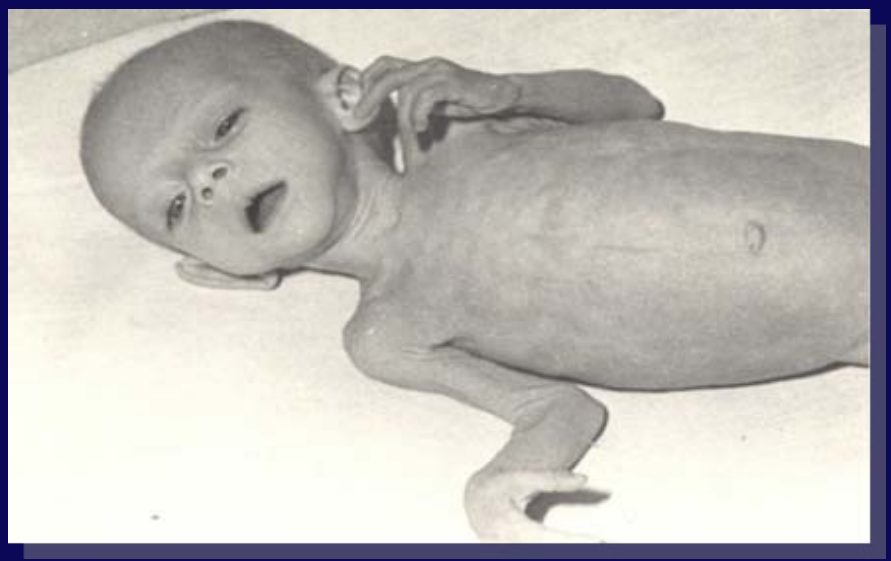
THE STORY OF CYSTIC FIBROSIS IN PRAGUE

VĚRA VÁVROVÁ
on behalf of the
CF Centre Prague - Motol

CF IN PRAGUE (1946-1959)



The 1st CF case was diagnosed in May 1946

First publication on CF: Svejcar J, Benesova D, Houstek J: Cystická fibrosa pankreatu. Cas Lek Ces 1948;87: 1116-22

During 1946-59, CF was diagnosed in 25 infants and 1 child, all but one died at the mean age 0.49 years

Josef Houštěk

CF after 1960

In 1958 prof. Houštěk spent several months in the US. There he realised that a large proportion of children, who were treated for chronic pulmonary diseases, had in fact CF.

Thus, after his return he asked me to set up diagnostics and therapy of CF at the former *Institute for Child Development Research*.

My first task was to estimate the incidence of CF and to introduce the sweat testing for its diagnosis.

Incidence of CF

Dagmar Benešová
"Czech Dorothy Andersen"

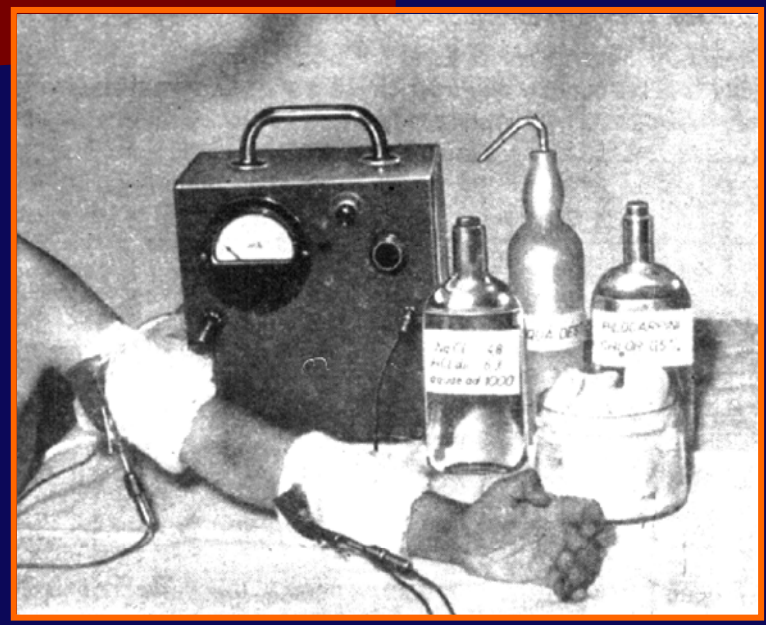
In the Central-Bohemian region, all deceased children were autopsied by prof. Benešová, who was interested in CF (in fact, she did not miss a single case with CF !).

Together, we had reviewed all clinical and autopsy protocols within 1946-1960 and found that the incidence of CF was

1 in 2,730 livebirths

Among the siblings of deceased children we also found one 11-year old misdiagnosed patient, considered to have " pulmonary fibrosis"

Sweat testing – “once upon a time“



In 1960 we started to use pilocarpine iontophoresis (Gibson and Cooke technique) by means of a *"home made"* device.

At the beginning, we measured chloride concentrations by 3 independent methods: manual titration

polarography (1959 CZ Nobel P.)

