Frédéric Chopin -- the great Polish composer and pianist--suffered from a chronic disease. Both during his life and after death physicians disagreed on the subject of Chopin's diagnosis. His contemporaries accepted the diagnosis of a disease common in the 18th century--tuberculosis. Description of new clinical entities provoked new dilemmas in the 20th century. The authors believe the most tenable seems to be the diagnosis of cystic fibrosis. In this work they present F. Chopin's case history and discuss cons and pros for cystic fibrosis as the cause of F. Chopin's suffering and death.

The dire psychological consequences of discovering an infant to be a CF carrier predicted by some are not born out by this small study. Six months after disclosure to the parents carrier identification of their infant was not perceived by parents to be problematic.

This trial of 300 mg tobramycin for inhalation twice daily (which seems to be a huge dose for young children compared to the effective 80 mg doses of inhaled tobramycin in some previous studies!) in 21 children less than 6 years for early Pseudomonas infection was stopped as there was a significant microbiological effect in all the treated patients. There was no 
P. aeruginosa
(PA) present in the 8 tobramycin-treated children but in only 1 of 13 in the placebo group had the infection cleared. The authors concluded that 28 days of tobramycin solution for inhalation, 300 mg twice daily, is safe and effective for significant reduction of lower airway Pseudomonas density in young children with CF”.

This study seemed to eventually convince many clinicians that early treatment of PA was effective in eradicating the organism first suggested in a letter to the Lancet from Leeds in 1985 nearly 20 years earlier (Littlewood et al, 1985) and later confirmed in Copenhagen in 1991 in a clinical trial (Valerius et al, 1991). We have found the delay of over a decade in adopting early eradication treatment of PA by many centres difficult to understand in view of the mass of evidence supporting the obvious deleterious effect of chronic PA infection on patients' ultimate health and even survival.

Dr Gibson (figure 30) is Director of the CF Clinical Centre at Seattle Children's Hospital and extensively involved in CF clinical care and research.

The variable definition of chronic Pseudomonas infection in various publications was problem in comparing experience between CF centres. Patients with CF in Leeds were classified into four groups on the routine culture results over the previous 12 months as follows-

- **Chronic** - more than 50% of cultures positive for Pseudomonas;
- **Intermittent** - less than 50% of cultures were positive;
- **Free** - previously had positive but clear for the past year;
- **Never** - patient has never had Pseudomonas.

Many previous studies used different definitions of chronic Pseudomonas infection making comparisons difficult. This "Leeds definition" was agreed by a number of experts including Neils Hoiby and later confirmed as useful in a published study from Belgium (Proesmans M et al. Eur

A 14-year-old boy with non-CF bronchiectasis secondary to chronic aspiration developed multiresistant *Pseudomonas aeruginosa* lower respiratory disease following several inpatient periods where accommodation and physiotherapy services were shared with CF patients known to be infected with the genetically identical strain of *P. aeruginosa*. Cross-infection with *P. aeruginosa* between CF patients and non-CF patients had not previously been described, and this finding raises significant issues relevant to the treatment of patients with non-CF supplicative lung disease. Spread of a highly transmissible *P. aeruginosa* to a CF patient already chronically infected with *P. aeruginosa* had already been described from Liverpool (McCallum SJ et al. Lancet 2001; 358: 558-560. [PubMed]) above.

The spread of infection to non-CF patients from CF patients is a definite risk in hospital wards, particularly if there are immunocompromised patients mixing with CF patients who have chronic *P. aeruginosa* infection. I have observed this on a paediatric ward on one occasion in the years before cross infection with *P. aeruginosa* was not considered to be a significant risk.

Dr Phil Robinson (figure 31) is Head of CF services and Respiratory Physician at the Royal Melbourne Children's Hospital and a leading Australian authority on cystic fibrosis.


