

# THE STORY OF CYSTIC FIBROSIS IN PRAGUE

VĚRA VÁVROVÁ

on behalf of the  
CF Centre Prague - Motol

# CF IN PRAGUE (1946-1959)



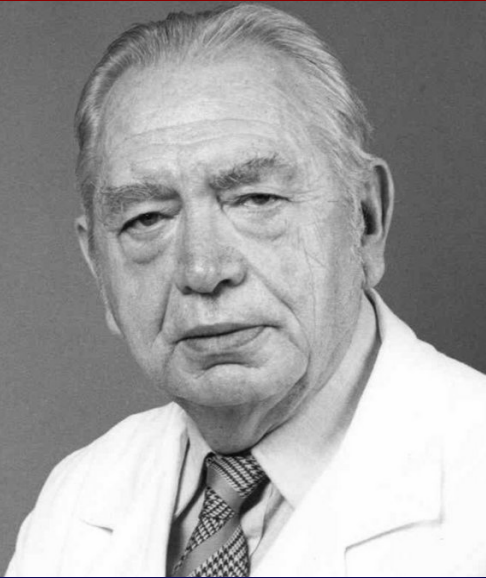
The 1<sup>st</sup> CF case was diagnosed in May 1946

*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**

## CF after 1960



Josef Houšťek

In 1958 prof. Houšťek 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 !).

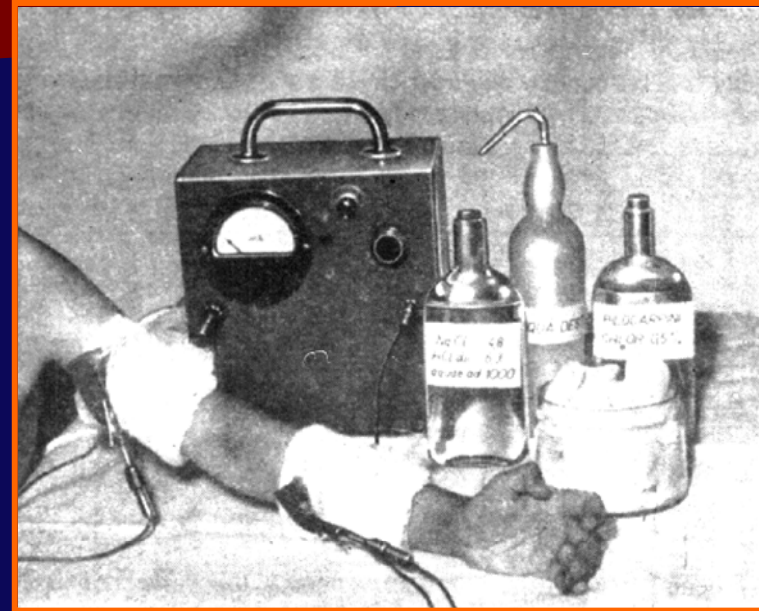
Together, we had reviewed all clinical and autopsy protocols within **1946-1960** and found that the incidence of CF was

