GLOBAL VOICES OF SCIENCE:

When Science Is Not Enough: Fighting Genetic Disease in Brazil

Mayana Zatz

Mayana Zatz
Brazil

Mayana Zatz has had a lifelong calling to help those with genetic disorders, mainly progressive muscular dystrophies. She has done so on fronts ranging from investigating the biomolecular bases of such diseases to establishing social institutions dedicated to improving the lives of those who are living with these afflictions. Except for a 2-year stint of postdoctoral work in neuromuscular diseases at the University of California, Los Angeles, Zatz's academic training and professional life have unfolded at the University of São Paulo in Brazil, where she now directs the university's Human Genome Research Center. In 1981, she founded the Brazilian Muscular Dystrophy Association (ABDIM) to improve the lives of children afflicted with muscular dystrophy, particularly those whose hardship is magnified by poverty. Now with its own clinical center, ABDIM serves more than 100 such children, providing physical therapy, psychological counseling, and training in arts and computer skills. In addition to her biomedical research and ABDIM work, Zatz has long been active in genetic counseling, fully embracing the ethical ambiguities that come with the ability to test for the likely onset of diseases for which there are no cures. In addition, Zatz has become socially active in issues that include the ethical use of genetic tests and the use of embryonic stem cells in research and medicine. Among her awards are the TWAS (The Academy of Sciences for the Developing World) Prize in Basic Medical Sciences, in 2003, and UNESCO/L'Oreal "Women in Sciences" Award, in 2001.

CREDIT: COURTESY OF MAYANA ZATZ

All essays appearing in this series can be found online at www.sciencemag.org/sciext/globalvoices/

In my country, Brazil, one out of five babies dies before their first birthday because of a gene-related disorder. The life-wrecking prevalence of these diseases is invisible only to those who close their eyes. It was during my undergraduate years in the 1960s, while pursuing my childhood dream of becoming a scientist who could cure some of these diseases, that I had a transformative experience.

All of us studying biology at the University of São Paulo at the time had read books by a professor there named Oswaldo Frota-Pessoa, an expert in human and medical genetics. More than his books, it was his example as a scientist that moved me. He became my teacher, scientific adviser, and intellectual father.

On one pivotal day, he ushered me into a world beyond books and laboratories by inviting me to take part in the genetic counseling of families with patients affected by genetic disorders such as Down syndrome or Huntington's chorea. I realized during that counseling session, which took place under Frota's supervision within the university's genetics department, that by entering the field of medical genetics I

could do scientific research and simultaneously help those who are suffering from genetic diseases.

At that time, few people envisioned that genetics was destined to become such a consequential science with so many applications in human health. Even fewer people imagined the ethical implications and conundrums that advances in genetic science and technology would bring,

I began laying the groundwork for my own subsequent involvement in these controversial developments as a graduate student and a fledgling genetic counselor. One day I was faced with a young woman who sought genetic counseling because her sister had three sons affected with Duchenne muscular dystrophy, a muscle-wasting disease with no cure. She was getting married and was worried that any sons she might conceive would be destined to develop the disease.

It was heart-wrenching that all we could do for this woman was to recite the statistics to her. All we could tell her was that she would be taking a gamble with any sons she conceived, and that it was up to her if she wanted to take the gamble. Wanting to do more to help this woman and others like her, I decided to focus my research on the disease that had placed her in such a difficult situation.

Raging Against Dystrophy

The era of molecular medicine was just beginning. For my part, I analyzed the activity of the muscle enzyme creatine kinase in about 1000 individuals from families with a history of Duchenne muscular dystrophy. We learned that women with high serum levels of creatine kinase had an increased risk of having sons with Duchenne muscular dystrophy. I chose this subject initially for my master's degree, but it also became the focus of my doctoral studies and then my life's work.

Even as I was doing research, my genetic-counseling duties kept me intimately connected to the clinical and social benefits that such research could have. I met daily with families affected by genetic disorders, mostly Duchenne muscular dystrophy. I tried to explain to parents and sisters of affected patients what the disease was, what the prognosis was, what risk they had of having additional affected sons, and what could be done to improve the quality of life for those living with Duchenne muscular dystrophy.

Even after getting my Ph.D., I continued to pursue parallel approaches to combating the disease--molecular studies with the goal of ultimately curing the disease and counseling to help those affected manage the disease. In 1978, I intensified my scientific studies by establishing a new research group at the University of São Paulo. At the same time, I was haunted by a nagging question: What had happened to the families I had counseled during my training period with Professor Frota? The answer, I suspected, would help me choose an area of research most likely to benefit those suffering from Duchenne muscular dystrophy.

