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Adult Cystic Fibrosis Committee of Quebec

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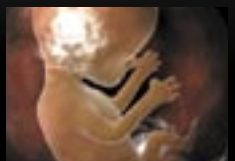



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CRITIQUE OF A DEATH SENTENCE

It is hard for most people to imagine just how much the situation of adults with cystic fibrosis (CF) has changed over the past 25 years. People with cystic fibrosis who are in their 40s can attest to that: all their lives, because of the statistics on median age of survival, they have been perceived as sentenced to death with a stay of execution. We are a far cry from the days when subjects such as employment, life as a couple, maternity and many other aspects of adult life could not be raised in the presence of young people with CF without creating a certain uneasiness. It was a time in which the future belonged to others.

Life has never been easy for today's forty-something adults with CF and they deserve the admiration of the CF community. Not only have they had to adjust to losing many of their peers, living in the constant shadow of death and dealing with a difficult, unpredictable disease, but they have also had to struggle with many prejudices that hindered their social integration.

The fact that our lives may be short, or at least shorter that other people's, necessarily influences our life choices, and it is hard not to take this into account when deciding how we want to live. However, taking it into account does not mean being paralysed by it. I will never forget the rage expressed by a woman in her early thirties with CF, who has since passed away, at having done nothing with her life because she was destined to die young. She came to this realization when she was 30, and began to live a life that was as full and active as she had always wanted it to be. This didn't prevent her from dying, but I'll bet that the second part of her life brought her more satisfaction than the first.

Unless they are unaware of the situation or in denial, no one with cystic fibrosis who is old enough to think rationally is indifferent to the statistics on median age of survival. Unfortunately, these data create unnecessary anxiety and pressure these people could do without, especially since only a few of them seem to really understand the true significance of these numbers. It is very upsetting to hear adults with cystic fibrosis refer to the median age of survival as though it were an "expiry date." In this regard, we should also be concerned about the general population's understanding of these data and ask ourselves whether or not this creates prejudice against people with cystic fibrosis with respect to their social and professional integration.

We agree that the concept of median age of survival needs to be more clearly understood by everyone. In the meantime, people with cystic fibrosis, rather than letting themselves be beaten down by statistics, would certainly stand to benefit by what the over 40 CF population has to say on the subject,. They would learn that as those people were turning 20, when the median age of survival was about 25, they never would have thought they would see the day when adults with CF would outnumber children with this disease. And they never would have believed they would see the day when some of them would become parents and maybe even grandparents; when lung transplants would be feasible and considerably increase the life expectancy of the CF population; when reproductive medicine would enable men with CF –98% of whom are infertile– to father their own children; and when adults with CF would excel in various fields, including the arts, dance, fashion, sports and business.

If the past is an indication of the future, people with cystic fibrosis have every reason in the world to be confident and to have an optimistic outlook on the future. What they shouldn't do is let themselves be intimidated by statistics on survival, because science will continue to surprise us! (21-12-06)

Laval de Launière

THE FOG OF MATH

I'm smiling as I tap away at my keyboard on this "little chat." Every year, I look forward to this delightful, joyful moment: that of writing "A Word from the Chair."

Today's adventure begins at the library. I was wandering in the stacks when I saw the least interesting book in our galaxy. No sooner had I picked it up than I felt a desperate craving for caffeine. This book is about mortality trends in Canada and Quebec over the last century. The authors give a detailed presentation of their scientific approach. They explain the difficulty in calculating the life expectancy of a low-density population. In order for this calculation to be reliable, the proportion of people aged 65 and over has to be greater than 4% of the total population. No wonder assessing the life expectancy of people with cystic fibrosis is a utopian feat. Now we understand why the Canadian Cystic Fibrosis Foundation (CCFF) opted for the median age of survival.

Unfortunately, the technical aspect of this datum is such that people don't really know what it means! It's not surprising that we use these expressions as though they were synonymous. This is a serious mistake, however. Admittedly, we wouldn't have much faith in a meteorologist who said: "Today, we have rain, and the temperature is 17°, so tomorrow and the days following, it will rain and the temperature will be 17°." Baseball is full of statistics: number of hits, home runs, strikeouts, etc. The batting average is the most commonly used datum. If a player has a .398 batting average, we know he has had an extraordinary season. However, this simple datum in no way predicts how many more seasons he'll be playing.

Life expectancy at birth is the calculation of the probable age that people in a population will die; in Canada, it is about 76 years of age. The median, however, is a statistical term. It is the value that divides a group into two equal parts.

Although statistics and probabilities are related, they differ conceptually. Statistics operate by deduction. Researchers analyse the data for a group and draw conclusions; they go from the general to the specific. Conversely, with probabilities, they go from the specific to the general; they predict probable results through induction. Life expectancy attempts to predict the future, while median age of survival gives information about the past.

The burning question is: "How do they calculate the median age of survival?" First, they need detailed knowledge about the Canadian cystic fibrosis population, which they then divide into age groups. They compile data on deaths over a given period (the CCFF uses five-year periods). Then, for each age group, they calculate the proportion of "survivors" out of the total number of subjects at the outset. The data are then calculated as a percentage (for instance, 89% of 10-year-olds with cystic fibrosis survived). A curve is then drawn using the values obtained for all the age groups. Then, they find the 50% mark on the curve. That point indicates the age at which the number of survivors equals the number of people who lost their battle against the disease. This value applies only to the period under observation. In 2002, the median age was 37 years.

Even after the difference between the two expressions has been established, the median age of survival still provides certain information. By looking at the changes in this value between 1977 and 2002, we see a significant improvement and can reasonably conclude that our life expectancy is increasing. The values are different but they follow the same trends.

Was it really necessary to make this subtle distinction? Yes, because the somewhat frantic desire to determine our life expectancy has distorted the concept of median age of survival. The distinction was made with good intentions, but it can cause confusion. My story, for instance, is very similar to that of the sailors who took part in Christopher Columbus' first expedition. At the time, people thought the earth was flat and, with each passing day, the sailors feared that their captain's obstinacy was bringing them closer to falling of the edge of the world. For me, the famous median age of survival mark represented the infernal abyss in which I was soon to disappear. When I was young, I was told I would die before I turned 18 and I wouldn't have children. I don't know why they didn't just say "have a good life in the meantime." My friends talked about becoming fire fighters, police officers, nurses or ballerinas, while I knew I was going to be in the restaurant business, providing dinner for the earth worms.

When I turned 31 in 1995, the median age of survival was 34 years. I floated through the storm, in quest of my America. The transplantation kept me from sinking into the "unlucky" half of the stats. Let me add that bad luck is a recurring trait in my family. You probably know that for two carriers of the gene, the probability of having a child with cystic fibrosis is one in four. Yet, my parents had eight children, and seven of them had cystic fibrosis. In baseball, that's a phenomenal average; in the day-to-day lives of a couple, it's another matter altogether. In some respects, my healthy brother isn't the lucky one in the family, I am. I have lived longer than my brothers and sisters, all of whom died before the age of two. At 42 years of age, I have passed the 50% mark. I'm a survivor. I feel like the Energizer Bunny beating its drum: I was lucky to have good batteries! It could be argued that I was unlucky to be born into a family with poor math skills. But rest assured of one thing: I would never trade my parents in. There's more to life than math! (21-12-06)

Christian Auclair

Genetics, Screening and Assisted Procreation: Ethical and Social Considerations

Interview with Chantal Bouffard

Chantal Bouffard is a professor in the Faculty of Medicine at the University of Sherbrooke. She has a PhD in Medical Anthropology from Laval University and a post-doctoral degree from the Centre de recherche en droit public (Public Law Research Centre) at the University of Montreal, and is interested in reproductive genetics and the delivery of medical genetics services. She participated in the development of the human genetics plan at the Quebec Department of Health and Social Services. Ms. Bouffard is currently setting up a research program on patient responsibility in medical genetics and reprogenetics.

Interview conducted by
Laval de Launière

Genetics is a relatively recent science that has evidently changed our relationship to life. Before you explain its applications in cystic fibrosis screening and assisted procreation, could you tell us exactly what genetics is?

Genetics is the science of genes, which has to do with heredity, evolution, speciation and individuality. Genetics basically refers to everything that has to do with genes. (See the glossary at the end of this article.)

Under what circumstances did genetics become an "applied" science?

Genetics gradually became an applied science as the techniques for studying genes and proteins were developed. Advances in cytogenetics, molecular genetics and biochemical genetics accelerated the acquisition of knowledge about genetics. Knowledge about genes, chromosomes and proteins, along with the possibility of testing individuals on a wide scale, changed genetics from a fundamental science to an applied science. It should be remembered that in the space of 50 years (1953 to 2003), we went from discovering the molecular structure of DNA to sequencing DNA's three billion letters. This remarkable feat was possible only because of the development of many study techniques. Given the clinical importance of genetics, technology transfers have always been quick and effective. Genetics will shape clinical practice in the 21st century as few disciplines have in the past.

Why do people have such strong feelings about genetics?

Genetics is a source of fear and hope because it can change our beliefs, our medical systems and our social institutions. It makes it possible to consider transformations in humans that once were the stuff of fantasy and myths. In addition, its connection to procreation and its use in eugenics prevent us from seeing it in purely scientific and medical terms. The power of genetics, as it shifts from the imaginary to the clinical, collides with the traditional values that are firmly entrenched in Western societies.

There is a fear that genetics undermines the integrity of humans by desecrating their divine or biological nature, depending on their beliefs, and distancing them from their assigned place. Genetic manipulations, cloning and genetic programming of unborn children are considered as the usurpation of God's creationist powers or a dangerous interference with what Nature took years to accomplish through evolution. Fuelling these fears are references to original sin, the trees of life and knowledge, *Brave New World*, clones, hybrid creatures and sorcerer's apprentices. There is also a fear of discrimination against people with diseases or disabilities, of eugenics and of stig-

matization of certain individuals and communities, not to mention that genetics generates feelings of guilt and vulnerability in persons who have, or who are carriers of, genetic or chromosomal diseases.

As for hope, we have to consider the fact that genetics was developed in societies in which myth and beliefs support the idea of resurrection and eternal life and youth. Such views make it possible to perceive genetics as a means of eradicating or preventing all diseases. Furthermore, genetics has created a new medical paradigm based on the genetic characteristics of individuals or communities rather than the characteristics of diseases. When genetics is associated with reproduction, it raises the fear of changing traditional family models and reproduction methods in order to create children who measure up to the desires of parents or societies. Lastly, the power offered by genetics and its potential in a market economy are also conducive to eliciting passion and competition.

Despite all the regulatory activity surrounding genetic research, do you think there is any reason to fear it? Should we distrust what's going on in our laboratories?

It isn't so much genetics we should fear, but the ways it will be used, the groups who will control it and the impact that genetics marketing will have on uninformed consumers. Out of concern for justice and fairness, we should also ask who will have access to genetic tests and treatments and under what conditions. That is why it is important for the public to acquire some knowledge about genetics and to ensure that citizens participate in genetic ethics and policy frameworks concerning genetics.

In Canada, university research projects are evaluated by peer committees who judge their scientific and ethical merit. For instance, a project involving genetic material or information has to be endorsed by an ethics committee in order to receive funding. Therefore, there is very little risk of unethical pursuits in public research. In the private sector there are fewer controls. Everything depends on the regulations in a given country. However, in Canada, researchers in both the private and public sectors are subject to the *Assisted Human Reproduction Act*, which regulates the production of human embryos, cloning and embryonic stem cell research, among other things.

In 1989, the discovery of the cystic fibrosis gene opened the way to screening for carriers of this disease. Why are some people reluctant to undergo a screening test for cystic fibrosis when all it involves is the collection of a small blood sample? What are the psychological, social or maybe even moral issues behind their reluctance?