This is the major CF Foundation multicentre study on azithromycin. The active group (n = 87) received 250 mg (if weight <40 kg) or 500 mg (if weight > or =40 kg) of oral azithromycin 3 days a week for 168 days; the placebo group (n = 98) received identically packaged tablets. The azithromycin group had a significant mean 0.097-L (SD, 0.26) increase in FEV1 at day 168 compared with 0.003 L (SD, 0.23) in the placebo group. Participants in the azithromycin group had less risk of experiencing an exacerbation and at the end of the study weighed an average 0.7 kg more than participants receiving placebo.

So here was further evidence that azithromycin treatment was associated with improvement in clinically relevant end points and the authors advised the drug should be considered for patients with CF who are 6 years or older and chronically infected. Following this trial the product was licensed and by 2005 no less than 53.6% of patients on the US CF Foundation Patient Registry were taking azithromycin.


The analysis was conducted using data from the Epidemiologic Study of Cystic Fibrosis from 1995 through 1996. Within-site rankings tended to be consistent across the three age groups. Patients who were treated at higher ranking sites had more frequent monitoring of their clinical status, measurements of lung function, and cultures for respiratory pathogens. These patients also received more interventions, particularly courses of IV antibiotics for pulmonary exacerbations. There were substantial differences in lung health across different CF care sites. Frequent monitoring and increased use of appropriate medications in the management of CF were associated with improved outcomes.

This study by Dr Charlie Johnson (figure 32) and colleagues confirmed the value of collecting data in a registry and analysis of that data to yield valuable information. Their findings reinforce the value of more frequent monitoring and interventions in achieving better clinical outcomes.


Immunotherapy with specific egg-yolk antibodies (IgY) may be an alternative to antibiotics for the prevention of PA infections. CF patients gargled daily with an IgY-antibody preparation, purified from eggs of hens immunized with *Pseudomonas* bacteria. These patients were compared to a group who did not gargle with the preparation. Both groups had their first colonization with PA...
eradicated by antibiotics. The basic treatment for CF was essentially the same in both groups. In the initial study, the period between the first and second colonization with PA was significantly prolonged for the treated vs. the control group. In the prolonged study, the treated group had only 2.5 sputum cultures positive for PA per 100 months of observation, and none of these patients became chronically colonized with PA. No adverse events were reported. In the control group, 13.7 cultures per 100 months of observation were positive for PA, and 5 (24%) patients became chronically infected with PA. This feasibility study shows that antipseudomonal IgY has the potential to effectively prevent PA colonization without any severe adverse effects.

Hans Kollberg (figure 33) from Uppsala has been attending CF meetings for many years. I first remember him giving a paper on CF in Sweden at the 1980 Toronto CF conference. He has published 79 papers since 1964 on a wide variety of CF topics. He has been developing this particular treatment for some years and it now seemed to be showing definite promise. Certainly one of the "long distance" CF doctors!! Further report of this IgY treatment (Nilsson et al, 2007 below) where 10 year progress is reported; a multicentre trial is planned in 2010 and likely to be funded.

The results of 15 patients (3 girls and 12 boys) with confirmed steatorrhoea during the control evaluation were analysed. Median age was 8.7 years (range 3.5-15.9 years). Median daily lipase intake was 13,500 U/kg per day (range 10,000-22,000 U/kg per day). During treatment with omeprazole, median faecal fat loss (g fat/day) decreased from 13 g (quartiles 11.5-16.5 g/day) to 5.5 g (quartiles 4.9-8.1 g/day) (P<0.01). The same improvement was noted when fat absorption was calculated: 87% (quartiles 81-89%) without versus 94% (quartiles 90-96%) with omeprazole (P<0.001). So omeprazole improves fat digestion and absorption in cystic fibrosis patients with residual faecal fat loss despite maximal pancreatic enzyme substitution.

A useful study showing a definite improvement in absorption with acid suppression.