conductivity

Sweat testing - “now“

Eva Kinclová

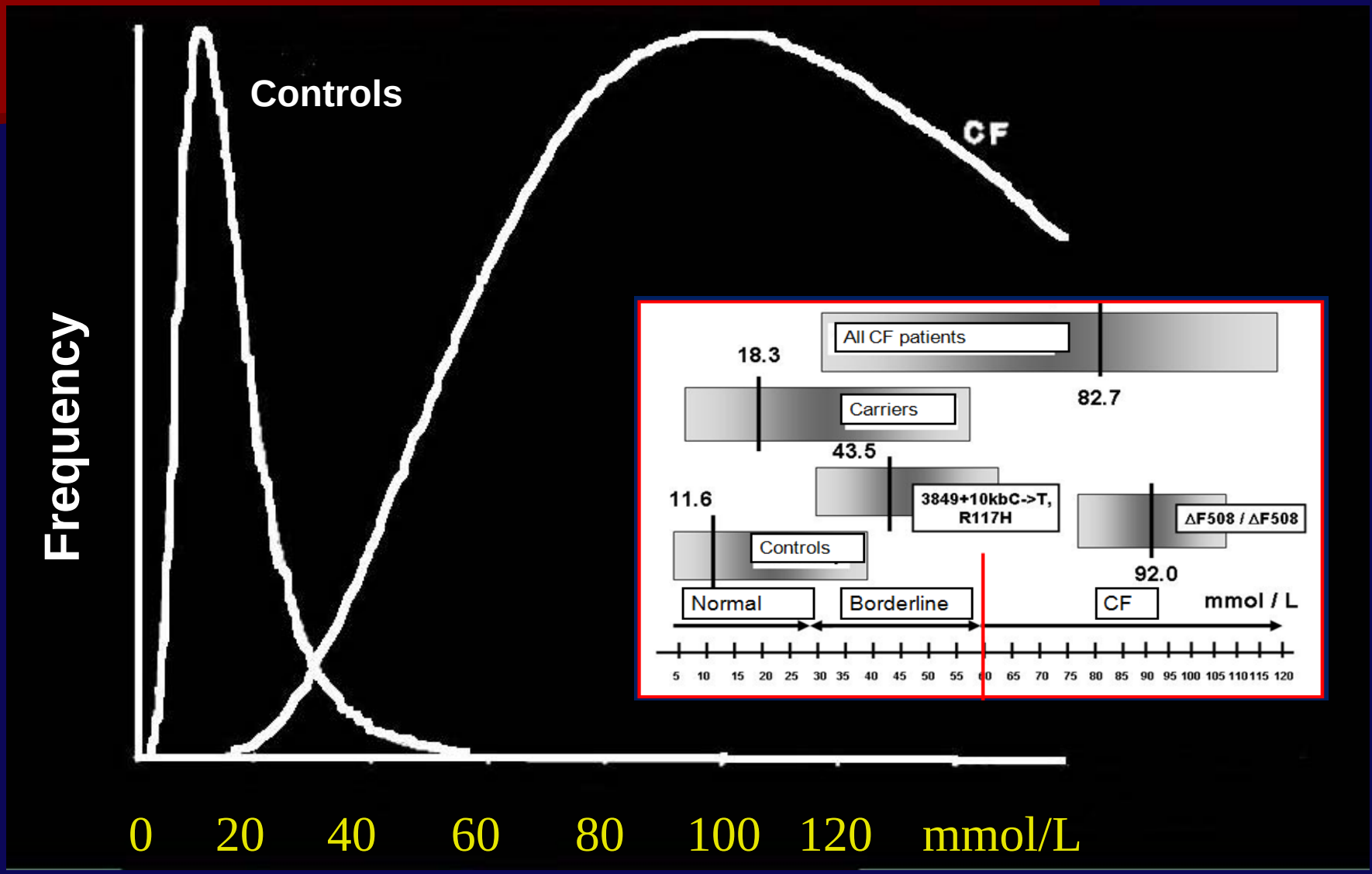
Helena Slavíková

Since 1976 we have utilised the commercial chloride titrator ®

Since then, our sweat testing facility has performed over 30,000 sweat tests. Nearly all of them have been performed by two technicians. Currently, the annual turn over has increased to 1,800 tests.

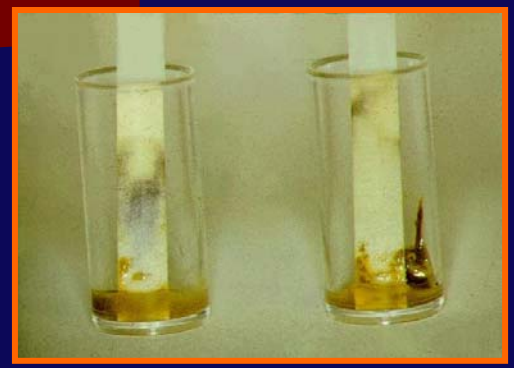
Statistical comparison of 4,974 controls versus 252 CF patients provided evidence that chloride concentrations over 31.5 mmol/L must be considered as borderline.

Sweat chloride concentrations in CF and controls (1985)

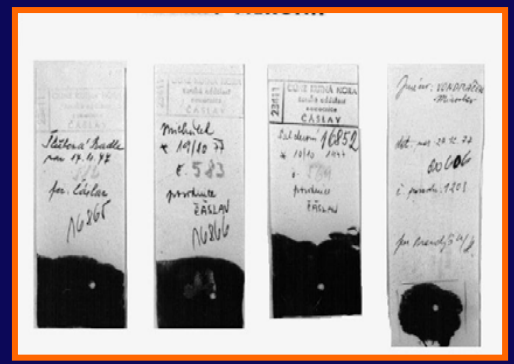


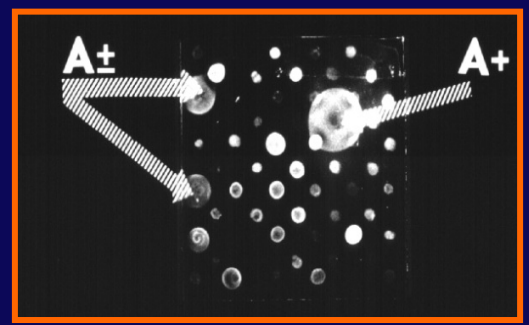
Neonatal screening - “once upon a time“

Test stripes for albumin with phenolphthalein blue were assessed between 1974-1975



Meconium albumin analysis by immunoprecipitation method was performed between 1976–1977: 44,285 meconium samples were analysed and sweat test performed in 1,307 newborns - 8 had CF, but the false negativity was too high (33.3 % !). Due to low sensitivity and specificity we did not recommend this test for population-based screening.





Neonatal screening - “now“

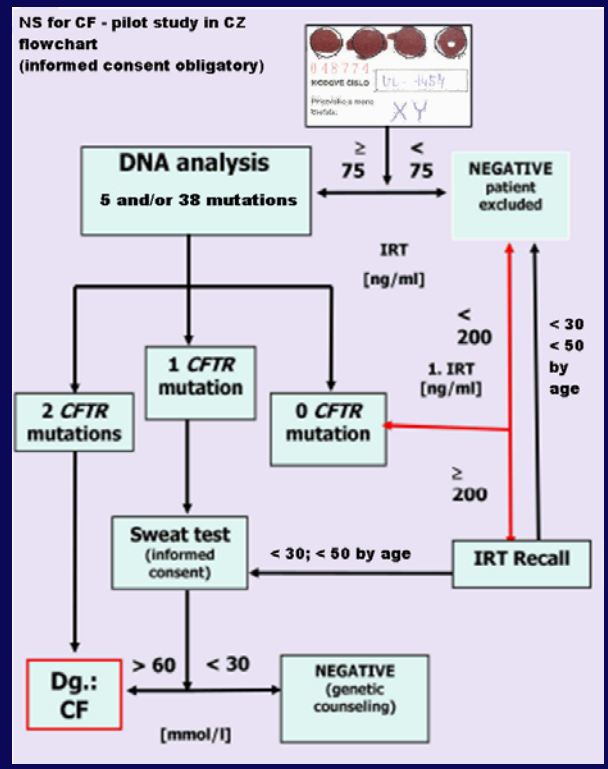
Felix Votava

Veronika Skalická

Miroslava Balaščáková

Czech pilot study of the IRT/DNA/IRT scheme (2005-2006)

- Number of examined newborns: 76,438
- IRT in dried blood spots over the “cut off“ (≥ 75 ng/ml): 800
- Number of diagnosed CF patients: 11
  - 10 of them had 2 CF-causing mutations
  - 1 of them had 1 CF-causing mutation and a positive sweat test
  - CF was diagnosed in 3 older sibs treated with other diagnoses
  - Negotiations are underway with the Czech Ministry of Health

