether they smoke or drink. Smoking interferes with the blood flow to the penis and it will cause the small arteries to close so the penis does not get adequate blood."

The medical establishment generally remains dubious of such procedures. The American Urological Association says there is no evidence that penis enlargement surgeries are either safe or effective. As a result, the association deems they should be considered investigational. "There is no evidence of either safety or efficacy and the reason there isn't is because there are no studies," says association spokesman Ira Sharlip, a clinical professor of urology at the University of California, San Francisco. "But those of us who see patients have the impression that there are a lot of complications from these surgeries."

Sharlip acknowledges that surgeons who promote these procedures will say critics are those seeing patients who have developed complications and are not seeing all the great results. That may be true, he concedes, but he asks that if there are great results, why doesn't someone put together objective evidence that would make the surgery respectable? "If somebody did that, then there would probably be a whole lot of urologists interested in doing it," he says. "But there's no data, and the impression that we in the mainstream of urology have is that the results are not good and that some patients have been harmed."

> There is no evidence of either safety or efficacy and the reason there isn't is because there are no studies. But those of us who see patients have the impression that there are a lot of complications from these surgeries.
>
> —*Ira Sharlip, Spokesman, American Urological Association*

Men who are worried that they fall short of the mark do have some less expensive and less extreme alternatives, experts say. If they are fat, they can lose some weight. If they are hairy, they can do a little trimming to help the tree stand out from the shrubbery. If they care to look at themselves, doctors recommend looking in a mirror sideways rather than straight down. If men are still concerned they are too small, they can educate themselves about what is normal outside of the porn industry. And if they remain obsessed enough to take a pill to try to fix their problem, they may want to pop a selective serotonin reuptake inhibitor. It won't make their penis any bigger, but it might make them feel better about what they've got. TJOLS

Roadmap for success: The anatomy of the penis is complex and botched, phalloplasty often occurs because plastic surgeons without a proper understanding of the penis perform the procedures, says urological surgeon Gary Rheinschild.

JOSH LOCKWOOD

Stimulating the Appetite

The pharmaceutical industry is chasing dreams of sexual dysfunction treatments for women that could rival the success of Viagra, but finding such wonder drugs poses lots of challenges. Critics meanwhile charge the industry is simply trying to "medicalize" female sexuality.

By Daniel S. Levine

When Pfizer scientists developed the compound sildenafil citrate in the early 1990s, they were hopeful they had struck upon a new treatment for hypertension and angina. But when the drug candidate known as *UK-92480* began clinical trials, the results were disappointing. It didn't do much for angina, but doctors did notice an unintended effect: subjects treated with the drug developed erections. In an effort to turn its failure into a success, Pfizer decided to pursue the drug as a treatment for erectile dysfunction, it gave the little blue pill the snazzy name "Viagra," and—after winning U.S. Food and Drug Administration approval for the drug in 1998—the drug giant quickly found it had a new blockbuster on its hands. Other drugmakers followed with their own so-called PDE5 inhibitors, such as Eli Lilly's Cialis and Bayer's Levitra, highly targeted drugs that increase the blood flow to the smooth muscle cells in the penis. Together they have built the category into a multibillion market.

But as drugs aimed specifically at treating male sexual dysfunction, PDE5 inhibitors were missing half the potential market. The success of Viagra launched a new pursuit—a treatment for what studies suggest could be an even bigger market—female sexual dysfunction. The target sounds simple enough, only getting there has been tougher than expected.

Female sexual dysfunction falls into four categories: desire disorder, arousal disorder, inability to orgasm, and pain during sex. Complicating treatment of these problems is the fact that each may be intertwined, or may be tied to psychological, social, or cultural issues. A landmark epidemiological study of sexual dysfunction in the United States, published in the *Journal of the American Medical Association* in 1999, found that sexual dysfunction is more prevalent for women (43 percent) than men (31 percent). Though it's an oversimplification, today male sexual function is viewed largely as a matter of hydraulics. The switch is thrown, blood surges, and the machinery gets into position. When the plumbing doesn't work right, a PDE5 inhibitor improves the flow in the pipes and everything gets back to working order.

> I don't think chronically administered drugs for sexual dysfunction, particularly female sexual dysfunction, are going to get through the FDA. Having had many meetings with the FDA, their level of safety concerns seem to be quite high for female sexual dysfunction in particular.
>
> *—Carl Spana, CEO, Palatin Technologies*

But women are different. As one therapists says, the desire circuitry for men is like a simple on-off switch while for women it is like the instrumentation panel for a 747. "The physiology and the understanding of female sexuality are much more complicated, and the various aspects of it are more closely interrelated," says Myron Murdock, a urologist and medical director of the Mid-Atlantic Institute of Clinical research. "With men, it's just getting hard and doing the act. With females there is a

much greater interaction with the psychological aspects of sexuality and the physical aspects of sexuality." If researchers unlock the mystery, the rewards could be huge. The market for the three leading erectile dysfunction drugs in 2007 reached $3.3 billion and the market for female dysfunction could be significantly bigger. But scientists face challenges beyond just the clinical complexities. The FDA seems more concerned about safety than they are about ensuring women are getting their mojos working. And there's a vocal group of critics who say the industry is just trying to "medicalize" female dysfunction—creating a cure for a disease that doesn't exist.

Our understanding of female sexual dysfunction is roughly 30 years behind that of the problem in males, Murdock says. One result of the development of successful treatments for males is a realization by many women that they have problems that need to be treated too, he says.

But women troubled by their inability to enjoy sex find little available to help them. For starters, clinicians say there are very few places to go to find out what is wrong with them, let alone treat them. And diagnosing the problem in women can be a challenge. Physical problems may be compounded by related psychological and social problems and sometimes it can be all three.

> Certainly the federal government doesn't care about people's sexuality in terms of making it more pleasurable, enjoyable, and functional. So they are not going to invest large amounts of money.
>
> *—Julia Heiman, Director, Kinsey Institute at Indiana University*

And when a psychological cause for a woman's sexual problems may be assigned, there may be an underlying biochemical problem in the brain that doctors don't yet understand. In the days before Viagra, Murdock notes, doctors believed that for about 85 percent of all men, a psychological problem was behind their erectile dysfunction. Today, he says, physicians generally agree about 85 percent of men with erectile dysfunction actually have a physiological cause.

In the case of women who suffer from hypoactive sexual desire disorder—a low interest in sex—he estimates about 25 percent have a hormone-related problem due to a lack of testosterone. It is a physical problem doctors can diagnose and treat with off-label use of the hormone. But for the other 75 percent of these women, there may be no physical problem, at least none science can detect. That can include such things as stress from work, exhaustion from raising kids, and a mate that is no appealing. "It's probably due to the fact that their husbands weigh 350 pounds, drink a six pack of beer every night, and every Sunday watch 10 hours of football on television," says Murdock. "If they are turned off by their husbands, they are not going to have a lot of sex, and they are not going to have a lot of interest in sex."

Even though there are clinics in the United States that are using drugs to treat women with sexual dysfunction, there is no drug yet approved by the FDA for the disorder. Instead, doctors are using a small selection of drugs approved for other purposes. For women with desire disorder, doctors will often try treating it with hormone therapy if they find evidence of a hormone imbalance. This can include the use of low-dose testosterone, estrogen, or DHEA, a precursor to both estrogen and testosterone. Some doctors also use the antidepressant Wellbutrin (Bupropion). Unlike selective serotonin reuptake inhibitors or SSRIs, which can cause sexual dysfunction, Wellbutrin has a different mechanism of action. It may improve sexual desire by raising levels of dopamine and norepinephrine—neurotransmitters that some studies have suggested may fuel sexual desire. For women with arousal disorders—a lack of blood flow to and lubrication of the genitals—doctors have turned to PDE5 inhibitors such as Viagra to treat the problem.

But while there is no FDA-approved dysfunction product for females, it's not for lack of trying. Among the products moving through pharma pipelines are two in late-stage clinical trials. BioSante Pharmaceutical's LibiGel is a once-daily transdermal testosterone developed to treat desire disorders. Meantime, Boehringer-Ingelheim's Flibanserin, a serotonin receptor agonists, was originally being developed as an antidepressant, but later was found to boost sexual desire.

Finding therapeutics that work hasn't been the only challenge. As drugmakers race to develop products that can be marketed to treat

the various aspects of the disorder, another problem has been convincing the FDA that these products are safe and effective. Proctor & Gamble won approval in Europe in 2007 for a testosterone patch as a treatment for hypoactive sexual desire disorder. Released under the brand name Intrinsa, the product is for women who have had their ovaries and uterus surgically removed and are receiving estrogen therapy.

