

September 27, 1994

CYSTIC FIBROSIS - WHAT'S NEW

Stacey Fitzsimmons, Ph.D

DR. WILLIAM BAKER: Two years ago at the 17th ICLAM meeting in London we had the pleasure of hearing an excellent presentation by Dr. Stacey FitzSimmons our next speaker. Stacey gave us good news and improving news about cystic fibrosis and later on, when we went on our tour through Kent and had a delightful lunch at The Oasthouse, I had the privilege of talking to her and signing her up for this meeting because we know that a lot has transpired in the last two years.

Stacey wants to be known as a Ph.D epidemiologist. She's held positions at NIH and the National Center for Health Statistics before she came to the Cystic Fibrosis Foundation over two years ago. She's the assistant director of the medical and scientific affairs department of the Cystic Fibrosis Foundation. I'm awfully happy that Stacey could come to address us and tell us the good news about cystic fibrosis.

DR. FITZSIMMONS: In my talk I want to cover three topics. First a brief description of cystic fibrosis. Second, a review of epidemiologic data from the Cystic Fibrosis Foundation's national patient registry which describes the incidence, the survival trends and rates of morbidity associated with CF. And three, an update on three new therapies being tested in CF patients, in particular gene therapy. This last year has been a tremendously exciting time for CF research and I'll provide some highlights.

Cystic fibrosis which I will refer to as CF, is the most common fatal genetic disease among caucasians in America today, affecting approximately 25,000 children and young adults in the US, and 55,000 individuals worldwide. Approximately one case occurs in every 3,000 live caucasian births and is much less common in non-whites. There are approximately 1,000 new cases diagnosed each year.

CF is inherited as an autosomal recessive disease, meaning that a child will develop the disease only if he or she inherits two mutant CF genes, one from each parent. When both parents carry the gene, the child has a one in four chance of having CF. A child who inherits only one abnormal gene becomes a carrier and can transmit the disease but will not have symptoms. Approximately 12 million Americans are carriers, or five percent, meaning that if there are 250 of us in the room today, 13 are carriers.

The gene was discovered in 1989 and is located on the long arm of chromosome seven. It's a very complex gene. More than 400

mutations have now been recognized. One particular mutation, the delta F508 allele, accounts for the majority of CF cases, approximately 75 percent of CF genes of people of northern European origin. The delta F508 mutation is clearly associated with what we call classic or severe CF with nearly universal pancreatic insufficiency.

Cystic fibrosis is a multi-system disorder, characterized by four things. You can summarize it by four things. First, chronic pulmonary disease leading to progressive destruction of the lungs. Second, pancreatic deficiency. Third, hepatobiliary disease and fourth, male infertility. CF is caused by a mutation in the gene and coating the CF trans-membrane conductants regulator, the CFTR protein. Mutations in the CFTR protein lead to the malfunctioning of the CFTR chloride channel and defective electrolyte transport across effected epithelium. In CF affected individuals, shown in the cell on the right side, the failure of chloride conductance by epithelial cells leads to too much sodium and chloride in the cell. This imbalance attracts excess water molecules into the cell resulting in dehydrated mucus secretions on the cell surface that are viscid and difficult to clear.

In the lungs these viscus secretions contain an enormous burden of bacteria and inflammatory cells and inflammatory mediators which in turn cause infection and more inflammation resulting in total lung destruction. The thick secretions make the patient particularly vulnerable to recurrent and persistent infections, notably with pseudomonas and staphylococcus bacteria. In the digestive system similarly the thick secretions block the small ducts of the pancreas, ultimately impairing delivery of pancreatic enzymes which are necessary to digest fat and absorb crucial vitamins and calories.

In the CF patients this results in undernutrition, poor growth and failure to thrive. Eighty-five percent of all CF patients have both respiratory and digestive problems while 15 percent have only respiratory problems. The clinical manifestations of CF vary tremendously. Although the mechanisms underlying this variability are not fully understood, there are a number of parameters which appear to influence outcomes, which I'll touch upon when I review the epidemiology of CF. The sweat glands are also affected by the CF defect and they secrete a much saltier sweat than normal. A sweat test has been used since 1959 to diagnose CF. Informal sweating testing, however, has been done for centuries. There was a folk belief in Europe in the middle

ages that "a child who tastes salty from a kiss on the brow is hexed and soon must die." And many parents still diagnose CF when they report salt after they've kissed their child. The modern Gibson-Cook quantitative sweat test employs the chemical pilocarpine to stimulate sweat glands to produce sweat in a process called iontophoresis. A CF diagnosis is confirmed by a sweat chloride concentration greater than 60 mili equivalents per liter.

