Fifty Years of PREDNISONE

This 20th-century wonder drug helped one of its first users to recover from an almost fatal bout of pneumonia and then live with chronic asthma and bronchitis. But prednisone's side effects are lengthy and often as debilitating as the many diseases it helps treat, leaving that user's daughter to question why, after half a century, there are no new drugs in the pipeline able to do a better job. by Cynthia Cushing

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It's not easy to keep a house quiet when five children under the age of eight live in it. When my mother was dying from pneumonia, my father accomplished this feat of crowd control with a scowl that was scarier than the closed bedroom door and the comings and goings of the doctors. My siblings and I sigh and roll our eyes about that time now because, although my mother was dying, she did not die. She was given a then new wonder drug and lived.

Prednisone is that wonder drug and it has been with us for 50 years now, more or less, depending on whether you start counting from the year it was discovered, isolated in the lab or made commercially available. In 1962, my mother, Lorraine Cushing, participated in the first wave of its widespread use; in her case, first for pneumonia and then for the asthma and bronchitis she developed thereafter. Prednisone was—and still is—used to treat a great number of diseases and conditions, many that may not be fatal but that can limit a life to a terrible extent. Before prednisone there weren't effective treatments for lupus, severe psoriasis, asthma, ulcerative colitis and dozens of other ailments from gout to bacterial meningitis. It is a superb anti-inflammatory and immunosuppressant and it acts quickly. It is used in the treatment of multiple sclerosis, the palliative management of leukemia and liver diseases, amongst dozens of others. Prednisone has made it possible for millions of people over the years to exchange death for life, or at least crippling invalidism for a chronic, debilitating condition. It has altered the lives of patients and the lives of their families, some in dramatic ways, which is what happened to mine.

The changes haven't all been good; there have been costs as well as benefits. Prednisone can have debilitating side effects and people who have no choice but to take it are right to wonder if 50 years isn't long enough. It seemed that there was a promise implied by prednisone: that the modern era of chemistry, and then later of biotechnology, would continue to reap harvests of new wonder drugs every decade. But will it turn out that prednisone was the end and not the beginning?

In Canada, prednisone is manufactured and distributed by Apotex, the largest Canadian-owned pharmaceutical company. Its generic name for the drug is Apo-Prednisone and the trade name on the bottles is Deltasone. It is dispensed in one, five and 50 milligram tablets. Apo-Prednisone was No. 37 on the list of most prescribed drugs in Canada in 2007, with 1,743,000 prescriptions for the little white pills filled that year (not including what was used in hospitals). This was a 7.5-percent increase over 2006 and theoretically enough to supply 5.4 percent of the Canadian population, although Apotex exports drugs to many countries. Besides pills, prednisone is available in creams, inhalers, nasal spray, injectable solution, eye drops and ear drops.

The drug is a synthesized version of the adrenal corticosteroid hormone, which is produced by the outer layer—or cortex, thus "cortico"—of the adrenal glands perched on top of the kidneys. It is a member of the larger group of molecules known as steroids. Steroids have a common chemical structure and the group includes cholesterol, estrogen, Vitamin D and the subset of so-called glucosteroids, which include the corticosteroid hormone. The corticosteroids are not the same as the infamous anabolic steroids that have been misused by some athletes. Like the naturally occurring hormone, prednisone works as a chemical messenger in the body. In a long and complicated chain of biochemical events, it travels through the blood and conveys its signals (for example, a signal to control inflammation) to cells far away by binding physically with receptors within the cells, which in turn leads to an alteration in the cells' biochemistry.

A little plastic vial of prednisone pills always sat on my mother's kitchen windowsill after that early bout of pneumonia. Her illnesses never really went away; she had severe asthma, chronic bronchitis and significant allergies and they were held at bay by the prednisone, except when they weren't. It could be a cold or a strawberry or exhaustion that sent her to the hospital for a week or more at a time. Hospitalizations occurred at least annually when I was a child, mostly in the winter, and the pressures and work of looking after a big family on a small budget must have been a factor. I can see her coming home from the hospital one Christmas Eve at suppertime, walking into the dining room and putting down her bag and taking off her coat, still wheezing and looking weary but smiling weakly, steeling herself for the onslaught. I remember making an effort to smile and sound happy, pretending not to see what I saw even as a child.

That's how we coped. Lorraine would be fine for stretches and then she would have weeks when she would sleep propped upright on the couch in the living room. The blankets and pillows would be put away by the time the rest of us got up in the morning. She might say, "I slept on the couch last night. I couldn't breathe." There would be a pause for a short beat and breakfast conversation would pick up from where it had been interrupted. It was the same with the cough, a cough that was literally gut-wrenching. You couldn't get away from it; you could hear it all over the house. I think we all perfected the cringe as an internal function, perhaps at most a shared glance. What could be said? The cough was there and no one wanted it to be there; we wanted to make it go away and we did so by ignoring it.