But in 2004, an FDA advisory committee rejected P&G's "Fast Track" request for Intrinsa because of worries over potential off-label use of the drug and safety concerns. P&G this summer licensed from Noven Pharmaceuticals a testosterone patch that releases a low dose of the hormone that is absorbed through the skin. But according to Noven's website, P&G has put the program "on hold."

The pharmaceutical giant Pfizer had even less success. It scrubbed attempts to develop a female version of Viagra to treat sexual arousal disorder after clinical trials failed to provide sufficient evidence of its benefits. Though the drug did show signs of improving arousal, the researchers could not find a connection between arousal and desire in women. In other words, the female test subjects showed physiological signs of arousal–blood engorged their clitorises and they became lubricated–but it seemed to have little effect on desire. They had no greater interest in having sex. In 2004, after 8 years of work and clinical trials involving 3,000 women, Pfizer threw in the towel and announced it would stop testing Viagra in women.

And then there's Palatin Technologies, which had stumbled on a promising drug dubbed Bremelanotide, part of a new class of drugs known as melanocortin receptor-specific peptides. Melanocortin receptors regulate a wide range of functions including skin color, food intake, and immune response. Bremelanotide has its origins in work at the University of Arizona where researchers sought to develop a sunless tanning agent to protect people in desert climates from exposure to ultraviolet light and the development of skin cancer. When researchers gave the drug to healthy volunteers in an early-stage clinical trial, they found it gave the test subjects spontaneous erections. Palatin licensed the technology and eventually developed Bremelanotide for both male and female sexual dysfunction. The drug had benefits over other treatments. Testing showed it worked not only on desire, but arousal as well.

In addition, it didn't require chronic therapy as testosterone does. It would only be taken when needed as a nasal spray. After meeting with the FDA to discuss the results from a mid-stage clinical trial, the company concluded it would be unlikely to gain FDA approval because of safety concerns. A small percentage of the subjects, about 0.5 percent, experienced elevated blood pressure. Palatin's partner King Pharmaceutical ended its alliance over the drug, Palatin announced it would not pursue the drug and the stock tanked.

Palatin, however, thinks it may have found a solution. With a different drug it is developing as an obesity treatment that acts on the same receptor, the company was able to avoid the unwanted side effect of raising blood pressure. It's now pursuing a second-generation compound similar to Bremelanotide and expects to move it into the clinic in the second half of 2009. That gives Palatin CEO Carl Spana confidence that the new compound, known as *PL-6983*, has the same activity profile as Bremelanotide without the adverse blood pressure effect. And because it would be administered only when needed, he thinks the drug stands a much better chance of passing muster with the FDA.

"It's an on-demand product, so it would not require chronic administration, which from a

Headache again? Sometimes women who suffer from female sexual dysfunction may not have a physical problem, at least not one of their own..

regulatory standpoint is a key," says Spana. "I don't think chronically administered drugs for sexual dysfunction, particularly female sexual dysfunction, are going to get through the FDA. Having had many meetings with the FDA, their level of safety concerns seem to be quite high for female sexual dysfunction in particular."

But a debate still rages among therapists and clinicians over to what extent, if any, female sexual dysfunction requires pharmaceutical treatments. Julia Heiman, director of the Kinsey Institute at Indiana University, says she believes medical interventions have a role in certain situations. For instance, she found that Viagra provided a benefit to women who suffered from sexual dysfunction as a result of using SSRI antidepressants, in a study she co-authored in July for the *Journal of the American Medical Association*. But she also cautions that while women may be helped with some sort of physiological intervention, it probably won't be a purely genital one. "I still think that Viagra may be appropriate for certain situations for women, but I don't expect it to have a broadband, hyper effect as it did for men, given that a genital response, particularly a clitoral response, is not the core of what most women notice," she says. "It's just not the same experience as men with their genitals. To expect it to have the same effect in women as men, probably wasn't a very thorough assessment of the situation."

Fed up: Bat Sheva Marcus, clinical director for The Medical Center For Female Sexuality, thinks federal regulators don't "get" female sexual dysfunction.

Finding treatments for female sexual dysfunction is complicated not only by the male-female differences in physiological, social, and psychological responses to sex. Corporate interests and the politics of regulation also frustrate efforts, some say. Heiman says if you take the average woman under 50 with desire dysfunction not caused by medication, a lot of the problem has to do with personal issues—such as stressors in their lives, job loss, and economic woes. For a lot of people, these factors make them less sexual.

Some critics of the pharmaceutical industry's efforts to develop treatments for female sexual dysfunction complain that the chase for a little pink pill has thrown the everyday life issues by the wayside. "They are reacting to that because they feel it takes away the relationship and all the psycho-social variables about which quite a bit is known," she says. "But there are not large scale clinical trials because, who cares really?" Certainly the federal government doesn't care about people's sexuality in terms of making it more pleasurable, enjoyable, and functional. So they are not going to invest large amounts of money."

Among the critics is Leonore Tiefer, a psychologist and clinical associate professor of psychiatry at New York University School of Medicine, who charges the pharmaceutical industry with "disease mongering." It's a term borrowed from author Lynn Payer to describe an effort to try "to convince essentially well people that they are sick, or slightly sick people that they are very ill." The question, says Tiefer, is what kinds of things constitute sexual problems and who is in a position to articulate or define what constitutes women's sexual problems? Where does the information come from, and who develops it and who disseminates, who corroborates, and what is done about it? She sees the pharmaceutical industry seeking to define female sexual dysfunction through conferences, researchers, and studies it funds.

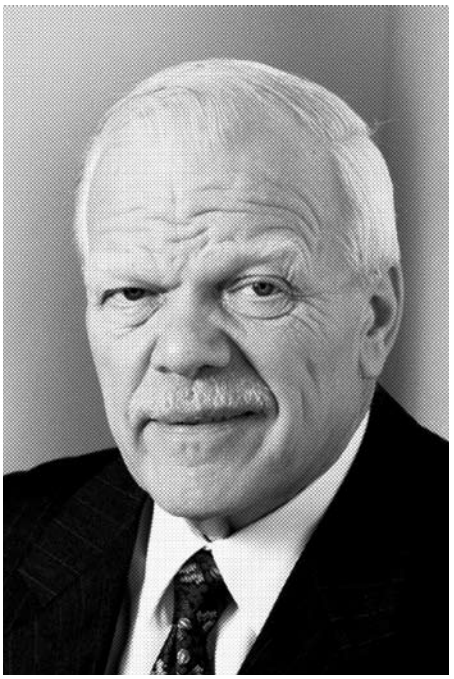
"If you have a sex life, how do you decide it's satisfactory?" she asks. "How did you used to decide 5, 10, 20 years ago? Who stuck their grimy little fingers in there to change your own sense of what is satisfactory or not, what your expectations are? That's really what disease mongering and medicalization are all about—it's changing expectations. Once the expectations are changed, the game is almost entirely lost at that point. Then getting a product through is child's play."

But some who treat women with sexual dysfunction say they are stymied in their efforts to help women who do suffer from physiological causes as opposed to social, relationship, or psychological reasons. The hurdles come from

an FDA reluctant to approve new therapies because of heightened safety concerns as well as the use of clinical endpoints that often fail to reflect whether a drug provides efficacy. What's more, they face lobbying efforts from therapists opposed to a pharmaceutical approach to the treatment of female sexual dysfunction.

Defining what works for females is ultimately a more elusive target than for males. Bat Sheva Marcus, clinical director for The Medical Center For Female Sexuality, says one study in which she enrolled patients had as its endpoint determining how often a subject had penile-vaginal intercourse. She notes such a requirement meant she couldn't include lesbians in the study. If a woman was having great oral and manual sex, it didn't count. "With male studies, it's erection up, erection down," she says. "That's a little easier. I don't think the FDA thinks of female sexual dysfunction as a serious problem. And I think that they don't get it. And I think they don't necessarily have a good handle on how you judge whether something is working or not."

But women with female sexual dysfunction may be fighting something more powerful than the FDA, the pharmaceutical industry, or the therapists lobby. Natural selection may be the real force to be overcome. Sociolgist Edward Laumann says he's been moving toward an interpretation that sexual desire is in fact a "potentially life threatening thing to women." Laumann is the University of Chicago professor who was the lead author on the epidemiological study published in *The Journal of the American Medical Association* in 1999 that first put numbers to female sexual dysfunction. He reasons that for most of the long sweep of human existence, mankind lived in hunter-gatherer societies where there was a regular struggle for survival. Following his logic, sex meant fertility, and being pregnant made a woman more vulnerable to predators and less able to care for herself. The more a women was interested in sex without paying attention to the optimal circumstances of carrying a baby and having a committed mate, he theorizes, the more at risk they would be of getting pregnant and being selected out of the gene pool because they would be more likely to die during pregenancy.



