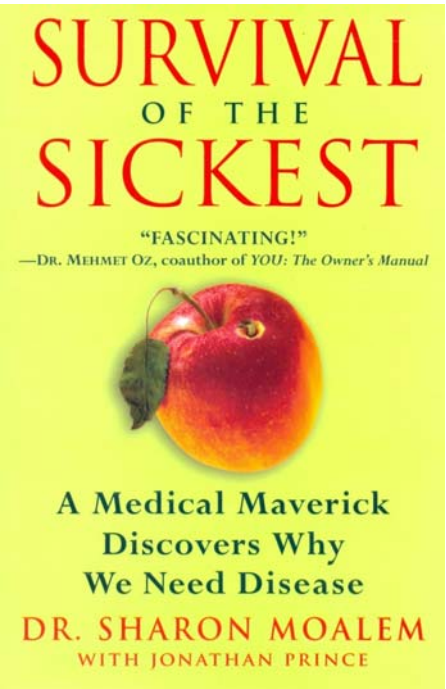
Book Review



Dr. Sharon Moalem
with Jonathan Prince

Survival of the Sickest: A Medical Maverick Discovers Why We Need Disease

Hardcover, 288 pages
William Morrow, February 2007
ISBN-10: 0060889659
ISBN-13: 978-0060889654

Survival of the Sickest: The Surprising Connections Between Disease and Longevity

Paperback, 304 pages
Harper Perennial, March 2008
ISBN-10: 0060889667
ISBN-13: 978-0060889661

Reviewed by U. Mohrhoff

Sharon Moalem's grandfather loved to give blood. No matter where his body hurt, all he needed was a good bleeding to make his aches go away. It turned out he had hemochromatosis, a hereditary condition that causes iron to build up in the body. When his grandfather was diagnosed with Alzheimer's, Moalem suspected a link between the two diseases. Nobody took him very seriously; after all, he was only fifteen. Soon after his graduation he learned that hemochromatosis had been linked to a genetic mutation.[1] He entered a Ph.D. program focused on neurogenetics, and after two years of collaborative work with researchers and physicians from many different laboratories they uncovered a complex genetic link between hemochromatosis and certain types of Alzheimer's disease.

When Dr. Moalem found out he had inherited hemochromatosis, he began to wonder

---

[1] One of the best-characterized genes regulating the amount of iron absorbed from food is called HFE. The HFE gene has two common mutations, C282Y and H63D. In the United States, most people with clinically measureable hemochromatosis have inherited two copies of C282Y — one from each parent. Mutations of the HFE gene account for 90% of the cases of clinical iron overload (Wikipedia).

why so many people would inherit a gene responsible for something potentially harmful? Why would evolution — which is supposed to weed out harmful traits and promote helpful ones — allow this gene to persist? Why would a gene that makes people sick still be in the gene pool after millions of years?

At first blush it doesn't make sense. Parasites hunt us for our iron; cancer cells thrive on our iron. For bacteria, fungi, and protozoa, human blood and tissue are an iron gold mine. This is why the places where we are most vulnerable to infection — apart from wounds and broken skin, these are our mouths, eyes, noses, ears, and genitals — are out of bounds for iron. In addition these openings are patrolled by chelators — proteins that lock up iron molecules and prevent them from being used. And when we are infected, our immune system not only floods the bloodstream with illness-fighting proteins but also locks away the iron.

What works in favor of people who have hemochromatosis is that they have a form of iron locking going on as a permanent condition. While most of their cells contain too much iron, the macrophages contain much less iron than normal. Dr. Moalem describes them as the police wagons of the immune system. They circle our systems looking for trouble; when they find it, they surround it, try to subdue or kill it, and bring it back to the station in our lymph nodes. . . When a normal macrophage gathers up certain infectious agents to protect the body, it inadvertently is giving those infectious agents a Trojan horse access to the iron they need to grow stronger. By the time those macrophages get to the lymph node, the invaders in the wagon are armed and dangerous and can use the lymphatic system to travel throughout the body. That's exactly what happens with bubonic plague: the swollen and bursting lymph nodes that characterize it are the direct result of the bacteria's subversion of the body's immune system for its own purposes.

