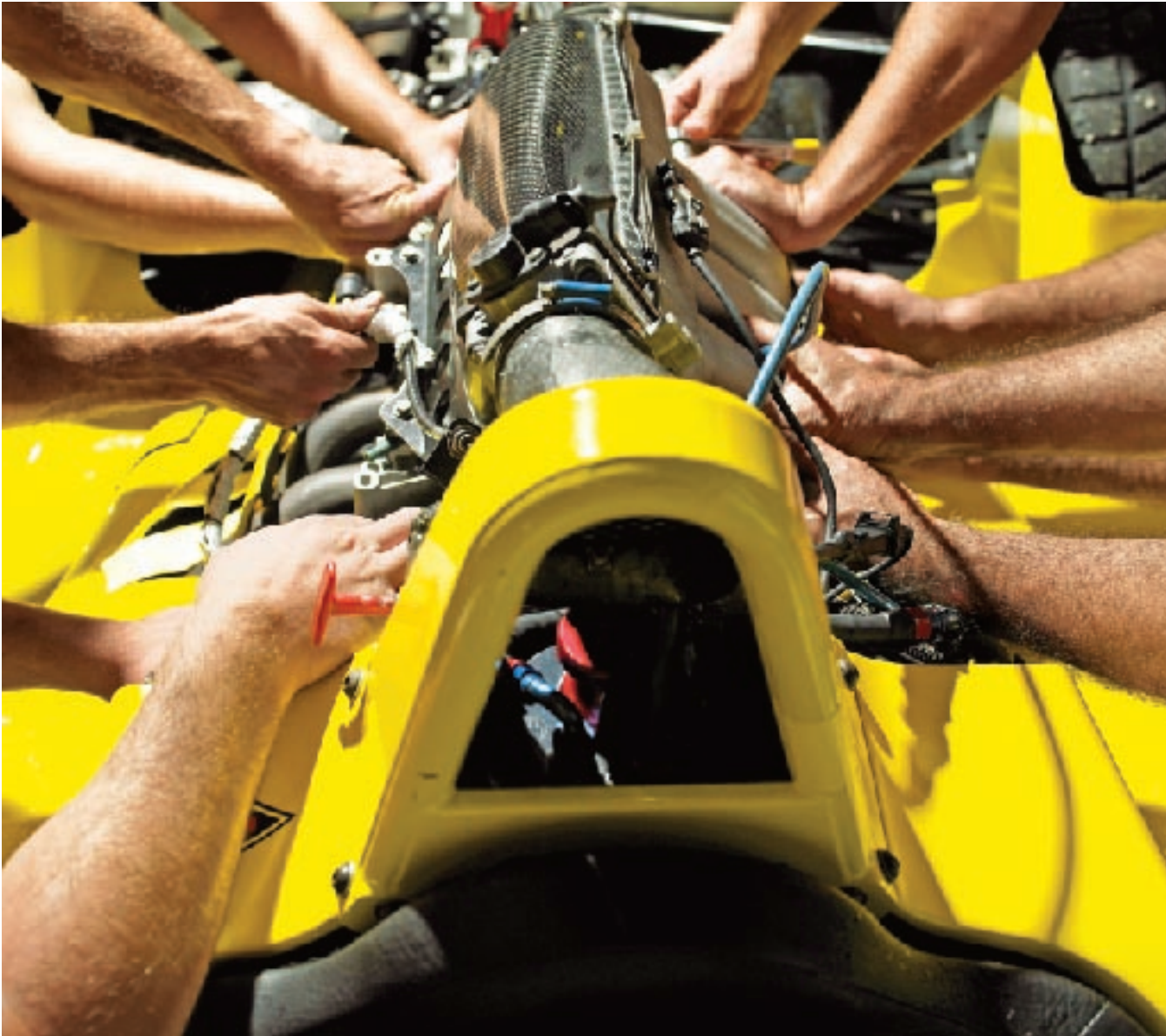


stat

COMING //

- **APRIL 24:** An FDA advisory panel makes its recommendations on the application for Pfizer's new HIV medication, Maraviroc, which belongs to a class of drugs that blocks the virus from entering white blood cells rather than fights the virus within cells. Thus Maraviroc may help patients who no longer respond to other HIV drugs.
- **MAY 4:** The International Museum of Surgical Science in Chicago unveils the art exhibit "Sympathetic Coordination" by Laura Splan. Using her own blood as the primary medium, Splan often depicts magnified nerve-tissue-like forms as an expression of the body's complex, involuntary responses.