"My argument is there is a relatively high adaptive response of sexual lack of interest and desire is really adaptive for women in the sense it actually protects them from what could be a life threatening circumstance," he says. "The fact that we now have a disconnect between sex and fertility doesn't mean that the hardwiring in the brain and the body and all that can change that quickly."

So for mates of women with female sexual dysfunction the answer might not be flowers and chocolate, getting in shape and cleaning up after themselves, or even finding a magic pill. It may be just a matter of having the patience to wait for the knuckle-dragger on the other side of the bed to evolve. TJOLS

> If you have a sex life, how do you decide it's satisfactory? How did you used to decide 5, 10, 20 years ago? Who stuck their grimy little fingers in there to change your own sense of what is satisfactory or not, what your expectations are. That's really what disease mongering and medicalization are all about—it's changing expectations.
>
> *—Leonore Tiefer, Clinical Associate Professor of Psychiatry, New York University School of Medicine*

Position evolving: Sociologist Edward Laumann, who first put the numbers to female sexual dysfunction, thinks natural selection may be to blame for the disorder.

A Loaf of Bread, a Carton of Milk,...and a Diagnosis

Although they've been around for years, health clinics located in grocery stores and retail pharmacies have expanded dramatically in the last two years as consumers seek easier access to doctors. Worried about being left behind, large hospital systems are now opening their own "doc-in-a-box" outlets.

By Eric Wahlgren

DANIEL S. LEVINE

When one of Hilario Aguirre's three daughters gets the flu or an earache, the heavy equipment operator says he no longer tries to get "squeezed in" at the family doctor's office. Instead, he or his wife Raquel takes the sick girl to a Rite Aid retail pharmacy about a 10-minute drive from their West Sacramento, California home. In the back of the store, just beyond shelves stocked with pet food and antifreeze, sits a new kind of doctor's office where the Aguirres can walk in seven days a week, and on most holidays, without an appointment. Like fast-food outlets, the clinic conspicuously posts a "menu of services" along with its flat fees: $63 for most visits, $25 for a flu vaccination, and $35 for a cholesterol screening, to mention a few. "Quick, convenient healthcare" reads a sign. Typical visits last 20 to 30 minutes and patients get pagers if they want to shop while they wait.

But there's a twist. This "Express Care" outlet is not the brainchild of some healthcare upstart but rather one of six such clinics opened by Aguirre's medical provider Sacramento-based Sutter Health, one of the state's largest health systems with roots going back more than a hundred years. Because a visit to Express Care is considered "in network," Aguirre's insurance requires him only to supply the $25 co-pay when he comes in. "You are always going to get in on the same day and you never have to wait more than 15 minutes," says the 35-year-old. "I'd hate to have to go to the emergency room and wait there for hours."

The doc-in-a-box concept, as it's called, is nothing new. The first retail-based clinic QuickMedx (now MinuteClinic) opened some eight years ago in the Minneapolis-St. Paul area. What is new, however, is the dramatic expansion of these clinics. In the last two years, their numbers have more than tripled to 1,104 clinics as of November 1, from 343 in the beginning of 2007, according to research and consulting firm Merchant Medicine in Shoreview, Minnesota. The growth comes as a faltering economy coupled with always-on-the-go lifestyles lead Americans to seek basic care that is cheaper and more convenient. "The reality is, many patients in the U.S. have difficulty accessing care from their primary care physician," says RAND Policy Analyst Dr. Ateev Mehrotra, who is also a professor at the University of Pittsburgh and has studied the emergence of retail clinics. "When they have something that is urgent but relatively minor, these retail clinics are trying to fill that niche."

Today, the market leader MinuteClinic is owned by CVS, but many clinics are owned by some two dozen independent operators, including The Little Clinic in Brentwood, Tennessee, RediClinic in Houston, and QuickHealth in San Mateo, California (See "Healthcare on the Go," p. 50). These clinics tend to be situated in high-traffic locations such as Wal-Mart, Kroger, Duane Reade, and Target stores. Growing particularly fast are clinics such as Express Care that are affiliated with large healthcare providers. That segment has nearly quadrupled, going from 30 clinics in the beginning of 2007 to 108 as of November 1."It is a defensive play," says Tom Charland, Merchant Medicine's CEO. "The hospital systems would like to neutralize competition in their markets by getting in before the big clinic operators get there. Secondly, they want to generate visibility for their brand out in the community, and as a result, bring new patients into their system."

As healthcare providers themselves tell it, opening clinics in pharmacies, big-box stores, and shopping malls is one way for the medical establishment to respond to the demand for quick and easy medical care. "The service is aligned with Sutter Health's vision to be a leader in healthcare access and affordability," says Pete Dzwilewski, program director for Sutter Express Care, which has six clinics in the greater Sacramento area. "You can get bread, milk, and a diagnosis all at the same time," says Andrelyn Almario, a certified nurse practitioner who sees patients at the Express Care in the Natomas neighborhood of Sacramento where the Aguirre family goes.

There's no doubt that cheap, in-and-out style clinics may have wide appeal, especially for many of America's 45.7 million uninsured. At these clinics, they can pay a flat fee for basic care such as a physical, a cholesterol check, or treatment for a urinary tract infection. There may be more than 6,000 clinics nationally by the end of 2012, according to forecasts cited by the California Healthcare Foundation, an Oakland, California-based organization focused on improving healthcare quality and access.

But if the numbers continue to grow, the medical establishment may be forced to rethink how best to provide primary care, given rising healthcare costs and a shortage of primary care physicians. Critics of retail-based clinics, including several prominent physicians organizations, have charged that they threaten the bedrock of the "medical home." Making sporadic visits to clinics only when health issues

Express healthcare: In the back of a Rite Aid pharmacy in Sacramento, Sutter Health's Express Care nurse practitioner Andrelyn Almario checks out 9-year-old Alexia Agurrie's ear while sisters Melania, 3, and Estrella, 12, look on.

BY THE NUMBERS | Retail-based Health Clinics

Number of retail-based medical clinics as of January 1, 2007	**343**
Number of retail-based medical clinics as of November 1, 2008	**1,104**
Number of retail-based medical clinics forecast for the end of 2012	**6,000**
Annual number of visits to primary care physician offices	**476 million**
Annual number of retail clinic visits	**Estimated 2 to 3 million**
Percent of retail clinic visits represented by patients ages 18-44	**43 percent**
Percent of visits to primary care physician offices represented by patients ages 18-44	**23 percent**
Percent of retail clinic visitors who have a primary care physician	**39 percent**
Percent of Americans who have a primary care physician	**80 percent**
Average family practice physician's salary	**$156,164**
Average nurse practitioner's salary	**$80,414**
Cost of treating a patient for strep throat in an emergency room	**$328**
Cost of treating a patient for strep throat in a doctor's office	**$122**
Cost of treating a patient for strep throat in a retail clinic	**$101**
Percent of retail clinic visits paid for out of pocket when the trend began in 2000	**100 percent**
Percent of retail clinic visits paid for out of pocket in 2007	**15.9 percent**

SOURCE: CALIFORNIA HEALTHCARE FEDERATION, MARY KAY SCOTT, SCOTT & COMPANY, HEALTH PARTNERS, TOM CHARLAND, MERCHANT MEDICINE, ATEEV MEHROTRA, RAND, SALARY.COM

> The hospital systems would like to neutralize competition in their markets by getting in before the big clinic operators get there. Secondly, they want to generate visibility for their brand out in the community, and as a result, bring new patients into their system.
>
> —*Tom Charland, CEO, Merchant Medicine*

come up could prevent patients from developing a relationship with a primary care doctor who can coordinate their care as they age, they argue. A majority of the clinics are staffed by certified nurse practitioners and physician assistants who provide carefully prescribed care for only a limited number of conditions.

With a debate simmering over the future of primary care, the retail clinic model that seems especially well positioned is that of clinics run by established healthcare providers like Sutter. Why? Belonging to a larger health network may blunt the argument that these clinics erode the concept of the medical home. At Sutter Express Care for example, patients seeking additional treatment or a physician to follow them can easily be referred to doctors in the Sutter network. An electronic medical record is created that details any visit and is immediately available to hospitals and physician groups within Sutter.