Ultimately, the ability to access iron within our macrophages is what makes some intracellular infections deadly and others benign. The longer our immune system is able to prevent an infection from spreading by containing it, the better it can develop other means, like antibodies, to overwhelm it. If your macrophages lack iron, as they do in people who have hemochromatosis, those macrophages have an additional advantage — not only do they isolate infectious agents and cordon them off from the rest of the body, they also starve those infectious agents to death.

The advantage of having a gene that will kill you by the time you reach what is now middle age is that it will protect you from a disease that is killing everyone else long before that. The bubonic plague — the Black Death, as it was called — swept across Europe from 1347 till about 1350. It killed somewhere between one-third and one-half of the population — more than 25 million people — and significantly increased the gene's frequency across the surviving population.

Like much else in the *New York Times* Bestseller *Survival of the Sickest*, this is fascinating stuff, with a sobering moral to boot. At the beginning of the twentieth century, the medical community

> considered bleeding to be the epitome of everything that was barbaric about prescientific medicine. Now, new research indicates that — like so much else — the broad discrediting of bloodletting may have been a rush to judgment.

> First of all, it's now absolutely clear that bloodletting — or phlebotomy, as it's known today — is the treatment of choice for hemochromatosis patients. . .
>
> It's not just for hemochromatosis, either — doctors and researchers are examining phlebotomy as an aid in combating heart disease, high blood pressure, and pulmonary edema. . .
>
> The lesson for medical science is a simple one — there is much more that the scientific community doesn't understand than there is that it does understand.

At a time when ignorance is admitted only euphemistically ("the details aren't completely understood yet") it is refreshing to read this.

There's an important story within the story that makes up the second chapter. Before the 1950s, most scientists believed that climate change took thousands if not hundreds of thousands of years. By the 1970s there was general agreement that the temperature shifts and climate changes leading into and out of ice ages could occur over mere hundreds of years. Finally, in 2003, in his book *The Discovery of Global Warming,* the physicist Spencer Weart could write:

> Swings of temperature that scientists in the 1950s believed to take tens of thousands of years, in the 1970s to take thousands of years, and in the 1980s to take hundreds of years, were now found to take only decades.

Over the last 110,000 years, around a score of such abrupt climate changes have taken place, and none of them was man-made. In fact, during this time span the *only* truly stable period has been the last 11,000 or so years.

Now to the chapter's main story. Type 1 diabetes, a.k.a. juvenile diabetes, is most common in people of Northern European descent. Finland has the highest rate of juvenile diabetes in the world. Sweden is second, and the United Kingdom and Norway are tied for third. As we head south, the rate drops lower and lower. It's downright uncommon in people of purely African, Asian, and Hispanic descent. While "we don't fully understand" (!) the causes of Type 1 diabetes, inheritance definitely causes a predisposition to the disease. But if a disease has genetic underpinnings *and* is significantly more likely to occur in a specific population, this almost certainly means that the genetic underpinnings of the disease once helped the forebears of that population to survive. To find out how, you need to read this chapter.

The third chapter is about cholesterol, vitamin D, folic acid, sunlight, and skin color. If you don't get to read this utterly absorbing book, in the interest of your health I'll pass on two pieces of advice:

> when the optic nerve senses sunlight, it signals the pituitary gland to kick-start the melanocytes. Guess what happens when you're wearing sunglasses? Much less sunlight reaches the optic nerve, much less warning is sent to the pituitary gland, much less melanocyte-stimulating hormone is released, much less melanin is produced — and much more sunburn results. If you're reading this on the beach with your Ray-Bans on, do your skin a favor — take them off.
>
> Today, the most widely prescribed therapy for high cholesterol is a class of drugs called statins. Although they are considered generally "safe" drugs, over time, statins can cause serious side effects, including liver damage. If you knew that you might be able to reduce your excess cholesterol by getting enough sunlight to convert it to vitamin D, wouldn't you rather hit the tanning salon before starting a lifetime of Lipitor?