A report a case of cystic fibrosis (CF) in a 14-year-old Chinese girl presenting with recurrent productive cough since birth with para sinusitis and otitis media was confirmed to have CF in Peking University First Hospital. Chest CT scan showed bronchiectasis, more severe in the right upper lobe. Sweat tests were taken three times, and the values of Na(+) and Cl(-) were (126.6 +/- 5.4) mmol/L and (108.9 +/- 3.3) mmol/L, respectively. The examination of the pancreas showed no remarkable cystic changes on CT scan and there was no pancreatic insufficiency. Sixteen patients with CF in Chinese reported from 1974 to 1999 were reviewed. Sixteen of the 17 patients (7 males and 9 females, aged from 6 months to 25 years) had clinical data available for analysis. Eleven of them had died, nine before the age of 13. They all suffered from frequent episodes of pneumonia, while 14 had malnutrition and 4 had jaundice. The diagnostic procedures included clinical features, sweat test and acute. Four of them had DNA screened and four kinds of novel mutations in the cystic fibrosis transmembrane conductance regulator gene were found. So Chinese patients with CF show similar clinical manifestations to patients in the European and North American populations, but the CFTR mutation was different.

We show that Pandoraea apista must be added to the increasing list of pathogens capable of causing chronic lung infection in cystic fibrosis (CF) patients. It is most likely that this strain of P. apista was transmissible among patients with CF, leading to spread of infection from the index patient to 5 other patients exposed during participation in winter camps and/or hospitalization. All patients developed chronic infection with high levels of antibodies, and 4 patients had a downhill course of lung disease. P. apista must therefore be considered a new and sometimes important pathogen for CF patients. Cohort isolation prevented further spread of P. apista in our CF center. One of the increasing numbers of unusual organism which are significant pathogens for people with CF. Such reports from large CF centres such as Copenhagen are useful for clinician who subsequently encounters such organisms.

To investigate routine sonaroscopy (US) as an early marker and to identify risk factors for the development of cirrhosis and portal hypertension (PHT) in cystic fibrosis (CF). 106 children with CF aged 5.9+/-2.3 years were followed for 10.4+/-0.2 years in a CF clinic. At enrollment, the US was
normal, but biochemical and/or clinical disease was present in 10%. By the end of the study, 19 had developed US changes, eight with evidence of PHT. At the time of the initial US change, only 36.4% of those had, at the end of the study, either a heterogeneous or a nodular parenchyma, and only 50% of those with PHT had biochemical and/or clinical disease. Of the 30 patients treated with ursodeoxycholic acid for biochemical and/or clinical disease with (n=15) and without (n=15) associated US changes, PHT developed in six of the former and two of the latter. Univariate analysis and logistic regression showed that children with more severe disease in terms of forced expiratory volume in one second were at somewhat greater risk (P<.06) of PHT developing.

CONCLUSION: US was an early marker of liver disease and more severe CF disease, a predictor of progressive liver disease. A controlled trial should be done to assess isolated US-detected disease as an indication for UDCA.

A record of experience and long follow up from a Montreal with extensive expertise in paediatric liver disease.

The authors treated nine CF patients (0.7-1.9 years) with nebulised rhDNase (2.5 mg) and NaCl 0.9% (10 ml) via jet nebulizer cross-over once daily during 2-week treatment blocks. Measurements were performed at baseline and after treatment blocks and consisted of lung function tests (plethysmography and tidal rapid thoraco-abdominal compression technique), overnight pulse oximetry, and daily symptom scores. The DNase treatment and the different assessments were well tolerated by all children and their parents. Lung function showed increased airway patency after treatment with rhDNase (P < 0.001), but not after NaCl 0.9%. This pilot study indicates that objective assessment of the effects of rhDNase is feasible in infants with CF who have little or no respiratory symptoms. Our results warrant a larger randomized placebo-controlled trial.

This small but detailed study showed definite short term benefit from inhaled rhDNase even in infants. At least one large paediatric centre in the UK tries CF infants on rhDNase as soon as they are able to inhale it.

The conclusions of this detailed study were that alpha1-AT genotype is not a major contributor to the variability of pulmonary disease severity in cystic fibrosis.