Lorraine didn't suffer from many of the common side effects of prednisone use. One of the most dreaded is the typical "Cushingoid" appearance, named after Cushing's disease. With Cushing's disease, tumours overstimulate the adrenal glands and symptoms include a puffy moon face, weight gain and weight redistribution to the upper back and neck and trunk. Because her last name was Cushing, this was always a great joke with each of the many doctors she saw. She didn't seem to mind the repetition; she regarded her avoidance of puffy cheeks as a victory of character and liked this achievement to be recognized. In fact, I think that she enjoyed her medical appointments overall. It was a chance to get out of the house and she knew more about her condition than many of her doctors and liked to prove them wrong when they made some ill-informed pronouncement.

Other potential side effects of prednisone use are diabetes, fragile skin, increased body hair, glaucoma, cataracts, osteoporosis, pancreatitis, high blood pressure, suppressed adrenal glands, suppressed immune responses and mood swings. There are many others, many of them serious, and the overall effect is said to be like accelerated aging. The side effects from localized use in inhalers and creams are generally fewer and less significant than those from pills, and nowadays, anyone who takes prednisone for an extended period has to have their blood counts, liver function and bone-calcium levels checked often and is monitored for infections. A book by Julie Ingelfinger and Eugenia Zukerman, *Coping with Prednisone: It May Work Miracles, But How Do You Handle the Side Effects* (St. Martin's Griffin, 1998), is a sympathetic handbook that would be useful for anyone taking prednisone for more than a week or two. Ingelfinger is a pediatric nephrologist and Zukerman is her sister, a flautist who took prednisone for an extended period to treat eosinophilic pneumonitis, a serious lung disease.

> **"Is there such a thing as the 'real' person we are apart from whom we become after life has had its way with us?"**

My mother certainly had the suppressed-immune-response side effect. On the one hand, this feature of prednisone is what has made organ transplants possible. Rejection of foreign tissue is a natural immune response that prednisone suppresses. This feature of the drug is also a good thing when it comes to the treatment of autoimmune diseases, such as lupus and multiple sclerosis, which cause the body to target its own tissue for destruction. For Lorraine, a suppressed immune response meant that a little cold always turned into a respiratory disaster. That usually meant an increased dose of prednisone for a time, followed by a period of tapering down to the old dose, which often led to further respiratory disaster, followed by a higher dose yet again.

Patients must taper their doses when they stop using the drug because prednisone overwhelms the natural functioning of the adrenal glands. Although prednisone mimics a naturally occurring hormone, it is used therapeutically in much greater amounts than the adrenal glands would ever produce on their own and they respond by shutting down shop. Without a gradual period during which natural production is allowed to start up again, the body is left without the hormones it needs. An abrupt withdrawal of the drug is usually painful, with low energy and acute aches. It can even be fatal. Blood pressure can drop to dangerous levels and the heart can beat irregularly. The condition that was being treated in the first place can get worse and mood swings can become more pronounced. And because the adrenal glands normally produce a large amount of steroids in highly stressful circumstances such as car accidents, the shutting down of the natural cycle leaves users exceptionally vulnerable. People who take prednisone for extended periods wear Medic-Alert tags to let EMTs and doctors know that they may need to be injected with a large dose of steroids in emergency situations.

The psychiatric side effects can be difficult for prednisone users and their families. I would have said that Lorraine was as free of these as she was of the puffy cheeks and the high blood sugar. (She died of pancreatic cancer at 61 and I do wonder if that could have been a "side effect", given the possibility of prednisone-induced pancreatitis.) But at her funeral, when we were walking away from the grave, my father said something like, "At least I had her for 35 years. It's too bad that you were too young to know her when she was really herself."

> **"With the prednisone my father had a wife who resembled my mother; without the prednisone he would have had no one."**

He was talking about the prednisone and I was furious. She wasn't only *your* wife, I thought but did not say, she was *my* mother, too, and she wasn't crazy. I held his remarks against him long after he, too, had died at a relatively early age. Then I began to wonder if my mother had been who I thought she was. Had I loved a stand-in? What does it mean to love someone who is transformed into someone else?

