**Patient, Heal Thyself**

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*Treatments from our own cells could cure many diseases—if Washington will only allow it to happen.*

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Emily Whitehead, a child given cell therapy for acute leukemia; her family says that she shows no sign of the cancer today.

Unlike conventional drugs, these cell therapies are created from scratch, one patient at a time, and many of the tools used to create them are simple, compact, and cheap enough to land in laboratories that serve hospitals, small clinics, and doctors in private practice. They have been landing there in growing numbers in the last decade, and Washington has been trying to keep pace. The Food and Drug Administration (FDA) has taken the position—upheld in February 2014 by a federal appellate court—that a patient’s cells become a “drug” when extracted and manipulated in a laboratory, and may not be used to treat the patient without FDA approval. But it is far from clear how the agency should set about approving a custom-made drug that will be prescribed to only one patient, in whom its safety and efficacy will be largely determined by how the patient’s molecular biology interacts with itself.

The widespread interest in human-cell therapies—together with the still-blurry lines between the broad statutory definition of “drugs,” which require FDA approval, and the “practice of medicine,” which does not—has set the stage for an extended and fractious [struggle for control](http://www.city-journal.org/2013/23_4_genetic-data.html), pitting many doctors and patients against Washington. At stake are extremely versatile treatment methodologies that can regenerate damaged tissues and organs and have the potential to cure many currently incurable diseases.

**T**wo types of cells perform the two most fundamental tasks involved in maintaining our health: stem cells spawn new healthy cells; and immune-system cells destroy unhealthy ones.

From our toenails to our brains, we owe every part of our adult bodies to a single stem cell that contained the two half-strands of DNA that fused at the instant of our conception. This “totipotent” stem cell had the power to reconfigure itself to spawn the next generation of more specialized stem cells in a process repeated until it culminated in the array of stem cells that built all our organs and tissues and that continue to lurk inside them, standing by to maintain and repair them throughout most of our lives.

Researchers have been harvesting stem cells from embryonic and fetal tissues for many years, albeit often in the face of much opposition. Viacord, a company established in the early 1990s, pioneered the banking of stem cells harvested at birth from the child’s umbilical cord and blood for future use by the child or, sometimes, a sibling. Several other companies now provide similar services. Some collect placental stem cells that have a unique capacity to control immune-system chemistry (a power they use to prevent the mother’s immune system from attacking the unborn child during pregnancy) and that have the potential to be used later in life to treat autoimmune diseases. Stem cells can also be harvested from adult tissues. And biochemists recently developed tools to reengineer mature cells back into stem cells that are as potent and versatile as embryonic cells.

In the United States and abroad, under widely varying degrees of regulatory oversight, stem cells have been used in attempts to treat many different disorders. There are promising indications that a patient’s own unmodified stem cells can regenerate nerves in severed spinal cords; or rejuvenate diseased heart tissue or retinal cells in patients experiencing macular degeneration; or treat burns, strokes, type 1 diabetes, Parkinson’s disease, multiple sclerosis, Alzheimer’s disease, some cancers, and osteoarthritis. Stem cells can also be used to grow healthy replicas of entire organs.

The patient can’t always supply the healthy stem cells that are needed. Donor stem cells have been used to regenerate immune systems since the late 1950s, when one healthy twin donated bone marrow (which contains stem cells) to a sibling whose bone marrow had been destroyed in the course of treating him for leukemia. Successful non-twin transplants began two decades later, after medicine learned how to match a donor’s immune-system genes with the patient’s. Biochemists now have the tools to dispense with donor cells and instead insert copies of healthy versions of the right genes into cells extracted from the patient’s own body. In the last few years, researchers have perfected flexible tools that can selectively add, delete, or replace genes inside stem cells as well as mature adult cells and can do in weeks what often required months or years of work using previous gene-editing tools.

No other currently known process has the potential to provide complete cures for the many rare but often deadly disorders caused by hereditary genetic mutations. In recent trials, for example, treatments with the patient’s genetically reengineered stem cells have cured “bubble babies”—born with a defective gene for an enzyme that plays a key role in the creation of a functioning immune system—and other children who rarely live more than a few years because they lack an enzyme required to create the sheaths that protect their nerves. Researchers are investigating the possibility of using the same approach to treat many other more common congenital disorders. In February 2014, an FDA advisory committee announced plans to consider the approval of human trials of a process for correcting genetic flaws in a woman’s unfertilized egg cells.

Other researchers are investigating a number of different vectors for reprogramming adult cells inside a patient’s mature tissues and organs. In a handful of early trials, for example, young adults blinded by a rare genetic flaw experienced substantial improvements in visual acuity soon after a viral vector was used to insert a healthy version of the gene directly into their retinal cells. Similar procedures are reportedly being developed to treat cystic fibrosis, brain cancer, and muscular dystrophy.