**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"



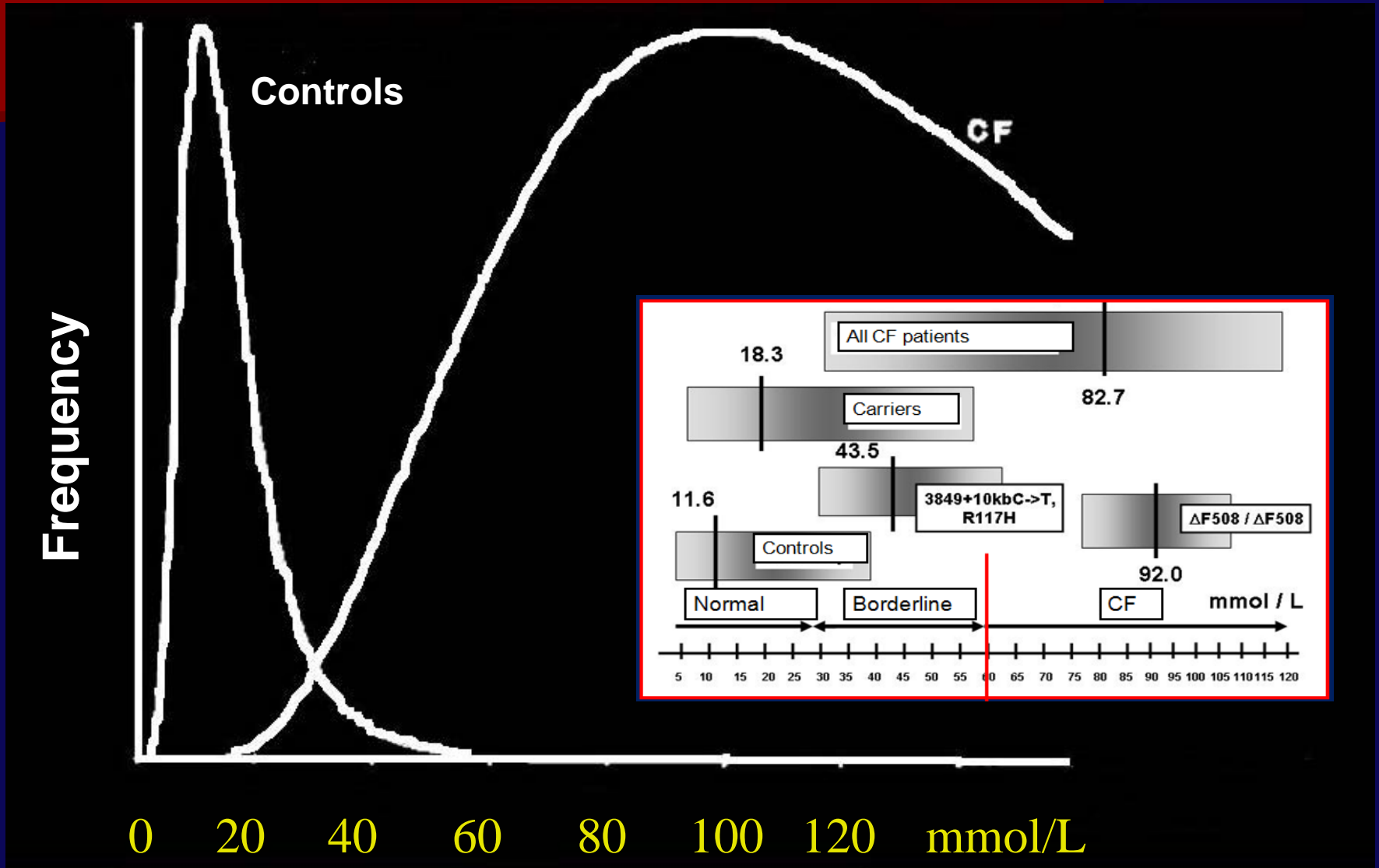
Eva Kinclová

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)

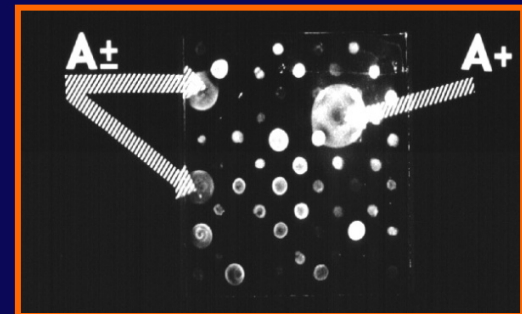
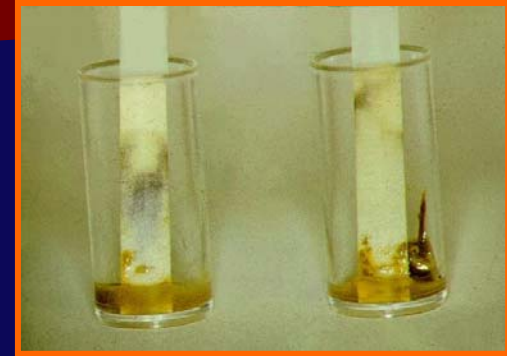




