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My word

Long odds

Anne L. Calof

I am by nature a conservative person, not much of a risk taker. Yet in life we take risks all the time, even if we don't know it. We take a chance in just crossing the street or driving to work. How great is the risk that something terrible will happen to us as a result? Very small, as we all know, or we'd never walk out of the door in the morning. We may even buy a lottery ticket (academic salaries being what they are), even though we realize that we are almost certainly wasting our money. In the California lottery, there's a pretty small chance of winning. To win a prize of any size requires correctly selecting five of six randomly chosen numbers between 1 and 51; the odds of doing this are only about 1 in 67,000.

Recently I asked a good friend if he would accept the bet that there was a 1 in 30,000 chance that he would die tomorrow. "Yes. Every day of my life — those are really long odds," he replied. And, after all, how often do we expect to win the lottery? But I didn't ask him this question because I was interested in his expectation of winning the lottery. I asked because there is a genetic disorder called Cornelia de Lange Syndrome (CdLS), which occurs at about this frequency (1 in 20,000 to 1 in 40,000) of live births. Children with CdLS have a wide range of physical and mental problems with varying degrees of severity, including growth retardation, limb abnormalities, kidney problems, defects of the digestive system, speech disorders, hearing loss and mental retardation. Many children with CdLS live into adulthood, but some live one or two years, and some live only weeks or months.

How do I know all this about such an obscure syndrome (raise your hand, everyone who has heard of CdLS)? I know because I had a daughter with CdLS. She had several of the rarer and more severe manifestations of the syndrome (which were undetectable prenatally despite all possible technology), and lived only 31 days.

Current wisdom (such as it is) says that CdLS results from a dominant mutation in an unknown autosomal gene. The mutation is thought to arise most often in the gametes of an unaffected individual, as cases of vertical transmission are extremely rare. Parents with one affected child have an increased chance — about 1 in 50 — of having a second child with CdLS. This has led to the hypothesis that there is mosaicism in the germline of some transmitting parents, with some fraction of that individual's gametes harboring the mutation and the rest being normal.

Events are making me reconsider the value I place on certain types of research

What all this means is that it would be futile to try to screen parental DNA from cells other than gametes for the mutation; foetal cells would need to be screened. But no screen exists because finding the affected gene is not going to be easy. There are no large pedigrees of individuals carrying the disorder that can be followed and analyzed. Indeed, there are very few affected individuals from whom lymphocytes have been immortalized and studied by molecular geneticists (one of the labs working on CdLS has managed, over years of work, to generate only about 100 such cell lines). This has been an intractable problem to study and I know of only two laboratories that are working on CdLS at the

molecular genetic level — one in the UK and one in the US.

In the past, I've had many discussions with my husband, who is also a biologist, about the relative merits of basic and applied research. Basic research — questions pursued for their own merits — always seemed to me more likely to yield results untainted by the bias that might arise from the desire for a 'cure' for a certain disease. After all, did the war on cancer, that much-vaunted US program of the 1960s and 1970s, give us a cure for cancer? No, but because of it, we now have a much better understanding of the complexity and underlying causes of cancer than we did when the war started, even if the research hasn't yet led to an outright cure.

When I told a colleague the story of my daughter, she asked me if having this happen made me want to work on CdLS. You bet it does. And it's making me reconsider the value I place on certain types of research. Even though my lab may never be involved directly in isolating the gene that is mutated in CdLS, or in developing a screen for the disease, I will forever more be intellectually involved with this research and emotionally vested in its outcome.

I used to think that basic research was somehow better than applied research, but now I've changed my mind. Now it seems entirely worthwhile to focus one's scientific curiosity on problems whose solutions will have a direct impact on our lives and the lives of our children. This is a self-centred opinion, I know. Because what I want is for someone to find a way to screen for CdLS. I want biologists like myself to work towards finding a way to prevent or cure this and other birth defects. One in 30,000 odds are no longer long enough, at least for me.

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