In Chapter Four it's fava beans, clover, sheep, birth control, malaria, and chemical weapons, of which plants are by far the biggest manufacturers. Favism is an inherited enzyme deficiency carried by 400 million people — the most common enzyme deficiency in the world. In extreme cases, people who have favism and eat fava beans experience rapid, severe anemia that often leads to death. Here's the mystery: favism is most common in exactly the places where fava beans are historically cultivated and consumed. "Well, if we've figured out anything so far," Dr. Moalem writes, "it's that evolution doesn't favor genetic traits that will make us sick unless those traits are more likely to help us before they hurt us." So where does favism help before it hurts? The answer: malaria.

Here's another bit that should make you think:

> Farmers who use synthetic pesticides, while creating a whole host of other problems, are essentially protecting plants from attack. Organic farmers don't use synthetic pesticides. So that means organic celery farmers are leaving their growing stalks vulnerable to attack by insects and fungi — and when those stalks are inevitably munched on, they respond by producing massive amounts of psoralen. By keeping poison *off* the plant, the organic celery farmer is all but guaranteeing a biological process that will end with lots of poison *in* the plant.

Chapter Five sets us straight about our relationship to microbes. An adult human contains ten times as many "foreign" microbial cells as mammalian cells. You have in your body more than 1,000 different types of microbial creatures weighing about three pounds and numbering somewhere between 10 trillion and 100 trillion. Their combined genetic material contains 100 times as many genes as your own genome does. While that relationship is mostly symbiotic, some microbes can affect our behavior in a most selfish manner — selfish from the microbe's point of view. It's called host manipulation. Take the Guinea worm. The victim relieves the sores caused by it by plunging them into cool water; this helps the worm to spread. Dr. Moalem goes on to examine some of the most extreme examples of host manipulation in nature, among them *dicrocoelium dendriticum*, a.k.a. the lancet liver fluke, a tiny worm made famous — for the wrong reasons — by Daniel Dennett (*Breaking the Spell*) and Richard Dawkins (*The God Delusion*).

According to neo-Darwinist doctrine, the potential for evolution is created when a random mutation occurs during an organism's reproductive process. Evolution actually occurs when this random mutation increases the "fitness" of its carrier, which of course is rarely the case. Chapter Six explodes two myths: the myth that random genetic mutations and natural selection are all there is to evolution, and the myth of a one-to-one correspondence between genes and traits.

> Geneticists originally believed that every single gene had a single purpose — a gene for eye color, a gene for a widow's peak, a gene for attached earlobes. When genes went wrong, you ended up with a gene for cystic fibrosis, a gene for hemochromatosis, a gene for favism. . . Suddenly, it's clear that genes don't have discrete jobs at all — there wouldn't be nearly enough genes to produce all the proteins necessary for human life if each gene only had one job. Instead, single genes have the capacity to produce many, many different proteins through a complex process of copying, cutting, and combining instructions. In fact, like a casino dealer who never stops, genes can shuffle and reshuffle

> endlessly to produce a huge array of proteins. There's one gene in a type of fruit fly that can produce almost 40,000 different proteins!

Nor is all this shuffling restricted to single genes: "the genetic dealer can borrow cards from other decks, combining parts of one gene with another."

> Instead of imagining genes as a set of discrete instructions, scientists have begun to conceive of them as an intricate network of information, with an overall regulatory structure that can react to change. Like a foreman at a construction site who directs a particularly fast welder to pick up the slack when his buddy doesn't show up for work, the genome system can react to a knocked-out gene and get a body built just the same.

So who is the foreman? To say, as Dr. Moalem does, that "the whole system is interconnected and automatically covers for its parts" doesn't begin to answer this question.

In the 1950s, Barbara McClintock discovered that whole sequences of DNA could cut and past themselves from one place to another, and that these "jumping genes" weren't behaving completely randomly, either. They even appeared to respond to outside influences. "In short, the corn plant seemed to be engaged in some sort of intentional mutation — neither random, nor rare." In 1983, McClintock received the Nobel Prize.