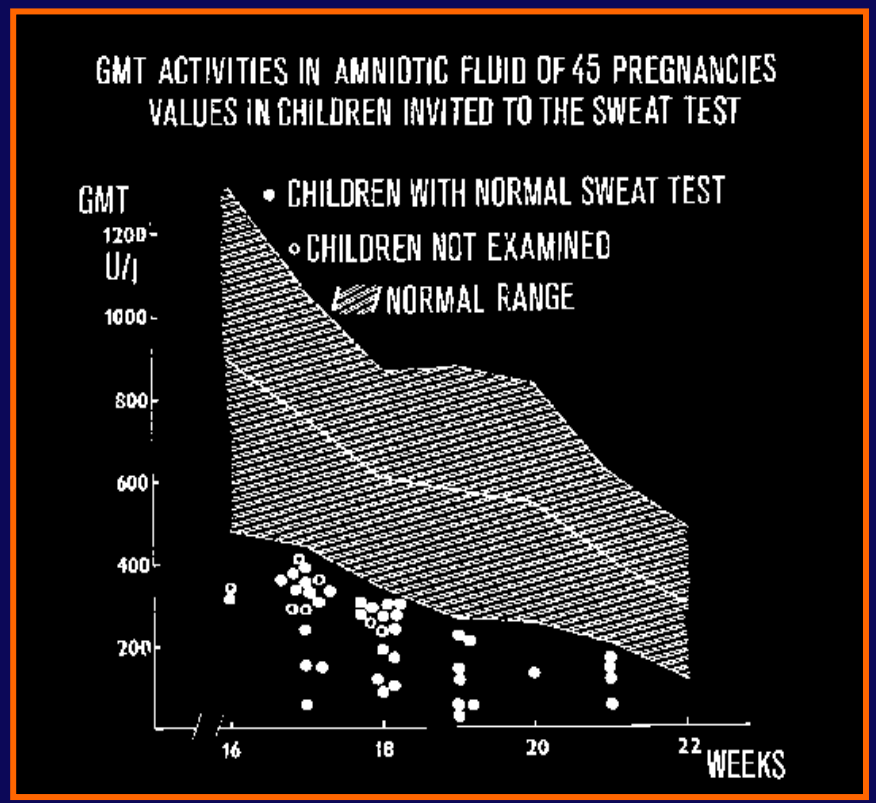


Prenatal diagnosis -“once upon a time“

From mid-eighties we started with the examination of microvillar enzyme (GMT/GGT) concentrations in amniotic fluid.

We defined population specific range of normal and abnormally low values and started to offer this examination to families with 25% risk of CF.

In collaboration with Prof. D. Brock (Edinburgh) and Prof. A. Boué (Paris)



Milan Macek Jr.

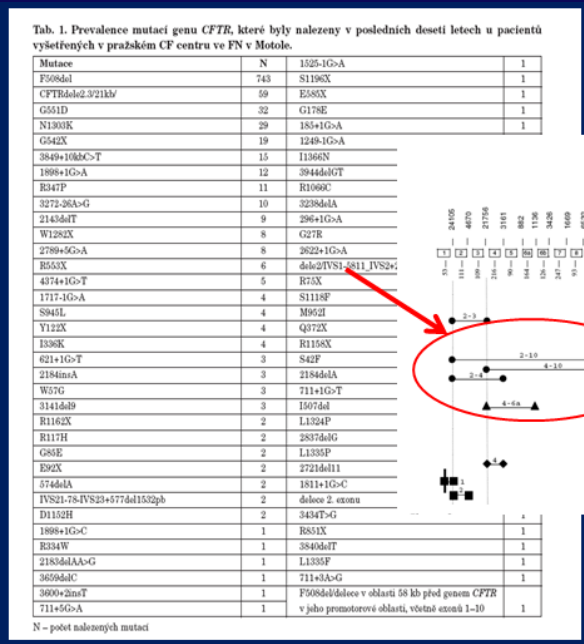
CF Genetics and DNA diagnostics

Milan Macek Sr.

Already in 1989 our genetists started with RFLP analyses and in mid-nineties they reached >98% population specific detection rate of *CFTR* gene mutations.

Alice Krebsová

Nowadays, in our CF cohort there is not a single patient with 2 unknown mutations and the small number of patients with one unknown allele decreases quickly due to international collaboration and introduction of novel methods (MLPA).



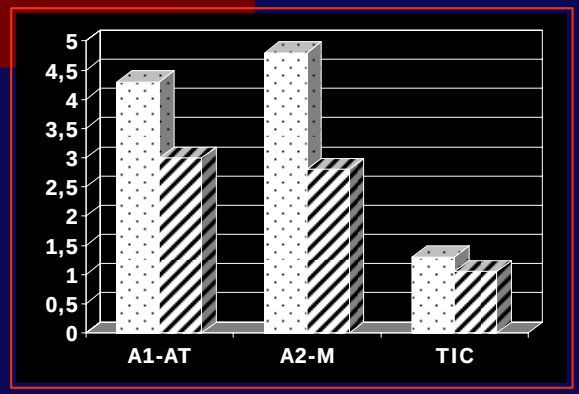
Tab. 1. Prevalence mutací genu *CFTR*, které byly nalezeny v posledních deseti letech u pacientů vyšetřených v pražském CF centru ve FN v Motole.

Mutace	N	Mutace	N
F508del	743	S1196X	1
CFTRdele2,3(21kb	59	E585X	1
G551D	32	G178E	1
N1303K	29	185+1G>A	1
G542X	19	1249-1G>A	
3849+10kbC>T	15	I1366N	
1898+1G>A	12	3944delGT	
R347P	11	R1066C	
3272-26A>G	10	3238delA	
2143delT	9	296+1G>A	
W1282X	8	G27R	
2789+5G>A	8	2622+1G>A	
R553X	6	dele2/IVS1-5811_IVS2+	
4374+1G>T	5	R75X	
1717-1G>A	4	S1118F	
S945L	4	M952I	
Y122X	4	Q372X	
I336K	4	R1158X	
621+1G>T	3	S42F	
2184insA	3	2184delA	
W57G	3	711+1G>T	
3141del9	3	I507del	
R1162X	2	L1324P	
R117H	2	2837delG	
G85E	2	L1335P	
E92X	2	2721del11	
574delA	2	1811+1G>C	
IVS21-78-IVS23+577del1532pb	2	delece 2. exonu	
D1152H	2	3434T>G	
1898+1G>C	1	R851X	1
R334W	1	3840delT	1
2183delAA>G	1	L1335F	1
3659delC	1	711+3A>G	1
3600+2insT	1	F508del/delece v oblasti 58 kb před genem *CFTR*	
711+5G>A	1	v jeho promotorové oblasti, včetně exonů 1–10	1

