Strides of a Century

THE FACE of MEDICINE in 100 YEARS

by Tamar Nordenberg

JOYFULLY ANNOUNCING THE BIRTH OF BABY BOY!
January 30, 2111, 10:15 a.m., Weight: 7 pounds 6 ounces, Length: 20 inches. Risk of a run-in with heart disease by age 50: 85 percent.

Along with the already-familiar measures such as weight and length that are tracked from birth, cardiovascular disease and other health susceptibilities of "Baby Boy" born a century from now will be catalogued right away—even before mom and baby check out of the hospital—by sequencing junior's genome in search of warning flags. And if the cardiac risk is realized and a heart valve or coronary artery is giving out on Baby Boy in adulthood, open heart surgery won't be in the cards, considered crude by 22nd-century standards. "It will be, 'Back in the day, they used to crack people's chests open!' " predicts Mukesh Jain, MD, the Ellery Sedgwick Jr. Chair and Distinguished Scientist, director of the Case Cardiovascular Research Institute and cardiologist at University Hospitals (UH) Case Medical Center.

Century-from-now approaches for diagnosis, prevention and treatment will bear little resemblance to the modern medicine of 2011, agree researchers from various disciplines within Case Western Reserve University School of Medicine. Among the quantum advances in store over the century ahead: Regenerative medicine will create new, working tissues and organs as substitutes for original parts that have degraded on their owners. Surgeries will become

progressively scarcer, with noninvasive procedures as the therapeutic mainstays. And in alliance with genomics and regenerative medicine, additional game-changing medical tools will obsolete the one-size-fits-all approaches that in 2011 are considered cutting edge.

Anticipating the state of medical care around the turn of the 22nd century requires imagination in spades, notes Hunter Peckham, PhD, professor of biomedical engineering and director of the Cleveland Functional Electrical Stimulation (FES) Center. "We have to envision what might be possible from our little inklings of today," says Peckham, who, along with Jain and other visionary medical school researchers, shared his forecast: What will we see from medicine in a century?

GETTING PERSONAL: GENOMICS

A focus shift is underway: Statistical generalities about the diverse patient population will be supplanted, over the next 100 years, by genetics-based personal assessments of susceptibility to diseases and individual responses to therapeutics.

The full knowledge of an individual's genetic makeup and their interactions with the environment, as well as understanding the implications of these factors for disease, will be the most significant advances of the next 100 years, says Mark Chance, PhD, director of the Center for Proteomics and Bioinformatics and interim chair of the Department of Genetics. "We'll be able to characterize our patients with multiple diagnostic and predictive biomarkers for understanding whether they're sick and with what, and what the right treatment is," Chance explains.

Chance's proteomics center studies the proteins encoded by a genome. Though current understanding of these proteins— which interact with the environment and are considered much more complex than their gene counterparts—is "primitive," Chance says proteomics could revolutionize medicine within a century by revealing targets for drug development and, ultimately, keys for curing disease.

Within a score or so years, the focus of medical care will be much less on therapy and much more on prevention and diagnosis, Chance says, thanks to a dramatically improved capability to accurately and rapidly assess not only the existence of, but the risk for, particular medical conditions. An example of this "predictive insight," from Robert Miller, PhD, director of the school's Center for Translational Neuroscience and vice dean for research: For diseases such as Parkinson's, which can progress for years before symptoms appear, a genetic analysis that signals a susceptibility would allow for regular screenings and early drug treatment when neurons are only starting to taper.

Within a century, too—and to a gradually increasing extent even over the next generation—a patient's molecular information will point the way to tailored treatments, researchers predict. The example offered by Krzysztof Palczewski, PhD, chair of the pharmacology department: "A person can be blind from a defect in 50 different genes, each one requiring a different treatment, and the day will come when a patient's specific genetic trait will determine the best therapy." In a century, the best therapies themselves will be leap-years ahead of the therapeutic options we currently know, adds Palczewski— progressive immunology-based therapies, for example, will

redefine disease treatment. "The vision is, your body can generate your own drug—a protein with the properties necessary to correct for your particular defect."

All of these advances rely on continuing rapid progress in technology, experts note. Ultra-sophisticated computers are needed, for example, to lead scientists to those exceptional DNA characteristics that have meaning for a person's health. (See "Computers as Key" on page 15.)

REBUILDING HEARTS AND OTHER BODY PARTS: REGENERATIVE MEDICINE

Though early inroads have been made in creating living replacements to repair or replace damaged cells and tissues, figuring out a biological fix for the problems caused by aging and disease is a long-term venture. Perhaps, within a century, simple treatments will be developed based on gene transfer or cell (including stem cell) transplantation.

Presaging Baby Boy's susceptibility to heart disease is one thing, but it's only helpful if methods are available to lessen the risk of damage or repair that is discovered. The good news for him: Within 100 years, researchers expect to be able to generate tissues made from a person's own DNA—"no need to obtain someone else's heart or eyes or kidneys like we do today," Jain forecasts. And no need for artificial organs, when a heart for Baby Boy—and blood vessels to feed the organ— can be grown in a petri dish based on his own molecular makeup.