So an organism has the "ability to react intentionally on a genetic level to environmental changes that threaten its ability to survive and reproduce." Indeed, "from an efficiency perspective, it makes a lot of sense for genes to be resourceful and to maximally utilize existing genetic parts" — provided that "gene" is a metaphor for something actually capable of being resourceful.

Jumping genes allow for much faster and more sudden evolutionary change:

> Instead of a minor spelling error in one word in one verse of the DNA songbook, whole melody lines could insert themselves all over the genome. Like a good hip-hop artist, the genome has the ability to "sample" itself, creating different, but similar, riffs. And a sturdy, networked genome. . . could. . . sometimes benefit, from such improvisation.

McClintock thought that "a challenge to survival triggers the organism to throw the mutation dice, hoping it will land on a change that will help." Nor did she think that it was just a matter of "hoping"; she had reason to believe that "the genome directed its jumpers toward those places in the genome where mutations were most likely to have a beneficial effect." What is at work here is neither Darwinian natural selection, which only acts on the phenotype, nor artificial selection, which requires a human breeder. Shall we call it supernatural selection?

Again, it's no big surprise that a challenge to survival makes genes more jumpy. But if the jumpers can be *directed* so as to maximize the potential for survival in times of stress, then they can be directed toward other goals at times of no stress. In other words, there is plenty of room for goal-directed evolution.

There is more. Jumping genes are most active in the early stages of brain development. Dr. Moalem surmises that

> all of that genetic jumping around may have a very important purpose — it may help to create the variety and individuality that make every brain unique. This developmental

> frenzy of genetic copy and paste only happens in the brain, because that's where we benefit from individuality.

Following Aristotle and Aquinas, John Locke held that at birth the (human) mind is a "blank slate." The *tabula rasa* concept was also central to the psychoanalysis of Freud, who held that one is largely determined by one's upbringing, and in the 20th century it became popular in the social sciences. Yet nothing could be further from the truth. Already at birth, every (human) brain is unique. What then accounts for the particular way in which each brain is unique?

Ever heard of reincarnation? Here is Sri Aurobindo's view on this matter:

> The soul needs no proof of its rebirth any more than it needs proof of its immortality. For there comes a time when it is consciously immortal, aware of itself in its eternal and immutable essence. Once that realisation is accomplished, all intellectual questionings for and against the immortality of the soul fall away like a vain clamour of ignorance around the self-evident and ever-present truth. *Tato na vicikitsate*.[2] That is the true dynamic belief in immortality when it becomes to us not an intellectual dogma but a fact as evident as the physical fact of our breathing and as little in need of proof or argument. So also there comes a time when the soul becomes aware of itself in its eternal and mutable movement; it is then aware of the ages behind that constituted the present organisation of the movement, sees how this was prepared in an uninterrupted past, remembers something of the bygone soul-states, environments, particular forms of activity which built up its present constituents and knows to what it is moving by development in an uninterrupted future. This is the true dynamic belief in rebirth, and there too the play of the questioning intellect ceases; the soul's vision and the soul's memory are all. (Sri Aurobindo, *Essays in Philosophy and Yoga*, p. 268)

Obviously this is a huge subject, but one of the many question it raises now has a plausible answer. Whatever it is that the soul contributes to its present incarnation, it could contribute it by directing the "frenzy of genetic copy and paste" that happens in the developing brain.

Chapter Seven deals with voles, water fleas, locusts, lizards, and juvenile obesity. One-third of American children are overweight or obese. Here is a possible, even probable, explanation:

> The junk food that fills so many American diets is high in calories and fats, but often very low in nutrients, especially those that are important to a developing embryo. If a newly pregnant mother spends the first weeks of her pregnancy eating a typical junk-food-laden diet, the embryo may receive signals that it's going to be born into a harsh environment where critical types of food are scarce. Through a combination of epigenetic effects, various genes are turned on and off and the baby is born small, so it needs less food to survive. . . According to the thrifty phenotype hypothesis, fetuses that experience poor nutrition develop "thrifty" metabolisms that are much more efficient at hoarding energy. When a baby with a thrifty phenotype was born 10,000 years ago during a time of relative famine, its conservationist metabolism helped it survive. When a baby with a thrifty metabolism is born in the twenty-first century surrounded by abundant food (that is also often nutritionally poor but calorie rich), it gets fat.