This paper from Okayama Japan reports experience in living-donor lobar lung transplantation for patients with various lung diseases including restrictive, obstructive, septic, and hypertensive lung diseases. From October 1998 to March 2002, living-donor lobar lung transplantation was performed in 14 patients with end-stage lung diseases. Diagnoses included primary pulmonary hypertension (n = 6), idiopathic interstitial pneumonia (n = 2), bronchiolitis obliterans (n = 2), bronchiectasis (n = 2), lymphangioleiomyomatosis (n = 1), and cystic fibrosis (n = 1). Bilateral living-donor lobar lung transplantation was performed in 13 patients and right single living-donor lobar lung transplantation was performed for a 10-year-old boy with primary pulmonary hypertension. All the 14 patients are currently alive with a follow-up period of 4 to 45 months. Although their forced vital capacity (1327 +/- 78 mL, 50.2% of predicted) was limited at discharge, arterial oxygen tension on room air (98.5 +/- 1.8 mm Hg) and systolic pulmonary arterial pressure (24.8 +/- 1.6 mm Hg) were excellent. Forced vital capacity improved gradually and reached 1894 +/- 99 mL, 67.4% of predicted, at 1 year. All donors have returned to their previous lifestyles. The authors suggest that living-donor lobar lung transplantation can be applied to restrictive, obstructive, septic, and hypertensive lung diseases. This type of procedure can be an alternative to conventional cadaveric lung transplantation for both pediatric and adult patients who would die soon otherwise.

This is an interesting paper for Japan with obvious success with this procedure of which there are few reports other than the work from Starnes group in San Diego in 2001.

Hyperechogenic fetal bowel is detected in 0.1-1.8% of pregnancies during the second or third trimester. This 1997-1998 multicenter study in 22 molecular biology laboratories identified 682 cases of hyperechogenic fetal bowel detected by routine ultrasound examination during the second (86%) or third trimester. The fetal bowel was considered hyperechogenic when its echogenicity was broadly similar to, or greater than, that of the surrounding bone. Karyotyping, screening for viral infection, and screening for cystic fibrosis mutations were performed in all cases. Pregnancy outcome and postnatal follow-up were obtained in 656 of the 682 cases (91%). In 447 cases (65.5%), a normal birth was observed. Multiple malformations were observed in 47 cases (6.9%), a significant chromosomal anomaly in 24 (3.5%), cystic fibrosis in 20 (3%), and viral infection in 19 (2.8%). In utero unexplained fetal death occurred in 1.9% of cases, toxemia in...
The History of Cystic Fibrosis by Dr James Littlewood OBE

1.2%, IUGR in 4.1%, and premature birth in 6.2%. This study demonstrates that this ultrasound sign is potentially associated with medically significant outcomes. Having established that the bowel is hypertrophic, recommended investigations should include a detailed scan with Doppler measurements, fetal karyotyping, cystic fibrosis screening, and infectious disease screening. After birth, newborns require pediatric examination because a surgical treatment may be necessary. This should be combined with clear counseling of the parents.

A very clear and practically useful paper from a large multicentre French study which indicates the significance of hypertrophic bowel during pregnancy.

2003 Mirakhur A. Walshaw MJ. Autonomic dysfunction in cystic fibrosis. J R Soc Med 2003; 96 Suppl 43:11-17. [PubMed]. This a useful review of the various work on the autonomic system in CF which has received attention over the years.


2003 Sheth S. Shea JC. Bishop MD. Chopra S. Regan MM. Malmberg E. Walker C. Ricci R. Tsui LC. Durie PR. Zielenski J. Freedman SD. Increased prevalence of CFTR mutations and variants and decreased chloride secretion in primary sclerosing cholangitis. Hum Genet 2003; 113:286-292. [PubMed]. This complex study concludes that the data indicate that there is an increased prevalence of CFTR abnormalities in PSC as demonstrated by molecular and functional analyses and that these abnormalities may contribute to the development of PSC in a subset of patients with inflammatory bowel disease.


Report of a Consensus Development Conference organised by the CF Foundation to which representatives from both USA and Europe were invited. The result is a very detailed paper full of information and nearly 400 references.