In all cultures, there is a tendency to consider the causes of diseases to be exogenous, that is, stemming from external factors. It could be wicked spell, the evil eye, defiance of a taboo, punishment for a sin, viral contagion, bacterial infection, etc. In all these cases, we can assume that the "evil" comes from somewhere else. With respect to how the causes of disease are perceived, genetics has introduced the notion that the causal factor is endogenous, that is, it comes from us or our families. Consequently, having a genetic disease or being a carrier always elicits feelings of responsibility, guilt and even shame, at least for a while. Since there is the assumption, in genetic diseases, that people have to bear the burden of having a defect and the guilt that they could or did transmit a serious disease to their children or grandchildren, many people may want to remain ignorant of their status.

Under these conditions, people who have been diagnosed with a genetic disease risk being abandoned or blamed by their spouses, and sometimes rejected by their families or social groups. Fear, stigmatization, guilt and self deprecation play an extremely important role in people refusing to acknowledge that they carry or have a disease. From a clinical standpoint, it is crucial to take into consideration patients' individual and family contexts if we want to assist them and their families during the genetic screening process and help them acquire the knowledge they need to understand their situation. This phenomenon underpins the importance of appropriate genetic counselling that is tailored to each patient.

In some US states and European countries, newborns are systematically screened for cystic fibrosis. Is anyone opposed to this practice? If so, on what basis?

First, it should be mentioned that, in Canada, systematic screening of newborns is done only in cases involving treatment for symptoms or therapeutic approaches that may make a difference in the child's development or health. Under these conditions, systematic incorporation of newborn screening into the health system would occur only if early identification of a disease were significant and early measures would help prevent serious clinical symptoms. However, those who oppose systematic newborn screening usually do so for two different reasons. They may be afraid that genetic information derived from the tests would be used, without the parents' consent, for research or for discriminatory purposes with respect to insurance, employment and so on. They may also disapprove of the fact that parents cannot, in an

informed manner, consent or refuse to allow their child to undergo the screening. However, the best interest of the child should always be kept in mind in the debate regarding newborn screening. It should also be determined whether this practice is a social or individual responsibility.

Overall, would you say that infertile couples who go to a fertility clinic understand the issues involved in assisted procreation? Do wishful thinking and the intense desire to have children lead them to underestimate the well-documented risks of multiple pregnancies, premature births, etc?

Let me start by saying that dealing with infertile couples is not my specialty. However, my continued involvement with reproductive genetics allows me to observe certain situations that are worth clarifying or improving. In the case of cystic fibrosis, even though infertility can be linked to the disease, it is important to make the distinction between assisted procreation used in cases of infertility and assisted procreation used to bear healthy children free from serious genetic diseases, in which case a preimplantation diagnosis of the embryo is required. Since in vitro fertilization is not covered by Quebec's health plan because infertility is not considered a disease, this distinction would make it possible to offer preimplantation diagnoses at no charge to persons who have or carry serious disabling diseases. Consequently, a two-tiered medical system has existed for a long time in Quebec as far as reproduction is concerned. On one side, there are couples who can afford in vitro fertilization or preimplantation diagnoses and, on the other, there are those who cannot. My experience in this field and the discussions I have had with infertility experts have made me realize that the desire to have children does not prevent couples from understanding the risks associated with these procedures. In addition, those who can afford assisted procreation are usually well educated and well informed about the techniques.

However, even though couples are quite aware of the issues and risks involved in assisted procreation techniques, they are worried or frustrated when they come to the genetics department because they don't really know why they have to meet with a geneticist. Obstetricians don't give their patients enough information about why they are being referred to a geneticist. Furthermore, I don't know if they discuss at any length the health problems caused by premature birth due to multiple pregnancies (two or more children). As for prenatal or preimplantation diagnoses, geneticists clearly explain the risks involved. The success rate for preimplantation diagnosis is about 25%, which is very similar to what happens naturally. With respect to reproduction, I don't think that wishful thinking is necessarily a negative thing when couples are properly informed. And I don't think that wishful thinking with respect to parenthood is exclusive to assisted procreation. Wishful thinking seems to be an inherent part of all procreation plans, whether natural or assisted.

Before a preimplantation genetic diagnosis (PGD) or a prenatal diagnosis is made, how do couples and geneticists come to an agreement as to which embryos to preserve or eliminate? Given that couples have to decide to eliminate the surplus embryos or those that might have genetic anomalies, aren't there considerable ethical issues involved?

In Canada, the decision to continue or terminate a pregnancy and the choice of which embryos to preserve or eliminate rest entirely with the parents. In no way are geneticists to try to influence their patients' decisions, as specialists do in other fields. However, they have an ethical and professional obligation to inform couples of the risk of transmitting a genetic disease to their children and of the options open to them should the fetus have the disease in question. The problem is different in the case of preimplantation diagnosis. For instance, in France, some couples prefer this technique because there is no risk of interrupting the pregnancy. There, as in Canada, only embryos that do not have or carry the disease are selected for implantation in the uterus. Surplus embryos can be kept frozen for future use or for donation to an infertile couple. At the end of a parenthood project, they can be destroyed with the patients' consent. However, couples generally prefer that the destruction of the embryos serve to advance knowledge or improve techniques rather than serve no purpose at all. Religious or other beliefs, and the way couples view the embryo are the strongest determining factors of the ethical position that will influence decisions in connection with prenatal or preimplantation diagnoses. These issues are intrinsically linked to values.

Do you think that the debate about assisted procreation in Quebec should be more prominent in the news? If it were, what aspect should the public's attention be drawn to?

I find that infertile people are discriminated against, compared to fertile people. From a social standpoint, infertility is not considered a disease in Canada, and even less so in Quebec. Yet, in some cases, genetics shows that infertility is often caused by genetic diseases or chromosomal anomalies.

This view is reflected in government in that the costs of in vitro fertilization and preimplantation diagnosis are not covered by the State. Yet, the government covers surgical procedures to reverse voluntary sterilization. It also sees no problem in paying for abortions of fetuses with genetic or chromosomal diseases, but refuses to cover preimplantation diagnoses for those who need them. In our societies, parenthood projects do not seem to be valued or supported. They are often seen as a narcissistic desire or a refusal to consider adoption. You would think that wanting to have children is rather capricious for someone who is physically incapable or who does not want to have to abort a fetus with a seriously disabling or fatal disease. In addition, the system is such that only wealthy families have access to these reproduction techniques. Lastly, in our societies, it is the status of the child and the importance we attach to it that are called into question. This seems to be the main ethical issue involved in reproduction techniques, whether genetic or not.

Glossary of key terms in understanding genetics

Genes

Genes are the units of information needed to synthesize proteins. The information is transcribed to produce messenger RNA, which transmits the information from the cell nucleus to the cytoplasm, where it is translated into proteins using ribosomes. The information stored in genes is transmitted from mother cells to daughter cell colonies. Genetic change is usually accompanied by a change in the characteristics of a cell. This is very clear in cystic fibrosis cells, which are deficient in transporting salt.

Heredity

Protein make-up determines the specificity of species and individuals. Genetics is thus directly connected with the transfer of characteristics from one generation to the next. The transfer refers to heredity. A genetic alteration found only in somatic cells may be transferred with each cell division and, if it ends up in the germ cells, can be passed on to the next generation.

Tools of genetic studies

Genetics includes cytogenetics, molecular genetics and biochemical genetics. Cytogenetics is the science that studies the organization of genes in the nucleus; chromatin and chromosomes are the organizational infrastructure for the thousands of genes in the nucleus of each cell. Molecular genetics is the study of DNA, the basic molecule that makes up genes in which information is stored, and RNA, which transports genetic information from the nucleus to the cytoplasm. Biochemical genetics is the study of proteins and metabolic pathways used to synthesize proteins and other molecules essential to cell function.

Population genetics

The science that applies these tools to the study of different populations in order to identify and understand the origin of diseases.

Shoot for the Stars

Mary-Pier Gaudet

Montréal, Quebec
Canada

My happy childhood began on December 15, 1983, in Ville Marie, in the lovely Témiscamingue region. When I was diagnosed with cystic fibrosis at 18 months, however, my life took a different turn. Yet my unflagging good spirits helped me navigate through life's obstacles. Between homework, friends, the hospital, figure-skating and dance lessons, coping with my parents' divorce and quarrelling with my little brother, no one could have sensed my deep discontent. Torn by an inner drive and a desire for self-fulfillment, I knew I didn't belong in that quiet corner of the world. My growing conviction that I could accomplish something special finally convinced me to take a chance, somewhere, elsewhere.

It was only after my first heartbreak that I mustered the courage to leave Témiscamingue and try my luck in the city. My dream at the time was to become a professional dancer. I used to quietly envy the beautiful dancing girls on television, moving to the exciting rhythms of pop music. I wanted to be one of them with all my heart.

As a newcomer to the big city, I was as curious and naïve as a child. I wanted to explore it all and try everything: going out at night under the bright city lights and partying until dawn. However, what I thought was the good life only seemed so on the surface. I had always been a little reluctant to accept my disease, so it didn't matter to me that I was overdoing things. And the situation got worse, I think, when I found out that I had diabetes. Alone in that egotistical metropolis, wounded by all the doors that were closing before me, I saw all my hopes crumbling. During those sad years, I could have filled the oceans with tears. I had no love, no job and no friends, and my health was poor. And to top it off, my good spirits had abandoned me, taking with them all my dreams.

The summer of 2005 was a turning point in my life. Weakened by my negligent behaviour, I had to put my life on hold, once again, behind hospital walls, hanging on to my IV pole for dear life. I was confronted with the cold, hard truth for the nth time, and my morale was crushed. My insulin levels had become catastrophically dangerous and my lung capacity, considerably reduced: my entire system was sort of like a time bomb, which didn't help my frame of mind.

During this tempestuous time, I was fortunate to meet a ray of sunshine: a source of light by the name of Alexandre, who made me realize for the first time that I was the captain of my own ship. I saw that my life was going nowhere and that, despite all my intentions, I hadn't yet accomplished anything. The example he set revived in me the impetus that had thrust me out of the shadows in the first place. An unknown force welled up inside me, making me want to prove, both to him and to myself, that I could succeed. That is how I came to fight my first battle.

Filled with anger at myself and the medical professional who recommended that I slow down, I vowed to start training seriously. I wanted to take control and change the course of my life. Staying motivated was a new challenge. Having never been very disciplined, especially because of the empathy my friends felt toward me because of my health, I had to swallow my pride and persevere every day. However, my new lifestyle brought about positive changes in all aspects of my life. Enthusiastic about this second life that I had been given through my own efforts, and spurred on by the results, I hired a trainer and set my first real objective: to enter a fitness competition. I was fascinated by all the work this required and completely taken with the idea of combining gymnastics, dance and flexibility. This time, I would achieve my dream, and no one was going to stop me!

As a result, my condition gradually began to improve. The training increased my lung capacity to a higher level than I had ever achieved in previous tests. In addition, my new diet helped me to understand my diabetes and how food affects my body.

The following changes occurred:

1) I went from 6 capsules of Cotazym [ECS 20] to 0-1 capsule of Cotazym [ECS 8] per meal.

> “This time, I would achieve my dream, and no one was going to stop me!”

2) I was able to considerably reduce the number and dosage of my daily insulin injections.

3) I improved my capacity for work-outs and my endurance.

4) My sleep became more restorative, so I could spend more time on my training.

5) I developed a sense of pride, which improved my morale.

My enhanced quality of life is a wonderful thing, naturally, but meeting my objective after putting so much effort into it was the greatest accomplishment in my life. Having known the joy of success makes me want to do even better. I now know that nothing is impossible, but that we sometimes have to exert a great deal of effort; if everything were always easy, everyone would be doing it! As for me, I want to be among those who try and who succeed. Since I am lucky enough to have that strength of character, the courage of a lion and an iron will, I might as well use it to make my life a series of victories.

In closing, I would like to give the following advice: It's important to believe in your dreams, no matter what they are, even if other people don't see eye to eye with you in that regard. The more effort you put into the endeavour, the more the dream becomes credible and important. Remember that the more time and energy you spend on your dreams, the less time there is to be sick! Shoot for the stars and look at the big picture, because the sky's the limit. The proof of this is that I took part in the championships in Miami in early November to defend my new title as Second World Champion in Fitness and Figure. Who would have thought!

Now it's your turn. Go for it!
(21-12-06)

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Today, I'm Celebrating Life!