---

[2] Sanskrit: thereafter one does not debate.

Time for a caveat:

> If you really want to understand how *little* we understand about possible epigenetic and maternal effects, consider the following. In the months immediately after the terrorist attacks on New York and Washington on September 11, there was a dramatic spike in the number of late-term miscarriages — in California. It would be tempting to assume that there is an obvious, behavior-related explanation for this — higher stress made it harder for some expectant mothers to take care of themselves. It is tempting to accept this except for one thing — the rise in miscarriages only affected male fetuses. In California, in October and November 2001, there was a 25 percent increase in the rate of male miscarriages. Something — and we don't know what — in the mother's epigenetic or genetic architecture sensed that she was carrying a boy and triggered a miscarriage.

In the final chapter Dr. Moalem asks where aging fits into the picture:

> Is it just wear and tear. . . ? Or is it the product of evolution? In other words, is aging accidental or intentional? . . . if a single genetic error can trigger accelerated aging in a baby or an adolescent, then aging can't only be caused by a lifetime of wear and tear. . . Are we programmed to die?

I should think so. Even if natural selection isn't all that it's cracked up to be, evolution depends on reproduction, and what kind of overpopulation would we be facing if our bodies would not age? Many scientists believe cancer prevention is the reason that, for normal cells, there is a limit on the number of times they can reproduce, the so-called Hayflick limit. But cancer cells aren't normal and have a way of getting around that limit, so this isn't convincing. Dr. Moalem thinks of it as a biological version of planned obsolescence, which makes more sense. There is however another possible reason: there's nothing like mortality to make us search for that in ourselves which is immortal.

Perhaps not least thanks to co-author Jonathan Prince, a speechwriter for former U.S. President Clinton, *Survival of the Sickest* is an absorbing read. It is also readily accessible, with a 43 page appendix of technical references and notes for the more enterprising. However, what I appreciate most is that it illustrates the schizophrenia at the heart of evolutionary research.

On the one hand, everything from genes to cells, from infectious agents to organisms, from species to evolution and Mother Nature, is said to have intentions and goals. "Every infectious agent has the same goal — to survive and reproduce by infecting new hosts." Evolution, who is "such a clever sort", "favors" certain traits. We are shown "how clever Mother Nature can be when she's doing the evolution dance." Aging is "intentional", "preprogrammed", "part of the design." In fact, when Dr. Moalem asks about aging, "Is it just wear and tear. . . [o]r is it the product of evolution? In other words, is aging accidental or intentional?" he *equates* being the product of evolution with being intentional. On the other hand, we are to understand the ubiquitous mention of intentions, design, goals are being purely metaphorical.

Even though the blurb celebrates Dr. Moalem, justifiably, as one of the "modern myth busters," and even though he presents his readers with plenty of evidence of true intentionality — never mind the elusiveness of the true agent, which also may be inten-

tional — he cannot quite free himself from the neo-Darwinist indoctrination to which students of biology and medicine are inevitably exposed. But he's trying hard and deserves credit for it:

> when you think of the amazing gift of your health and your life in the context of all the nearly incomprehensible forces of the universe pulling toward chaos — it reorients you, imbuing you with a deep respect for the immensely beautiful and intricate design of life on earth. Life that has been created and re-created again and again through billions of years of trial and toil. Something so complicated and time-consuming that it has to be a labor of love.

Indeed.

> The more we learn about the unbelievably complex, immensely varied, and yet simultaneously simple origin and development of life on earth, the more it looks like a miracle, and one that is still unfolding. The miracle of evolution.