Tough choices. In genetic counseling sessions like the one shown here, the author helps prospective parents at risk of having children with genetic disorders to make reproductive decisions.

CREDIT: COURTESY OF MAYANA ZATZ

Joined by my students, I started to visit my former counselees at their homes. By 1981, we had reestablished contact with about 300 families. During these visits I had two surprises. The good one was that very few children had been born to mothers who had a high genetic risk of having sons with Duchenne muscular dystrophy. Most of these mothers had understood the risks we had outlined in the genetic counseling sessions. To my dismay, however, we witnessed the terrible living conditions of those children with Duchenne muscular dystrophy who were born before the counseling sessions with their parents. Most of them could not leave their houses because they had no wheelchair. They were not accepted in schools because no one wanted to carry them from place to place. They had no access to physical therapy because there was no hope that they would regain mobility. They were completely excluded from society.

I decided that something had to be done for these children. So in 1981 I founded the Brazilian Muscular Dystrophy Association, or ABDIM. My goal was to improve the quality of life of these children and their families by providing education and counseling. The effort grew slowly and steadily, and in 1988, we inaugurated the ABDIM center so that we could directly provide services to at least some of Brazil's most needy children suffering from genetic disorders. Today we use our vans to pick up about 100 children from their homes and bring them to our facility, where they are attended to by a multidisciplinary team. Our staff provides many services for the boys, including physiotherapy, hydrotherapy, psychological support, and art and computer lessons. We are currently raising funds to enlarge the center so that we can serve up to 400 patients.

In the late 1980s, thanks to two former students, Rita Passos-Bueno and Mariz Vainzof, who are currently both faculty members in our department, we introduced molecular genetics technology in our laboratory. This action rekindled my interest in solving the long-term problem of finding a cure for Duchenne muscular dystrophy and other genetic disorders by uncovering the biological bases of these diseases. With these and other collaborators, I was able to publish more than 200 scientific papers, most of them related to neuromuscular disorders.

The Testing Dilemma

As we carried out our studies over the years--mapping new genes and trying to understand their role in the disease process--more genetic tests became available. The introduction of molecular technology brought great advances in the diagnosis and identification of couples at risk of having affected offspring. However, the same tests raised new ethical issues that called for the development of responsible protocols for their use. For many years we had tested the sisters of patients with Duchenne muscular dystrophy to determine if they carried the defective gene responsible for the disorder. Those identified as possible carriers were assured that they themselves would not develop the disease, but they were informed that they were at high risk of having sons who would. Although it is debatable whether the sisters of patients with Duchenne muscular dystrophy should be tested before child-bearing age, I felt that knowledge of the test results would give parents a basis for encouraging their daughters to have a profession and a broader role in life beyond motherhood. Although knowing that one is a carrier of a pathogenic mutation may have a negative emotional impact, our follow-up sessions with the women we counseled revealed that such information helped most of them in their reproductive decisions and, following prenatal diagnosis, in preventing the birth of affected children.

Testing for genetic disorders where asymptomatic carriers may themselves be affected later in life revealed a completely different ethical conundrum. The first example that we encountered was myotonic dystrophy, a disorder that may cause

baldness, cataracts, and infertility, as well as muscle weakness and atrophy. For many years, understanding genetic anticipation, that is, the phenomenon in which certain genetic diseases such as myotonic dystrophy appear to become more severe in each successive generation, had been a puzzle. The discovery of dynamic mutations in which a specific short sequence in the gene increases in length from generation to generation was a breakthrough. We were eager to study this type of defective gene in the families of patients diagnosed with myotonic dystrophy. We contacted those who already had been diagnosed with the disease and asked them if they wanted to be tested. Most of them accepted and came with their young children to the laboratory at the University of São Paulo.

We analyzed blood samples from all of the family members, and surprisingly we found that many asymptomatic children carried an expanded form of the gene. This meant not only that they would have a 50% chance of having affected offspring but also that they themselves would develop the disease later in life. Because there is currently no cure or treatment for myotonic dystrophy, the genetic information carried a terrible price. Should we reveal test results to the parents of those children who tested positive if it meant they would be unable to help their little ones?

We decided that this particular type of genetic information exacted too high of an emotional burden. It became our policy not to test children for myotonic dystrophy, Huntington's disease, or other disorders with a relatively late onset and for which there is no cure or treatment. Another ethical argument that we use to justify our policy is that when you test a child for a genetic disease, you deny him the option of deciding in the future whether he wants to be tested or not. Our experience has shown that most young at-risk people prefer not to be tested when we tell them that nothing can be done if they test positive for the disease.