Manon Fontaine

Terrebone, Quebec
Canada

In 1994, it was confirmed that I had cystic fibrosis. I was 40 years old at the time. I say "confirmed" because my sister had been diagnosed with this disease a few years earlier and, given my family's medical history, the probability of my having it also was quite high. But even though I was expecting it, the confirmation of this diagnosis came as a shock. My first visit to the cystic fibrosis clinic at the Hôtel-Dieu Hospital was very disturbing: I suddenly felt weighed down by the burden of this reality. However, after a few months of treatment for my condition, I noticed an improvement in my quality of life: less coughing and fewer lung infections. I also began to see myself as a more conscious being. Knowing the symptoms of the disease affected my reaction to it. I was no longer merely a sick person; I was gaining some control over my situation!

I am now 52 years old. In December 2005, a biopsy confirmed that I had breast cancer. After routine examinations associated with this type of cancer, I found out that it had metastasized to my bones and liver. Once again, I was in a state of shock! I discovered the world of oncology and now spend time with a number of people who have cancer, many of whom are grappling with the uncertainty of how the disease will progress. The spectre of death is ever present.

> "...trying to second-guess the future, because an attitude like that can fuel fear."

The weeks following this diagnosis were gloomy indeed: chemotherapy, waiting for examination results, pacing the oncology ward hallways I felt as though my life were on hold. All that waiting, and for what? Well, I'm quite alive today!

I've had 19 chemotherapy sessions since December 2005. These treatments depress the immune system, and in that period, I had to take antibiotics three times for minor lung infections. In spite of this, my lungs are holding up: I'm thrilled!

After that trying experience, I decided to act, so I surrounded myself with people who could help me improve my situation. My first move was to find an oncologist whom I could trust in every respect, someone who was medically skilled and compassionate. I found one, and his thoroughness, respectful manner and open-mindedness all contribute to my well-being.

Then I started seeing a psychologist who has been helping me identify my strengths and channel my energy. As a result, I am gaining a better understanding of fear: I recognize all its facets and this is helping me to overcome it.

To this end, I am learning to live each day to the fullest. This requires a certain amount of training. I have to learn not to waste my energy harping on the past, which I can't change anyway, or trying to second-guess the future, because an attitude like that can fuel fear. When my mind is fully alert and I see, hear and live in the here and now, I feel happy most of time.

Meditation is a great tool for learning to live in the present because it disciplines the mind. After five minutes of introspection, my thoughts wander in every direction and I'm often oblivious to what is going on around me. Daily meditation is a wonderful exercise, especially because it boosts my morale and my energy level.

I don't feel isolated because my spouse, my son, my family, friends and co-workers support me. I appreciate their attitude: they don't pity me, they aren't in denial, and they support me by acknowledging my strength. Furthermore, they are willing to listen and to give me comfort when I'm going through difficult periods.

I'm grateful for what life has to offer.

Today, once again, I'm celebrating life!
(21-12-06)

In Vitro Fertilization: A Unique Adventure

Martin Lemire

St-Bruno-de-Guigues, Quebec Canada

I have always dreamed of becoming a father, and how I achieved this –adoption, having children with my spouse or artificial insemination– made no difference to me. I was lucky to meet the most wonderful person in the world: my spouse, Isabelle. At the beginning of our relationship, I didn't know whether I would be able to have children naturally. Since Isabelle also wanted children, I had a spermogram a few months after we started seeing each other. Since I have only a mild form of cystic fibrosis, I was hoping to be among the 2% of men with this disease who are fertile. Unfortunately, I was disappointed when the physician called to give me the results: statistics do not lie. In the meantime, Isabelle had undergone genetic screening to find out if she was a carrier of the CF gene. The good news was that she was not a carrier of the two most common CF genes in Quebec and Canada.

A few years later, we went to a fertility clinic. The first meeting was promising, and we were told what we already knew, namely, that we had three options: adoption, artificial insemination with a donor's sperm or in vitro fertilization. Since Isabelle wanted my child, I came up with what I thought was a brilliant idea: I had a striking resemblance to my father, so why not inseminate her with his sperm? But Isabelle disagreed, and my bright idea quickly fizzled out anyway, because Quebec law prohibits this type of practice. In hindsight, I admit that it wasn't a very good idea for a number of reasons, including moral considerations. We left that meeting with all the necessary information and decided to think it over for a year.

During this time, we visited another clinic, the OVO Fertility Clinic in Montreal. We felt very comfortable and confident right from the outset. This was in April 2005. Our meeting with the physician was very informative and led to the decision to try in vitro fertilization. We started the process a few days later, with much enthusiasm. First, we had blood tests, and my spouse had an ultrasound; both procedures went very smoothly. Before going back home to Témiscamingue, we made a second appointment for the next step, which involved meetings with a gynecologist, a urologist and a geneticist.

We made our second trip to Montreal in May. Our meeting with the gynecologist was positive and things were looking good. Our meeting with the urologist was a little more stressful; he said the vas deferens was absent, but there were sperm in the epididymus. What a relief! Everything was still going very well. However, the meeting with the geneticist shook us up quite a bit. Before we started the process, he wanted to make sure that our future child would not have cystic fibrosis, so he told us that, as responsible parents, we should have Isabelle undergo a CF gene sequencing test. This is a more advanced test to find out if the person has one of the numerous CF genes found in North America, and it takes three or four months to obtain the results. This made us very sad and disappointed, because we had been planning to start the in vitro cycle in July, and I had chosen my vacation time accordingly to be able to travel to Montreal. Our plans were dashed. My spouse was outraged and asked me: "Why is it so hard to have children? Why can't we have them naturally? We went back home, broken-hearted.

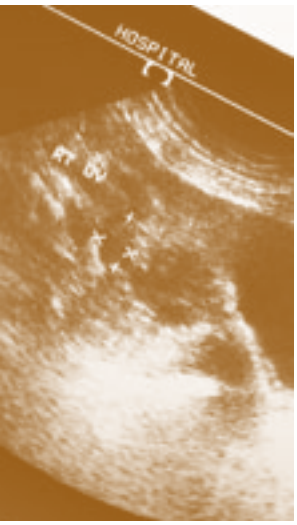
In early June, Isabelle had a blood test for the gene sequencing in a local hospital. Right before our vacation was to begin, we got an unexpected call from the geneticist: the results were perfect. According to him, there was almost no risk of having a child with cystic fibrosis. We were ecstatic! We immediately contacted the OVO Clinic to tell them we wanted to start the in vitro process because, as if my magic, it was the right time in my spouse's menstrual cycle. We couldn't have been happier. Our friends were encouraging, although some of them weren't in total agreement with us, because the process can be hard on a women's health and trying for the couple. In addition, it is expensive and doesn't guarantee results. Nevertheless, after we reassured them, they gave us their full support and encouragement. We went to Montreal and, a few days after taking the prescribed drugs, we went to the clinic. All the professionals (physicians and nurses) were very friendly and made themselves available to answer our questions and address our concerns. They explained that the process would last six weeks. We began our in vitro adventure with confidence and optimism, yet remained realistic: we were aware of all the possibilities.

We went back home with an armload of drugs and filled with hope. Because we lived so far away from the clinic, they facilitated the process by arranging for us to undergo tests in our area. The first drugs we took were in pill form, but the second batch

“ We began our in vitro adventure with confidence and optimism, yet remained realistic... ”

had to be injected, which was painful. We were both worried and nervous. We then prepared to go back to Montreal because, for the two following weeks, we had to be near the clinic. In the meantime, the drugs were doing their job and everything was going well. The day that the ova and sperm would be harvested was approaching and we awaited that day with trepidation.

Finally, on August 15, the physician harvested 24 ova from Isabelle, 14 of which were mature. Fortunately, this wasn't a painful procedure because Isabelle was on sedatives. Then, it was my turn. I panicked: I was afraid I wouldn't measure up. The nurse explained the procedure in detail, and all went well: the sperm were there, thank goodness! A few hours later, the clinic confirmed that our ova and sperm had produced nine embryos. However, that was not the end of our troubles. The ovarian hyperstimulation that Isabelle had undergone had caused severe abdominal pain; if it got any worse, they would have to delay implanting the embryos. Finally, on August 18, a very difficult day, the physicians implanted two embryos into Isabelle's uterus. The procedure was practically painless. The remaining embryos would be allowed to develop to a certain degree of maturity, and the ones that survived would be frozen. Now, all we had to do was wait and stay calm.



We went home two days later. On our way back, we found out that none of the embryos had survived. We had very much been counting on those embryos so as not to have to repeat the entire procedure in case Isabelle had a miscarriage or in case we decided to try to have another child. We had to wait two full weeks for the results of the pregnancy test; they were the longest weeks in our lives. We were happy, worried and confident all at once. The patiently awaited results of the first pregnancy test were positive, with hormone levels indicating that only one embryo had survived. We were happy, but also disappointed, because we were selfishly hoping that both embryos would survive; that way, we would have had our family in one attempt. This event made us realize that the success of this procedure hung by a thread; that the whole thing was really quite fragile, which is a difficult concept to swallow. I was torn between the positive result and the fact that nothing could be taken for granted until our child was born. I was apprehensive because there was a risk that Isabelle, like any pregnant woman, could miscarry. I was still afraid of getting bad news. It had not yet sunk in that we were indeed going to have a child.

Then we got the results of the second pregnancy test, which were also positive. We were going to have a baby! But I was still worried. Furthermore, Isabelle had a hard time early in the pregnancy, because the procedure provoked another episode of ovarian hyperstimulation, which was even stronger than the first one. She had serious abdominal cramps that made us fear the worst. But about two months into the pregnancy, things became normal and the rest of the pregnancy went off without a hitch. Each new stage –her expanding abdomen, the baby moving and hiccupping, the ultrasounds– brought us joy.

The wonderful day we had been so anxiously awaiting finally arrived. Was I finally going to realize that we had a child? The birth went very well. When I saw that rosy little baby wiggling and crying on my spouse's belly, I burst into tears of joy at the beauty of this miracle.

And now we have a lovely baby girl. The sweat test ordered by my physician indicated that she doesn't have cystic fibrosis. She is now six months old and she, along with my spouse who made it possible for me to live through this adventure, is the best thing that ever happened in my life. The process certainly wasn't easy, but we had been well prepared. A few days after the in vitro process was over, if anyone had asked my spouse if she would go through it again, she would have said no. But time goes by and the memory of the pain fades away. Today, with this little bundle of life and love, we cannot imagine what our lives would be without her. We would love to have more children, and if life is willing to grant us this wish, we're ready. Who knows, maybe in a few years' time, science will have made advances that will alter the process, and even make it easier. In the meantime, we are happy and make the most of every minute with our daughter, who fills our lives with joy.
(21-12-06)

Thoughts About Cystic Fibrosis

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The inherited problem presently known as cystic fibrosis ought to still be called by its original name, cystic fibrosis of the pancreas (CFP). Preventive pulmonary treatments have created a majority of older CF patients who have pulmonary function tests in the normal range. In contrast, over 97% have pancreatic insufficiency, over 70% have abnormal glucose tolerance tests and about 40% have diabetes.

Forty years ago the simplest calculations of life expectancy showed that the survival age for CF patients was two years. In contrast, a snapshot of the survival of the 496 patients in our database at the University of Minnesota in 2005 suggests that 67% of them may survive to age 65. The reason for our success in Minnesota is the prescribing and practising of known prophylactic pulmonary treatments for as long as possible to prevent CF-associated lung disease.

All the following are my thoughts. You should not consider that what I believe about how to treat cystic fibrosis of the pancreas is the "right" and the "only" way CF care should be given. There are many opinions, held by very good CF doctors, which are different from mine.

I hope that your CF doctors will not be offended if what they believe or do differs from what I do. If we all thought the same, then only one of us would be needed.

There is an old English saying: "Opinion between good men is knowledge in the making."

Physicians disagree with some of the things that I have written; thus, knowledge will be in the making.