07



FOCUS // **DURING A FORMULA ONE PIT STOP**, there's no room for mistakes, as the crew pitches in with practiced precision. Surgeons at London's Great Ormond Street Children's Hospital, after calling in a Ferrari team for a critique, devised a protocol to smooth the transition from operating room to intensive-care unit, when a forgotten message about a vital statistic or an unprepared piece of equipment could cost a patient's life. The changes, ranging from banning inessential chatter to disconnecting wires in a specific order, have noticeably cut errors. ■

INTERVIEW //

The Real Gender Gap

■ BY RACHEL GOTBAUM

By now it's an old saw: Men are from Mars, women from Venus. Yet according to Marianne J. Legato, a physician and professor of internal medicine, science is only beginning to uncover just how different the sexes really are. Here, the founder of the field of gender-specific medicine explains how this research has effected changes both profound (saving women's lives) and basic (showing men and women how to communicate better).

Q: How did you come to create the Foundation for Gender-Specific Medicine?

A: I had been studying the molecular biology of the heart at Columbia University for 20 years when in 1990 a journalist asked me to collaborate on a book about women and coronary artery disease. I replied, "What are you talking about? There's no difference in how men and women experience the disease." She responded: "My mother died of it. Many of her complaints were written off as silly or hysterical." We wrote *The Female Heart*, the first book on the topic.

Q: What are the differences, then?

A: Men's and women's heart muscles are composed of different proteins, and their hearts' electrical systems are not wired in the same way—which can make them function very differently.



■ One of my patients complained of her husband's ineptitude when she sent him to the store for peanut butter and expected him to get jelly and bread too.

For example, 20% of women having a heart attack don't feel chest pain; instead, they have symptoms that an inexperienced emergency room physician might mistake for a gall bladder attack. Women have died in the hospital parking lot because they were sent home.

Q: As you wrote *The Female Heart*, your thoughts turned to how other organs might differ, such as the brain. Could you explain the title of your new book, *Why Men Never Remember and Women Never Forget*?

A: In prehistoric times women had to remember where to find the best food

and where danger lay; as a result they are still hardwired to retain exquisitely detailed memories. Men, on the other hand, had to hunt dangerous animals, so it didn't behoove them to have detailed memories of painful experiences. But it did behoove them to take risks without undue anxiety or fear. It also helped that their pain was dulled by testosterone.

Q: How is it that a man and a woman can experience a quarrel completely differently?

A: During an argument, both men and women secrete the stress hormone cortisol. Men secrete a burst of the

hormone that lasts just an hour, after which they feel upbeat and energized. In women, estrogen prolongs that secretion for almost 24 hours, clouding their ability to think clearly. So when a woman, who is still anxious the next morning, says, “I’d like to return to this issue,” her husband might well answer, “What issue?”

Q: In light of these differences, what should women do?

A: Keep a conversation factual and brief. One of my patients complained of her husband’s ineptitude when she sent him to the store for peanut butter and expected him to get jelly and bread too. Men do exactly as they are told.

Q: And what can men learn?

A: It’s important not to shut a woman down when she wants to talk. Many women verbalize a problem to arrive at a solution.

Q: Do these brain differences have an impact on depression?

A: Researchers say that women are twice as likely to suffer from depression than men are—probably because they assume that both genders have the same symptoms. In fact, I think that depression is tremendously underdiagnosed in men because their symptoms are different: Men tend to become quiet and solitary, drink more and become irritable, even violent.

Q: There are times in life when hormones cause men and women to become a bit more alike.

A: In the first throes of infatuation, men and women are most alike; they have heightened levels of norepinephrine and epinephrine, which make them sleepless and obsessive. When a woman is about to give birth, her husband’s testosterone levels fall, making him less likely to roam and more likely to bond with his wife and new baby. And as testosterone levels dwindle in older men, they become dependent on their wives’ companionship.

Q: Could innate differences between men and women be a reason fewer women succeed in science?

A: No. Men and women can accomplish the same things; they just use different brain systems—and thus different techniques—to do them. When NASA put people into a virtual maze, women used landmarks, whereas men used what are called Euclidian principles—akin to using a compass—to find their way out.

Q: What changes do you hope to achieve with your work?