"To my way of thinking, cardiovascular disease is solvable within a century by cell replacement," says Horst von Recum, PhD, assistant professor of biomedical engineering, who studies how stem cells become cardiac or other cells that perform a specific function. "If we can make new heart tissue by replacing cells, heart failure from heart attack or tissue death can become largely a health problem of the past: Get to someone fast enough, and they needn't die."

For all its intricacy, heart disease is a straightforward challenge compared with cancer or neurological disorders, notes von Recum, based on the complexities of the latter conditions themselves and the organs that are compromised. Still, von Recum says, a century's progress in cell therapy is also sure to fortify the armory for facing down these conditions, as well as spinal cord injuries and other neurological conditions that stymie today's scientists.

RESTORING FUNCTION IN SPINAL CORD INJURY: ELECTRICAL, BIOLOGICAL BEST BETS

About a decade after a Super Bowl ad showed Christopher Reeve walking—while in reality the late actor and activist remained wheelchairbound from a devastating spinal cord injury— the commercial is still remembered for the controversy it caused, some saying it raised false hopes that a cure for paralysis was within reach. Is a cure likely to be found, even in the next century, to allow people with severe spinal cord injuries to walk again?

A team of researchers, including Peckham and other university experts in biomedical engineering and medicine, has already figured out how to restore lost abilities such as grasping, standing and coughing less severely to some paralyzed patients. The concept: produce an artificial nervous system of sorts within the body that mimics the natural one, using electrical signals sent by an external computer to substitute for the signals that in a working nervous system would travel directly from the brain or spinal cord.

Peckham, who is now collaborating with other biomedical engineering experts on a fully implanted "network neural prosthesis" (NNP) to restore multiple functions to a person with paralysis, hopes that within 50 years this technology, combined with other things like biological restoration and exercise approaches, will see people with "fairly severe cervicallevel spinal cord injuries" able to stand, use their hands, have good balance and move from one surface to another, such as from a wheelchair to a bed.

Anticipated use of the implantable device, Peckham emphasizes, is not limited to spinal cord injury, but is likely to be expanded to stroke and other neurological disorders. And conceptually, the device could be triggered to deliver a drug, along with the electrical current to the brain, whenever a tremor occurs. But what of enabling someone with Christopher Reeve-extent injuries to walk? According to Peckham, such an accomplishment could take decades to fully achieve.

In company with Peckham in the promising efforts to restore function and independence to those with paralysis is neuroscientist and School of Medicine professor Jerry Silver, PhD, whose two recent breakthroughs in biological therapies have so far worked in biologic models and in 100 years may translate into greatly improved health and autonomy for the thousands of people paralyzed each year.

In one experiment, Silver sent signals through severed spinal cords and restored breathing by shining pulses of light from a light-sensitive protein cloned from algae. In another study, Silver re-established nerve connections and restored some movement in biologic models with partial paralysis by grafting a piece of the sciatic nerve to the spinal cord and inducing nerve fibers to produce a gap-filling neural "bridge," and also delivering the enzyme chondroitinase to the site to prevent additional scarring.

Based on these and other promising studies of potential paralysis treatments, Silver predicts that within 100 years, "We may have the expertise to fairly simply restore function of some simple muscles, help people get off their respirator and breathe on their own, and return their bladder function."

THE INSIDE STORY: IMAGING

Since the discovery of the x-ray more than a century ago, imaging has allowed a noninvasive look-see into the human body for clues about disease or injury. But current medical diagnoses can miss the mark because of incomplete information from x-ray and even other, more sophisticated 2011 imaging technologies.

Even with MRI, x-ray computed tomography, ultrasound and other imaging technologies that are available for modern medical diagnosis, current imaging methods, overall, are crude compared with the expert-predicted imaging methods of the next century. "A hundred years is a long time, and what seems far-out now could become reality in that timeframe," says Jeffrey Duerk, PhD, chair of Case Western Reserve's biomedical engineering department and director of the Case Center for Imaging Research. "Imaging could resemble a Star Trek episode, where they run a wand over somebody's head and uncover a huge aneurysm."

Diagnostic capability may be redefined within a century, Duerk says, by imaging's emerging ability to detect specific molecular interactions occurring inside the body and unambiguously characterize a pathology. In the case of a would-be cancer patient, according to the biomedical engineer, "I believe we will be able to detect the earliest cellular and molecular changes before the patient goes on to actually develop a tumor, with imaging contrast agents and advanced imaging systems, designed together to provide the required sensitivity." In Baby Boy's case, the ultramodern methods could spare him the discomfort of cardiac cauterization to capture particularized pictures of his heart. "Within 100 years, imaging devices will provide much higher spatial and temporal resolution," Duerk predicts. "We may be able to routinely see the entire beating heart at an ultra-detailed 1,000 frames per second."