CF is the inheritance of a gene mutation from both father and mother. These two inherited genes produce an increased risk of acquiring a large number of diseases that are common in the general population. These include bronchitis, pneumonia, sinusitis, nasal polyps, pancreatic insufficiency, diabetes, male infertility and, less frequently, cirrhosis, symptomatic gallstones and even kidney stones.

While this seems like an unpleasant number of unwanted problems, there is a good side. A person who has genetic CF and the CF doctor know the illnesses at risk and both will be able to take preventive precautions.

There is another problem faced by young parents, which can perhaps be summed up in the following way. "What about having another child now that we have a child with CF?" There is no shortage of unsolicited advice concerning this question, but the decision ought to be left entirely up to the family.

My advice is only to the family.

1. Put your plans for another child aside for two years.

2. After two years, ask: "Can we take care of two children with CF?"

3. If the answer is "No," then you may decide not to risk another pregnancy or to try another year or two of care for your child.

4. If the answer is "Yes," then answer my second question: Would you want to take care of a second child with CF?

5. If your answer is "No," then perhaps you will need another year or two to care for your child and then ask again.

6. If you answer both questions "Yes", then go ahead with your family.

I believe that every patient with CF has the potential to improve lung function with aggressive airway clearance twice a day; even those patients

whose lung disease has progressed to the point that they have been advised to consider a lung transplant have this potential.

I have seen so many successful transplants that I support lung transplantation. Still, while there are many reasons for recommending a lung transplant, I favour only one, namely, to improve the quality of life. When I recommend that patients consider a lung transplant, I advise them to work as hard as possible to become so healthy that they and their doctors recommend delay. I believe that many patients considering lung transplantation have the potential to improve their lung function with improved HFCC airway clearance and with a determined and optimistic approach to treatment.

Thoughts About Living With CF

All patients should go to college to get a degree and make the same effort to find a job, to work and to plan for a normal career. Along with this, they should expect to marry, have children and later, grandchildren to enjoy. For males, the classic CFP infertility need no longer prevent fatherhood and, furthermore, adoption is a wonderful alternative.

Every patient or parent should maintain a record of all clinical visits, lab work, x-ray reports, cultures, prescriptions and hospitalizations, of the same quality as their CFP centre's medical records. The importance for every parent and later, every patient, to maintain their own records bears repeating. Such records can be critical when travelling and will be useful many times when moving to new jobs or homes and when seeking the care of new CF physicians.

Growing Old With CF Requires Both Knowledge And Hope

The classic tools of medicine are advice, prescriptions and manipulations or surgery. The tools most needed now are information, compassion and hope. In the doctor-patient relationship, compassion is where knowledge can be created and hope can be born and nourished. In the absence of compassion and hope there exists for the patient only despair.

The "Good Things About CF" is the intellectual background for hope:

- CF is not a disease.
- The illnesses that hurt CF patients are diseases that occur in patients who do not have CF and these diseases can be treated.
- New medicines and equipment are being developed.
- Patients and parents can experiment with treatments to obtain optimum results.
- Patients and parents can partner with CF doctors to fight the genetic component of CF.
- CF is treatable.
- With CF you do not have to worry about cholesterol.
- You meet wonderful families and friends.
- Having CF gives a better understanding of people who have other health problems.
- Having CF in the family has helped us enjoy every day and to appreciate our child.
- CF taught us not to take things for granted.
- CF helped us appreciate support from family and friends.

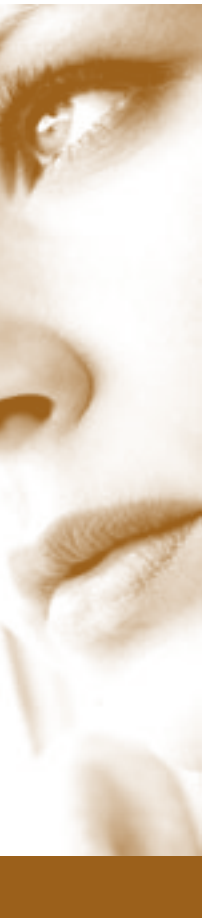
I always add three answers, based on my observations in caring for over 1,000 patients.

- Children with CF are on the average smarter than other children.
- They have better lungs before they acquire the CF-associated airway diseases.
- CF is a genetic risk factor for catching several common diseases; preventive therapies are needed and can work.

Hope

I see hope and despair as the extreme poles of a difficulty. Despair is focus on an unwanted outcome; hope is focus on a desired outcome.

In the 1960s and 1970s, when CF was seen as a probable forecast of death, there was a uniform belief among physicians and families that autopsy was our joint final battle against a condition which was, at that time, fatal. Almost all we know about the treatment of children and young adults was subsequently discovered, diagnosed and used to improve our treatment. In Minnesota, I cared for about 350 patients who died in those years and nearly every family joined the battle against CFP by granting permission for an autopsy to find out what we missed and to be better prepared to fight a more successful battle with future patients. That joint approach helped to make our CF Center recognized as among the best in the world.



We have lost that vision. Now, autopsies are performed on fewer than one in five deaths to learn the things that were missed or should have been done differently, or which prophylactic treatments ought to have been started to prevent deaths as they used to occur in the fifties, sixties or seventies. I believe the reason for this failure is threefold. First, there is poor communication between parents or families and their CF doctors. Second, there is a lack of trust on behalf of the deceased patients' families towards the CF doctors. Third, there is a lack of compassion demonstrated by CF doctors worldwide. Members of both the medical team and the family may be guilty of waiting for the development of new treatments and gene therapies, and not taking advantage of what is available both for prevention and treatment.

I am confident that improved communication in both directions, meaning between doctors and patients, and the earnest application of present technology, will prove my hope that most patients with CF will, in our times, achieve normal life expectancy.

Until then, many will die prematurely and will need to learn how to face death with hope. Aside from their faith, I see another hope that may support both patients and families. This is the hope that through an autopsy, they will have made a contribution to continue their fight against the acquired CF diseases which took the lives of their loved ones. The results of their autopsies will reveal still unknown answers to how better to fight the same problems in other patients with CF, and what to look for in future complications among all aging CF patients.

We (patients, families, husbands, wives, children, physicians, nurses, respiratory technicians, dieticians, secretaries, researchers, foundations and friends) can, working together, achieve this.

Practise hope.

Promote hope.

Never do anything that may take hope away from any patient or family.

Why!

Always ask "Why?" when you have a question about anything.

Enough is now known about CF to help patients achieve a near normal life and life expectancy. However, patients and families must insist on full answers to all of their questions, and frequently and persistently ask "WHY?" They must also give to their CF doctor the unasked-for full disclosure of what they do, how they do it, when they do it, what happens when they do it, what happens when they don't do it, what problems they have doing it, what they think needs to be done to improve it and what is wrong with it.

The advantages and difficulties concerning CF need to be diagnosed and analysed together. These include cost, advantages, dangers and risks, application, what may be accomplished and the duration of benefit. The entire CF community, including CF caregivers, patients, parents, siblings and partners, must be involved. When all options are identified and analysed, then we will accomplish our goal: the ability of all patients with CF to lead a normal life.
(21-12-06)

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Cystic Fibrosis and Fertility

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Many young adults with cystic fibrosis (CF) hope to become parents, and while the fertility of women with CF seems almost unaffected by the disease, over 95% of men with CF are sterile. Pregnancy in women with CF often raises numerous medical, social, and ethical problems. However, advances in reproductive medicine have allowed access to an array of very effective treatments.

Fertility problems

In men

Men with CF have totally normal capabilities for sexual function, but most of them are sterile (95 to 98%, according to estimates).

These men have normal testicles and produce sperm cells, but manifest an absence or shrinkage of the vas deferens. The vas deferens are the tubes that transport sperm cells from the testicles to the ejaculatory ducts. As a result, sperm cells are prevented from reaching the urethra during ejaculation. Men who have congenital bilateral absence of the vas deferens (CBAVD) usually produce a sufficient quantity of sperm cells, but these cells are not present in the ejaculated semen. This medical condition, which is present at birth, is not due to abnormal development of the vas deferens, but rather, to degeneration caused by obstructions similar to those found in the pancreas or salivary glands of people with CF. (Figure 1)

We will see that the existence of sperm in the testicles makes it possible, in some cases, to consider in vitro fertilization (IVF) by recovering the sperm from the epididymis or directly from the testicles.

In the past decade, a link has been established between CF and CBAVD. This has made it possible to determine a genetic cause for CBAVD which is, in most cases, considered to be a benign condition secondary to CF. Doctors now look for a mutation of the CFTR (Cystic Fibrosis Transmembrane Regulator) gene when CBAVD is diagnosed. CBAVD is a relatively frequent cause of male infertility, accounting for 1% to 2% of all cases. Both parents have to carry this gene for their son to be at risk of CBAVD (a 25% chance). Conversely, the CFTR mutation is present in 98% of people with CF. Given this fact, almost all men with CF are sterile because of CBAVD.

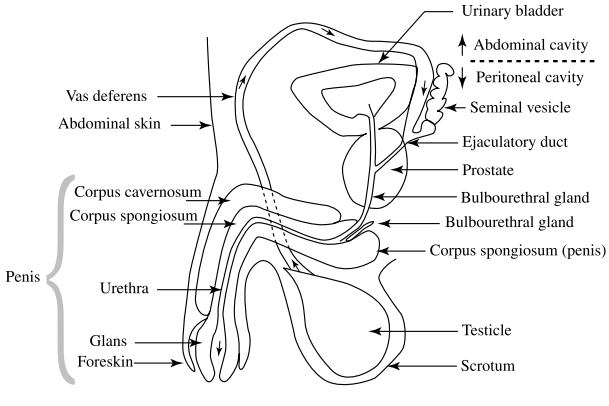
In general, several male fertility disorders have been associated with the CFTR gene, and men with these disorders are highly likely to be carriers of the CFTR gene, even if they do not have CF. These disorders include CBAVD, severe oligoasthenoteratospermia (low sperm count, decreased sperm movement, and abnormal sperm cell appearance) and azoospermia (absence of sperm in the ejaculate). Thus, 85% of men with CBAVD show no signs of CF. In most cases, CBAVD is the only symptom. This finding is important in the context of treating infertility in couples where the man has CBAVD. It implies that about one such couple in twenty-seven is at very high risk of having a child with CF (considering that one person in twenty-three in the general population of European origin carries a CFTR mutation).

Young's syndrome is a genetic disorder that affects specific mechanisms in the body's ducts and canals. In men, this syndrome can cause chronic respiratory problems (dilatation of the bronchi) and the inability to expel sperm (obstructive sterility). This association could constitute an elementary form of CF.

In women

Unlike men, women with CF are not sterile. However, it is generally acknowledged that these women are less fertile than women in

Figure 1 › Male Reproductive System



the general population. In principle, women with CF do not have any abnormalities in the structures of the reproductive tract that could prevent them from having children. Their reduced fertility can be due to one of the following factors:

- poor quality or lack of ova (female reproductive cells or egg cells) especially in women who are very undernourished;
- thickening of the cervical mucus, making it more difficult for sperm to pass through the cervix into the uterus;
- presence of polyps in the cervix.

It might also be mentioned that the concept of reduced fertility in women with CF has not really been proven by proper studies. Furthermore, some medical researchers are currently saying that up to 75% of women with CF who want to get pregnant do so without the need for assisted reproduction. However, it would seem reasonable to perform medical tests in women who have been having unprotected sexual relations for more than six months and have not gotten pregnant.

Medical recommendations

It is essential to consider whether or not pregnancy would endanger the health of a future mother with CF.

Birth control

If a woman with CF does not want to have children, she should use some form of birth control. This is an important point because too many young women with CF think they are sterile and do not take any precautions. This attitude is unreasonable, because even women with advanced CF have become pregnant. Oral contraceptive pills are commonly used, and are contraindicated only in rare cases of severe liver involvement. However, if a woman wants a child and does not become pregnant, she should undergo an examination of her reproductive tract and consider intra-uterine insemination or even in vitro fertilization (IVF).

Discussing the possibilities

The first thing a couple should do is to think about the future of the family and the child. They should take into consideration what impact the disease will have on them in the future, and the risk of transmitting the disease to their child. Genetic counseling should definitely be suggested to people with CF who want to have a family. The partner should be checked to see if he or she carries a CFTR mutation, in order to assess the risk of transmitting CF to the child. The couple should also be informed about the risks associated with pregnancy in women with CF.