Versatile tools for reprogramming our genetic code also open a broad range of possibilities for fortifying bodies, much as vaccines do, well before a disorder materializes. The HIV retrovirus, for example, pries its way into our immune-system cells by latching on to a protein on the cells’ surfaces. A recent trial demonstrated that genetically engineering a patient’s T cells to introduce a variation on the gene that codes for the HIV-entry protein can provide a durable cure. Rare variations in a single gene make some people prone to develop very high levels of cholesterol and suffer heart attacks in their teens. A different, more common variation in the gene has the opposite effect, and researchers are investigating the possibility of reprogramming cells to replace the high-cholesterol version of the gene with the low. An array of tumor- suppression and DNA-repair genes protects most of us from cancer for most of our lives. Hereditary variations in those genes affect how well those genes perform, and some are strongly linked with the development of specific cancers—breast, skin, or colon cancer, for example—or, in rare cases, a propensity to develop cancers throughout the body. Genetic therapies administered early enough could offer many people a significant, lifelong reduction in their risk of succumbing to what is currently the second most common cause of death in the United States.

Hereditary defects in DNA-repair genes are also associated with premature aging. The senescence and eventual death of stem cells in general is probably the dominant cause of normal aging. Last year, Mayo Clinic researchers announced that they had identified certain molecular factors that play a significant role in stem-cell aging and its link to age-related deterioration of various tissues. A recent genomic study of a woman who lived until the age of 115, disease-free and with her mental faculties largely intact, revealed that, at the time of her death, most of her remaining white blood cells were very old and were the progeny of just two surviving stem cells.

Progeria, a rare genetic disorder whose victims age so fast that they die in their teens, has given researchers access to cultivated stem cells that can be used in laboratories to investigate the molecular process involved in the onset of specific age-related disorders and the aging process in general. With the tools to manipulate the genes that control those processes now in hand, it is reasonable to foresee a future in which progeria is a curable disease and normal aging can be systematically retarded. Craig Venter, the entrepreneur who played a large role in the first sequencing of a human genome, recently announced that he and some highly qualified partners are setting up the world’s largest gene-sequencing facility, with the objective of working out the molecular etiology of aging and developing stem-cell therapies to “make 100-years-old the new 60.” Google has set up a company that “will focus on health and well-being, in particular the challenge of aging and associated diseases.”

On the nearer-term horizon, stem-cell technologies may provide organ-by-organ rejuvenation. Laboratories have already used human stem cells to grow small-scale hearts, livers, kidneys, windpipes, and a pair of lungs, and are exploring the possibility of reengineering stem cells to regrow entire organs inside a patient’s body. A recent study indicates that infusing imperfectly matched donor organs with a patient’s own stem cells can prevent rejection and thus expand access to donor organs and save recipients from a lifetime on immunosuppressive drugs.

**O**ur immune-system cells, even more so than our stem cells, have to keep reconfiguring parts of their chemistry throughout our lives because infectious microbes are quick-change artists that keep reconfiguring their own biochemistry to evade our defenses. Biochemists are now extracting the patient’s own immune-system cells, reengineering them in a laboratory to home in on a designated molecular target, and dispatching them to attack the patient’s cancer.

In April 2012, for example, oncologists at the Children’s Hospital of Philadelphia used a genetically engineered form of the HIV retrovirus to insert new genes into healthy immune-system T cells collected from six-year-old Emily Whitehead. She had been fighting leukemia for two years and was on the brink of death. The new genes allowed Emily’s T cells to recognize and attack a target expressed on her cancerous B cells. The T cells were also modified to generate a signaling molecule that stimulates self-replication of other killer cells, multiplying their numbers at least 1,000-fold inside each patient, and each T cell can kill thousands of cancer cells. In one of the first adult patients treated, the killer cells destroyed pounds of cancerous cells within a month, leaving no detectable trace of cancer in his blood or bone marrow. In Emily’s case, the attack was so violent that it nearly killed her, but her doctors slowed it down by using an arthritis drug to suppress the signaling molecule. She awoke from a coma on the day she turned seven, and the staff in the intensive-care unit sang “Happy Birthday.” As of March 2014, according to her family’s website, Emily, the first pediatric patient to receive this treatment, has “been doing great and her blood work has looked perfect!”