A: Assuming that women and men are identical without testing that hypothesis is against everything we have been trained to do as scientists. In testing that hypothesis with coronary artery disease, we have saved hundreds of thousands of women. With research into a number of diseases and organ systems, we will be able to save more lives and develop more effective medications. By applying this science, we will improve the quality and length of life for both sexes. ■

BY THE NUMBERS //

All Too Common



2-4 Number of colds adults typically catch each year

6-10 Number of colds kids typically catch

180 million Number of school days children with colds miss each year

196 million Number of days workers miss to care for children with colds or to nurse their own colds

\$40 billion Total annual economic impact of the common cold, including such direct costs as physician visits and indirect costs because of lost productivity

110 million Number of doctor’s visits for cold-related treatment each year

0 Effect that antibiotics have on viral illnesses such as the common cold

\$1.1 billion Annual amount cold sufferers spend on antibiotics (possible reasons doctors prescribe them: force of habit, pressure from patients and efforts to prevent secondary infections caused by bacteria in the throat and nose)

110 Number of distinct types of rhinoviruses, which cause an estimated 30%–35% of all adult colds and would defy any catchall vaccine because they constantly mutate

0 Number of days the antiviral drug BIRR 4 spent on the market. Despite shortening rhinovirus colds, the drug was not considered commercially viable, in part because it had to be administered too early in the infection process to be practical and because it targeted only about a third of colds. ■

INFOGRAPHIC //

At the Extremes of Life, Extremes of Cost

■ BY ERIC L. REINER // INFOGRAPHIC BY FLYING CHILLI

There's no quick fix for skyrocketing health care costs. But focusing on the beginning and end of life, the two most expensive periods, may point to ways to save substantial sums to everyone's benefit. Here, a look at where costs might be cut, or at least redistributed.

10

WHAT WE SPEND WHEN

(2006 figures)

\$408,105

Total lifetime health care expenditures per capita



Cost of prenatal care and delivery
\$10,865



Health care costs in first year
\$6,872



Annual health care costs at age 20
\$1,618



Annual health care costs at age 40
\$2,487



Annual health care costs at age 65
\$9,929



Health care costs in last year of life
\$55,367

SOURCES: MARCH OF DIMES, HEALTH SERVICES RESEARCH, ARCHIVES OF INTERNAL MEDICINE, JAMA, DARTMOUTH ATLAS PROJECT, NEW YORK STATE MEDICAID/DEPARTMENT OF HEALTH, MEDICAID, NATIONAL CENTER FOR QUALITY ASSURANCE, PUBLIC HEALTH REPORTS

CHECKING IN

Investments in prenatal care and education improve the health of the mother and child and thus reduce medical expenditures.

About one in eight U.S. births is preterm. Prematurity causes one-third of infant deaths and...



...with low birth weight, nearly half the cost of all births:



\$18.1 billion

Total cost of all births: \$36.7 billion

The cost of a baby's hospital stay if...

(2006 figures)

...the mother had prenatal care

\$1,958

...the mother did not have prenatal care

\$4,843

What should change?

Although prenatal care plus the costs of delivery and a hospital stay (\$12,823) are about equal to those for a woman who did not have prenatal care (\$12,832), redistributing those dollars means the chance of a healthier baby—and less cost to society. If more pregnant mothers could kick the nicotine habit, that would help too.

\$1 spent on smoking-cessation interventions for pregnant women



\$3 saved in neonatal intensive-care costs

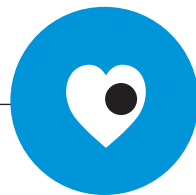
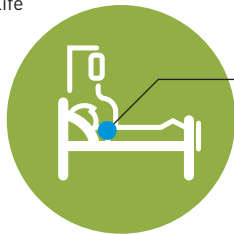
Such measures will be given a boost by the PREEMIE Act, which allocates \$91 million in new federal funds for research and education over the next five years—though there's no telling how long it will take to see a return on the investment, both in costs saved and fewer premature births.

CHECKING OUT

Medicare devotes about one-fourth of its total annual expenditures to individuals in their final year of life, with as much as half spent in their final 60 days. The more favorable the person's health-risk profile, however, the fewer resources required.

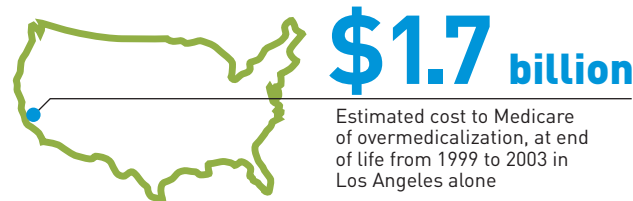
Extra Medicare expenditures in the final year of life for a high-risk patient:

\$15,318



\$10,367
of which is related to cardiovascular disease

Dramatic savings are possible by rethinking end-of-life care. A significant body of research shows that more care (read: more cost) does not better the patient's health, ability to function or survival time, and, in fact, may extend pain and suffering. Drastic attempts to save patients' lives, such as feeding-tube placements, are often futile.