The list of questions that a person needs to consider before deciding to be tested is growing all the time. What disorder are they being tested for? What are the implications of a positive or a negative result? What can and should be done in each case? What are the benefits of genetic testing? In the context of genetic counseling, a discussion of these issues may take hours, and new dilemmas appear all the time. For example, what should be done when the results of genetic tests reveal awkward information about paternity? Or when the test results of one person reveal the risk status of a relative who does not want to know this information?

Another acute dilemma is how to deal with prenatal diagnosis. With the exceptions of rape or to save the mother's life, abortion is forbidden by law in Brazil. Despite the legal restrictions, the reality is that in the past, many women who had close relatives with Duchenne muscular dystrophy or other genetic disorders chose to terminate their pregnancy, often at great danger to themselves, rather than risk passing the defective gene on to their child. Would it have been unethical to withhold the possibility of prenatal diagnosis to these women, even though the technology to do so was in hand?

For us, the pivotal ethical issue is this: If genetic testing were to reveal that a fetus did not carry the defective gene, we might prevent the termination of the pregnancy. Therefore, in the 1990s we decided to offer prenatal diagnosis to women who would interrupt their pregnancy if they feared their fetus might be affected. Since then, we have done hundreds of prenatal diagnoses. In most cases, the test revealed that the fetus had not inherited the pathogenic mutation present in their family. As a result, prenatal diagnosis has encouraged more women to carry their babies to term than to terminate their pregnancies.

I vividly remember a young pregnant woman who came to us for prenatal diagnosis because she had lost two brothers and three uncles to Duchenne muscular

dystrophy. It had been an unplanned pregnancy, but she told us she wanted to have the child if we could assure her that the baby would not be at risk of contracting the disease. Unfortunately, our tests showed that the fetus had inherited the defective gene. Her mother, who had accompanied her, immediately said: "You have to interrupt this pregnancy! You don't have to go through what I did." With tears in her eyes, the woman turned to me and asked: "Do you think God wants me to abort this pregnancy?" For a nonreligious person like me, it was not an easy question to answer. "The only thing I can tell you," I said, " is that when your mother was pregnant she did not know she could pass this gene to you and to your affected brothers. But in your case, God wanted you to know. He is putting the decision in your hands."

I found out later that she had terminated the pregnancy, and I think that was the right decision. I believe that we have to keep fighting to change the law in Brazil to allow abortion of fetuses with genetic or untreatable disorders, mainly those incompatible with the ability to lead an independent life. The decision whether to keep or terminate a particular pregnancy has to be primarily the mother's because it is she who will bear all the burden of raising an affected child.

Stemming the Tide

Meanwhile, stem cell research and the prospect of being able to replace defective tissues through stem cell therapy offer enormous hope for patients with disorders such as Duchenne muscular dystrophy. Even so, in February 2004, the Brazilian Congress rejected the scientific or medical use of embryonic stem cells. With a group of scientists and patients' associations, we fought to have the law changed. We also have been waging a public awareness campaign through the media in which we have tried to explain what stem cells are, why research with embryonic stem cells is so important, and the difference between using stem cells from an aborted fetus and using stem cells from frozen embryos obtained as part of fertility procedures and that eventually would be discarded. On 2 March 2005, we learned that our efforts paid off: The legislators approved research with embryonic stem cells. It is hard to describe the emotion that we felt when the results of the vote were announced (352 for and 60 against), and we joined together in holding hands and singing the Brazilian national anthem.

Vote vigil. A group of patients and advocates for stem cell research in Brazil wait to hear the result of a vote by the country's legislators on whether to change a law forbidding such research.

CREDIT: VALENTINA FRAGOSO

Even as I continue to push for policy reform, I know that success will bring its own difficulties. If the research is permitted, hundreds of desperate patients will beg us to inject stem cells into their bodies, hoping to be cured. Explaining the difference between basic research, therapeutic trials, and proven treatment will be a hard and necessary task that will deflate many people's hopes of a timely cure. However, in my opinion, telling patients that there is no cure for their disease would be a worse frustration. I think people want to know that we scientists are doing our best to rid the world of terrible diseases.

The father of a boy with Duchenne muscular dystrophy once told me: "We are special! We have been blessed because we were chosen to take care of these

children." I consider the ability to work as a scientist and as a genetic counselor also to be a great blessing.

The author is at the Biosciences Institute, University of São Paulo, Rua do Matão 277, sala 211, São Paulo 05508-090, Brazil.