The couple's first option consists of trying to conceive with their own gametes (sperm and egg cells). If pregnancy is achieved but there is a risk of transmission, a prenatal diagnosis should be obtained on the fetus through amniocentesis (genetic analysis of the cells in the amniotic fluid). If the fetus is found to have CF, a decision would have to be made as to whether to terminate the pregnancy. It is also possible now to obtain a pre-implantation diagnosis, which consists of genetically testing the embryos conceived in vitro and implanting only the healthy ones. Couples can also opt for using donated sperm, or for adoption. It is up to each couple to make this decision, and it is a tough one to make, so psychological counseling can be helpful.

CF and pregnancy

In women with CF, it has been found that the number of pregnancies is rising along with increased life expectancy. In the 1960s, the first reports of pregnancy in women with CF were alarming, and researchers concluded that pregnancy was not recommended for these women. These days, health care teams are in a better position to educate couples who want to have children. In addition, thanks to improved assisted reproduction techniques, more and more men with CF are able to become fathers.

Pregnancy in women with CF is a relatively new phenomenon. Patient registries, such as the one kept by the Cystic Fibrosis Foundation, have recently begun keeping track of the number of these pregnancies and their progress.

It should be noted that pregnancy does not accelerate deterioration of lung function or increase the risk of complications, and it is not specifically associated with mortality. However, this lies partly in the woman's state of health before pregnancy. For a patient who is clinically stable, pregnancy may be considered under strict medical supervision. Should her condition worsen, termination of the pregnancy could be considered.

Treatments and possibilities

Artificial insemination by donor (AID)

In cases of CBAVD, artificial insemination by donor may be suggested. Frozen sperm from a donor is placed in the woman's uterus. It is essential to use frozen sperm to ensure that the specimen is not contaminated. The donor must undergo screening and after the sperm is donated, it is quarantined for at least six months. Then the donor undergoes a complete screening again before the sperm can be used. This is to ensure that the donor did not have a disease nor had he been exposed to one at the time of donation. Thus the possibility of the donor passing a disease on to the receiver is eliminated.

In vitro fertilization (IVF)

In cases of CBAVD, when the couple wants to use the spouse's sperm, it is possible to use in vitro fertilization (IVF). Currently, the great majority of IVF is done with stimulation of the woman's menstrual cycle in order to retrieve more than one oocyte (egg cell) per cycle. Ovarian stimulation must be closely monitored through the results of ultrasound examinations of the ovaries and tests for blood hormone levels. This monitoring allows many ovarian follicles to mature while avoiding excessive stimulation of the ovaries. Ovarian follicles are tiny sacs that develop on the ovary, and each follicle contains an egg cell.

When the follicles seem large enough, ovulation (release of the egg cells) must be triggered by an injection of chorionic gonadotropin (a group of hormones). Thirty-six hours later, the fluid which is in the ovarian follicles is aspirated. It is from the follicular fluid that the embryologist retrieves the mature oocytes that are necessary for fertilization.

In cases of CBAVC, the sperm cells have to be retrieved directly by inserting a needle into the scrotum, or through a testicular biopsy, which is usually done under local anesthesia.

Using ICSI (intracytoplasmic sperm injection), a single sperm is injected directly into each egg, which is then placed in an incubator at 37°C. The next day, it is possible to see the number of fertilized oocytes (also called embryos), but it is only the day after that, i.e. 48 hours after follicular aspiration, that it is possible to know how many embryos have been obtained.

Two days following the aspiration, the embryos have an average of four cells. They can then be transferred into the uterus, but often, they mature in vitro for about one to four more days. This makes for a better selection of embryos, which increases the chance of pregnancy.

Currently, in the great majority of cases, two embryos are transferred. The transfer process is not painful: a fine, flexible plastic tube is introduced into the cervix and the embryos contained in a tiny amount of fluid are delicately deposited into the uterus. A pregnancy test is performed about 12 days later.

Natural-cycle IVF is a new solution that consists of aspirating the single follicle that is produced naturally every month (without ovarian stimulation), then fertilizing it with the father's sperm, which has been retrieved from the testicles. Unfortunately, this technique is still quite rare in Canada.
The results of IVF have clearly improved over the past few years. The following table, featuring statistics from the OVO Fertility Clinic, indicates that the most important predictor is still the woman's age.

Pre-implantation diagnosis

Pre-implantation diagnosis makes it possible to select embryos for transfer into the uterus. With this technique, prenatal diagnosis becomes unnecessary and the possibility of therapeutic

abortion is avoided. Technically, pre-implantation diagnosis requires IVF to obtain embryos. The testing is done using cells retrieved from the embryo through an embryonic biopsy, generally performed when the embryo is three days old. Genetic anomalies are diagnosed using specialized laboratory techniques. Only embryos that have no genetic disorders are transferred to the uterus.

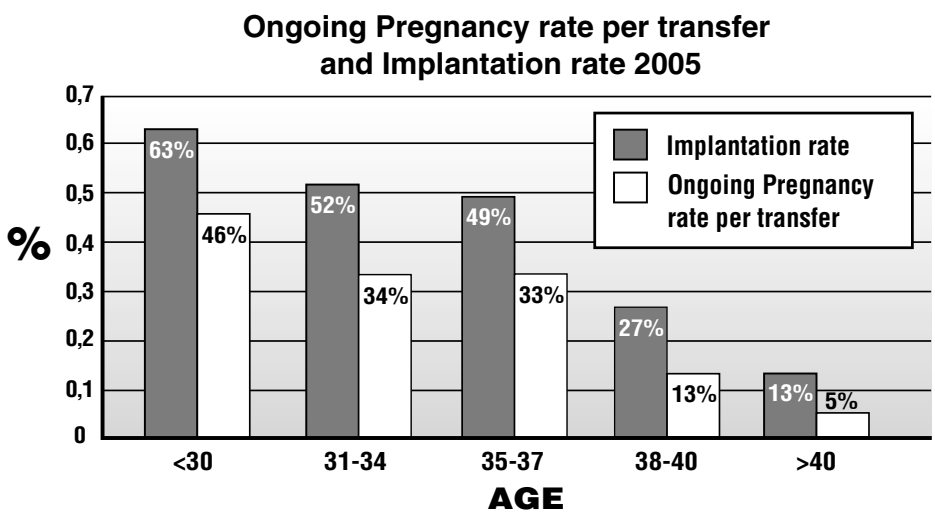
Conclusions

Today, 30 to 40% of persons with CF are adults of reproductive age. These days, the majority of people in this situation can have one or more healthy children, without compromising their own health. A multidisciplinary approach is necessary, bringing together all the physicians involved in medically assisted conception (gynecologist, urologist, geneticist, etc.), which makes the overall management of the couple possible.

Lastly, it is important that the couple take the time to discuss the various treatment options in private. The role of the medical team does not consist of imposing its personal convictions, but of providing the couple with the information they need to make an informed decision.
(21-12-06)

(*) Dr. Jacques Kadoch's profile is available at the following Web site : http://www.cliniqueovo.com/biographie5.asp

Table 1 ›



Grossesse évolutive définie comme étant un cœur fœtal intra utérin après 10 semaines

Antibiotic Therapy In Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is the most common lethal hereditary disorder with autosomal recessive heredity in white populations. In the lungs, the basic CF defect causes chronic bacterial infections which contribute the most to sickness and mortality in CF patients. The majority of CF patients suffer from chronic respiratory infection with the bacterium *Pseudomonas aeruginosa*, which takes advantage of the condition of the patients' airways. Antibiotic therapy is thought to be responsible for improving the clinical condition and quality of life of CF patients. This review focuses on antibiotic treatment strategies, including diagnosis of infection, antibiotic dosages, subinhibitory concentrations of antibiotics, emergence of resistance, routes of administration, adverse effects of antibiotics, home treatment and early antibiotic treatment.

Introduction

Cystic fibrosis (CF) is the most common lethal hereditary disorder in white populations, with an incidence of approximately 1:2,500 live births.[1] Disease is caused by over 1,000 mutations in a gene encoding a membrane-bound chloride channel.[2] The mutations affect ion and water transport in cells that line the respiratory, digestive, liver, biliary and reproductive tracts. In airways, this leads to an impairment in the mechanism that keeps the inner surfaces of the airways clear,2 and this causes chronic bacterial infections that may start early in the life of CF patients.[3] These secondary infections have the greatest impact on illness and mortality in CF. While *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Haemophilus influenzae* remain the most common bacteria, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Aspergillus* species, non-tuberculous mycobacteria and respiratory viruses can also be present. The vast majority of CF patients are infected with *P. aeruginosa*.[3] Mucoid *P. aeruginosa*, characterized by the formation of its sticky biofilm (the exopolysaccharide alginate), is predominantly present in chronic infection.[4] The development of chronic *P. aeruginosa* lung infection in CF is characterized by the production of a lot of antibodies, the formation of antibody clusters (immune complexes) and a large influx of white blood cells (neutrophils).[4,5] These cells form large areas of pus around the persisting bacteria, leading to obstruction and destruction of the airways.[5] Uncontrolled progression of infection will result in progressively severe lung damage, respiratory failure and death. Children with CF and infected with *P. aeruginosa* have lower pulmonary function, lower chest x-ray scores and lower 10-year survival than uninfected children.[6]

Infection control policies

P. aeruginosa is a widely found water organism. Studies of groups of patients have been conducted using several genotyping methods to study the bacterium. These studies suggest that transmission of *P. aeruginosa* to CF patients may occur by direct patient-to-patient contact or via contaminated sources in the patients' surroundings.[7] Many studies have found *P. aeruginosa* in the hospital environment.[7] Particularly, washbasin sinks may be contaminated, and hand washing at contaminated sinks has led to contaminated hands.[8] Hygienic measures to decontaminate these reservoirs of *P. aeruginosa* have been recommended. CF centers have separated CF patients with and without *P. aeruginosa* infection in order to limit cross-infection.[4] In the Copenhagen CF centre, separation of patients with or without *P. aeruginosa* infection, introduction of hygienic measures for patients and health care workers, and the move to a modern clinic led to a decrease in the number of new and known cases of *P. aeruginosa* infection.[9] Hand disinfection for CF patients and hospital personnel has been emphasized.[10] Importantly, if the hands of CF patients are contaminated with infected respiratory secretions, their exposure to *P. aeruginosa* is significantly prolonged.[11] How-

ever, infection control policies vary from one CF centre to another, and therefore these policies can generate controversy and anxiety among members of the CF community. Unfortunately, hospital personnel do not always conform to recommended hygienic practices.[10] Protection from *P. aeruginosa* infection may also be obtained by vaccination.[12,13] *P. aeruginosa* infections are generally diagnosed by taking sputum or throat swabs and identifying the bacterium by routine methods. Blood tests to detect the presence of *P. aeruginosa* have been especially useful in patients that do not produce sputum.[14] There is increasing evidence that early diagnosis of *P. aeruginosa* lung colonization may be beneficial, since early treatment can be initiated (see below). Therefore, it is recommended that all CF patients, regardless of clinical status, should have a respiratory tract culture performed at least once every three months.[15,16]

Antibiotic therapy regimens

Antibiotic therapy is thought to be responsible for improving CF patients' clinical condition, pulmonary function, *P. aeruginosa* load in sputum, parameters that reflect inflammation, quality of life and nutritional status [e.g., 17]. Besides antibiotics, improved agents to thin the mucus, airway physiotherapy and improved nutrition have contributed to increased life expectancy in CF patients (the usual survival in 1969 was 14 yrs; in 1996 it was 31.3 years[3]). However, since mucoid *P. aeruginosa* is usually located in isolated mucus plugs deep in the airways,[18] high doses of antibiotics are recommended (Table 1).