Dzwilewski says about half the patients the clinics treat are new to Sutter's network, and up to 10 percent make subsequent visits to primary care physicians in the network. "I think that's an advantage for us," he says. "We can provide continuity of care. We don't want to be a patient's medical home. But we have the ability to use our network to find patients a medical home." The West Sacramento father of three Aguirre says he likes the flexibility. "We all have the same primary care doctor and we go there for regular physicals," he says. "But when something comes up, the clinic is a little closer and it's quick, easy, and thorough."

Not surprisingly, the retail clinic concept was not an easy sell at first to physicians within large health networks, says Kimberly Hodgkinson, director of finance and operations for Milwaukee-based Aurora Health Care's QuickCare, which has 19 clinics. Aurora has 14 hospitals and

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The reality is, many patients in the United States have difficulty accessing care from their primary care physician in a timely manner. When they have something that is urgent but relatively minor, these retail clinics are trying to fill that niche.

—Dr. Ateev Mehrotra, Policy Analyst, RAND

more than 1,100 physicians in Wisconsin, she says, and in 2006 became the first hospital system to open retail medical clinics. "We ran into a lot of different opinions," says Hodgkinson. "We told them this was the trend. If we weren't going to step up to the plate and provide the service, someone else would. When we put it like that, they kind of backed off."

The retail-based health clinic got its start eight years ago when MinuteClinic's founders reckoned there might be a better way to get care for ills like strep throat, the flu, or aches and pains than going to an urgent clinic or emergency room. "They were frustrated by the fact that they had to go to urgent care and wait for two hours when they thought it wasn't rocket science," says Charland, who was part of one of MinuteClinic's early executive teams. They opened clinics that would handle basic care for a prescribed number of conditions inside of Cub Foods, a grocery chain.

Despite several different models, the general concept is the same. "Convenient care" clinics, as they're also called, generally don't require appointments, are open longer hours including nights and weekends, and are usually located in high-traffic locations such as Wal-Marts and retail pharmacies. Although all clinics have supervising physicians, most professionals providing the care are non-physicians, such as physician assistants or nurse practitioners—a choice that saves on staffing costs. A family practice physician makes $156,164 on average compared with $80,414 for a nurse practitioner, according to Salary.com.

In the clinics, practice guidelines published by physician organizations are used to help properly diagnosis and treat a limited set of condi-

Andrelyn Almario is a nurse practitioner with Sutter Health's Express Care retail clinic located in a Rite Aid in Sacramento: "You can get bread, milk, and a diagnosis all at the same time," she says of the clinic.

tions. Although patients used to have to pay out of pocket for visits, more clinics these days are accepting insurance. "This is one of the rare innovations we've seen recently in healthcare delivery," says healthcare consultant Mary Kay Scott, a principal of Scott & Company who has studied the field extensively. The cost of treating strep throat, including drugs, amounts to about $101 in a retail clinic, versus $122 in a doctor's office and $328 in an emergency department, says Scott, citing a survey by Health Partners, a Minnesota HMO. "You've taken this group of customers and you're serving them better, cheaper, and more conveniently," she says. "It might be crass, but this is what Jiffy Lube did with its auto maintenance customers."

Obviously, retail-based clinics are still only a tiny player in providing basic health services. Clinics log an estimated 2 to 3 million visits annually, versus 476 million visits to primary care facilities, says Scott. But surveys suggest that nearly 20 percent of American adults are very likely or likely to use a retail clinic in the future, Scott says. The bulk of clinic users don't have regular healthcare providers, according to a recent RAND study, which appeared in the September/October issue of *Health Affairs* and is the first to look at the types of patients who use these clinics. In fact, just 39 percent of the patients—among the 1.3 million visits analyzed between 2000 and 2007—had primary care physicians, compared with 80 percent of people nationally. "I think clinic users are less likely to have a relationship with a primary care physician and less likely to be going to see a doctor regularly," says Mehrotra, the study's lead author.

> We as a city have invested an enormous amount in creating this very comprehensive system of community health centers. If there are problems with those sites, would we not be better off fixing those problems than adding retail medical clinics?
>
> —*Dr. Barbara Ferrer, Executive Director, Boston Public Health Commission*

Healthcare on the Go

Unlike other retail-based clinics, QuickHealth relies on actual doctors and doesn't take insurance. Some of its service policies take inspiration from Starbucks.

David Mandelkern likens the medical clinics he runs in Wal-Marts and pharmacies to Starbucks outlets. When the former high-tech entrepreneur opened the first QuickHealth in San Mateo, California in 2005, he sought to emulate the coffee chain's reputation for being convenient, offering a warm atmosphere, and providing high levels of service. "At Starbucks, you are going to get a consistent quality product, no matter who the barista is that day," says Mandelkern. "We're a doctor's office run like a Starbucks."

Like other retail-based medical clinics, his are open seven days a week, don't take appointments, and post prices for basic care services for all to see. But unlike many other clinics, Maldelkern's don't accept insurance—a choice that reduces overhead costs. Another big difference: each clinic is staffed with at least one physician, whereas many other chains rely on nurse practitioners and physician assistants. The reason for the difference? Some 80 percent of the patients who visit QuickHealth outlets are uninsured, suggesting few have primary care doctors. What's more, some 60

COURTESY OF QUICKHEALTH

The clinics seem to be responding to a growing demand. The study found that the bulk of the users—43 percent—were patients aged 18 to 44—a group that makes only 23 percent of the visitors to primary care physician offices. "As opposed to older people, clinic users are probably more likely to have a job and other commitments, including childcare," says Mehrotra. "That makes it more difficult to miss work and get to the doctor at an inconvenient time."

And they're becoming more than just a safety net for people without adequate insurance, Mehrotra says. Originally, most retail-based clinics required out-of-pocket payment, but they are increasingly accepting insurance. In 2000, 100 percent of visits were paid for out of pocket, versus only 16 percent in 2007, Mehrotra says. "I think the patient population that is being served is slowly expanding, going beyond to a larger segment that is more likely to be insured," he says.

In a finding that may provide some reassurance to physicians worried about the clinic's growing reach, the study says their services appear to remain circumscribed. Nearly 90 percent of the visits were for 10 simple acute conditions and preventive care, according to the RAND study. Those were upper respiratory infections, sinusitis, bronchitis, sore throat, immunizations, inner ear infections, swimmers ear, conjunctivitis, urinary tract infections, and other a screening lab test or a blood pressure check. Meantime, the same conditions accounted for 18 percent of visits to primary care physician offices and 12 percent of emergency room visits.

Despite the clinic's limited services, concerns about the potential lack of continuity of care remain. The American Medical Association and other physician groups have publicly expressed reservations about the growth of the clinics and have issued suggested guidelines. These include offering only a limited scope of clinical services as well as protocols for ensuring referrals and continuity of care.

Most vociferous, perhaps, has been the American Academy of Pediatrics, which is strongly opposed to the use of retail clinics by children and adolescents. Among the concerns are the potential for lack of follow-up care if a retail clinic diagnoses a child with a condition. The AAP is also worried about the potential public health

percent are Latino, a reason for which six of the 11 clinics are located in Farmacia Remedios, a pharmacy chain that caters to Latino customers.

"For the scope of the services that we needed to provide, our patients really need to see a physician," Mandelkern says. As a result, QuickHealth is able to offer more extensive services than many other retail-based clinics, including wound suturing, STD tests, and pelvic exams.

QuickHealth and clinics like it ease the burden on the health system, Mandelkern argues. Since the company began seeing patients, he estimates QuickHealth has saved about $12 million in medical costs by diverting patients from emergency rooms. "I was trying to serve people who were having a difficult time getting primary medical care," he says. "Too many were showing up at the emergency room. What they really needed was a medical office." If it weren't for QuickHealth, Mandelkern says, some 40 percent of his patients say they would go to the emergency room for basic care and another 40 percent would tough it out. "The problem is, when those who try to tough it out at first end up at the emergency room, they are train wrecks," he says. "That is not good."

QuickHealth does all it can to ensure continuity of care, Mandelkern adds. Like other clinics, records of QuickHealth visits are saved electronically and can be printed out so that patients can take them if they need follow-up care. QuickHealth has a referral network to help patients obtain ongoing care. "I don't make claims to be the Mayo Clinic," Mandelkern says. "However, when you compare us to the alternative, we're a lot better than trying to get continuing care from an ER visit. We may not be the perfect medical home, but at least we're a medical condo that people can rent for a while."