N – počet nalezených mutací

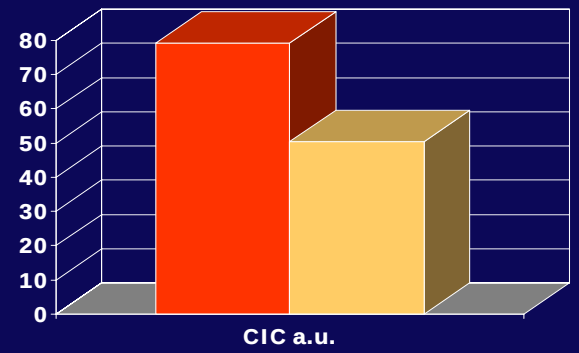
Biochemical studies

Helena Tomášová



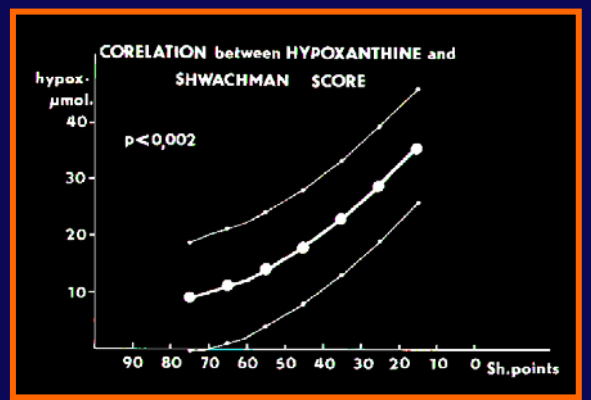
Protease-antiprotease activity

Proteases were 3x more elevated in CF, while antiproteases (A1AT, A2M, TIC), also elevated, coud not compensate their effect.



Circulating immune complexes

were elevated in *Pseudomonas aeruginosa* infected patients



Hypoxantine concentrations

correlated with the Shwachman score

Anna Šedivá

CF and immunity

- no primary immunodeficiency in CF
- secondary changes in immune reactions due to the CF basic defect

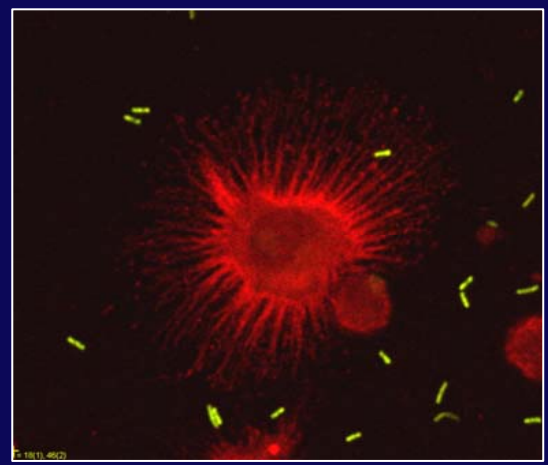
Autoantibodies C-ANCA positive in a subset of patients

ANCA mediated inhibition of *P. aeruginosa* killing by neutrophils *in vitro*

Disbalance in cytokine production with negative influence on lung functions

TGFβ-1 as a disease modifying gene

Dendritic cells and infection with *P. aeruginosa*



Anthropometry and nutrition

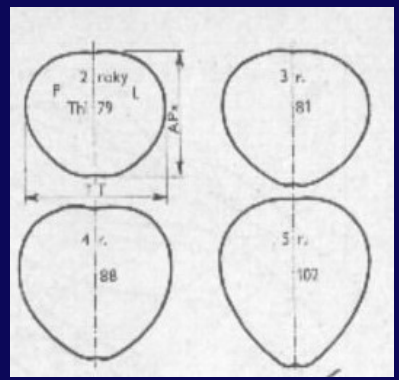
Daniela Zemková

Božena Tomášková

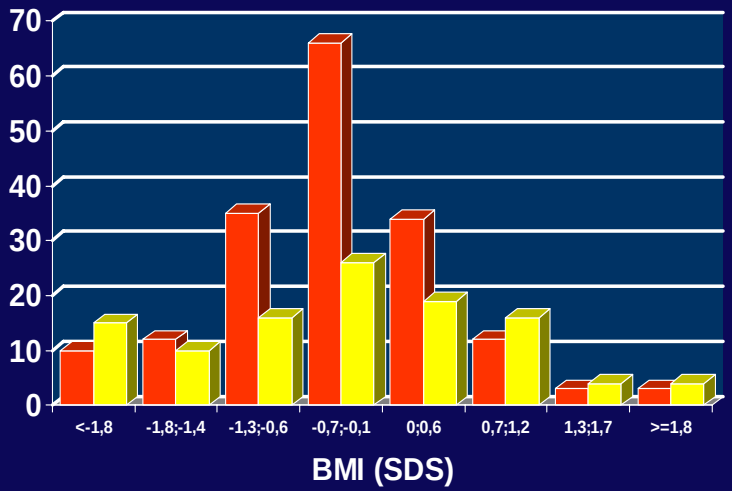
Assessment of the nutritional status is performed at every clinical examination