To obtain high levels of antibiotics in the airways, antibiotics such as tobramycin and colistin have been given by the aerosolized route. A review of five randomized controlled trials showed benefit for nebulized antipseudomonal antibiotics with no demonstrable undesirable effects.[19] Among doctors and researchers, there is much agreement over the advantages of aerosolized antibiotics in CF patients,[15,20] which has been published in consensus reports. Nevertheless several antibiotics, including aminoglycosides and cephalosporins, are still intravenously administered in high dosages (Table 1) and therapy is generally scheduled for approximately two weeks. Combination therapy with antibiotics has been favored because it may slow down the emergence of drug-resistant bacteria, and may result in increased effectiveness.[15] Only fluoroquinolones are given orally,[21,22] and in children.[23]

Eradicating mucoid *P. aeruginosa* in patients with chronic infection has been shown to be virtually impossible, and only a reduction of the load of *P. aeruginosa* can be generally achieved. This implies that the concentrations of antibiotics which are present in CF airways may be low, although this may still positively affect the clinical condition and the lung function of CF patients.[24] However, these lower concentrations may also increase the rate at which *P. aeruginosa* mutates, leading to the development of resistant variants.[25]

Chronic *P. aeruginosa* infection necessitates many courses of antibiotic therapy, but this carries the risk that the bacterium will develop resistance towards a given drug. Emergence of drug resistance after intravenous and aerosol therapy has been noted in several studies.[15,26,27] Antimicrobial resistance may diminish and the bacterium may become susceptible again over time, when the selective pressure of a given antibiotic is removed.[28] To avoid resistance, CF patients receive combination therapy with *P. aeruginosa*-specific antibiotics that have different modes of action. For aerosol therapy, intermittent on-off cycles of four weeks are recommended.[15,16]

Large amounts of aerosolized antibiotics may be swallowed during treatments, and studies have been proposed to investigate the effects on bacteria in the digestive tract.[29] Usually, a nebulizer is used to inhale a liquid mixture of the antibiotic, although dry powder inhalation, which is faster, has also been reported.[30] Since many CF patients re-use their disposable jet nebulizers, hygienic problems related to contamination may arise. Therefore, patients must learn to clean and dry their nebulizers. Furthermore, the patient should exhale through a separate tube that leads to the outside air or to a filter, to avoid contaminating their immediate surroundings. Some hospitals recommend that inhalations be performed in a separate area.[31]

CF patients are treated with antibiotics for most of their lives and drug side effect may well occur. The aminoglycoside class of antibiotics, which includes tobramycin, may have toxic effects on the hearing and the kidneys due to accumulation of the drug within susceptible cells.[32] The ß-lactam class of antibiotics, particularly penicillins, may cause allergies.[33]

Prophylactic administration of antibiotics against *Staphylococcus aureus* has been suggested, since *S. aureus* may pave the way for *P. aeruginosa* infection. Continuous prophylactic flucloxacillin in CF

patients diagnosed early was associated with improved clinical progress during the first two years of life.[34] However, this treatment was found to increase the rate of *P. aeruginosa* infection[35, 36] and therefore it does not seem to be recommended.

Initiating antibiotic therapy shortly after the diagnosis of *P. aeruginosa* lung colonization is a very promising concept.[37,38] Based on the observation that the bacterium is usually non-mucoid at the time of colonization and that sputum volumes are low, eradication seems to be possible. Indeed, the combined treatment of aerosolized colistin and oral ciprofloxacin significantly reduced the onset of chronic *P. aeruginosa* infection in treated CF patients, compared to an untreated group of patients.[37] Similarly, a placebo-controlled, double-blinded, randomized study of tobramycin inhalation showed that after the start of *P. aeruginosa* colonization, sputum culture became negative much sooner with active treatment. This suggests that early treatment may prevent *P. aeruginosa* pulmonary infection in CF patients.[38] In a follow-up study,[39] it was demonstrated that this approach prevented or delayed chronic *P. aeruginosa* infection in 78% of the CF patients for 3.5 years. Furthermore, aggressive treatment maintained or increased pulmonary function during the year, whereas in untreated patients, pulmonary function declined.39 Several studies now demonstrate that early antibiotic therapy indeed eradicates the bacterium from CF airways.[40,41]

Home therapy permits more normal activity for the CF patient, including uninterrupted school attendance or employment.[42] Home intravenous antibiotic therapy in CF patients is a feasible, cost-effective alternative to inpatient therapy. However, patient guidelines concerning hygiene and physiotherapy need to be established.[43] In addition, stringent quality control and assessment of effectiveness is mandatory.

Several centres treat chronic *P. aeruginosa* infection in CF patients with intravenous antibiotics regularly, three or four times a year, with daily aerosolized antibiotics such as colistin and tobramycin in between. There are still concerns that this intensive and aggressive antibiotic treatment may eventually result in the emergence of multiresistant *P. aeruginosa* strains or may increase undesirable drug reactions.[44]

Conclusion

New antibiotic therapy regimens have improved the clinical condition and quality of life of CF patients. Based on the way in which *P. aeruginosa* lung infection develops in CF patients, early antibiotic therapy which may eradicate the pathogen is most promising. This aim can only be achieved when *P. aeruginosa* lung colonization is diagnosed regularly in all CF patients.
(21-12-06)

Table 1.
Recommended dosages for antibacterial agents in the management of *P. aeruginosa* lung infections in CF patients [from ref 15].

Antibiotic	Route of administration	Dose (mg/kg/day)	Number of administrations per day	Maximum daily dose (g)
amikacin*	i.v.	30	2	-
aztreonam	i.v. i.v.	150 100	4 continuously	8 8
cefepime	i.v.	100-150	2-3	6
ceftazidime	i.v.	150-250	3-4	12
ceftazidime	i.v.	100-150	continuously	12
ciprofloxacin	p.o.	30	2-3	1,5-2,25
colistin	inhal. i.v.	80-160 § 6	1-2 3	0,320 § 0,48
imipenem/ cilastatin	i.v.	50-100	3-4	4
meropenem	i.v. i.v.	60-120 60	3 continuously	6 3
netilmicin*	i.v.	10	2	-
ticarcillin	i.v.	500-750	4	30
tobramycin*	i.v. inhal.	10 150-300 §	2 1-2	- 0,6

*: Dose based on measurements of serum concentrations
§: Absolute dose (dependent on age and situation).
Recommendations may not coincide with dosing recommendations as approved by regulatory authorities in different countries.

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Everybody Up!

Exercise and Physical Activity In Cystic Fibrosis

Patients with cystic fibrosis (CF) are living longer and better than ever. The median survival in Canada is now more than 37 years. Current projections suggest that young CF patients have an even brighter future. Along with increases in longevity, CF patients are busy accomplishing more than ever before. In the realm of sports, there are now CF patients performing at, or close to, national and world class levels. When you consider that there are only 70,000 CF patients worldwide, having several elite athletes amongst the CF population is truly a significant accomplishment. Their feats attest to the heights that CF patients can achieve.

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Who Should Be Active?

So, who should be physically active? If we look at the general population, everyone can benefit from a healthy, active lifestyle, even people with chronic heart or lung conditions.[1] This also holds true for patients with CF.[2] So everyone can be active and can profit from increases in regular physical activity.

Factors Limiting Exercise Ability

There are several factors which can impose limitations on maximal exercise ability. It should be remembered that it is rare for anyone to exercise for any prolonged period at maximal levels. However, maximal ability is a good marker of what people can readily tolerate on a daily basis.

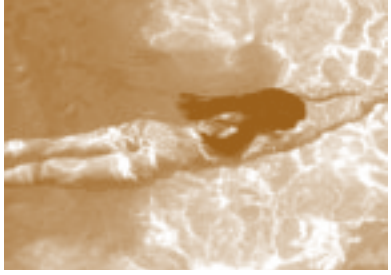
In people without heart or lung disease, exercise ability is generally limited by muscular ability. Muscular ability depends on both the amount of muscle available and the level of physical conditioning. In other words, the more muscle we have and the more exercise we do, the more we can do, and the less active we are or the less muscle we have, the less we can do.

Respiratory Factors

In CF patients with moderate or more advanced disease, ventilatory or breathing capacity can also potentially limit exercise ability.[3] When lung disease progresses in CF, there is difficulty exhaling air fast enough (expiratory flow limitation). This is because the airways become narrowed from secretions and inflammation. In patients with bronchiectasis, the airways lose their stiffness, and may narrow even more when breathing heavily. If air does not come out quickly enough when exhaling, there can be a build up of air in the lungs (air trapping).[4] Patients with air trapping often look barrel-chested. When there is air trapping, the muscles used to inhale must work harder. Patients often sense this increased work of breathing, and it is not unusual for patients with advanced disease to complain of difficulty breathing during exercise.

Muscular Factors

Muscular ability is also often limiting in CF patients. In CF, besides the amount of muscle and physical conditioning, other factors can influence muscular ability. The mutation in the CF gene appears to impact upon the mitochondria (the body's power house, present in virtually every cell), and its ability to generate energy.[5] The mitochondria is where the fats and sugars derived from our diet are turned into energy to allow our muscle to contract or shorten, allowing us to move. Generally, not much of the protein we eat is used for energy production. Instead, it is used for building and renewing the body's tissues. Other energy-generating processes may also be limited in CF



patients for unknown reasons. Some of these aspects are being currently explored in a research project being done in Montreal and Toronto.

It is well recognized that CF patients have a lot of inflammation in their lungs. However, the inflammatory response is not solely confined to the lungs, and there is a spill-over effect, with increases in certain markers of inflammation in the blood.[6] These markers (cytokines) can lead to loss of muscle tissue and decreased muscular function.

Finally, another factor influencing muscular ability is medical therapy. Some CF patients receive oral corticosteroids over prolonged periods of time. While corticosteroids can help decrease inflammation, they can also sometimes cause significant muscular weakness. Patients and their medical team must be on the look-out for this and try to limit the dose of corticosteroids.

The Benefits of Physical Activity in CF

The most important benefit to be gained from an active lifestyle is quality of life; you'll feel better. Increased exercise ability seems to have a bigger impact on quality of life than changes in lung function.[7]

We found that in children, patients who were more physically active on a daily basis had a better maintenance of lung function, regardless of their initial lung function.[8] This may be partially due to the enhanced removal of secretions that accompanies physical activity. So, being active can really help, in addition to regular chest physical therapy, although exercise does not replace regular chest physical therapy.

Exercise can also have a positive influence of growth hormone, which helps maintain muscle bulk and function.[9] The changes seen with exercise are similar to what is seen with growth hormone injections.

Exercise is safe and can be well tolerated by all patients, provided it is geared to the appropriate level. Often the clinic physiotherapist can give guidance on exercise and training programs. The most successful programs are those that get people doing the types of physical activities that they want to do. Treadmills, stationary bikes or free weights can get really boring so it's important to mix up and combine fun activities, such as group sports. It's also important that patients replenish the salt and water they lose through sweat.

Exercise is particularly important for patients with respiratory limitations. Exercise training reduces the amount of carbon dioxide and lactate that is produced in our body. Carbon dioxide and the acid produced from lactate force us to do more ventilatory (breathing) work. So if we get fit through more regular exercise, we can decrease the production of carbon dioxide and lactate for the same amount of work, and we'll breathe easier. As mentioned earlier, it is quite common for people to stop exercising because they feel that they are breathing too hard and they are short of breath. If people become more physically active, activities become better tolerated and even enjoyable.

Other Factors That Can Enhance Exercise Ability

As mentioned, there are several modifiable factors, aside from muscle bulk and conditioning, that can have an impact on exercise ability.

Decreasing the systemic inflammatory response with antibiotics or high dose ibuprofen may enhance weight gain and muscle performance, in addition to improving lung function.[10] Nutritional supplements that can increase antioxidant defences may also be of some help.[11] These therapies should be discussed with the CF treatment team, as they require specific dosing and monitoring on a regular basis.