Lorraine didn't suffer from acute anxiety or have violent mood swings as far as I know, and she certainly didn't experience the psychosis that is a rare side effect of prednisone, but I think that her relentless activity was brought on by the drug. There was never an unwashed dish, an untidy room, or an un-ironed sheet in the house. She mowed an acre and a half of grass every week, much of it on steep banks; kept the long gravel driveway in good repair; cleared the ditches alongside the driveway; pruned the apple trees, picked the apples, preserved apple sauce and took the apple sauce to neighbours. She cleaned her mother-in-law's house as well as her own, gardened, babysat grandchildren, cooked three meals a day and worked in retail for many years, asthma lurking all the while.

It's not that she didn't have a sense of humour or couldn't be distracted enough to, say, go for a walk or have a cup of tea. She enjoyed the company of her family but any pauses were only ever just that. To distract her was to know that the work would be compressed into a shorter span of time. It created a tension in the household that felt like guilt. She did so much, many things that the rest of us did not think were necessary, and she inevitably would overdo things and become ill. She was intolerant of indolence in others and everyone was indolent, at least relatively. That intolerance gradually extended to all faults and all people. As children we avoided bringing friends home. Lorraine would be polite to them while they were in the house but would later pinpoint their faults: their looks, manners, parents, grammar. My father used to go to the Legion to drink in the evenings.

Is there such a thing as the "real" person we are apart from who we become after life has had its way with us? We marry and our spouse becomes someone new just with the passage of time apart from anything else. They become older, they get new ideas, they get sick or lose their memory. We marry and promise to stay forever but a long marriage is a serial event. It's a series of promises to the new spouse who awakes in your bed every morning or once every decade or so. My father stayed and adapted. I think he missed the woman he married in 1954 and I wonder if he stayed for her sake, loving the woman who, he believed, was somewhere there beneath the prednisone. His clumsy but well-meaning comments at her funeral seemed to indicate that he did. With the prednisone he had a wife who resembled Lorraine; without the prednisone he would have had no one.

Centuries before prednisone was isolated in the lab, it was known that women with rheumatoid arthritis felt better when they were pregnant. The long process of developing prednisone began with the thought that a naturally occurring hormone could be the reason why. This idea led to research in several countries. Clinical trials in the U.S. in 1949 showed that a corticosteroid, cortisone, greatly improved the symptoms of patients with the disease, although even then the side effects were worrisome. It was around 1950 that a team at a major pharmaceutical company, Schering Corporation, succeeding in converting cortisone into prednisone. The patent was granted to the team's leader, Arthur Nobile, in 1964 when production of the new drug was already under way.

Prednisone is just one of the 20th century's many wonder drugs. Like penicillin and many others, it was developed by following a long process. This process begins with learning about diseases and conditions at the biochemical level and then investigating many compounds that show promise of interrupting an abnormal series of biochemical events. Almost all of these promising compounds were derived from natural sources with long histories as natural remedies: plants, bacteria, moulds and animals. Cortisone was initially processed from an extraction of ox bile. It was later obtained from wild yams and then a mould. Each new source led to a simpler and less expensive production process.

The same process that was involved in the development of prednisone is at work today: there is basic research to elucidate the biochemical sequences responsible for disease, the screening for biologically active molecules from plants and microorganisms, the development of compounds that can effectively and safely interrupt the abnormal sequence. Taxol, an anti-cancer drug derived from the yew tree, is a late-20th-century example of this painstaking approach. Research into the human genome promises more targeted remedies for a great number of maladies.

Given all the new technology and advances in medical research, where are all the new drugs? Why is prednisone, with all its shortcomings, still one of the most prescribed drugs in the world? At least part of the answer can be found in the economics and politics of the pharmaceutical industry.

Marcia Angell describes the industry in *The Truth About the Drug Companies: How They Deceive Us and What To Do About It* (Random House 2004). Angell, a doctor, former editor-in-chief of the *New England Journal of Medicine*, pathology-textbook author and member of Harvard's Medical School, makes a strong case that the $200-billion American pharmaceutical business, despite its claims to be a font of research and innovation, is neither.

The industry has been turning out so-called "me too" drugs for decades. These supposedly new drugs are often merely variations of older drugs, created so that new patent rights may be obtained. To keep expanding the markets for pharmaceuticals, new diseases such as "erectile dysfunction" are created, while the clinical guidelines that determine the levels at which certain conditions—such as high cholesterol and high blood pressure—are deemed to require treatment are reassessed. People who would have been encouraged to start by making changes to their lifestyles a few years ago suddenly need to take pills every day. The pharmaceutical companies pour money into marketing and lobbying instead of research, and these activities buy influential friends in medical and political circles, a strategy that has been profitable for decades.