Marie Nováková

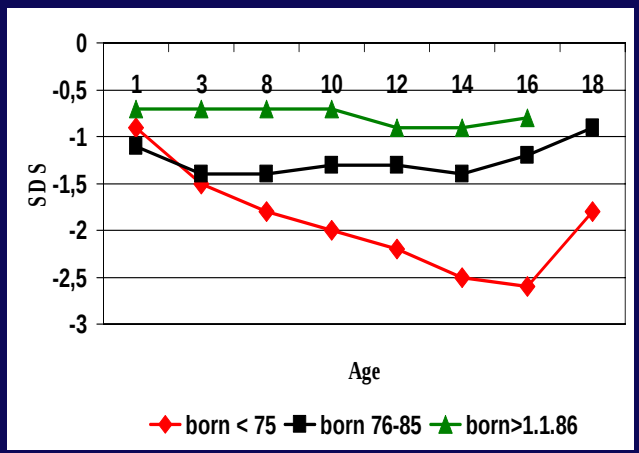
Kyrthometry



Longitudinal follow up of all patients



Mid arm circumpherence Improvement due to modern therapy

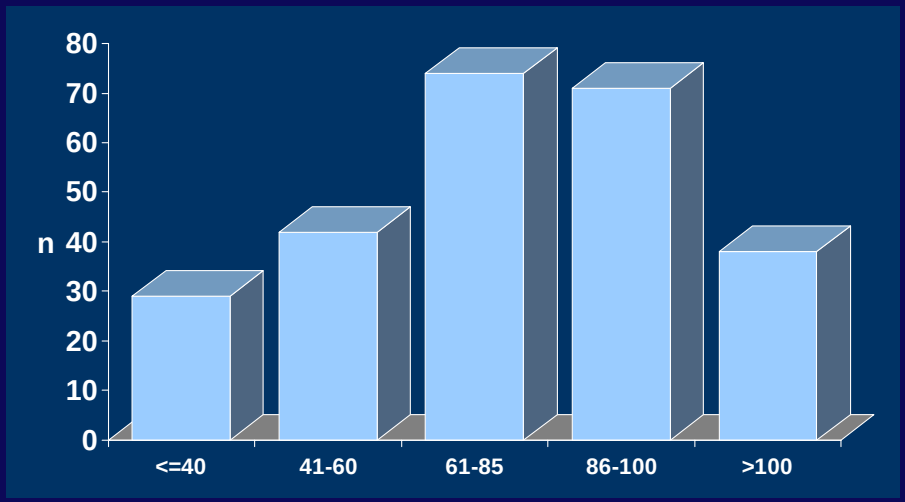


Alois Zapletal

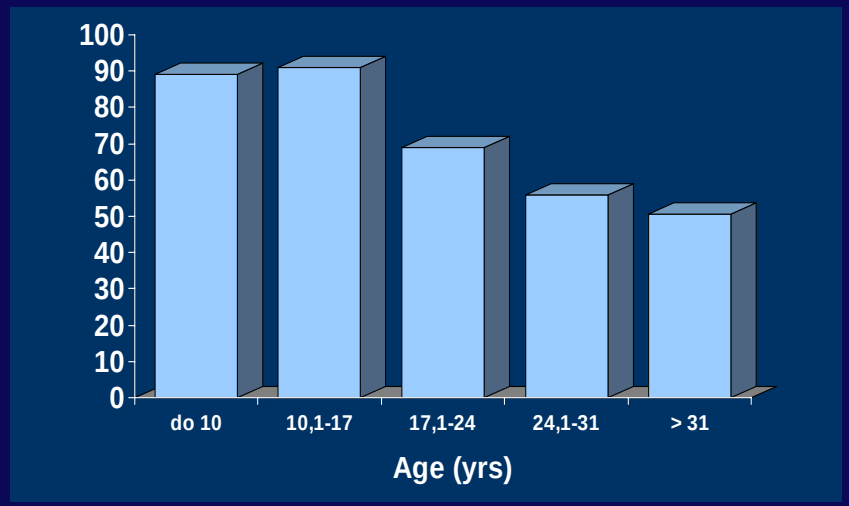
Lung function tests

Spirometry and oximetry is performed at every clinic

FEV_1



Median FEV_1 in different age groups



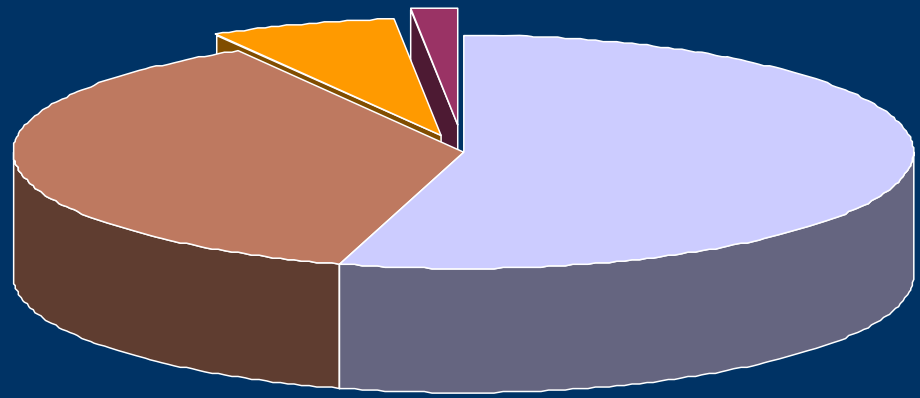
Pavel Dřevínek

Bacterial infection

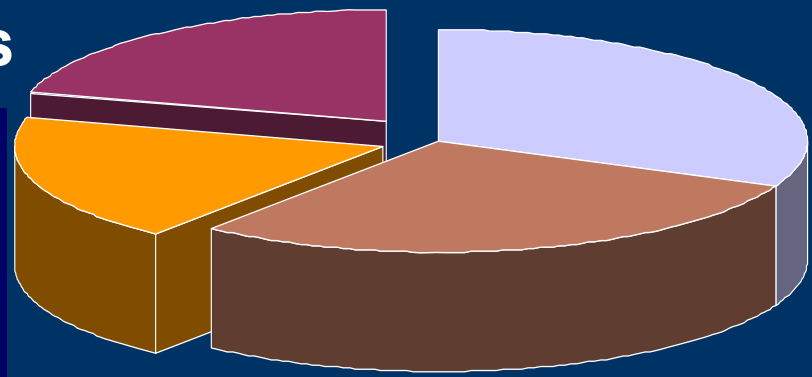
Pseudomonas aeruginosa
Burkholderia cepacia complex

Šárka Vošahlíková

Children



Adults

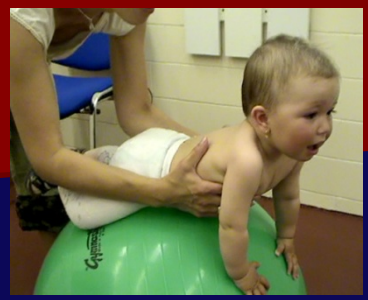


PCR-based diagnostics and separation of patients had a beneficial effect on respiratory tract infections in children


PSEUDOMONÁDA
BOJ ANTIBIOTIKY
CEPACIE
STAFYLOK
OK
A JE TO!
BOJ
INHALÁTOREM

Physiotherapy

Libuše Smolíková



Respiratory handling

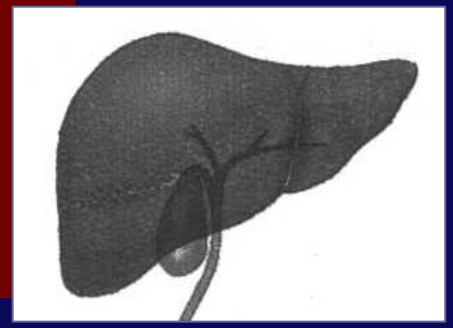
Jana Šimoničková

Respiratory physiotherapy

- Autogenic drainage
- Active cycle of breathing techniques
- PEP mask, Flutter
- Acapella choice
- Inhalation therapy
- Incentive spirometry
- Assisted AD, bouncing
- Physical exercise

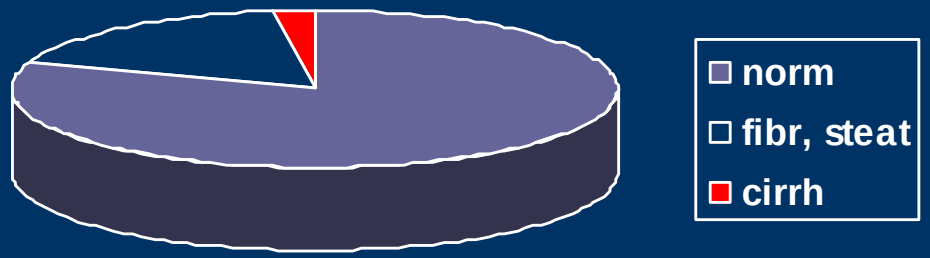
Radana Kotalová

Complications (1)