The future presents both opportunities and challenges for the business model, he says. Mandelkern plans to expand to 250 stores, with target states including California, Arizona, Texas, and Nevada, where immigration patterns all suggest an attractive market. Plus, he says, "the number of people who need our services tends to increase with the worsening economy." But Mandelkern, who is in his third phase of funding, says the "stores" take a while to break even. "This is not a get-rich-quick scheme," he says.

—E. W.

threats that could arise when patients with contagious diseases—think mumps or measles—show up in a busy grocery store for treatment.

What's more, even though the clinics are set up just to treat minor conditions, the academy argues that such appointments are what give primary care physicians the opportunity to strengthen the relationship with their patients and find out if anything else is going wrong, says Dr. Robert Corwin, a pediatrician in Rochester, New York who helped draft the academy's policy recommendations. "When children come into our practice is when we get to know the families," he says. "If they're coming in for an acute illness, we're also looking to see if they're behind in vaccinations and whether there are any other things to worry about."

Opposition exists for other reasons. In Boston, Mayor Thomas Merino and members of the Boston Public Health Commission have opposed retail pharmacy chain Walgreens' plans to open one of its Take Care health clinics in a neighborhood where there are already three comprehensive community health centers. The city-run clinics are open extended hours and at least one weekend day and do not turn away people who cannot afford to pay. "We as a city have invested an enormous amount in creating this very comprehensive system," says Dr. Barbara Ferrer, the commission's executive director. "If there are problems with those sites, would we not be better off fixing those problems than adding those clinics?"

> Retail health clinics are able to take care of our well population while the physician practices can focus on more chronic and complex services.
>
> *—Kimberly Hodgkinson, Director of Finance and Operations, Aurora QuickCare*

Among other worries, Mehrotra says, are concerns that clinics run by pharmacy chains may be more likely to prescribe drugs. But he says that's unlikely if staff members follow the established protocols by using evidence-based guidelines (not using antibiotics for colds for instance). In fact, overprescribing is more likely to happen at a family doctor's office, he says. "There is evidence that out in the community, physicians are actually less likely to use evidence-based guidelines and more likely to use antibiotics," he says.

Medical experts also wonder whether care people receive at the clinics—admittedly for a limited number of conditions and services—is as good as what one would receive at a primary care doctor's office. Future studies should investigate the quality of care provided as well as the likelihood that patients receive follow-up care, Mehrotra says.

But if patient satisfaction is any guide, retail clinics are successful, as most leading operators report satisfaction scores of 95 percent or higher, Scott says. "Either the bar is really low" when compared to regular doctors offices, says Scott, "or after several years of being mainstream, they have maintained really high satisfaction."

Indeed, clinic proponents say the model responds to a critical need. While they agree that encouraging the public to find a medical home is a laudable goal, they say it's not always a realistic one with so many people without sufficient insurance coverage. What's more, they argue the clinics keep patients seeking care for minor problems out of expensive emergency rooms. "The statements from the medical establishment are disingenuous," says Wanda Jones, president of hospital consulting firm New Century Healthcare Institute in San Francisco. "They feel they may be losing their precious referrals from the system. We need the alternatives." The retail-based clinic model takes the provision of basic care out of a high cost setting, she says, freeing up primary care physicians to focus on preventive care and managing more complex and chronic conditions.

Perhaps just as challenging to the retail clinics as some of the practice concerns is the business model. "This is not a get-rich-quick scheme," says David Mandelkern, CEO of QuickHealth, which owns 11 clinics in California. "It takes a certain amount of time to break even." The startup costs for a multi-exam room clinic can approach $145,000, not including staffing and overhead costs for managers, medical records systems, and other expenses, says Scott. Individual clinics usually break even within 18-24 months but nothing is assured—and there have been quite a few flameouts. San Ramon, California-based Wellness Express closed its four clinics in northern California in 2006, about 18 months after opening, after running out of cash. "We could not maintain a consistent level of consumer traffic to maintain long-term viability," CEO Paul Kaufmann told the *Silicon Valley/San Jose Business Journal* at the time.

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Even clinics developed with the backing of big healthcare systems aren't immune to the challenges. Key is building awareness of the new offering, says Sutter Express Care's Dzwilewski. "People aren't accustomed to going to [retailers] for their healthcare needs," he says. The business is not yet at breakeven, he says, but he has seen "steady growth with our volume performance." A hopeful sign for Sutter? The company is "exploring growth opportunities" around Northern California at other Rite Aids and potentially at some employers, Dzwilewski says.

Whether retail clinics expand as much as predicted will likely depend at least as much on their financial success as on their acceptance by the medical community. "They are able to take care of our well population while the physician practices can focus on more chronic and complex services," says Aurora Healthcare's Hodgkinson, expressing one of the clinics' chief rationales. No doubt that argument may become increasingly compelling if healthcare cost inflation as well as the primary care physician shortage continue. TJOLS

> This is not a get rich quick scheme. It takes a certain amount of time to break even.
>
> —*David Mandelkern, CEO, QuickHealth*

A la carte health: Like most retail clinics, Express Care posts all its services and costs in a conspicuous spot. Patients are given pagers if they want to shop while they wait to be seen by a healthcare professional.

From Rags to Royalty

Paul Capital Healthcare offers companies an alternative to debt or equity as a way to raise capital at a time when markets may be unwelcoming to companies seeking cash to fuel growth.

By Daniel S. Levine

In 2004, privately held Acorda Therapeutics was in a bind. The Hawthorne, New York company had suffered a setback on a late-stage clinical trial for its lead compound Fampridine-SR to treat patients with spinal cord injury. Acorda had reported encouraging results in a mid-stage trial of the drug in patients with multiple sclerosis. But the drug failed in its goal of showing effectiveness in treating chronic spinal cord injury in two late-stage trials.

Because of the clinical disappointment, Acorda's venture investors were unwilling to inject new capital into the company. Just a year before, these same investors had stopped the company from going public because they thought the valuation was too low. Despite the promise of Fampridine, the company found it was in need of funding to continue drug development and to prove to new and existing investors that it could make it as a commercial company.

To save itself, Acorda turned to an unusual option: a financing mechanism championed by Paul Capital Healthcare, a boutique Wall Street firm that is becoming an important player in biotech. Acorda's gambit called for swiftly transforming itself from a development company

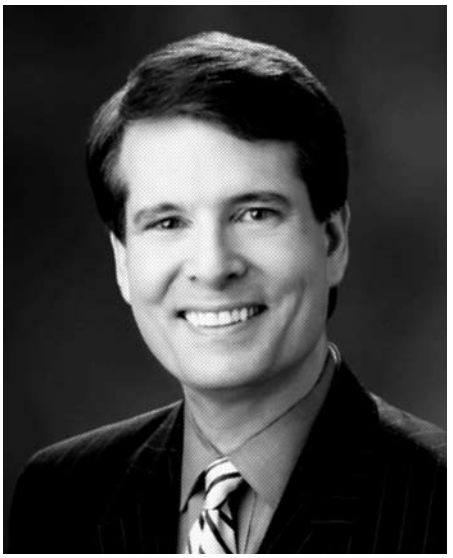
into a commercial one. Although Acorda didn't have access to sufficient capital to advance Fampridine and its other products to market, it did have enough in its piggy bank to acquire the motor neuron inhibiting drug Zanaflex (tizandine hydrochloride) from Elan Pharmaceuticals. For the relatively small upfront outlay of $2 million with milestone payments tied to sales of Zanaflex over several years, it got the short-acting drug to treat spasticity.

The company hoped to use the product to support the development activities, but it still needed upfront investment to get its sales operation up and running, as well as pay for the asset. Here's where Paul Capital came in. In exchange for a revenue stream from Zanaflex, Paul provided Acorda $15 million. The terms provided for staged returns based on the sales volume of Zanaflex. The deal also limited the upside for Paul Capital, in case Zanaflex performed beyond the company's expectations.

"At the end of the day, I don't think we would have survived without it," says Ron Cohen, Acorda's CEO. "It bought us time. It was something where our VC investors were rocked back on their heels because of the setbacks we had had on our lead clinical program. This bolstered everybody because it showed a way for us to re-craft the business plan in a very productive direction to become a commercial stage company. Everyone saw that would potentially open the door in a number of directions."

The risk appears to be paying off. This year, Acorda expects its Zanaflex franchise, with its sales staff of 65, to turn cash flow positive. What's more, it expects to file an application with the U.S. Food and Drug Administration in 2009 for its MS drug Fampridine, now that it has completed two successful late-stage trials of the drug.