It has been government-funded agencies and universities, not the drug companies, that have been doing the expensive basic research since the 1980s, when new legislation in the U.S. allowed for what was called technology transfer. This meant that discoveries developed in public institutions, discoveries that formerly would have remained in the public domain, could be patented by researchers and then licensed to drug companies in exchange for royalties. Many small biotech companies in this era were started by university researchers. They became wealthy and the drug companies no longer had to rely on their own research. Then the research that was done began to have a pro-industry bias, with the emphasis on readily available commercial opportunities.

Now it is widely believed that the pharmaceutical industry is in trouble. There have been few blockbuster drugs in recent years and the pipeline of new and important drugs is dwindling, while the current big sellers have been on the market long enough to no longer qualify for patent protection. One result has been a flurry of acquisitions by the major firms within the industry. Merck & Co. has recently agreed to buy Schering-Plough for $32.6 billion US. Pfizer is buying Wyeth for $68 billion US, and Roche Holding AG is expected to buy Genentech for more than $46 billion US. The giant European pharmaceutical companies are adopting similar tactics. The general idea is to merge operations for similar product lines and thereby reduce costs. These are the tactics of a greying industry, not one that is young and innovative. Small biotech companies, once a source of much hope for new treatments, have mostly been externally funded and they are now being gobbled up by the major players or left to wither away from lack of financing as the recession takes hold.

In the current economic environment, especially as the new Democratic administration talks up reform of the U.S. medical system, the astounding salaries of executives and the retail prices of the drugs themselves are being attacked, along with the marketing approaches that had become accepted industry practice. It was announced in January of this year that the pharmaceutical giant Eli Lilly would pay a fine of $1.4 billion US related to illegal marketing of the anti-psychotic drug Zyprexa. And now American prosecutors are targeting physicians who accept lucrative consulting or speaking fees from manufacturers and then tout the drugs. Penalties will include fines, jail, loss of medical licences and exclusion from public medical-insurance plans.

Canada can be proud that its homegrown manufacturers, such as Apotex, produce lower-priced drugs relative to those south of the border. But while there is important experimental work going on here, such as in the field of stem-cell research, the journey from the laboratory to the doctor's prescription pad is a long and expensive one that travels through several levels of clinical trials. It remains a conundrum that large pharmaceutical firms seem to be the best placed to manage the production process, and yet the more stringent the testing, the less immediately profitable the drug becomes. It seems likely that it will take years before reform results in truly innovative drugs in the bathroom medicine cabinet.

And that makes it even more likely that prednisone will hang on to its place on the drug bestseller list for decades to come. There isn't anything substantially different in the pipeline to replace it. First it was the regulatory and moral environment that sent pharmaceutical progress down a side road in the '80s and, just when it seems it might get back on track, the economy is putting up a roadblock. It's like the old joke about people in the '50s thinking that by the year 2000 everyone would be flying around with jet packs, when it turns out instead that the newest innovation in personal transportation is a car—but a really small car. Yes, prednisone is now being used in combination with other drugs and, yes, there have been improvements in tailoring doses to individuals. Still, it seems that prednisone will endure, which means millions of us must continue to endure its shortcomings.

If I had lived 200 years ago, my life expectancy would have been 45 years and I would have been old long before that. I probably would have lost at least one child during childbirth or to a childhood illness. A cold or the flu would easily have become pneumonia and a little scratch might have gotten infected and led to the amputation of a limb or to a painful death. I might also, like so many, have wasted away from tuberculosis.

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Life is different now that we have drugs like penicillin and statins and prednisone. The prospect of a long life has changed how we think about our bodies and our health. Old age—now called middle age, thank you—used to be a truncated affair. Now old age is a half-century long and an owner's mentality has taken over from the renter's devil-may-care attitude. We look after our teeth, eyes, bones, backs, feet, digestion, skin and general safety like a responsible landlord protecting his investment property. There is so much to lose. Yet instead of glorying in the delights of extra decades of life, it seems that we fret those decades away and are more than a little indignant when death shows up all the same.

Lorraine spent a few weeks in a palliative care ward near the end, 27 years after she lay dying but not dying in our upstairs bedroom. Her children and her brothers and sisters came to say goodbye and she lay there in her hospital bed with her eyes closed and didn't speak. One of the nurses said that, yes, she was dying of cancer but she shouldn't be doing this poorly. She looked at her chart and noticed that she had been taking large daily doses of prednisone before she had been admitted and that she had had none since. They began to give her injections of prednisone in the hip and within a day she was feeling well enough to go home. For two or three days everyone sat around the living room and her brothers and sisters talked and joked about growing up on their farm and the people they had known and things they had done. Lorraine didn't say much but she laughed and kept her hand poised by her face as if she was always about to shush everyone else and throw in her own story. She was sparkling, vibrating with happiness. I thank prednisone for that.