Conclusions

Everyone feels better being more active. CF patients can particularly benefit from a more active lifestyle. Physical activity is a lifestyle choice, and not another treatment. Put down this article and get out there!
(21-12-06)

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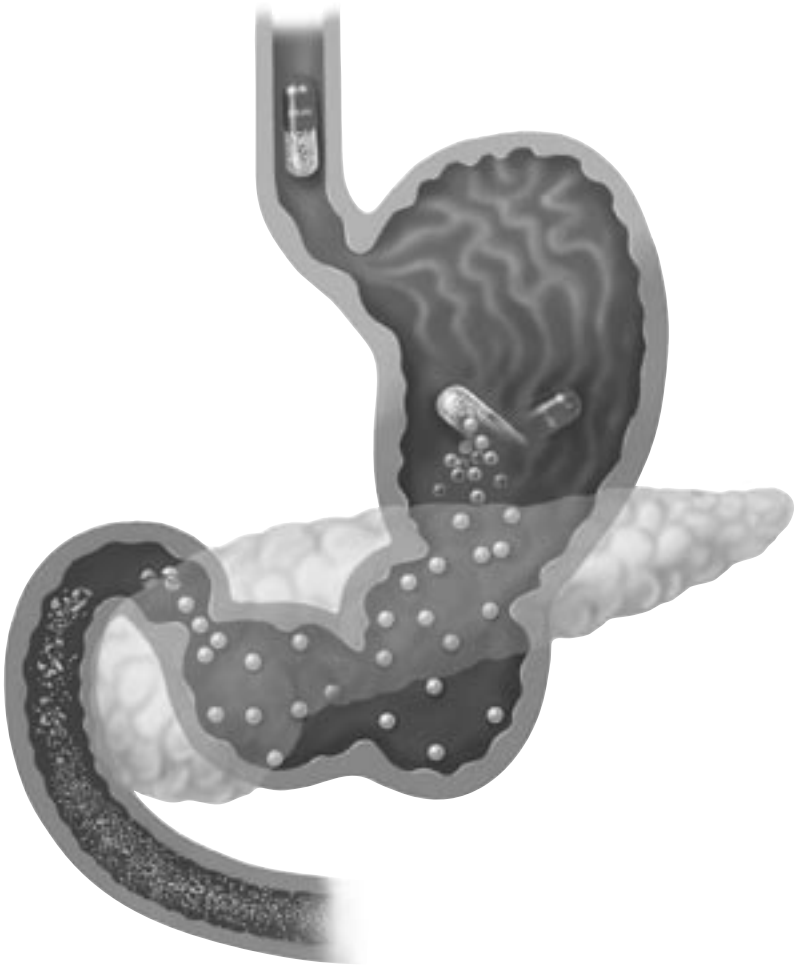

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People with cystic fibrosis (CF) born after 1990 now have a life expectancy of over 40 years.[1,2] However, as they grow older, end-stage lung disease becomes the most common cause of morbidity and mortality.[3] Transplantation has been considered a viable therapeutic option for such patients since 1985. Before 1990, heart-lung transplantation was performed but nowadays bilateral sequential lung transplantation is preferred, leaving people with their own hearts. This has proved an increasingly effective form of treatment and results are improving all the time. Recent figures show a survival rate of 81% at one year, 59% at five years and 38% at ten years.[4] For children and adolescents, cumulative international survival figures are slightly lower, being around 78% at 1 year and 49% at 5 years.[5] The surgery is known to have a substantial effect on health-related quality of life.[6]

Decisions about the need for transplantation have to be addressed about two years before the operation is likely to be essential, allowing sufficient time for assessment at the transplant centre and donor lungs to become available. However, the process of referral, listing and waiting is lengthy and the psychosocial and physical stress for patients and their relatives, at all stages, are well documented.[7] The task of the referring CF centre is, therefore, to balance medical and psychological considerations when raising the prospect of transplantation. Early referral gives people and their families more time to assimilate complex information, to emotionally come to terms with the issues and to make an informed choice. It also allows the referring centre more time to prepare and support the family. However, referring too early may be unnecessarily psychologically distressing.[8] Referring too late can result in optimal care being compromised, the surgery being deemed an inappropriate treatment option, people being listed at their first visit to the transplant centre with limited time to discuss options or dying before donor organs become available.

The time-line of transplantation can broadly be divided into six main stages; (i) the initial discussion, (ii) the decision, (iii) the assessment, (iv) the wait, (v) the call, and (vi) the operation and beyond. As the process unfolds, people with CF and their relatives can experience a range of psychological and behavioral difficulties, consequently continual support is vitally important, especially in the early stages.

The initial discussion

Introducing transplantation can be a distressing experience for people with CF and their relatives, who can experience a range of emotions including shock, denial and anger. There is evidence that "getting the news and making the decision" is particularly traumatic within pediatric settings, with 25% of young people,[7] 14% of fathers and 21% of mothers,[9] demonstrating clinically significant levels of distress. People want to know, "Are we really at this point?" "Do we really have to rush into this?" and "How much time do we have to decide?" Despite these problems, relatives report thinking that discussion helped them face the reality of the situation. In particular they valued receiving information and talking about treatment options in a gradual and informal way to help them feel better prepared and supported. Having a good relationship with the clinician introducing the option was also seen as essential.[10]

The first few messages presented to parents are crucial to understanding, as people tend to be able to recall these more clearly than later ones (known as the "primacy effect"). Initial messages form the foundation of understanding

subsequent ones. Consequently, communication about transplantation needs to begin with as many clear, positive messages as possible, giving people with CF the best chance of assimilating complex information. It is this that helps individuals make informed decisions.

The decision

Making the decision whether or not to proceed with transplant assessment can be a harrowing experience. It places enormous pressure on individuals as they consider, amongst other things, "Will it really be worth it?" and "For whom would I really be having the transplant?"

It is during this stage that psychological assessment is vital. Indeed, current guidelines recommend that this is an essential duty of psychosocial professionals working directly into CF teams.[11] Assessment needs to include both individual and family interviews so that everyone's views, thoughts and feelings can be aired. It is also valuable to review their quality of life, coping skills and support mechanisms.

How people go on to prepare themselves psychologically depends ultimately on their comfort with having made the right choice. Having had the opportunity to discuss this in a facilitated way is enormously beneficial, and psychological support, if wanted, needs to continue regardless of the choice an individual makes. For some, transplantation is simply not for them. Yet, saying no can be psychologically challenging for relatives and teams, however, it is a decision that must be respected. For others, opting for transplantation can be based on the belief that it is the only option to prolong their life with quality. What lies ahead is a series of challenges, each of which needs to be successfully negotiated and psychologically prepared for.

The assessment

Once the decision has been taken, referral is made to the transplant centre where people undergo a series of tests to determine whether or not they are appropriate candidates. Here the transplant team has an opportunity to consolidate individuals' knowledge and explore their uncertainties, taking time to answer questions and talk about worries or problems.

The assessment results in one of three options. The first is that the person is deemed not to be a suitable candidate for medical reasons. This occurs in approximately four to ten percent of people assessed. Having emotionally prepared for being accepted onto an active list, this outcome can be emotionally devastating. People may experience feelings of anger, disappointment, loss, hopelessness and sorrow. The second outcome, one which clinical experience suggests is most preferred, is that they are provisionally accepted. This means that they are deemed to be a suitable candidate but thought to be too well at the present time. Typically, people are kept under review, with appointments being brought forward if rapid physical deterioration occurs. The third outcome is that the person is accepted on to the active waiting list, beginning the next stage of the journey.

The wait

Waiting for surgery can last from a few days to over three years[12] and is known to be very stressful, leading to further psychological dysfunction.[13] People have often referred to this period as "putting their life on hold." They need to be contactable at all times (often having a "bleep") and be able to reach the transplant centre within a specified period of time. In some larger countries, for example, the USA and Canada, people may need to relocate, leaving home, relatives and social networks behind. Often increased financial demands lead to further pressure on time and changes in roles and jobs. Common emotional problems arise from feeling isolated and having to deal with and acknowledge jealousy ("Why did Sarah get the call before me?") and from trying to maintain hope in the face of further physical deterioration and an increased treatment burden. Some people and their relatives have commented on actively trying to minimize the impact of negative information as a coping strategy by focusing only on the positive.[14] Pre-existing psychosocial

issues that may impinge on post-operational care, for example, procedural distress or partial adherence, also need to be addressed and built into management plans during this time.

People with CF need to be able to acknowledge these effects in a confiding relationship if they are to maximize their quality of life pre-transplant. However, psychosocial support is often unavailable or deemed too expensive. The use of telephone-based interviews has gained increasing attention as a real alternative to conventional counselling and has been evaluated in over 90 people awaiting lung transplantation. Early results suggest this is effective in improving global well-being, psychological functioning, social support and health-related quality of life.[15] Given that high levels of psychosocial distress are linked to adverse health outcomes[16,17] and psychological adjustment[18] after lung-transplantation, addressing these issues successfully, before people undergo the operation, may further improve clinical outcomes.[15]

The call

People with CF and their relatives often remember in vivid detail where they were and what they were doing when the call to say that potentially suitable donor organs have become available. Whilst false alarms are common, such recall can become intrusive in similar ways to other post-traumatic stress reactions. Vivid thoughts and images are often referred to as "flashbacks," sometimes leading people to feel "as if" the experience were happening all over again. Whilst certain aspects of the process can be traumatic, true Post-Traumatic Stress Disorder after transplantation is rare.

The operation and beyond

Surgery is followed by a short period in intensive care, then a subsequent, lengthier in-patient stay. Physical recuperation is variable. Some do so rapidly: others less so. Whilst people and their relatives are often euphoric immediately afterwards, emotionally this can be a period fraught with increases in health anxieties and hypervigilance. ("What if something goes wrong?" "What if I pick up an infection?" "I have a high temperature – does that mean I am going into rejection?") However, by far the most difficult psychosocial challenge is rehabilitation and adjustment, which inevitably involves a re-appraisal of "Who am I?" as individuals find ways to reconcile feelings of pre-transplant vulnerability and post-transplant health and optimism. Whilst the desire for freedom from healthcare may be strong, people need to accept that they need to continue with a different treatment regimen.

Conclusion

Early referral for lung transplantation is thought to be like "taking out an insurance policy," giving people with CF time to assimilate and emotionally process information, consider the risks and benefits and make informed decisions. In Leeds, psychological support is available throughout this process and we believe that this can help maximize quality of life in the pre-transplant phases and help individuals and their relatives make positive emotional adjustment afterwards. Using health-related quality of life measures in all phases will allow clinicians to evaluate the effectiveness of such support mechanisms and perhaps facilitate greater understanding of the reality of transplantation for people with CF, their relatives and friends.
(21-12-06)

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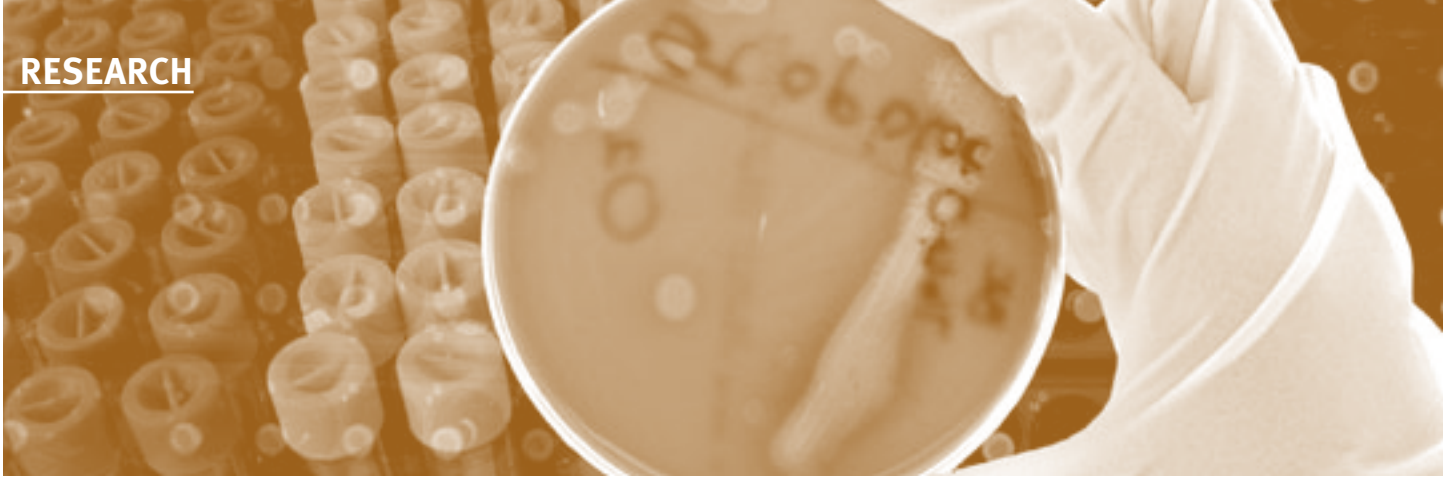

Applications of Genetic Knowledge In Cystic Fibrosis

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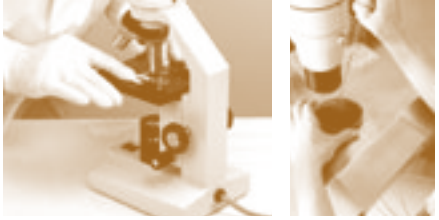
Cystic fibrosis is an autosomal recessive genetic disease. The word "autosomal" indicates that the defective gene is located on a chromosome that is neither the X nor the Y chromosome. The term "recessive" is used for all genetic disorders in which symptoms appear only if a defective gene is inherited from both parents. When only one defective gene is inherited, in the case of a recessive disease, the person is said to be a carrier of the gene, but does not have the disease. Carriers of a recessive genetic disease have no symptoms, but can transmit the defective gene to their children. If a man and a woman are both carriers of a defective gene that causes cystic fibrosis, for instance, the probability that one of their children will have the disease is one in four, while the probability that one of their children will be a carrier of the defective gene (without having the disease) is one in two.