Paul Capital is not the only player in the royalty and income revenue financing space. Though it is one of the largest and oldest, rivals are moving in. Among the recent entrants is Cowen Healthcare Royalty Partners, a fund launched by Cowen Group and former Paul Capital partners in 2007. The interest in this type of financing comes at a crucial time. The battered capital markets have resulted in what is perhaps the worst financing environment for biotechnology companies in the history of the industry. It's been roughly a year since there was a biotech IPO of any consequence, as private investors are reticent to fund companies without a clear exit strategy. It also comes as the maturation of the biotechnology industry provides a growing number of marketed products with revenue and royalty streams that companies can use to access financing.



A pathway to profit: Ron Cohen, CEO of Acorda Therapeutics, says he doesn't think his company would have survived without the Paul transaction.

At the end of the day, I don't think we would have survived without it. It bought us time. It was something where our VC investors were rocked back on their heels because of the setbacks we had had on our lead clinical program. This bolstered everybody because it showed a way for us to re-craft the business plan in a very productive direction to become a commercial stage company.

—Ron Cohen, CEO, Acorda Therapeutics

"It provides another source or potential avenue for companies to raise money that given market conditions, reputations, or a myriad of factors might not be able to get the best financing they can from the street," says John McCamant, editor of the *Medical Technology Stock Letter*. "You will see more of it as there are more of it as more products are developed and there are more revenue streams to access."

Paul Capital was founded by money manager Philip Paul in 1991 when he had the opportunity

The nice thing about what we do is we are non-dilutive to equity and we are not dependent on equity returns. We don't view changes in equity markets as a necessary factor in how we change our healthcare revenue stream purchase. People use their products in good times and bad.

—Ken Macleod, Principal, Paul Capital

to acquire 42 venture capital and leveraged buyout fund positions from The Hillman Company, once the biggest player in the private equity market. Paul viewed the secondary market as a way to mitigate risk by eliminating the most volatile elements of a portfolio. Such an approach would lose out on the big early winners of a portfolio, but also the spectacular blow-ups that can occur. By the time Paul invests, the bad companies in a portfolio have generally disappeared, as have the really good early successes.

The secondary market has steadily grown and Paul has grown with it. But in 1998, Paul Capital was approached about purchasing a royalty stream in the cancer drug Taxol from Florida State University. Paul Capital saw the transaction as not unlike what it was doing in the secondary market as a way to mitigate risk. The product was already on the market and was being sold by a large pharmaceutical company, Bristol Myers Squibb.

By 1999, Paul decided it needed to set up a dedicated team if it wanted to pursue other similar opportunities and launched Paul Capital Healthcare in 1999. A year later, it had closed its first fund. Today, it manages $1.6 billion in assets, with offices in New York, London, and San Francisco. The firm has closed more than 20 investments across the pharmaceutical, biotechnology, medical device, and diagnostic space.

A man for all seasons: Paul Capital's Ken Macleod says the beauty of the royalty and revenue financing deals is they function independently of equity markets.

Obviously this form of financing is not for every company. For starters, a company needs to have a revenue stream either through a revenue-producing royalty or sales of a product already on the market. Paul provides an upfront payment to the company in exchange for a percentage of the future product revenues for a defined period of time. The transactions don't dilute equity, and tend to be more flexible than traditional debt because they carry fewer covenants than a lender typically would impose on a company. Paul also accepts the risk that the sales of a product might not meet expectations. If the product fails to perform, Paul suffers.

"The nice thing about what we do is we are non-dilutive to equity and we are not dependent on equity returns," says Ken Macleod, a Paul Capital principal in London. "We don't view changes in equity markets as a necessary factor in how we change our healthcare revenue stream purchase. People use their products in good times and bad."

Obviously, the financing mechanism is not one all companies can take advantage of. "Either you have a royalty stream to sell or you have a drug on the market or about to enter the market. For certain companies, that's a part of the ecosystem," says Glen Giovanetti, Global Biotechology Leader for Ernst & Young. "It is a viable financing tool, especially if you are able to monetize a noncore asset and redeploy the proceeds from that into something you perceive as a higher value, such as advancing an R&D stage asset, without immediate dilution to your stock," he says.

One advantage of such an instrument, says Giovanetti, is that it could provide a way for a public company to realize greater value from an asset. Wall Street might not be giving it much credit for having the asset, instead focusing on the company's clinical pipeline to determine it valuation. It also provides a means of using an asset to fund a promising product in the pipeline without partnering and independent of market conditions.

That is precisely what Avant Immunotherapeutics did in 2005 when it entered into an agreement to sell Paul Capital up to a $61-million interest in the net royalties it would receive on worldwide sales of Rotarix. It was an oral live-attenuated human rotavirus vaccine that the company had licensed to drug giant GlaxoSmithKline. At the time, Avant needed funding to expand its vaccine pipeline, but with a roughly $100-milion market cap, the value of the royalty wasn't being priced into the stock. It needed to raise money for clinical develop-

ment, but at the low valuation it didn't want to dilute its shares.

Avant was able to monetize the revenues from Rotarix, while still retaining a sizable interest in the royalties above a cumulative threshold to preserve the vaccine's significant upside potential. The company got $10 million upfront, with the remaining payments made upon the achievement of milestones, including the product's launch in the European Union and in the United States. With the proceeds from the transaction, the company was able to advance its cardiovascular immunotherapeutic program, get a new manufacturing facility up and running, and advance a pipeline of oral vaccines to combat a wide range of bacterial threats including avian flu and typhoid fever.

"Rotarix underscores our ability to develop commercially successful oral vaccine products," Avant president and CEO Una Ryan said in a press release at the time. "By entering into this agreement with [Paul], we are reaping the benefits of that success today so that we can create more and higher value products tomorrow."

The transactions are not without risk for Paul. The firm's Macleod notes that people often imagine that the risk in the pharmaceutical industry relates to the drug development process. But the risk doesn't disappear when a drug gets approved or introduced to the market. There are risks with the challenges of the marketplace, the competitive environment, pricing, and post-approval regulatory issues. All this leads many drugs to underperform rather than overperform. Because of that, Paul's team may appear to be more like a business development group within a pharmaceutical company rather than a group of investment bankers. Many of its members come out of academia and industry. "What we try to do is work with the companies," Macleod says. "We look at each individual transaction on a deal by deal basis."

Because of that, it's difficult to say precisely what the cost of a Paul transaction would be for a royalty or revenue-financing deal would be for a given product. Representatives of the firm say the cost of a transaction falls between the cost of accessing capital through a mezzanine financing and a public offering. Others, however, estimate the rate of return at roughly 20 to 25 percent.

Though Paul often shares in the upside of the product, it does limit the upside and, depending on the needs and concerns of the entity it is funding, will put a firm limit on what it can make on a deal.

"Sometimes we have what we call a step down," says Walter Flamenbaum, managing partner of Paul Royalty Funds. "When we reach a certain return, we say 'Great. We've had a good run.' We don't believe we should continue to participate ad infinitum so we will step down. Maybe we took 10 percent of revenues, but we've reached a return level and now we will take 1 percent. Sometimes it's actually fully limited."

That was the case when The Wistar Institute wanted to expand it research capabilities by capitalizing on the royalty stream from Merck's RotaTeq rotavirus vaccine it jointly developed with the company. It was concerned that a transaction would force it to lose the upside potential of the vaccine. In exchange for $1 million upfront and a $44-million milestone payment when the vaccine won approval in the United States, Paul purchased a royalty related to the first $300 million in worldwide sales.

Wistar retained all worldwide royalties on annual sales in excess of $300 million, an amount the vaccine has shattered. The deal allowed Wistar to increases its endowment and accelerate research programs. "We are fully capped," says Flamenbaum. "Once the level is achieved, we make no more money."

Though some have viewed royalty and revenue financing as a tad steep, the question is, compared to what? What other capital does a company have access to at a given time and what would a given transaction allow it to accomplish? In the case of Acorda Therapeutics, "If we had had the ability to raise equity at a price, that would have made the cost of capital lower than the Paul deal, we would have done that. If we could have raised debt at a price that was lower, we would have done that, but we couldn't," says Acorda's CEO Cohen. "You just do the analysis." TJOLS

Term limits: Paul founding partner Walter Flamenbaum, says the firm will put a limit on what it can make on a deal.

COURTESY OF MATT ISEMAN

Finally A Doctor Who Works Nights and Weekends

Matt Iseman left the medical profession to become a comedian in Hollywood. Life is good, he says, because he now gets to laugh at work.