There are also strong signs that these treatments can provide long-term protection against recurrence. The killer cells continue to circulate in the patient’s blood well after the cancer cells can no longer be detected. The methods used to cultivate the cells may also stimulate the generation of “memory” cells that can relaunch the attack if cancer cells resurface. With the engineered cells still circulating in their bodies, two of the three adult patients who were treated before Emily remained in full remission more than two years later.

The Pennsylvania team is now working with Novartis to continue developing these “chimeric antigen receptor” cancer therapies and commercialize their use in the U.S. and abroad. They have initiated a clinical trial to test the leukemia-treatment protocol against several other cancers that present the same target and have also reengineered white cells to attack a different target typically found on mesothelioma, ovarian, and pancreatic cancer cells. Similar procedures will likely prove effective against a wide variety of other disorders. In three trials involving 43 HIV-positive patients enrolled over a decade ago, the Pennsylvania team reengineered T cells to target a protein found on HIV’s outer surface. All the patients remained healthy 11 years later, and in almost all of them, the modified T cells were still present in their bodies.

Other researchers have found a way to rely entirely on a patient’s own un-engineered cells. Our immune systems often spontaneously produce some T cells that target cancer cells but rarely in sufficient quantities to destroy the cancer completely. Researchers extracted T cells from a patient suffering from late-stage bile-duct cancer that had metastasized to her lungs and liver, found a match between one T cell and a mutant protein associated with her cancer cells, and cultivated enough copies of that T cell to boost her immune system to the point where about 25 percent of the T cells targeted the cancer. Her lung and liver cancers stabilized for about 13 months, and then began to progress again. The regression resumed when the doctors boosted the dosage to 95 percent, and, at last report, the cancer had continued to regress six months later.

**H**aving taken over a decade to finalize a first set of rules addressing when human-cell therapies will be regulated as drugs, the FDA is now scrambling to catch up with laboratories and doctors who began developing and administering them without waiting for permission, on the assumption that when treating patients with their own cells, doctors are engaged in nothing more than the “practice of medicine.”

The recent case upholding the FDA’s authority to regulate human-cell therapies as drugs involved a procedure developed by two doctors to treat joint, muscle, bone, and related conditions with the patient’s own stem cells that had been cultivated and thus transformed into a “drug” in a laboratory that the doctors had set up to serve their clinic. The doctors still provide same-day stem-cell treatments in Colorado, using procedures that involve extraction and isolation but no cultivation of stem cells, but they now offer the cultivated cell procedures through an independent company that they set up in the Cayman Islands.

Another group of doctors in Texas neglected to obtain FDA approval of a similar procedure they used to treat arthritis. When the agency threatened to take them to court, they announced plans to shift their operations to Mexico. Their procedure used “mesenchymal” stem cells (MSCs), which many experts agree are safe and can help a significant number of patients by modulating overactive immune-system responses to damaged tissues and accelerating the formation of healthy new blood vessels. Hundreds of MSC clinical trials have been launched, among them at least one for treating multiple sclerosis. Many patients with degenerative diseases such as MS view existing treatments as inadequate but usually aren’t allowed to join the stem-cell trials that are already under way. In significant numbers, as *Nature* reported in 2013, they are traveling abroad to receive treatments provided by largely unregulated laboratories and doctors. Arnold Caplan, a pioneering MSC researcher at Case Western Reserve University, says that if he had MS, he would get the stem-cell therapy, going abroad if he had to.

The FDA clearly has an important role in overseeing the standard tools and processes used by laboratories that prepare human-cell therapies, and its statutory authority to do so dates back to the Biologics Control Act enacted in 1902, in response to a disaster caused by the distribution of diphtheria serum contaminated with tetanus spores. There are other more fundamental reasons for caution—much the same reasons that make many doctors and patients eager to forge ahead without waiting for FDA approval. Live cells can do things that conventional drugs can’t because they exploit the full power of the human genome that controls them. But they also have the potential to be equally flexible and potent in causing unwanted effects. One paraplegic patient whose injured spinal cord was treated with stem cells extracted from her nose developed mucus-containing cysts eight years later, in the area treated. Some of the bubble babies developed leukemia following treatment because the viral vector used to reengineer the treatment cells sometimes activates cancer-causing genes. The most potent stem cells have the potential to differentiate into forms that can colonize any part of a patient’s body. As the National Institutes of Health (NIH) has noted, metastatic cancer cells behave in ways “highly reminiscent of the classical properties of stem cells.”

There is, however, no scientifically rigorous process for evaluating and making one-size-fits-all yes/no calls regarding the efficacy of treatments that are custom-manufactured from each patient’s own, biochemically unique cells. It is not even clear how any attempt to do so can be reconciled with key language of the federal drug law. A provision enacted over 50 years ago requires drug-approval calls to be anchored in “adequate and well-controlled” clinical trials. The FDA’s long-established view is that this language and related statutory clauses are grounded on the assumption that a “drug” is an “article of commerce” that has a fixed, rigorously controlled chemical composition, the efficacy of which must be established by prescribing it in some standard way to a group of patients large enough to provide a statistically robust, one-dimensional correlation with a desired change in a clinical condition.