The defective gene in cystic fibrosis is the CF gene coding for a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is an essential protein for transporting chloride and bicarbonate molecules. Chloride molecules determine the concentration of salt in mucus on the surface of mucous membranes and bicarbonate molecules are essential in pH adjustment, thus determining mucus acidity or alkalinity. The pH adjustment and the concentrations of salt and water are essential properties in determining the appropriate mucus viscosity. A deficiency in CFTR causes significant thickening of mucus in all organs with mucous membranes, such as the sinuses, bronchi, intestines, pancreas, liver and reproductive organs.

The CFTR gene was discovered in 1989, in Toronto, through the support of the Canadian Cystic Fibrosis Foundation. Since this discovery, researchers have identified over 1,200 different mutations of the same gene, all of which can cause CFTR deficiency. However, about 70% of the defective genes in Canada have the same mutation, namely, delata F508. This mutation is responsible for the absence of an amino acid at position 508 in the CFTR protein. The protein is thus severely defective and cannot be expressed normally on the surface of the mucous membranes. Among other mutations that account for 30% of the defective genes, about 40 mutations have been identified in almost all CF genes that do not have the delta F508 defect. It is possible to identify the types of changes caused in the CFTR protein, based on the various mutations, and to classify the mutations according to the severity of the resulting disease.

Thus the type of mutation in the CFTR gene can explain some of the variability in cystic fibrosis symptoms. However, not all variations in clinical symptoms can be explained solely by the type of mutations in the CFTR gene, and it is becoming increasingly obvious that all the other genes besides CFTR strongly influence the severity of clinical symptoms. This is a particularly interesting point in that research has begun to identify other genes besides CFTR that play a critical role in modulating the severity of the clinical symptoms of cystic fibrosis. If there are therapies that can increase or reduce the number of those genes, then it stands to reason that some people with cystic fibrosis could benefit from treatments that are based on the modulation of these other genes.

Newborn screening is another important application of genetic knowledge in cystic fibrosis. Since the discovery of the various mutations in the gene responsible for cystic fibrosis, particularly since the scientific community has developed effective tools for identifying many possible mutations, national cystic fibrosis newborn screening programs have been launched. Newborn screening



makes it possible to identify children with cystic fibrosis in the first weeks following birth. Quebec and all the Canadian provinces already have newborn screening programs for serious genetic diseases. Up until now, cystic fibrosis was not among the serious genetic diseases screened for, primarily because of the lack of data and efficient technology.

Many researchers, however, have developed a two-step cystic fibrosis screening technique that is very sensitive and highly specific. At birth, a small blood sample is routinely taken from all newborns, usually from the heel. Blood cells in the few drops of blood contain plasma and DNA proteins. Part of the blood sample is initially analysed to determine the levels of a protein called immunoreactive trypsinogen. Trypsinogen is normally synthesized by the pancreas, and only small traces can be found in plasma. However, when the pancreas is diseased, part of it is destroyed through the release of trypsinogen into the plasma. This protein can therefore be measured through antibodies using a technique called immunoreaction. The great majority of children with cystic fibrosis have high levels of immunoreactive trypsinogen in their plasma. This is therefore an excellent screening test that is especially sensitive in detecting cystic fibrosis.

However, high levels of immunoreactive trypsinogen are not specific to cystic fibrosis, so it is necessary to do a second test in all newborns who test positive for this. The same drop of blood is used for the second test, which identifies mutations on the CFTR gene that could cause cystic fibrosis. Given the cost of identifying many types of mutations, laboratories that specialize in this type of screening test for a restricted number of mutations that correspond to those most frequently found in a specific population, based on the data for that population. The genetic test that is done only in children who have a high level of immunoreactive trypsinogen confirms whether there is an anomaly specifically associated with CFTR gene mutations, which is strongly suggestive of cystic fibrosis. The information is then sent to the mother and newborn's care-giving team. The team includes physicians, nurses and counsellors who specialize in genetic diseases and, specifically, cystic fibrosis.

One may wonder what advantage there is in diagnosing cystic fibrosis at birth, rather than later on. Many groups have studied this issue, and it is clear that the prognosis, that is, the course of the disease, is more favourable in members of the CF population who are diagnosed early, compared to those who are diagnosed later on. Even now, there are people with cystic fibrosis who are not diagnosed until adulthood, and this situation is often associated with a degree of permanent damage that could have been avoided had the diagnosis been made at birth. In addition, cystic fibrosis newborn screening programs have shown that the majority of children diagnosed at birth already have very significant nutritional deficiencies, and many suffer from pancreatic insufficiency

necessitating interventions to prevent growth retardation and, in particular, delayed brain development, as measured by the cranial perimeter. Based on this information, experts are stating that there are excellent reasons for instituting cystic fibrosis newborn screening programs across Canada.

Currently, Alberta is only province to have a one newborn screening program, but discussions are under way in other provinces to add cystic fibrosis to the list of genetic diseases screened at birth. The Canadian Cystic Fibrosis Foundation believes that it is important to share this information with the public and government officials and to encourage the application of cystic fibrosis screening programs in order to avoid prejudice to patients with this genetic disease.

To sum up, we see that genetic knowledge has practical applications that will help change the lives of patients with cystic fibrosis and of those who are not yet born. These examples of genetic applications in cystic fibrosis underline the importance of maintaining strong support for medical research so that, together, we can conquer cystic fibrosis.
(21-12-06)

HEALTH COLUMN

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PANCREATIC ENZYMES

My physician is having a hard time specifying the quantity of pancreatic enzymes I should be taking with meals. How do you determine the right quantity and proper concentration of enzymes for patients? Is it better to take these enzymes before, during or after meals?

The quantity of pancreatic enzymes required for proper digestion and food absorption can be roughly estimated by the quantity of fat ingested at each meal. However, there are significant differences from one person to the next for reasons that are not always properly understood. Some of my patients need only 20,000 units of lipase per meal, while others take 10 times more. The dose is usually adjusted on the basis of clinical criteria: we gradually increase the dose until the symptoms of malabsorption (stomach cramps, diarrhea and foul-smelling, greasy stool) disappear. However, there may be other causes for stomach pain and diarrhea besides insufficient pancreatic enzymes. When an increase in dosage fails to make the symptoms go away, it is necessary to look for other potential causes and, sometimes, measure the amount of fat in the stool.

Lastly, pancreatic enzymes should be taken at the beginning of meals that are not too copious or drawn out. For longer, more abundant meals, it is better to take some enzymes before and some in the middle of the meal.

VIAGRA

I have been having significant coughing fits for almost a year. I cough more during intercourse, which makes it difficult to maintain an erection. I find this very annoying. Do you think that Viagra could help me maintain my erections?

Erections are the result of a complex process involving physiological and psychological phenomena. On the physiological level, erections occur as a result of an accumulation of blood in the *corpus cavernosum* (erectile tissues) of the penis. This involves vascular elements (blood is transported through the contraction and dilatation of blood vessels), hormonal elements (mostly testosterone, the male hormone, but other hormones also) and neurological elements (the spinal cord and peripheral nerves that transmit electrical stimulation to the blood vessels). Psychological factors also play an important part in triggering and maintaining erections, although the mechanisms are not as well known. These factors include libido (sexual desire), fatigue, stress, depression and performance anxiety.

In young men with cystic fibrosis, the vascular, neurological and endocrine mechanisms are usually intact. Regarding the situation you described in your question, deteriorating health caused by severe respiratory infection could be the cause, but psychological factors are certainly also involved. Coughing would be an embarrassing, annoying distraction that could trigger performance anxiety. One of the solutions would be to control your coughing through better treatment of your lung condition. Also, you might benefit from counselling by a psychologist or sexologist. If the problem persists despite these interventions, you might find phosphodiesterase inhibitors (Viagra, Cialis, Levitra) helpful. These drugs work by producing smooth muscle relaxation in the corpus cavernosum of the penis and allowing inflow of blood to produce an erection. The main contraindication for these drugs is concomitant use of nitroglycerin, a drug used in treating arteriosclerosis.

SPERM

Some of my ex-partners have pointed out that I produce very little semen compared to other men. Is that normal? If the problem is related to cystic fibrosis, as the disease progresses, will I stop producing semen and will this affect my orgasms? Are there any drugs that increase semen production?

Regarding your first question, that is, whether it is normal for a man with cystic fibrosis to produce less semen than other men, the answer is yes. Semen is made up of spermatozoa and fluid secreted by the testes. This fluid is transported in the vas deferens and, just before it is expelled, secretions from the seminal vesicles and prostate are added. We know that in 97 to 99% of men with cystic fibrosis, the vas deferens have either atrophied or disappeared, most likely because of obstruction *in utero*, so the important contribution of the testicles is missing in these men. However, although they produce less semen, production is constant, and the quantity and quality of orgasms are not affected in any way. To my knowledge, there are no drugs for increasing semen production.

HAIR REMOVAL

I would like to have my underarm and leg hair permanently removed using laser technology. Is there any danger in this for a person taking oral or intravenous antibiotics? Is laser technology contraindicated for people who have had a transplant? What is your opinion about electrolysis?

According to a dermatologist colleague of mine, laser technology for permanent hair removal appears to be safe and not to present any dangers for people taking oral and intravenous antibiotics. Also, there is no contraindication for transplant patients, at least not once their medical condition has become stable following surgery. As for electrolysis, this technique appears to be just as safe.

VACCINES AND TRAVEL

I plan to travel after my transplant. Some of the countries I want to visit require certain vaccinations. Should I get these vaccines before my transplant, even though I'm quite ill?

It is important to consider that following a lung (or any organ) transplant, immunosuppressive drug therapy is administered to prevent rejection of the transplanted organ. Consequently, vaccination with live viruses or even live attenuated viruses is contraindicated. Before transplantation, however, even if lung condition is poor, there is no immunosuppression, so there are no contraindications to vaccinations.

I therefore advise that, before your transplant, you update all the childhood vaccinations you may have missed: measles, mumps and rubella, polio, diphtheria, whooping cough and tetanus. The chicken pox vaccine could also be included if you have never had that disease. For travel, you should add vaccines for tropical diseases, such as yellow fever and Japanese encephalitis, depending on your destination. However, following your transplant, I would not recommend that you travel to countries where medical care is rare or non-existent. Even if transplant patients are physically fit at first, it should never be forgotten that they are always in an immune suppressed state, so they are more vulnerable than the general population to unusual infections.
(21-12-06)

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COTAZYM ECS 8

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COTAZYM 65B

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