CFLD

Cirrhosis 2.3% - 2 patients Tx

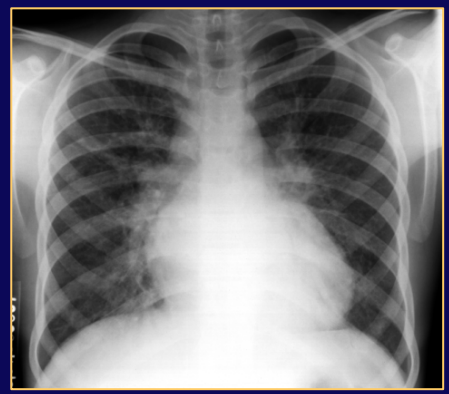


Meconium ileus

11.5 %

Cardiomyopathy

18 patients
4 alive
1 of them after heart transplantation



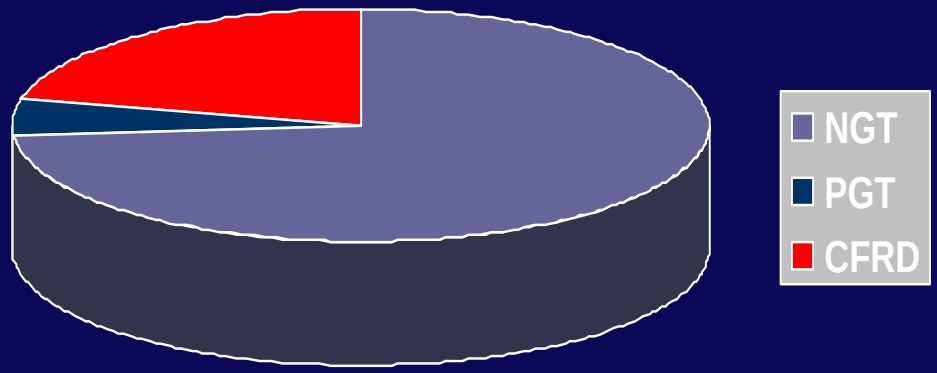
Věra Hroboňová

Stanislava Kolouškova

Complications (2)

CFRD

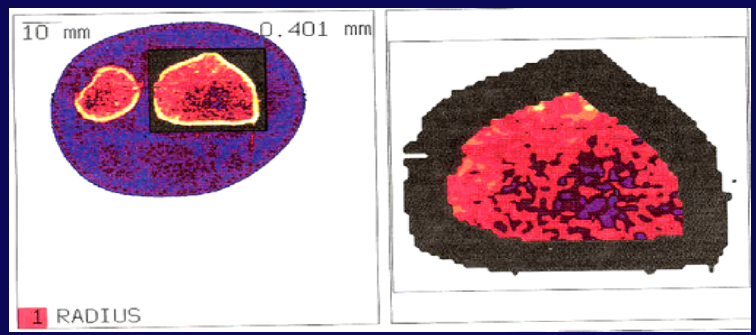
29.4% of adults



Regular oGTT screening since the age of 10 years

Osteoporosis

12.8% of adults



Czech CF Club

Psychological and social support for patients and families

"Marching with a Chick": increasing awareness of CF

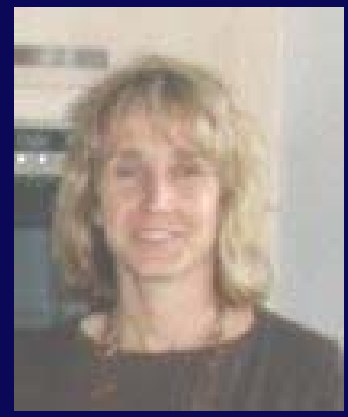
Auctions of patients´ drawings

Summer camps (cancelled due to infection control)