There are four mainstays in the management and treatment of CF. First is chest physio-therapy or that is chest percussion by hand or clapping or use of vibrators or mechanical vests to mobilize the mucus secretions and improve clearance of infected secretions. Recently a flutter device and autogenic drainage techniques have proved to be effective airway clearance methods.

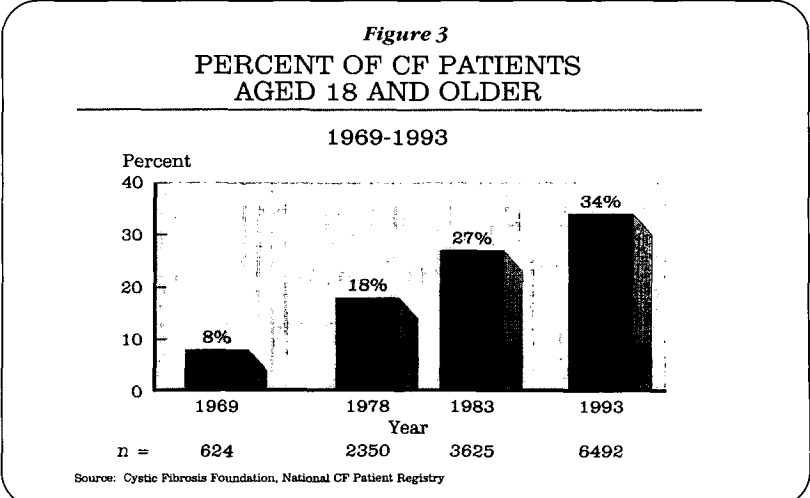
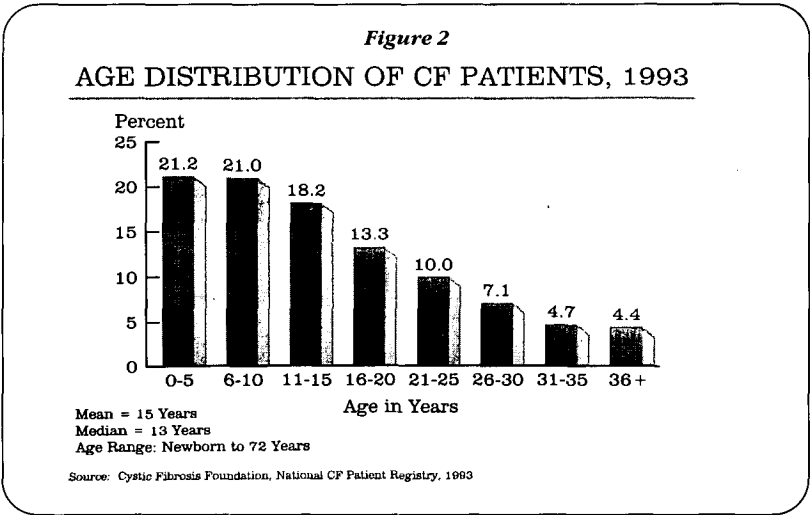
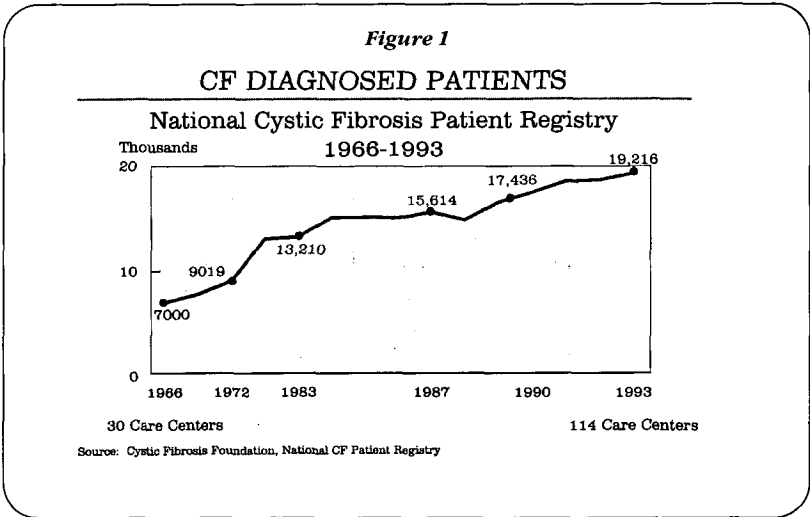
Second, use of antibiotics. In CF antibiotics may be administered orally, intravenously or in an aerosolized form to treat the infections. Third, pancreatic enzyme replacement to facilitate fat absorption and improve nutrition, and fourth, vigorous attention to nutritional status with daily nutritional supplementation and often reliance on enteral and/or total parenteral supplementation. The enteral supplementation is most frequently accomplished using a gastrostomy tube or button, a nasal gastric tube or a jejunal tube.