By Eric Wahlgren

As perhaps one of the few, if only, doctor-turned-comedians, Matt Iseman has an unusual background that often makes its way into his material. In one act, he recalls becoming indignant after a date tells him that being a real doctor isn't as good as playing one on TV. "I couldn't believe it," he fumes. "I was hurt. That made me want to take her home and treat her like a doctor: Make her wait outside my bedroom for two hours, spend five minutes with her, and send her a bill for $575."

But Iseman may get the last laugh. With his latest job hosting the newly launched *Sports Soup* series on the Versus network, as well his movie debut in *Transformers 2* due out in July, the former doctor is probably not going back to medicine. He's having way too much fun, he says. Plus, he may end up better off in showbiz than he would have sticking with a career in internal medicine. "Regardless of the dollars and cents, I would say my lifestyle is much better than it was when I was in medicine," says the 37-year-old.

These days, he's got an agent, a Hollywood zip code, a live-in girlfriend, and a job he loves: getting paid to make people laugh. "I miss interacting with patients," he concedes. "I miss having the impact where you change a person's life for the better. That's a powerful thing. But I think on a much smaller scale, I'm doing that anytime I make somebody laugh."

Since moving to Los Angeles nearly a decade ago, the Denver native has appeared on scores of shows including *The Drew Carey Show*, *NCIS*, and *General Hospital*, where ironically, he did not play a doctor. It is as host of *Clean House* on the Style network, where some of his physician's bedside manner can come into play. On the show, Iseman and his crew sweet-talk chronic clutter-bugs into ridding their homes of junk, using the proceeds raised from yard sales to refurbish the houses. "The show is not for the faint of heart," says Iseman. "If you have a little mess, don't bother. We had a house with 30 pounds of dried cat turds in it and the cats had been dead for two years."

In another episode, Iseman helps a confirmed pack rat clear out her kitchen cabinets. Upon spotting an ugly plate with a cherry motif, Iseman grabs the china and sends it crashing to bits on the floor as he cries "Opa!" like they do in Greek restaurants. "That was spur of the moment," says Iseman. "We never try to break any of their stuff, but that plate had to go."

All of this on-camera buffoonery is a world away from the solemnity of the exam room—and Iseman likes it that way. It was during his first year of residency at the University of Colorado in 1999 when Iseman began to have second thoughts about his medical career. One night, while working the overnight shift in the intensive care unit, he had an epiphany as he and his colleagues rushed to deal with all the patients being admitted. "I just kind of realized that in the next few months, I was going to be the one making the decisions that really affected peoples' lives," he says. "I wasn't passionate enough about it to where I was going home to do all the research and reading that I needed to be doing. I felt like I was just trying to get by."

Iseman had followed in his father Mike Iseman's footsteps, first attending Princeton and then Columbia College of Physicians and Surgeons for med school, ending up at the University of Colorado Hospital where his father is a pulmonologist. "I had a pretty good sense of how he was doing," says his father. "Everything I heard said he was a good physician." But his father also realized that although Iseman appreciated the intellectual challenges of the profession, he seemed to lack the emotional commitment that makes it possible to deal with the demands of being a physician. "He looked around and didn't see many people who were having fun," his father says.

When Iseman's internship ended in July of that year, he decided to take a year off to clear his head. So he moved to Los Angeles to try something totally different: stand-up comedy. During medical school in New York, a friend had dragged him to open-mike nights, but he had gotten up the nerve to actually perform only a few times, he says. Once in LA, however, he just dove in, hitting the city's clubs on open-mike night on a daily basis. "I was so excited to be doing something else that I didn't know how bad some of those shows were that I was doing," he says.

But he kept at it, he says, and on the circuit, crossed paths with pros like Chris Rock, Jerry Seinfeld, and Dane Cook, which helped him hone his craft. "You're learning at the feet of giants," Iseman says. In 2002, he joined The Groundlings, the improvisational comedy troupe that helped launch careers of the likes of Will Ferrell and Lisa Kudrow.

Then came a lucky break. A friend invited him on *The Drew Carey Show* as an extra. There, he met an agent who got him work appearing in national commercials—among the more lucrative work in Hollywood. Iseman, 6-foot-3 and a pitcher all four years as a Princeton under-

Comedian Matt Iseman says he loved the defibrillator while working as a doctor. "I used it on all my patients," he jokes in one of his routines. "I didn't care what they had. 'Your leg looks broken alright. Clear! Congratulations, it's a beautiful baby boy. Clear! He's been constipated for two weeks? Clear!'"

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grad, has an athletic, all-American look, which made him a natural in ads for Pontiac, PlayStation, and Bank of America, among others. "That was sort of a marker to me that 'this is tenable,'" he says.

The work has been steady and growing ever since. In addition to his TV gigs, his voice has been featured in campaigns for DirecTV, Land Rover, and Six Flags theme parks, as well as in the video game *Command and Conquer III: Kane's Wrath*. But he remains proudest of his stand-up. "It's nobody but me," he says. "I write all the material. I perform it. I make the choices on stage. So if it bombs, it's on my head. But when it goes great, it really is the feeling of 'I did this. I took these people on that ride.'" He's traveled the national comedy club circuit, but also the world, performing for U.S. troops in hotspots like Iraq and Afghanistan.

Both on and off stage, Iseman is a study in contrasts. Trained to make life and death decisions, he has settled instead on the life of a professional jester. An Ivy League grad who earned honors in American History, in performances Iseman appears more like the kid who got by on an athletic scholarship. "Immature and enthusiastic are two words to describe myself on stage," he says. He's a practitioner of observational comedy, poking fun at life's little peculiarities—dating woes, motorist mishaps, celebrity train wrecks, and his own personality quirks—audiences all relate to. "It's about paying attention," he says. "It's usually what makes me or my friends laugh."

> I miss interacting with patients. I miss having the impact where you change a person's life for the better. That's a powerful thing. But I think on a much smaller scale, I'm doing that anytime I make somebody laugh.
>
> —*Matt Iseman, Comedian*

Where Iseman's Ivy League education does show up is on a late-night Fox News Channel talk show called *RedEye* where he is a regular guest. Host Greg Gutfield introduces random topics—Sharia law, transgendered politicians, pole-dancers, and North Korean nukes—to which Iseman responds rapid fire with informed snark. After news that now President-elect Barack Obama had "experimented" with drugs, Iseman on *RedEye* brays "Like he's Marie Curie? 'Barack, you didn't experiment. You partied with drugs.' This has got to be the first time a guy has confessed to using drugs and ended up sounding like a bigger loser afterwards."

Still a licensed physician, Iseman also uses his background in medicine and comedy to speak to groups in the healthcare industry about an issue that is important to him: being able to laugh at yourself. "Healing people is a serious business," Iseman says. "You take that seriously. But you don't have to take yourself seriously all the time. You need to be able to let yourself go and vent."

When he speaks to nursing organizations, medical conferences, or pharmaceutical company events, he often highlights the countless idiosyncrasies of the medical field. "We end up communicating with each other in the chart via notes," he says in one "Prescription for Laughs" segment. "How fifth grade is this? We're grown adults communicating by passing notes."

The funny doctor act seems to be a hit with industry crowds. "He kept us in tears of laughter the whole time," says Danna Thompson with the National Arthritis Foundation, which hired Iseman to speak at a meeting of national fundraising staff and volunteers in Tucson, Arizona in 2006. For Iseman, there was a personal connection with this appearance: at age 31, he was diagnosed with rheumatoid arthritis, but he has responded well to treatment, he says. As for Thompson, she says the foundation was a little apprehensive at first, as it had never had a comedian address its meeting. But Iseman brought the house down, she says. "The takeaway was, you just can't take life so seriously," she says.

Indeed, Iseman seems to be taking his own advice to heart. Though he says he regrets not having started his comedy career a little earlier, going to medical school was one of the best things he's ever done, he says. Being exposed to the life and death situations doctors face gave him a little bit more grounding, he adds. "In Hollywood, it's pretty easy to lose perspective and get wrapped up in things that really aren't that significant," he says. "At the end of the day, we're just trying to make people laugh. If the show gets canceled or something goes wrong, it's not the end of the world." TJOLS

The Professional Guinea Pig

For some, participating in clinical trials is a selfless act of altruism that involves doing their small part to advance medical research. For Robert Helms and others like him, it's a living.