2003 Ballmann M. Junge S. von der Hardt H. Low-dose methotrexate for advanced pulmonary disease in patients with cystic fibrosis. Respir Med 2003; 97:498-500. [PubMed] In the year before starting with low dose methotrexate (MTX), FEV1% decreased (median: 10% FEV1; range 9-15% FEV1; P<0.005) after starting with MTX, FEV1% increased (median: 9% FEV1; range: 2-15% FEV1; P=0.05). IgG changed (median: -2 g/l; range: 0.2 to -7.3 g/l) in the first year with MTX. The authors suggest that these preliminary data suggest a beneficial effect of MTX even in advanced pulmonary disease in CF patients.


Nontuberculous mycobacteria (NTM) are potential respiratory pathogens in cystic fibrosis (CF). To assess the species-specific prevalence and risk factors for acquisition, we conducted a prospective, cross-sectional study of the prevalence of NTM and clinical features of patients at 21 U.S. centers. Almost 10% of patients with CF who were 10 years or older were included (n = 986). The overall prevalence of NTM in sputum was 13.0% (range by center, 7-24%). Mycobacterium avium complex (72%) and Mycobacterium abscessus (16%) were the most common species. When compared with patients with CF without NTM, culture-positive subjects were older (26 vs. 22...
years, p < 0.001), had a higher FEV1 (60 vs. 54%, p < 0.01), higher frequency of Staphylococcus aureus (43 vs. 31%, p < 0.01), and lower frequency of Pseudomonas aeruginosa (71 vs. 82%, p < 0.01). Molecular typing revealed that almost all patients within each center had unique NTM strains. In summary, NTM are common in patients with CF, but neither person-to-person nor nosocomial acquisition explained the high prevalence. Older age was the most significant predictor for isolation of NTM. The clinical significance of NTM in CF is incompletely defined, but patients with these organisms should be monitored with repeat cultures.


The prevalence of nontuberculous mycobacteria (NTM) is high (approximately 13%) in sputum of patients with cystic fibrosis (CF), but the impact on lung disease is unknown. We followed 60 incident NTM-positive and 99 culture-negative patients with CF for 15 months and assessed clinical impact of NTM by FEV1 and high-resolution computed tomography (HRCT) of the chest. Mycobacterium avium complex was seen in 75% of NTM-positive subjects. The annual rate of decline in FEV1 was not different among control versus NTM-positive subjects who did not, or did, meet American Thoracic Society microbiologic criteria for NTM disease (3 +/- 1, 3 +/- 2, and 5 +/- 2%, respectively). More subjects with three or more positive cultures for NTM had two or more characteristic findings on entry HRCT (60%, 9/15) as compared with subjects with two positive cultures or less (32%) or negative cultures (19%; p < 0.02). All subjects with three or more positive cultures and exit HRCTs (n = 6) showed progression of HRCT findings, whereas only 17% of subjects with two positive cultures or less had progression (p = 0.0006). In summary, no significant short-term effect on FEV1 was detected in patients with multiple positive NTM cultures, but an abnormal HRCT was predictive of progression. Patients with CF and multiple positive NTM cultures, characteristic HRCT findings, and progressive HRCT changes should be monitored closely and considered for antmycobacterical therapy.


Nasal polyps are common, affecting one to four per cent of the population. Their cause, however, remains unknown and it is possible that it is not the same in all patients. They have a clear association with asthma, aspirin sensitivity and cystic fibrosis. Histologically they demonstrate large quantities of extracellular fluid, mast cell degranulation and an infiltrate of inflammatory cells, usually eosinophils. The authors believe that an endoscopic approach using a microdebrider facilitates accurate removal of polyps with preservation of normal anatomy.

This is a detailed review of polyps in general but it contains no new information.