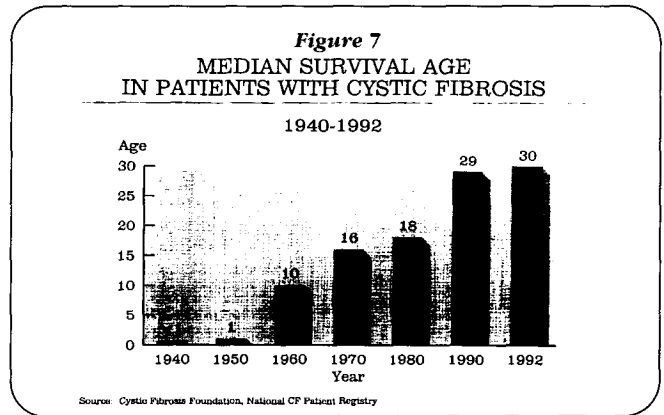
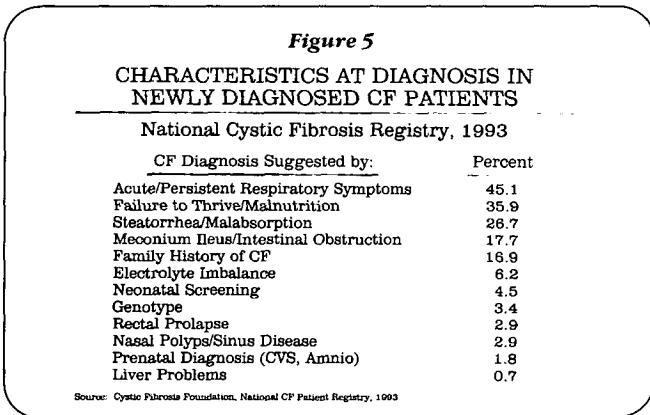
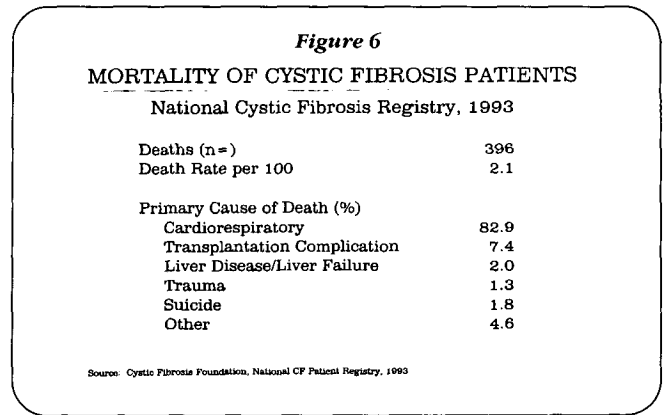
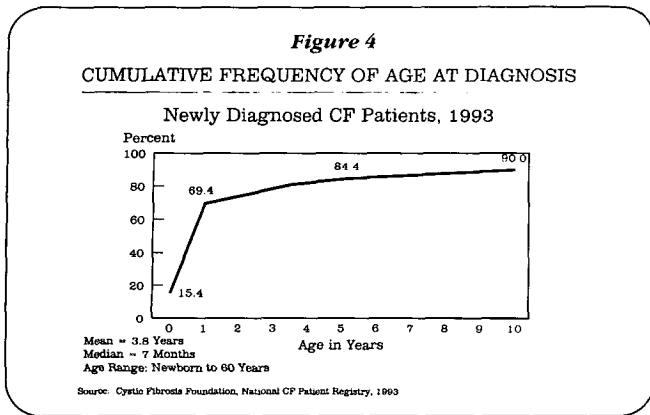
My second objective this morning was to provide a description of morbidity and mortality associated with CF. In 1966, 28 years ago, the CF Foundation established a national patient registry with about 7,000 patients reported at that time.

Figure One. Today 19,216 patients are reported from 114 accredited CF care centers throughout the US. These comprise a national network of treatment and research centers that serve as focus for CF clinical and basic research, funded by NIH, the CF Foundation and others. The CF Foundation serves as the coordinating center for data collection, data quality and data analysis for this national CF registry, contacting the CF care centers, for example, to retrieve or correct missing or out of range values. The CF care centers report every patient that attends their clinic to the national registry.

Figure Two. Distribution of age among our patients is shown in this slide. In the first three bars on the left, the majority or about 61 percent of our patients are under 15. But in the United States patients are surviving into their third and fourth and fifth and sixth decade. Our oldest patient last year was 72 years old and she died. Our oldest patient now is 67 years of age. The median age of patients in the United States is 13 years.