What should change?

Of Medicare dollars spent during the last year of life, 54% goes toward hospital stays, whereas just 2% is directed to (less costly) hospice care. A shift in the balance could mean less cost for Medicare and more comfort for the patient. Likewise, if more regions use hospitals and physician services in a manner similar to that of Salt Lake City, a metro area that is exemplary for its high-quality, low-cost care. Of the \$123 billion in Medicare spent on end-of-life patients, \$40 billion less would have been spent using the Salt Lake City benchmark.



MILESTONES //

Stopping Seizures

For centuries epilepsy was thought to have supernatural, usually evil, origins. To drive out the dark spirits that made them shudder with seizures, epileptics were subjected to exorcisms (even Jesus cast out an unclean spirit from a probable epileptic), prodded with hot pokers (to release "pernicious humours") and plied with poisons (arsenic).

By Victorian times, masturbation—an evil practice by the day's standards—was considered a principal cause of the disorder. This notion, more the product of straitlaced values than of scientific inquiry, prompted the discovery of the first effective anticonvulsant.

In 1857 Sir Charles Locock, Queen Victoria's obstetrician, read that potassium bromide calmed sexual appetites. After he tested the drug on several female patients prone to seizures prompted by "sexual excitement" (or so he thought), the seizures ceased. Locock revealed his discovery at a Royal Medical and Chirurgical Society meeting, and by the 1870s bromide was widely prescribed. It remained the only effective anticonvulsant for more than 50 years.

While certainly an improvement on earlier treatments, bromide produced serious side effects, including boils, lethargy and dulled mental function (hence the origin of the word's meaning as a dullard or a platitude). In 1912 bromide was superseded by phenobarbital, a central nervous system depressant that proved highly potent with



fewer side effects. The drug is still widely prescribed in the developing world, but in the West dozens of medications have replaced it.

"There are lots of choices," says Carl Bazil, director of clinical anticonvulsant drug trials at the Columbia Comprehensive Epilepsy Center in New York City.

"Though they've minimized side effects, none have been proven more effective than drugs that came before." Even now, 30% to 40% of patients have seizures that cannot be controlled with treatment.

For those patients, a high-tech option is in the pipeline. One such device, a responsive neurostimulator, is in clinical trials. Embedded in one's skull, the device emits shocks to stop seizures.

Researchers' ultimate goal—to find a cure—is a complicated endeavor, not least because epilepsy may not be just one disorder. Its symptoms are different from one patient to the next; its causes are myriad (from head injuries to infections); and for about two-thirds of epileptics, the cause is unknown. Much about epilepsy remains a mystery. And that's no bromide. ■



POINT/COUNTERPOINT //

Should prisoners be permitted to participate in medical research trials?

POINT: *If one respects the tenets of science and of human rights, the answer is clear, says Vera Hassner Sbarav, founder of the Alliance for Human Research Protection (AHRP), which advocates responsible and ethical medical research practices.*

In 1973 the journalist Jessica Mitford famously summarized why prisoners were the preferred medical research subjects in the United States. They were “cheaper than chimpanzees,” she wrote in *The Atlantic Monthly*, quoting a physician involved in prison research.

More than three decades later, inmates are not only less expensive than chimps, they have fewer government protections. Annual reports submitted to Congress document the number and disposition of every chimp (and dog and hamster) used in research trials. But no federal law requires anyone to keep track of the number of humans used—or harmed—in clinical trials. In fact, the only protection prisoners have against being subjected to experimental abuse hangs on the thread of a

single federal regulation, Subpart C of the Common Rule, and that regulation governs only federally funded research.

The recent Institute of Medicine recommendations to the Department of Health and Human Services, which commissioned the study on research involving prisoners through its Office for Human Research Protections, aim to strengthen federal oversight of human research. Yet the report, “Ethical Considerations for Research Involving Prisoners,” fails to fathom a fundamental truth: No matter what safeguards are put in place, the incarcerated can never freely give voluntary, informed consent because the fear of retaliation from prison officials precludes them from saying no to experiments.