Weekends with parents

Helena Chladová

Tereza Tesařová

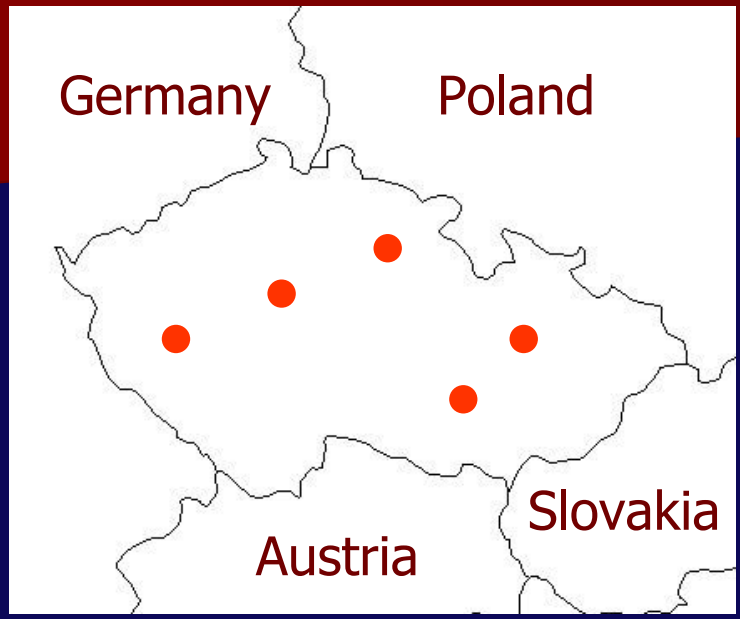


Kamila Šmídová

Alice Picková

Czech CF Registry

Ondřej Cinek



Český registr cystické fibrózy

www.cfregistr.cz

5 CF centres:

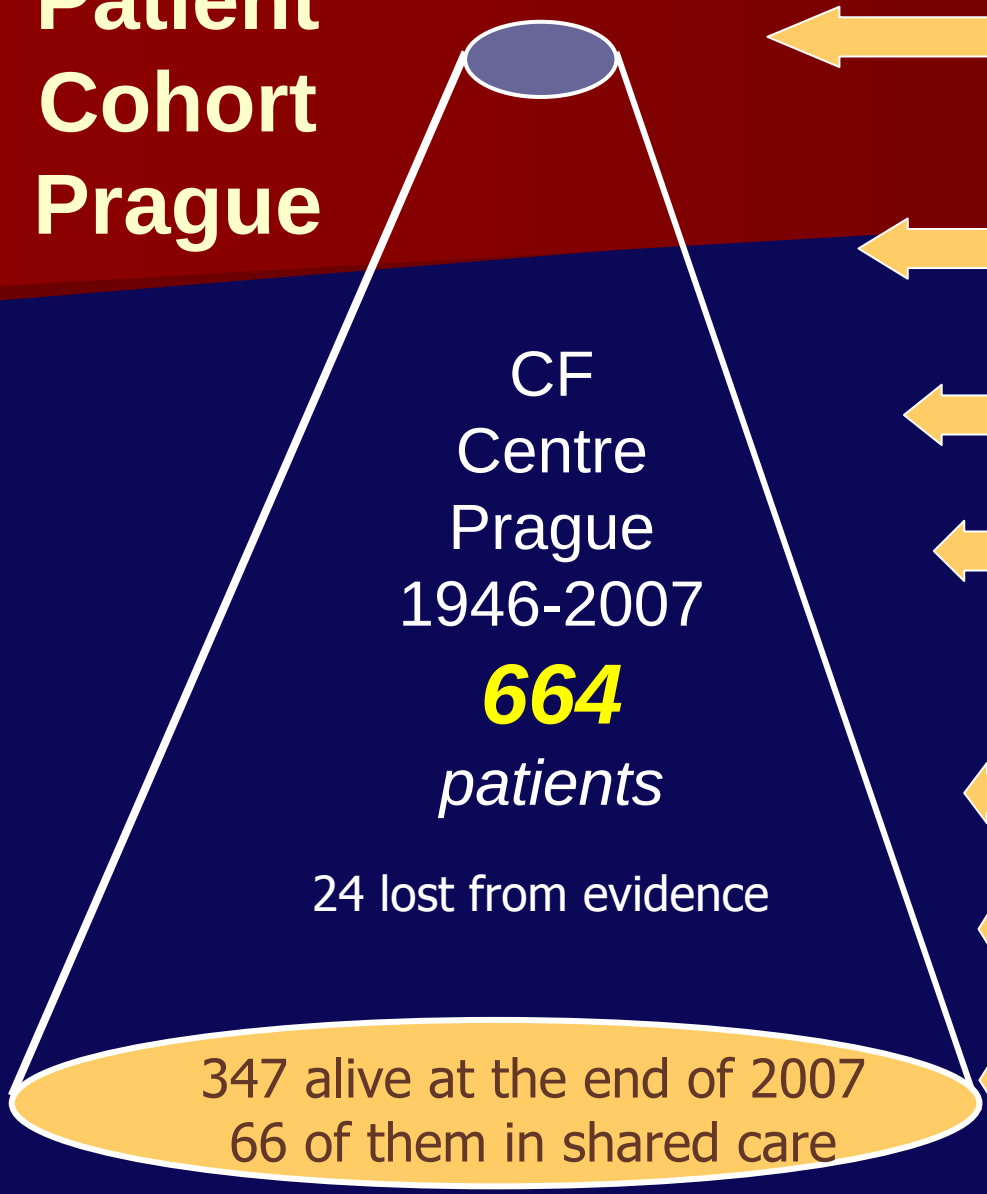
- 276 pts
- 35 pts
- 54 pts
- 17 pts
- 45 pts

EU Projects

EuroCareCF European Coordination Action for Research in Cystic Fibrosis

www.eurocarecf.eu

Patient Cohort Prague



1946 – 1959
26 infants diagnosed

1960: Sweat testing

1978: i.v. ATB treatment

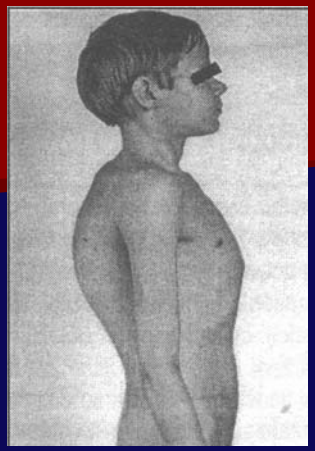
1989: *CFTR* gene ->
DNA diagnostics

1990: modern CF therapy

1995: rhDNase

1998: lung transplantation

Influence of modern therapy on the course of CF



1. Before 1975; number of pts = 187

Low fat diet
Limited antibiotics choice
Conventional physiotherapy (clapping)

2. Between 1976 - 1985; number of pts = 165

Modern therapy since school age or puberty: 1978 - i.v. ATB
1985 - preventive therapies
1987 - Prolipase

3. Since 1986; number of pts = 287

Modern therapy since early childhood: new forms of pancreatic enzymes, 1995 - rhDNase, better choice of antibiotics, nutritional support, modern physiotherapy.
Since 1998 **lung transplantation** by the team of prof. Pafko in 20 CF patients

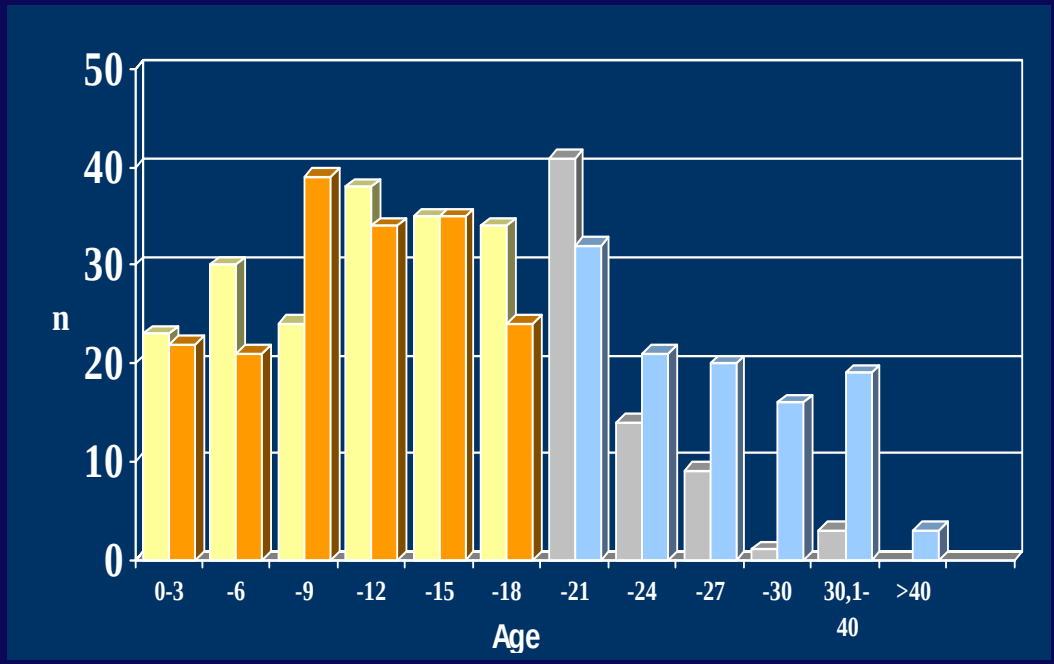
Age of patients

Libor Fila

1998 vs 2007

Children
183 vs 184

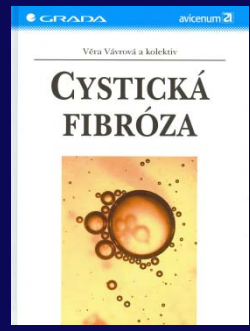
Adults
68 vs.93



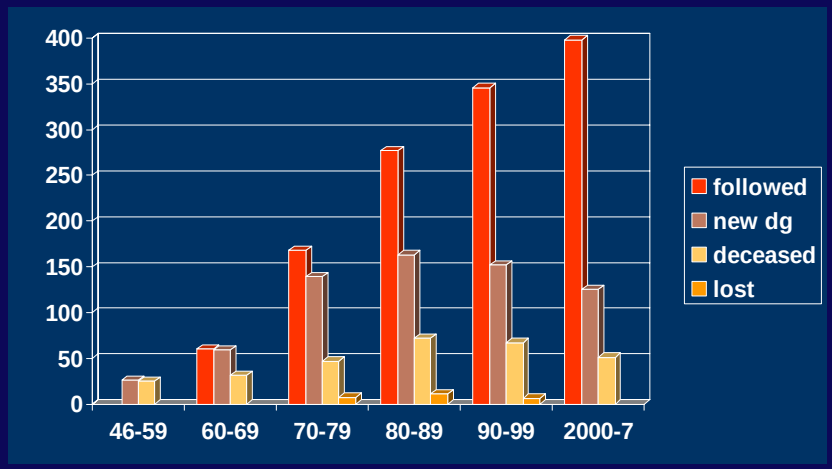
Kateřina Austová (Pediatric nurse)