Figure Three. People think of CF as a pediatric disease but the proportion of CF patients who are adults has increased every year. In 1969 the proportion of patients of 18 years and older was eight percent and today the proportion who are 18 years and older is 34 percent. These 6,490 patients present new and continuous challenges to the pediatric pulmonary community in transitions of care from the pediatric units to the adult respira-





tory units, as they have very special social and financial, emotional and medical problems that need to be addressed.

Figure Four. The cumulative frequency of age at diagnosis for all newly diagnosed CF patients in 1993, numbered 889. Age of diagnosis is very young. At birth 15 percent of CF patients are diagnosed when they present with meconium ileus. By age one 69 percent have been diagnosed, by age five 84 percent and by age ten, 90 percent of CF patients have been diagnosed. The oldest patient diagnosed last year was 60 years of age. This person had a mild mutation and thought all his life that he had chronic bronchitis. The median age is seven months. We investigated the characteristics at the time of diagnosis and among these narrowly 1,000 newly diagnosed patients in 1993 and these 1,000 patients represent five percent of all previously diagnosed patients. We asked what symptoms and events preceded the ordering of the sweat test. The presenting manifestations of CF show a very marked heterogeneity.

Figure Five. The categories are not mutually exclusive. Patients were most often referred because they had acute persistent respiratory symptoms, 45 percent. Second, failure to thrive, malnutrition, 35.9 percent. Third, steatorrhea or malabsorption, 26.7 percent and meconium ileus or intestinal obstruction, 17.7 percent and fifth, family history of CF, almost 17 percent. Other presenting reasons are electrolyte imbalance, neonatal screening, genotype information, rectal prolapse, a history of nasal polyps or sinus disease, prenatal diagnosis and finally liver problems, less than one percent.

Figure Six. Last year there were 396 deaths for an accrued monthly death rate of 2.1 percent. The primary causes of death are cardio-respiratory representing the vast majority, 83 percent, with lung transplantation applications representing the second. A proportion of these are liver transplants as well. The third leading cause of death, liver disease, liver failure, two percent of our patients, with trauma and suicide and other reasons. One interesting thing to note about the death rate is that mortality rate, 2.1 percent, is smaller than the rate of new patients which is five percent, hence the CF population is growing or increasing three percent a year.

Figure Seven. There have been very remarkable advances in CF patient survival over the last four decades. The median survival has increased from less than one year of age in 1940 to 30 years of age in 1992, with a life expectancy plotted on the life tables of about 45 years of age. There have been many therapeutic advances that contributed to this.

Figure Eight. The median survival, for males, has consistently been three to five years greater than that of females. The reasons for this are not very well understood surprisingly and it's one of the few diseases where survival of male patients is greater. Further analysis are underway to investigate possible predictors of this improved survival for males, and some of the reasons include psycho-social reasons, gender differences in airway secretions, differences in airway reactivity by gender, differences in bacterial adherence by electrical properties, expression of the CFTR itself, differences in growth philosophy by males versus females and differences in pulmonary function. The national

patient registry records the first calendar year spirometry test results for all patients age six and older who are seen in the clinic and able to perform a reliable test using the American Thoracic Society standards.