The history of U.S. prison research confirms abuse, not benefit. Prisoners were exposed to cancer-causing and radioactive chemicals at Holmesburg Prison in Pennsylvania between 1951 and 1974. Juvenile inmates at Stockton Prison in California were subjected to psychotropic drug tests in 1997 despite regulatory prohibitions. A federal investigation in 2000 documented gross violations in prison research conducted by the University of Texas at Galveston. Inmates should be off-limits except for noninvasive research aimed at improving prison conditions, such as how to prevent staph infections.

The push for prison experiments is motivated by business priorities. The biotech and pharmaceutical industries are addressing the shortage of volunteers by dipping into a deep pool of captive subjects with limited rights, housed in inherently coercive environments. Prisoner research is about exploitation, profit and expediency, not the benefit of prisoners.

What’s more, when the subjects are inmates, a study’s scientific conclusions are highly suspect. Although it’s hard to know how often lockdowns occur—according to a California study, one facility underwent 391 in a year—just a few can seriously disrupt a trial. During a lockdown, prisoners are denied access to their medicines, including lifesaving ones. So whatever results are eventually reported are little more than junk science.

COUNTERPOINT: *The vulnerable status of prisoners should not be compounded by systematically excluding them from the benefits of science, says Lawrence O. Gostin, professor of law and public health at Georgetown University Law Center and chairman of the Institute of Medicine committee that issued “Ethical Considerations for Research Involving Prisoners.”*

Unquestionably, there’s something wrong with how research is conducted in prisons. But if we can correct the problems,

then such research will yield a world of good. Sound research can profoundly improve the welfare of inmates. For example, if prisoners were enrolled in studies of such diseases as HIV/AIDS, hepatitis C and tuberculosis—which afflict prisoners in disproportionately high numbers—they could benefit from any finding or treatment discovered. Of course, research should never be conducted on captive populations simply to advance the greater good. Researchers should be required to demonstrate how prisoners themselves would benefit from a proposed experiment.

It's true that current regulations have brought about an untenable state of affairs: No one has a complete picture of what's being studied, by whom (whether private or federal agencies) and upon whom. Thus federal oversight needs to be strengthened in significant ways. Gaping regulatory loopholes must be closed and more safeguards established (such as ensuring the privacy of patient information). Prisoners must be uniformly protected, regardless of the source of research funding.

The recent report by the Institute of Medicine would create a national system of oversight and a public database to track studies. The institute's report also recommended that prisoners not be allowed to participate in Phase I and II studies when safety has not been established. Furthermore, at least half of the research subjects in any clinical trial should be non-prisoners so that inmates are not singled out for research that the general public won't volunteer for.

It's true that a significant percentage of trial subjects aren't protected by regulatory restrictions, but that can be remedied

in two ways: Congress could mandate uniform guidelines that would govern all research that enrolls prisoners, and the definition of prisoner could be expanded to include people on probation and parole. In addition, institutional review boards should be assisted by independent prison research advocates, who would work on-site to quickly detect and report problems—and ensure that subjects have not been coerced.

The issue of voluntary consent and the question of whether prisoners can truly exercise independent choice are fundamentally important. Research proposals that cannot ensure this protection should not be approved.

Finally, the argument that trial protocols cannot be followed in a prison environment subject to lockdowns and other disruptions is disingenuous. Research is never perfect, regardless of the setting. Protocols get disrupted in ordinary trials. It is both harder and easier to conduct science in prison; harder because there are lockdowns, but easier because subjects generally aren't lost to follow-up.

For all these reasons, I'm confident that research conducted in prisons can be both scientifically and ethically sound. I don't deny the threat of exploitation, but with rigorous legal oversight and consistently applied standards of protection, we can banish it. ■



THE CUTTING EDGE // A Useful Cavity

Often, drugs don't work for the simplest of reasons: People forget to take them. To bypass our faulty memories, European scientists have devised a prototype for a dental prosthesis that regularly releases medication, which is either absorbed through the cheeks or swallowed. Two joined artificial molars contain a drug-filled reservoir (into which saliva flows to dissolve the drug), two sensors (which monitor the volume and concentration of the drug flow), a valve (which opens and closes when signaled by the sensors) and electronic components (which control all the parts) powered by two batteries. A remote control can be used to set dosage and indicate when the patient is due for a refill (which means another doctor's visit).

Clinical testing will begin later this year in Berlin, Madrid and Palermo using the addiction-withdrawal drug naltrexone. As researchers point out, two groups that might benefit most from this device—addicts and Alzheimer's patients—often have missing molars because of problems spurred by inadequate dental care or aging. For the rest of us, let's hope a model hits the market that doesn't require pulling a few good teeth. ■