There is controversy about the need for postural drainage physiotherapy in asymptomatic infants with cystic fibrosis (CF). In this study Brenda Button and her colleagues compared the effectiveness of standard postural drainage chest physiotherapy (SPT) with a modified physiotherapy regimen without head-down tilt (MPT) in 20 young infants with CF. Patients receiving SPT had more days with upper respiratory tract symptoms than those on MPT (70 +/- 38.8 vs. 37 +/- 24.9 days; P = 0.04) and required longer courses of antibiotics (23 +/- 28.5 vs. 14 +/- 11.2 days; P = 0.05). Chest x-ray scores were similar at diagnosis but were worse at 2(1/2) years for those receiving SPT (P = 0.03). Forced vital capacity and forced expired volume in 1 sec (FEV1) at 5-6 years was lower for SPT than for MPT (P < 0.05). In conclusion, MPT was more effective than SPT in this small study of infants with cystic fibrosis. Patients receiving SPT had more days with upper respiratory tract symptoms than those on MPT (70 +/- 38.8 vs. 37 +/- 24.9 days; P = 0.04). They required longer courses of antibiotics (23 +/- 28.5 vs. 14 +/- 11.2 days; P = 0.05). Chest x-ray scores were similar at diagnosis but were worse at 2(1/2) years for those receiving SPT (P = 0.03). Forced vital capacity and forced expired volume in 1 sec (FEV1) at 5-6 years was lower for SPT than for MPT (P < 0.05). In conclusion, MPT was associated with fewer respiratory complications than SPT in infants with CF.

Brenda Button’s work has been largely influential in most physiotherapists omitting the head down position in the physiotherapy recommendations for infants with cystic fibrosis. [PubMed].


Lung transplantation is now available for patients with cystic fibrosis (CF) and end-stage lung disease. While pulmonary graft function is often considered the major priority following transplantation, the nonpulmonary complications of this systemic disease also continue. GI complications after lung transplantation were common in patients with CF, and the authors advised that attention should be paid to the risk for DIOS in the early postoperative period. Prevention and early medical treatment are important in order to avoid acute surgery. Close collaboration with the GI disease. While pulmonary graft function is often considered the major priority following transplantation, the nonpulmonary complications of this systemic disease also continue. GI complications after lung transplantation were common in patients with CF, and the authors advised that attention should be paid to the risk for DIOS in the early postoperative period. Prevention and early medical treatment are important in order to avoid acute surgery. Close collaboration with the CF clinic, in order to diagnose and treat CF-related complications, is recommended.

The gastrointestinal aspects of treatment may receive insufficient attention if there are serious respiratory problems. This report of extensive experience from Toronto of patient after lung transplantations documents this advice and records experience of 27 of 75 patients. The present writer is aware of an instance where failure to give enzymes in the post operative period resulted in fatal systemic candida infection.


Sixteen of 51 (31%) patients had low RBC zinc levels compared to 4 of 40 (10%) with low plasma
zinc concentrations (P < 0.01). Thirteen of 38 patients (34%) in whom both values were obtained had low RBC zinc concentrations compared to 4 of 38 (11%) with low plasma zinc levels (P < 0.022). Neither low RBC nor plasma zinc levels correlated with nutritional status or lung function. In conclusion, about one third of patients with CF had low RBC zinc levels. Plasma zinc concentrations may not adequately reflect overall zinc status. This deficiency did not appear to be related to either nutritional status or lung function. The significance of low RBC zinc in CF is unknown.


Methotrexate (MTX) is known as an effective anti-inflammatory treatment in asthma and in juvenile rheumatoid arthritis. The question was: Is an improvement in pulmonary function achievable with low-dose MTX in patients with cystic fibrosis and advanced pulmonary disease? We treated five CF patients with advanced pulmonary disease, who deteriorated in spite of intensive conventional therapy on an individual basis with low-dose MTX. FEV1% and immunoglobulin G (IgG) serum levels were followed from the year before to the year after starting with MTX. In the year before starting with MTX, FEV1% decreased (median: 10% FEV1; range 9-15% FEV1; P<0.005) after starting with MTX, FEV1% increased (median: 9% FEV1; range: 2-15% FEV1; P<0.05). IgG changed (median: -2 g/l; range: 0.2 to -7.3 g/l) in the first year with MTX. These preliminary data suggest a beneficial effect of MTX even in advanced pulmonary disease in CF patients and supports the need for a controlled prospective study.