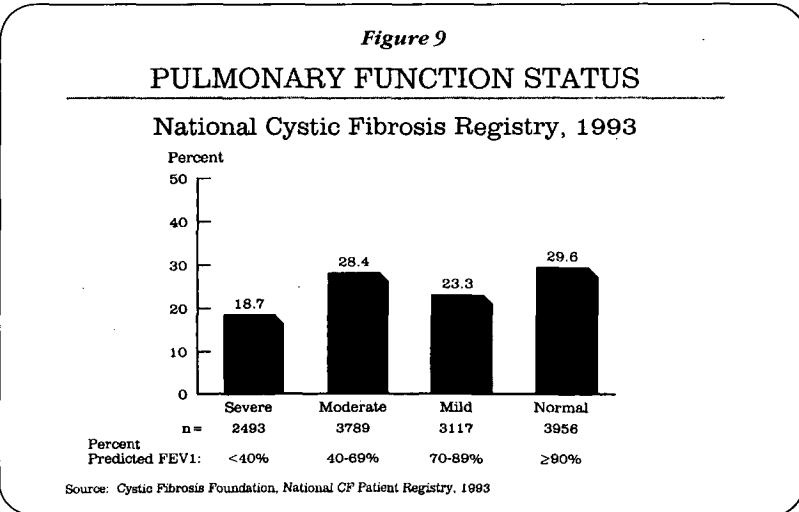
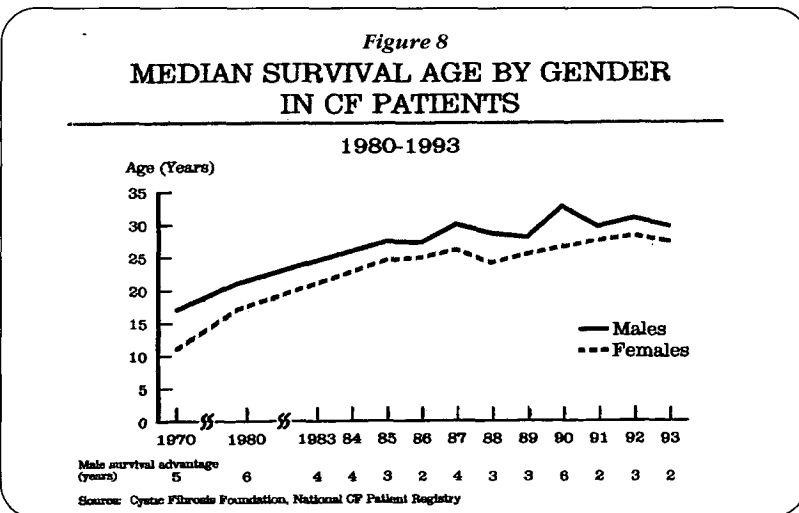
Figure Nine. On the far right, the CF patients whose FEV1 is greater than the 90th percentile predicted are listed as normal or considered normal and they comprise 29.6 percent of the total. Twenty three point three percent are in the mild range and considered an FEV1 of 70 to 89 percent. Twenty-eight percent are in the moderate range, considered an FEV1 of 40 to 69 percentile and finally in the severe range, 18.7 percent whose FEV1 is less than the 40th percentile. Disability claimants in all likelihood would comprise a subset of this category.

There are about 11 percent who are continuously on oxygen and this is also the subset who are on wait lists for lung transplantations. The other thing that is interesting is that in the US and North America there are over 50 percent of CF patients who really could be considered to have mild to normal pulmonary functions. In the US registry we also plot the height and weight of CF patients, using the National Center for Health Statistics and Center for Disease Control normalized weight for age and reference curves, calculated by gender.

Short stature and poor nutritional status has long been observed in CF patients. Approximately half of all of our patients are below the 10th percentile for height as well below the 10th percentile for weight, and only a very small minority, about a sixth, achieve the 50th percentile or greater for either height or weight.

Respiratory cultures are performed on 88 percent of CF patients seen in the clinic and include sputum, throat, bronchoscopy cultures. The organisms are identified by standard bacterial logic according to the American Society for Microbiology standards. Pseudomonas aeruginosa is the most common pathogen, 58.1 percent. It's well recognized that the majority of CF patients developed broncho-pulmonary infection with pseudomonas aeruginosa contributing to bronchiectasis and progressive obstructive airway disease. The age when colonized and the course of infection is highly variable, although by adulthood, in the case of pseudomonas aeruginosa, this slide plots the age specific infection rate. By adulthood 73 to 80 percent of all CF patients are colonized with pseudomonas aeruginosa. Staphylococcus aureus, shown in the orange line, which 30 years ago was the most frequently isolated organism in the sputum of CF patients, was cultured in only 29 percent of our patients.

Other pathogens are listed; hemophilus influenza, cultured in ten percent; aspergillus at 4.6 percent. And five, bicolteria cepacia, formerly called pseudonoma cepacia, cultured in 2.9



percent. It's considered a much more virulent strain of pseudomonas and is associated with significant mortality. Acquisition of cepacia in some patients, particularly adolescents and adult females with moderate or advanced pulmonary disease is associated with shortened survival.

The CF patient registry provides a very unique opportunity to examine the frequency of complications in the national samples rates which might only be anecdotal in any individual clinic and here can be examined to see if there are trends over time, associations with age, emerging new complications and so forth. These data, for the most part, validate clinical impression.

The leading complication is diabetes requiring insulin in 4.6 percent of cases, with the highest rate in adults: 10 percent of adults have diabetes. Next four leading complications: nasal polyps requiring surgery, 2.3 percent; distal intestinal obstruction syndrome, two percent; liver disease requiring GI consult, two percent; and allergic bronchial pulmonary aspergillois, 1.6 percent. Others are hemophylsis, massive hemophylsis requiring transfusion, cirrhosis with portal hypertension, one percent, arthropathy, arthritis and pneumothorax requiring chest tube. Diabetes and liver disease are associated with significantly poorer survival.

Patients with diabetes have a median survival of 9.7 years compared to patients who do not have diabetes. Similarly patients who have liver disease requiring a GI consult have a median survival of 6.4 years compared to the rest of the patients, 31.2. There used to be a difference in patients born with meconium ileus. Now these differences are no longer statistically significant.