Advanced imaging techniques being researched today will support new treatments within a century where adequate therapies are so far lacking, Duerk foresees, by exposing early whether experimental treatments are effective or failing. For Alzheimer's disease, is a treatment combating the implicated plaques and tangles? In multiple sclerosis, how well is the myelin being repaired? If a treatment being studied—or one used therapeutically—isn't working, says Duerk, "We'll be able to stop and move on to something with greater possibility earlier."

OUTWITTING INFECTIOUS DISEASES: VACCINES FOR HIV AND OTHER ILLNESSES

Vaccines have already achieved sweeping success in infectious disease control in the U.S. and around the world. Credited for the eradication of smallpox, the elimination of polio in much of the world, and the dramatic decline in diphtheria, whooping cough and measles, immunizations are the best hope over the next 50 to 100 years for gaining the upper hand on communicable disease threats.

Will we ever be able to cure HIV infection? It's a question that has been put repeatedly to Michael Lederman, MD, since soon after HIV was identified in the early 1980s. "I used to be very pessimistic," recalls Lederman, co-director of Case Western Reserve/UH Case Medical Center's Center for AIDS Research and the Scott R. Inkley Professor of Medicine. "But based on new inroads, it's plausible we could eradicate HIV at some point in the future." For now, notes global infectious disease expert James Kazura, MD, who heads up the school's Center for Global Health and Diseases, "The fantastic antiretroviral drugs available today in the United States have turned HIV into a chronic disease."

Not so in the developing world, including Africa, Kazura is quick to point out. As an influential country in the global community— and with its population always susceptible to additional infectious diseases such as swine flu and avian flu—the United States will increasingly focus, over the next century, on finding cost-effective solutions to globally significant infectious diseases including HIV, tuberculosis and malaria, Kazura says. He and Lederman agree: In the next century, there may be a very effective immunization not only for HIV, but TB and malaria. Eradication around the world, however, is something that neither expert is counting on.

While HIV and some other current health challenges may well be controlled, new diseases are bound to pop up in their place, school experts caution, as various microbes evolve to outwit prevention efforts. According to Lederman, "It's a constant race between us and the bugs—their genetic selection versus our scientific smarts."

OF HUMAN BEHAVIOR AND OTHER VARIABLES

Add to bugs' wily evolution another challenge to medical progress: the complexities of human nature. Behavioral changes, experts point out, are in some cases required to realize the promise of advances in medical understanding. Chance illustrates, "Say your gene sequence says that if you smoke, you'll have a 95 percent chance of getting lung cancer in a certain timeframe. Having this 'answer' doesn't mean behaviors will change and that health will improve."

"The trouble with the current advice to avoid high-fat foods, cigarette smoking and other risk factors for disease," expands Miller, "is we're talking about statistic susceptibility: If you smoke, you're more likely to get lung cancer. People can cop out, saying 'Doesn't mean me.' Not so if you tell someone, 'If you smoke, you *will* get lung cancer by age 30.'"

Based on this important distinction, some researchers express hope that the ability to provide personal—not only statistical— information about disease risk will motivate behavior change in those who, like Baby Boy, have a high risk of a disease that lifestyle changes could abate.

Given all these incalculable variables, Lederman sums up the exercise of foretelling the state of medicine in a century: "It's hard to predict the pace and path of science." But one thing, he says, is observed across the whole history of medical discovery: "Some things happen at a slow and measurable rate, then all of a sudden there's a huge breakthrough observation that changes the rules. Slow and steady progress is vital, but big paradigm shifts are the things that transform medicine." If school prognosticators are right, these metamorphoses could be driven by newscience disciplines such as genomics and regenerative medicine, as well as modernized approaches to imaging and infectious disease control.

(Sidebar)

Computers as key

In genetics research, as in all areas of medical study, computers are expected to play an all-important role over the century to come, experts agree. "Computer science will completely take over biological science as the key field in medicine," predicts School of Medicine proteomics specialist Mark Chance, PhD. In the estimation of professor of international health James Kazura, MD, computers will have a starring role if medicine's healing potential is to be realized: "Gathering information is one thing, but computers are needed to make heads or tails of it and translate it into systematic ways of attacking a medical problem."

In the case of Baby Boy born in 2111, all data relevant to his medical care—from his health history and charts to intricate diagnostic images of his body—will be available to any of his doctors at a moment's notice, thanks to the high-powered computers that will be run-of-the-mill by his time. And with elaborate satellite technology supporting instant information-sharing around the globe, a doctor won't need to be nearby to offer a specialized diagnosis—if, for example, Baby Boy lives in a rural area without easy access to medical attention or wants to consult a hometown caregiver about concerning symptoms while away from home.

This kind of remote, computer-assisted "telemedicine" can support not only health diagnoses, but also medical procedures such as robotic surgeries, points out cardiovascular expert Mukesh Jain, MD. "Already, one of our own electrophysiologists has performed a computer- and robot-assisted ablation for arrhythmia of someone in Europe from here in the United States," Jain

says—an exceptional circumstance today, but expected to become commonplace over the next 100 years.

For good or for bad, Jain foresees less and less human contact between physician and patient as an inevitable side effect of the increasing prominence of computers in medicine. Virtual house calls may be the closest thing to the personal tradition of years long past.