But little is fixed, standard, or one-dimensional when cell therapies are derived from the patient’s own cells. When the cells are cultivated, the patient’s own biological code controls that process, and it doesn’t end in the laboratory—the patient is treated with a live drug that can continue to replicate itself or use molecular signaling systems to enlist other healthy cells in advancing its mission. The efficacy of the therapy is determined by how the whole cell performs. Therapies that use the patient’s own unmodified cells are controlled entirely by the patient’s own unique code. When cells are reprogrammed, the modified code controls only a small part of the cells’ behavior. And the performance of the new code may be influenced by other code already inside the same cell and by noncoding stretches of the patient’s genome that play a role in activating and deactivating genes. In the last decade, researchers have discovered a large group of noncoding ribose nucleic acids (RNAs) that regulate gene expression. In the words of MIT Nobel laureate Phillip Sharp: “There’s a whole new world of RNA that’s layered on top of a gene and is involved in regulation that we know very little about, and I’m confident it’s going to tell us a lot about how cells respond to oncogenes and tumor suppressor genes and developmental signals.”

Stem-cell performance will also be influenced by neighboring cells. To repair or regenerate complex organs and tissues, stem cells must activate and deactivate different parts of their code to perform different functions as their work progresses. The FDA’s own scientists are focusing their laboratory research on how stem cells interact with their “microenvironment”—other cells in their immediate vicinity. In its list of important unresolved questions about stem-cell science, the NIH includes “the characteristics of their ‘niche’ that controls their behavior.”

Laboratory research with human-cell cultures can advance our understanding of some of these issues, but the science that can reliably predict when cell therapies will perform well can come only from the accumulation of clinical experience with a wide range of patients. We may well find that standard manufacturing and treatment protocols sometimes suffice to ensure similar outcomes in most patients. But manufacturing protocols are difficult to standardize when live cells are being processed one patient at a time, and quality assurance still hinges on monitoring and refining the methods used to reprogram and cultivate cells. And cell therapies can be used in countless ways. They may be prescribed at many stages in the development of a disease, or they may perform a wide variety of regenerative tasks in organs and tissues damaged in different ways by injuries, degenerative disorders, or infections. It is already clear that patient responses will often vary significantly and that safety and efficacy will often hinge on monitoring responses, repeating treatments, adjusting dosages, and, at times, intervening with conventional drugs to address unintended side effects. Rigidly scripted trials that don’t allow doctors to monitor and adjust treatments patient by patient are likely to end up rejecting many therapies that could benefit significant numbers of patients when used flexibly by skillful doctors.

**B**y and large, rigidly scripted trials remain the norm at the FDA. Responding to the advent of drugs precisely designed to modulate specific molecular targets, the FDA has gradually come to accept that the drug-approval process must take into account the relevant patient-side molecular factors as well. The FDA has, however, been slow to accept trial protocols that systematically investigate those factors and incorporate them into prescription protocols that increase the likelihood that the drug will be effective. With rare exceptions, the agency requires that the molecular factors that might affect a drug’s efficacy be identified by studying the disease before a clinical trial begins, or by analyzing the drug’s performance in short, early-phase trials that involve few patients—far too few to provide a full understanding of how variations in patient chemistry may affect a drug’s performance.

This has already been recognized as a serious problem in the testing of certain categories of conventional drugs. Cancer drugs don’t reconfigure themselves on the fly, but they target diseases that involve fast-mutating cells that do. A 2010 paper summarizing a report prepared by a coalition of cancer experts drawn from the American Association for Cancer Research, the FDA, and the National Cancer Institute concluded: “Many [cancer] drug candidates fail in early clinical development because outdated trial designs are used for their clinical testing and evaluation.” Two years later, a report issued by President Obama’s Council of Advisors on Science and Technology (PCAST) noted that many conventional FDA trials “imperfectly represent and capture the realities of the clinical care setting in which health care is delivered and do not include the full diversity of patients with a disease or the full diversity of treatment results.” Both reports recommend broader use of “adaptive” clinical trials in which patient responses are analyzed and modified at interim points in the trial to home in progressively on criteria for selecting the drug-patient combinations that work. The PCAST report would go a step further, suggesting the possibility of “[i]ntegrat[ing] clinical trial research into clinical care . . . [to] provide important information about how specific drugs work in specific patients.”