Although adults comprise only one third of all the patients, they do represent the source of most of the CF morbidity and mortality. When you consider the ratio of complications of adults to children, for some of these complications, adults have seven to 11 times higher rates of arthritis, pneumothorax, peptic ulcer disease, hemophysis and diabetes.

Adults have slightly higher rates of cirrhosis with portal hypertension and ABPA and distal intestinal obstruction syndrome and issues of nasal polyps and liver disease occur at about the same rate in adults and children.

There's a growing trend towards the increased use of home intravenous therapy in the United States. One third of all CF patients are hospitalized each year, representing a total of about 8,000 patients. While many are hospitalized for an acute exacerbation, a large proportion are hospitalized for a ten day course of antibiotics. In 1993 home IV therapy was used for nearly 3,000 patients which generally saves a patient in the health care system 50 percent of the hospital cost.

Thirty three percent of our patients have now been genotyped by DNE analysis and their specific CF mutation identified. Remember delta F508 is found in caucasians of northern European heritage, as is G542X. G551D is found in people of Celtic heritage, Irish. W1282X is found in Jews and I303K is found in individuals of southern Mediterranean heritage. R553X is found in African-Americans and 621+1G-T in French Canadians.

Discovery of the gene for CF in 1989 and the subsequent identification of a very broad spectrum of CF gene mutations prompted extensive research to determine possible associations between specific mutations and clinical characteristics of the disease. This genotype/phenotype research may provide a basis, not only for more accurate clinical prognostication but also for the development of novel therapeutic approaches.

As I mentioned earlier, prior to the 1990s, there were really only four major therapies for CF patients. The therapies had merely treated the symptoms of the disease and these included physiotherapy, antibiotics, pancreatic enzymes and aggressive nutritional interventions. Well, since 1989 such great strides have been made in understanding the basic molecular defect. Our ability to propose new therapies has really been enhanced. Each new therapy directed toward different aspects of the pathophysiology of CF. And I'll review the pathway.

The abnormal gene causes the abnormal CFTR protein which causes altered ion transport in the cells and abnormal mucus secretion on the top of the epithelial cell lining. The abnormal

mucus secretions in turn creates an environment for infection and inflammation and eventual tissue destruction culminating in organ destruction and respiratory failure.

I'll talk about three therapies that focus on specific aspect of this pathway. I'd like to talk about the potential for gene therapy to transfer the normal gene into the epithelial and second amiloride and amiloride coupled with UTP to alter the ion transport part of the defect of the cell and finally just briefly a little bit on DNAs, now called pulmulzyme that a very tremendous influence on the abnormal mucus as well reducing the resulting infection.

Let me first discuss the recent exciting advances in gene therapy or more correctly termed as gene transfer. This gene transfer is not a cure. It is exactly as it sounds, a transfer of a correct copy of the gene. There are six phase one protocols underway right at this moment in 74 adult CF patients in the United States. They're underway at the NIH, Cornell, at the University of Iowa, the University of Pennsylvania, University of North Carolina, University of Cincinnati and the University of Washington.

This University of Washington protocol was just approved two weeks ago by the NIH and the FDA and they already have attempted gene transfer in one of their five patients. These phase one safety protocols have been designed to address the question how to best deliver correct copies of the CF gene, at what site, at what dose, with what side effects.

Only phase two and phase three gene transfer trials will begin to address clinical efficacy. These six protocols will attempt to transfer normal genes by using mercominant adenovirus delivery system. The strategy, insert a corrected CF gene to the genetic material of a cold virus, the adenovirus, which is modified or disarmed to stop it from causing an infection.

The researchers aerosolize the virus into the lungs or in some protocols into the nasal epithelium. Preliminary results show that the corrected copies of the CF gene have been successfully transferred into the epithelial cells. The hope is that the healthy gene will express over a matter of weeks.

Normal epithelial cells turn over every 35 to 40 days or so. And thereby correct the defect. This will enable the lung's cells to regain their ability to transport chloride, salt and water normally, creating the normal or optimal volume of airway surface fluid. The cilia involved in muco-ciliary clearance should then successfully clear mucus and bacteria from the airways.

Results from the first two protocols, University of Iowa and NIH, have been published. In October of 1993, results from Dr. Michael Walsh's lab at the University of Iowa, achieved a milestone in CF gene therapy when they determined that the gene treatment had repaired the defective cells in the nasal tissue. This September, this month, results from Dr. Ron Crystal's lab from the NIH appeared in Nature Genetics and reported initial results from the very first four patients to undergo CF gene therapy.

These patients were given different doses of the virus and monitored very carefully. He reported normal gene expression in the lungs of one of the patients for up to ten days. One of the largest studies is at the University of Pennsylvania where they will be studying 22 patients. They have treated eight patients to date. None of the patients treated, 36 of the 74, have suffered any long term inflammatory response. There was no recombination or complementation or shedding of the viral vector.