Božena Mottlová (Adult nurse)

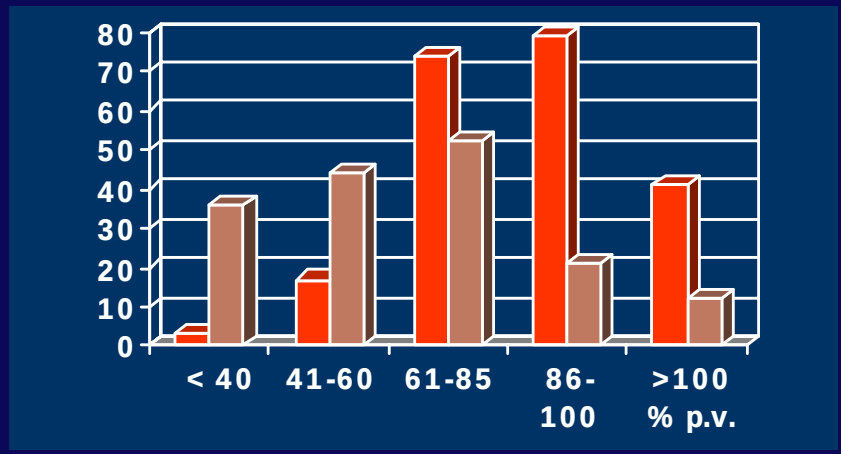
Results of implementation of modern treatment schemes after 1990

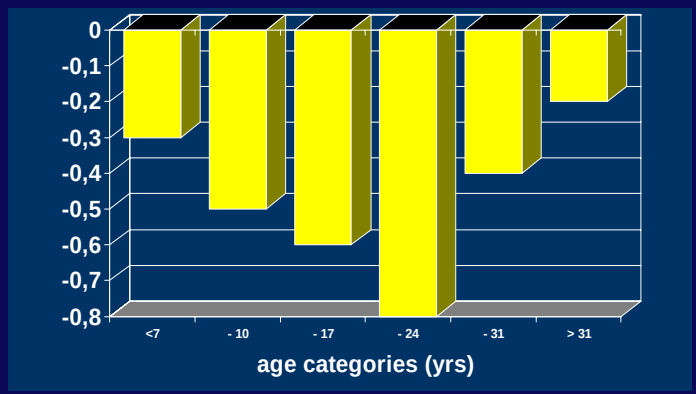


Number of newly diagnosed patients and their survival steadily increases



Lung function (FEV_1)





Nutritional status (median BMI in SDS)

The overall quality of life has markedly improved !

CF patients and their “Prague doctors“

Petr Pohunek

Pavel Dřevínek

Jana Bartošová

Jitka Brázová

Luděk Pelikán

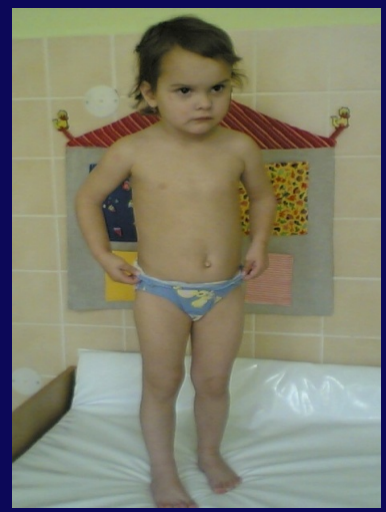
Veronika Skalická

Libor Fila

Kristýna Böhmová

Tereza Fischerová

Věra Vávrová



Summary

Due to political and socio-economic restrictions optimal treatment was not accessible to us prior to 1990.

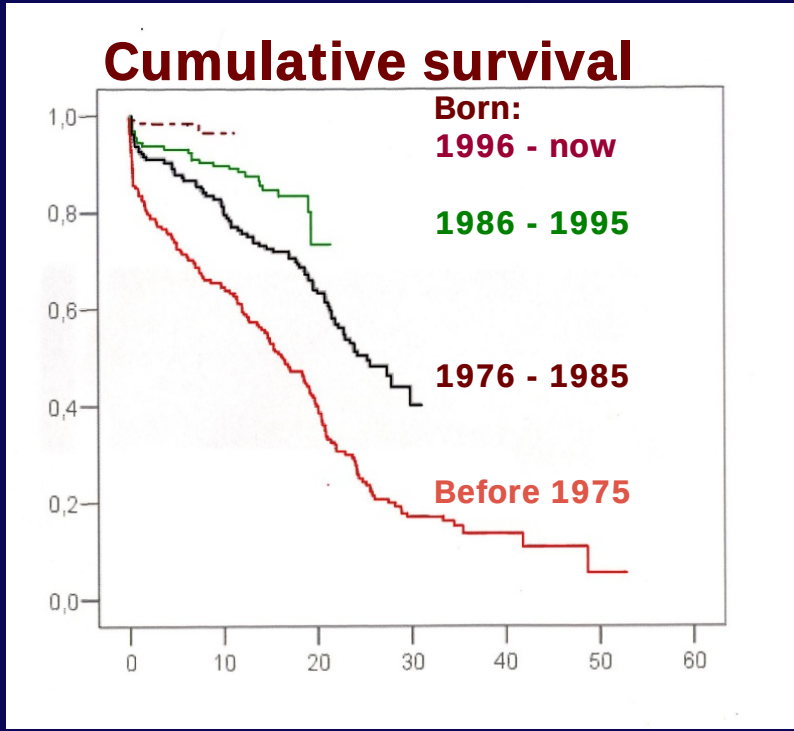
Since then, there has been steady improvement of:

nutritional status

pulmonary function

quality of life

⇒ increased survival



Personal conclusion: inspiration from CF families

CF life behind the Iron Curtain was rather difficult and often sad …

Nevertheless, my personal life was enriched by meeting many wonderful and brave people suffering from CF !

Nowadays, I am happy to work within a comprehensive CF team that provides specialised care to them, equivalent to that in developed EU countries

Let me express my deepest gratitude to them - they showed me true life values and inspired me all the time !

Thank you for your attention !

… and to ECFS once again for giving me the

"2008 Award"