The FDA already has in place a “treatment-investigation” framework for doing just that. Developed in 1987, as part of the agency’s early response to a dreadful new disease called AIDS, the new rule authorized designated hospitals and clinics to prescribe as-yet-unapproved drugs to patients with “immediately life threatening conditions” as soon as short-term safety testing had been completed and “some evidence of therapeutic benefit” had been obtained. In applying the new rule, however, the FDA made no serious effort to integrate the investigation with the treatment. The objective was “not primarily to gain information . . . but to treat certain seriously ill patients”—particularly, members of demographic groups that were unlikely to have the opportunity to participate in ongoing trials. A second objective was to catch up with medical scofflaws. In their desperate search for ways to treat the many diseases that afflicted them when their immune systems collapsed, patients had organized buyers’ clubs to import drugs that were available in other countries. This was illegal, but prosecuting AIDS patients was politically inconceivable. So, for a time, the FDA applied the new rule to “drugs or therapies currently in wide use—whether they’ve been formally studied or not.”

Cell therapies have the potential to cure many currently untreatable diseases that are as lethal as AIDS—and for desperate patients, medical tourism is fast emerging as the alternative to waiting for the FDA’s permission to use them. Those factors alone make a strong case for adopting trial protocols that integrate clinical trial research into clinical care, as the PCAST report suggests; and there is also a compelling scientific case for doing so. When each patient is treated with a biochemically unique drug manufactured for use by that patient alone, any scientific demonstration of both efficacy and safety must involve a single-patient trial. The only way to develop a reliable foundation for prescribing such drugs safely and effectively to future patients is to begin with trials that systematically study the molecular factors that can affect how treatment cells interact with patients, and identify the combinations of treatment cell and the patient molecular profiles that perform well. Every combination of treatment and patient is biochemically unique, but similar combinations of the molecular factors that matter will recur in groups of patients. As the PCAST report notes, modern statistical methods and tools can handle large amounts of complex data and explore multiple causal factors simultaneously—including “individual patient responses to a drug, the effects of simultaneous multiple treatment interventions, and the diversity of biomarkers and disease sub-types.” As data accumulate, the powerful analytical tools of the digital age will progressively improve medicine’s ability to predict when specific combinations of molecular configurations in the treatment cells and the patient’s body make it likely that the treatment will be effective.

To that end, the FDA should develop flexible trial protocols that promote the comprehensive collection of molecular and clinical data and ongoing reporting to the FDA or independent supervisory bodies that the agency would designate. These bodies would have the authority to analyze data as they accumulate, promptly share what is learned with any doctor involved in the investigation of similar treatments, and decide when trials should be shut down on the strength of indications that the treatment is likely to be unsafe or ineffective in too many patients. Cell therapies have been made possible, in part, by tools that enable us to investigate and track what’s happening at the molecular and cellular levels and develop a mechanistic understanding of the molecular causes of a disorder. These same tools enable us to evaluate a drug’s ability to control those causes and thus obtain early, objective indications of whether the drug is likely to be clinically effective.

Safety issues are intrinsically more difficult because they can involve unanticipated drug-patient interactions anywhere in a patient’s body. But as the FDA has already recognized, the only practical way to deal with drug safety systematically is to begin with an array of laboratory tests, and then carefully monitor patients for side effects during clinical trials and thereafter, if the drug is approved. Trial protocols that integrate clinical trial research into clinical care would do the same and would include a systematic search for the molecular factors that can be used to predict when a patient is likely to experience serious side effects.

**D**efenders of the regulatory status quo worry—not unreasonably—that, absent strict regulatory oversight, the whole field might be discredited by disasters caused by inept practitioners. What they should fear at least as much is spectacular success, whether in FDA-approved U.S. clinical trials or in trials conducted in other countries, or from the relentless accumulation of favorable case reports from doctors and patients who dodge FDA strictures in other ways. If engineering white blood cells to target one specific protein works extremely well, there will be enormous pressure to engineer them to target many other proteins associated with other disorders. If stem-cell therapies work well for some disorders in even a minority of patients, the FDA will face pressure to make similar therapies immediately available to patients who are suffering from the many lethally degenerative diseases that are currently untreatable. Statutory definitions notwithstanding, many ordinary people will find it difficult to accept that they may not be treated with their own cells by their own doctor without Washington’s permission.

Some will go abroad for treatment, and others will find their way to U.S. doctors who are willing to ignore FDA rules and who may well be less qualified than those who aren’t. Many other patients may suffer and die because they do neither. The broader risk is that the United States permanently surrenders its role in leading the development of these radically new and extremely promising forms of treatment.

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