These protocols will answer important safety questions. There are many, but I have listed two of the critical ones. First, will the patients develop significant or debilitating inflammation? As I said results from the first 37 of the 74 patients to undergo gene transfer therapy are very encouraging. None to date have developed any long term inflammatory response.

And two, the central question, can the adenovirus safely be administered on a repeat basis, since the cells turn over every 40 days and then a new CF cell then emerges, and you would have to re-infect the patient with the copy of the gene, can this be administered on a repeat basis or will this cause an antibody response that would defeat the transfer process? This, of course, would severely limit the effectiveness of this type of gene transfer. None of the patients to date have shown any evidence of a rise in neutralizing antibody. Other questions under expression, how many corrected genes need to be delivered to cause sufficient expression to replicate sufficiently to correct the entire respiratory system? Another question, what regions of the lung or nodes are the best to target? Some believe that simple treatment of the nasal epithelial cells can be adequate because the infections typically express down to the lung.

How can we develop more sensitive ways to evaluate gene expression than the current measures of potential difference, electrical measures of ion voltage changes? New parameters include possibly bacterial adherence, mucociliary clearance. And finally, what will be the most effective and the safest and the least expensive delivery vector. And of course the longest term challenge is to identify the parent stem cells responsible for making the CF cells. Current CF gene transfer therapy is at the somatic cell level. Ideally we would like to affect the immortal cells that give rise to the normal epithelium.

Two upcoming protocols include the adeno-associated virus and liposomes, each with advantages and disadvantages. The seventh and eighth gene transfer protocols were approved by the NIH two weeks ago and they await FDA approval before they can begin. One at Johns Hopkins, proposes to use the adeno-associated virus as the delivery vector. The advantages are the small size of this virus, the potential to deliver the gene without posing any risk of causing disease or being rejected by the body. The disadvantage is how to produce the adeno-associated virus in large quantity. The other protocol from the University of Alabama, we use liposomes to deliver corrected copies of the CF gene to CF patients. Simultaneously two of these first sites have begun repeat dose studies to determine the immunological response.

The liposomes are tiny capsules of fat that provide a very novel vehicle to correct the CF gene. In the protocol advance today, they'd be sprayed into the lungs. Liposomes offer several advantages over the adenovirus. They do not carry the risk of disease causing a cold or of any allergic reaction, no viral immunity. They adhere better to all types of tissue and may in fact provide the best delivery system to all organs and include the pancreas and liver and enable those manifestations of CF to be corrected, not just the airway. And they're one tenth as expensive. A group of British scientists confirmed the feasibility of this exciting gene therapy. A study of 15 patients showed that liposomes transferred the healthy gene into human nasal passages.

Another potential therapy that I believe holds very great promise is underway in a nearly completed randomized placebo control multi-center clinical trial of amiloride, and second trial evaluating the potential combination of amiloride with UTP.

These trials seek to correct the ion transport defects of CF. The phase one and phase two studies have demonstrated that amiloride, a common diuretic which blocks the excess sodium absorption, will in part correct this ion defect related to CF, as will UTP, uridine triphosphate. UTP is a normal chemical compound found in human airways that moves chloride across airway cells. While the administration of amiloride and UTP to CF patients would not cure CF, it could treat a very significant portion of the basic defect and the therapy will be very inexpensive.

A third new therapy was proposed to decrease the viscosity of the thick mucus ubiquitous to most CF patients' lung epithelial cells called dlanase, now marketed as pulmozyme. Massive infiltration of neutrophils into the airways of patients with CF leads to the release of DNA which contributes to the viscosity, further contributes to the viscosity and tenacity of the sputum.

Recombinant human dlanase cleaves the excess DNA present in the CF mucus and literally chops it up, rather dramatic ability to thin and liquify sputum and improve a patient's ability to mobilize the mucus and expectorate and thereby ridding themselves of some potential risk of infection and subsequent inflammation.

The results of the largest CF randomized placebo controlled phase three trial to date, the dlanase trial, included 968 patients, demonstrated that pulmozyme reduced the risk of various respiratory tract infections by 28 percent and improved lung function with a six percent improvement in FEV-1 after dlanase treatment of 168 days at an administration of either once or twice a day.

Results of this trial appeared in the *New England Journal of Medicine* this month. This study represented really a logistical tort of force and a landmark effort of cooperation with the FDA in expediting the review and approval process of the first new therapy for CF in 30 years. The development and approval process took five years, not the more typical seven to 12 years. Dlanase is costly, however, due to the new technology which had to be created at \$27 a dose or almost \$1,000 a month.