For much of his adult life, Robert Helms worked as a professional medical test subject. He chronicled his experiences, and that of others, in his zine *Guinea Pig Zero*. Excerpts of the publication are available in the book *Guinea Pig Zero: An Anthology of the Journal for Human Research Subjects*. Now 51, Helms has been forced into retirement as most studies are interested in subjects between the ages of 18 and 45. The full podcast of the interview can be found on the *The Journal of Life Sciences*' website at http://www.tjols.com/article-793.html

"When I rent my healthy body to medical science, I am the temporary employee of a research team, paid as a contractor for each job," he says in the book. "I do my bleeding, pissing work in a blurry area between patient and subject. This blurry area has made for intense public debate, and the questions relating to the guinea pig as a worker are not even considered by lawmakers in this country (yet they are in Canada or France)."

The *Journal* recently spoke to Helms about his career choice, the-day-to-day lives of professional guinea pigs, and the role of human

test subjects in modern medical science. Edited excerpts of the conversation follow.

Q: What is *Guinea Pig Zero*?

A: Guinea Pig Zero was a printed zine from 1996 to 2000. We did eight issues. It was a journal for human research subjects and I always concentrated on people like myself who were healthy subjects volunteering for pay in Phase I drug trials, which are conducted so that new drugs can approved by the U.S. Food and Drug Administration and be put on the market.

Q: It was a zine for workers?

A: That is the key to the approach that I took. Being a human guinea pig for pay is an occupation in the little universe I belonged to until I turned 46, which made me too old for the better, more worthwhile studies.

Q: How does someone become a professional medical subject?

A: The first things one learns are the ropes and the rules of the game. The rules of the game are one thing when it's on paper and explicitly stated between the researcher and the guinea pig. And it's something else when you're in the real practice of it and you're actually trying to make a living this way.

> "There are some people who are doing it for altruistic reasons...the overwhelming majority is doing it for the money"
>
> —*Robert Helms*

Q: What type of rules are we talking about?

A: First thing you have to do is make yourself known to the recruiters who sign you up, screen you, stay in touch with you, and know you are a reliable person—who is not going to come in with heroin in the blood or even over-the-counter drugs in the blood. You are going to have to have a clean physical exam, your health is going to be good, and your height and weight are not going to be off the charts. You have to understand that you are in competition with other people who are going to be saying the right thing.

Q: What constitutes a good study for a research subject?

A: Well, a lousy study is one that says you are going to come in for two hours a day, three times a week, and it's going to extend over four months. And you are going to get around $500 for the whole thing. That is a ridiculously bad deal.

A great study would be checking into the research unit, after you've been screened, on, say, Monday morning January 1, and you're there continuously for six weeks or something like that. That is a lot of paid time concentrated into a period and it turns out to be $4,000 to $6,000.

Q: Are there people who are actually able to make a living from this?

A: There's a lot of them. How many? That's the great question of the age—exactly how many. But it's not a glamorous living. It's a modest living. You're living out of a duffle bag. You have an address. You may only have a tiny room. Or you might be living out of your car and you just go from one study to another. The critical thing is in order to make a real living, you have to do as many studies as possible.

Every time you do a study, the question that will come up is "when was you last study?" The answer they are looking for is, "I haven't done a study in three months or six months." If you say "I just got out of one two weeks ago," you are not going to get into the study.

Q: What kind of living did you make?

A: I never kept track of how much money I made in drug studies. I didn't do it as a workaholic. I didn't do it back to back. But some people make over $30,000 a year.

Q: What type of studies did you participate in?

A: Most were drug trials. Some were physiological things like the behavior of the stomach under certain circumstances.

Q: How do research subjects spend most of their time?

A: Watching TV, waiting for the next blood draw, talking to their friends on the phone, and shooting the breeze with their other guinea pigs.

COURTESY OF ROBERT HELMS

Human guinea pigs have been the physical beings that have helped enhance the knowledge of the human body that has created the whole field of medicine as we know it. We deserve credit and we deserve to respect ourselves. We deserve to cherish our history such as it is.

—Robert Helms

Q: What makes a good or bad place to be?

A: That was the key. It's how good is the food? Is it edible or is it totally cheap garbage that we're expected to eat? What kind of facilities do they have? Do they have things to keep you distracted like a pool table or a decent television set? Do they have phones available in the rooms? How crowded is it? Sometimes it would be over-crowded and you would end up in a fold-out cot or a fold-out chair and you could only get into the regular beds when it was time to get your drugs. You were paid extra for that. Also in one place, there was no hot water.

Q: How good a job do they do in these experiments at explaining the risks?

A: Some do a great job and some do a horrible job. A real great place to do a study is Thomas Jefferson University. They are a medical college. The people are the same who are developing the drug and working on them directly with the drug manufacturers. The people I would interact with in person would really be on top of the science.

They would be delighted if we started asking questions about the drugs and what they do to the body. My favorite question was "What is the half life of the drug?" The reason I was asking was to know when the drug would be out of my body. It makes it easier to know when I can get into another study.

Q: Did you ever have an adverse reaction to the drug?

A: Not an unexpected one. I would get the predicted side effects. I watched other people have adverse reactions.

A friend of mine was in the bed next to me and they were testing a blood thinner. We were among the first humans ever to take the drug, which was designed to extend the time it takes for your blood to clot. It's used for things like organ transplants. They gave both of us the same drug and same dose. The normal bleeding time is three to four minutes. Mine went up to 11 or 12 minutes. That's what they were shooting for.

My friend's went up to 21 or 22 minutes. So they became slightly concerned for his safety and raised up the rails on the side of bed and told him to lie still. He was basically a hemophiliac for that period. They took him out of the study and paid him in full for the study. So he made like $2000 bucks for about two days work.

Q: How did you first get into this? Did you see a want ad?

A: I knew people who had already been doing it for years. They gave me the phone numbers of recruiters and taught me the ropes. They told me "ok, when they ask you about your medical history, you tell them you have never been sick in your life, nobody in your family has ever been sick at all. You don't smoke. You only drink two cups of coffee a day."

I was really drinking about three pots of coffee a day. I didn't quite understand in the beginning why they were asking that question. But if you drink a huge amount of caffeine and all of a sudden you don't get any caffeine, you get very bad migraine headaches or you get muscle cramps in your lower back and thighs. And my body happened to go with the muscle cramps.

During the first couple of studies, I was pacing the floor all night long. Later, I figured I would just taper off before I went into the study and then a drink a big cup of coffee right before I went in.

Q: Was there something satisfying in doing these experiments or was it just a job?

A: There are some people who are doing it for altruistic reasons, either they have some spiritual orientation—sometimes nuns volunteer—or they are doing it to advance medical science. They might be raising money for some charitable cause. Or it might be somebody they know who had a horrible disease. But the overwhelming majority is doing it for the money.

Q: Do you miss the job?

A: As far as my life goes, there was certainly an appea l in the flexibility of it. After I stopped, I was a freelance house painter. I did light carpentry. Now I'm a union organizer. I plan my own schedule.

That was the appeal of doing studies. When I was done with the study and I got this paycheck, I could go to Europe for a while. That's the only part I miss. As far as doing it, it's boring.

Q: Any advice for anyone embarking on a career as a research subject?

A: Be either extremely cautious with any psychiatric drug experiment or don't do them at all. One advantage of a normal drug study is that your body is earning the money while your mind is doing whatever you want. You could be reading, writing, or doing business over the phone or by email. You could be earning two paychecks at the same time. If you are doing a psychiatric drug study, you are not in your normal state of mind.

Human guinea pigs have been the physical beings that have helped enhance the knowledge of the human body that has created the whole field of medicine as we know it. We deserve credit and we deserve to respect ourselves. We deserve to cherish our history such as it is. TJOLS

COURTESY OF ROBERT HELMS

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Australia at a glance

- Ranked first as a location for clinical trials and second overall in a recent international benchmarking study of the pharmaceutical industry.[1]
- Over US $33 billion market cap of life sciences companies at end September quarter 2007.[2]
- Over US $640 million raised in calendar year to date 2007.[3]
- Ranked first in the Asia Pacific for the number of biotechnology companies.[4]
- 11 Australian companies have products in final stages of clinical development.[5]
- In 2006, 67% of biotechnology partnerships were with overseas companies or agencies.[6]

Imagine a brighter future Australia

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1 The Economist Intelligence Unit, November 2005 **2** Bioshares, 2007 **3** ebd. **4** Ernst & Young Report, 2006 **5** The Bulletin (17. September 2007)
6 Hopper und Thorburn, 2007 Die Bildrechte für die Darstellung des *Helicobacter pylori* liegen bei Luke Marshall.

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