So let me close by thanking you for your attention. In conclusion I ask what does the future hold for CF patients. It's been estimated that an individual born with CF in the 1990s can be expected to live into their 40s or 50s, and I would say if we add to this projection, the potential advances from current clinical trials now underway and the advances potentially yielded from gene transfer therapy in the United States, the outlook for CF patients is very, very optimistic. Thank you very much.

(Applause.)

AUDIENCE MEMBER: Very good talk, doctor. I have two questions and I would like you to address them in a futuristic fashion if you would, and perhaps even beyond cystic fibrosis. The first one you're eminently qualified to address because it's an epidemiologic question and I had already planned to ask even before I saw your last slide. What happens to the gene pool when we start to have people reproducing that would have typically died at much younger ages and with all the diseases that we have now, when suddenly they're living much longer, what happens in 100 or 200 years to the gene pool? Secondly, almost all genes we're discovering now, you seem to see there are so many different mutations and you don't know which one is important. There's always concern that certain ones are disastrous and other ones could allow you to live to an old age, and I wonder is there work being done on functional assays of gene protein products that would allow you to see the gene and say this particular decrease in function has certain prognostic implications so you could lump 300 of your 400 mutations into that group and the rest you say they're pretty benign?

DR. FITZSIMMONS: Good question. Let me take the latter question first. The genotype/phenotype research has been very exciting for all my colleagues and among the geneticists. We've really only identified the 400 mutations in the last year and the international gene consortium continues to identify the mutations. The question is very much to identify which of the genotypes are correlated with the phenotype of the altered ion transport, therefore you want to target ATP therapy, amiloride therapy to them and there might be very different actuarial curves produced. I would suspect five years from now, depending on the genotype for CF that a patient had, I'm always struck when adult patients call the CF Foundation and say, "I thought all these years I had chronic sinusitis or I had chronic bronchitis. I'm dumbfounded to find out that I have CF." Certainly it would make sense in the actuarial industry to determine with more specificity the mortality and morbidity components of each of the genotypes and we're very earnestly pursuing that.

Your first question, what happens to the gene pool. That one is harder to answer because the frequency of CF has been very stable, as I understand from my genetic colleagues, over the past 100 years. What we're seeing in the detection and depiction of genotyping is as parents have their own genotype revealed only a fourth are choosing to abort their child and another fourth are choosing to adopt. So you could say that could slightly affect the gene pool. Not that many CF patients are becoming preg-

nant because it's virtually impossible for the males to pass on their gene, although with some new therapies it is becoming possible. It's estimated about 75 percent of the women and 99 percent of the men are infertile. So I don't know the long term impact on the gene pool. I wouldn't imagine there would be any real change in the next 50 to 100 years at all.

AUDIENCE MEMBER: I really enjoyed your presentation. I wanted to ask you, this might be a hypothetical question. You mentioned that there was one patient recently diagnosed who was age 60 something and a thought came to my mind, is there perhaps a cohort of people out there that may have chronic bronchitis because they have one of those minor mutations?

DR. FITZSIMMONS: Oh, there are.

AUDIENCE MEMBER: There may be a series of mutations that cause chronic bronchitis and I thought about alpha 1 antitrypsin deficiency and maybe there's a combination between that and a CF mutation, maybe smoking or some kind of smog or environmental, maybe those come together to produce chronic bronchitis. One in itself might not, but a series of things might do that. Would you comment on that, please?

DR. FITZSIMMONS: You've hit upon one of the iceberg kind of questions that is afflicting CF researchers right now. In fact, it's not only just those who are asymptomatic for CF symptoms but in fact carry the gene. They don't go order a genotype and their sweat test may presumably be negative so they have no idea that they can pass on the CF gene if they marry someone else who carries the gene. Even a more important component of that, and a big debate in the genetic community is the definition of CF. Men who have congenital absence of the vas deferens actually represent a mild mutation of CF and we say there are 25,000 people with CF. There are approximately 50,000 men in the US who have congenital absence of vas deferens and so the big debate is do we now enlarge the definition of CF and what does that do to insuraneability.

The men who have that or others who have the alpha one antitrypsin deficiency definitely can pass it on. If they marry someone who carries the CF gene, they can cause CF in their progeny so it's becoming an important question. I leave it to the geneticists to define how along the spectrum it will be defined. CF is very difficult because although the delta 508 represents 75 percent of our patients, there are many who live and die and they're never diagnosed with CF, never registered in our registry and they never know that they carry the disease.

(Applause.)

DR. WILLIAM BAKER: Stacey, we knew you'd have good news and you did it in such an excellent manner. Thank you. We will now take time for lunch in the French Room. While we can't go to lunch at The Oasthouse, we will try to imagine it.

(A recess was taken.)