# Neonatal screening - "once upon a time"

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



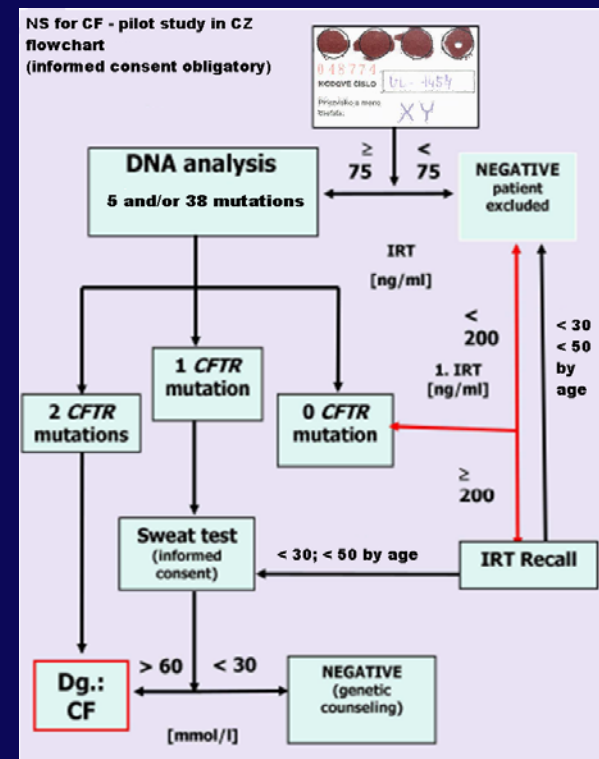
Veronika Skalická



Miroslava Balašćáková

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" ( $\geq 75$  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

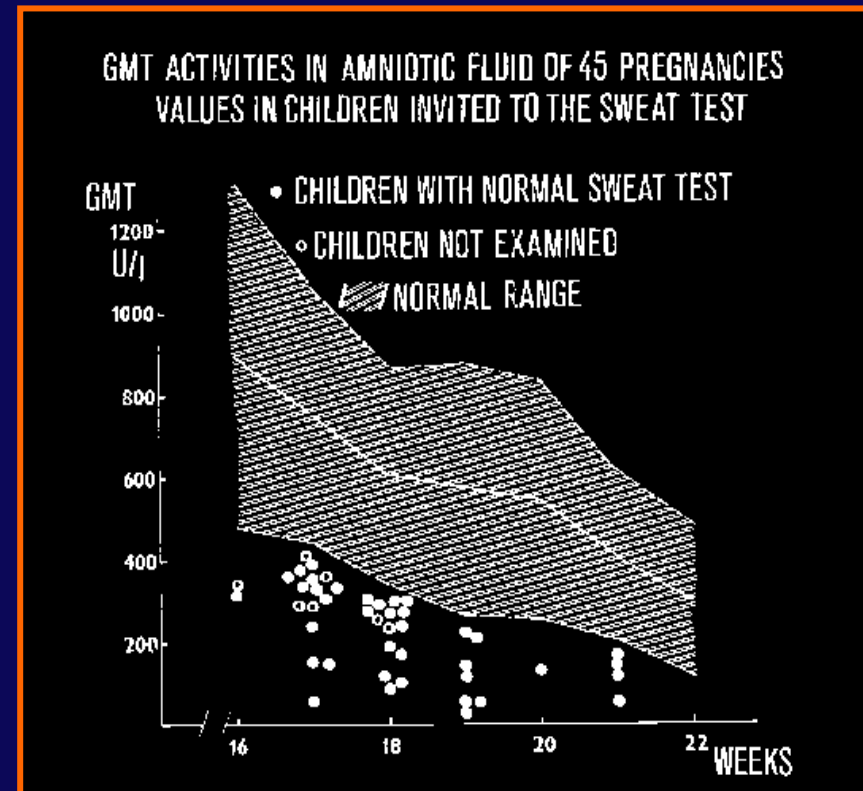


# Prenatal diagnosis - "once upon a time"

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)





# CF Genetics and DNA diagnostics



Milan Macek Jr.

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.

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)**.

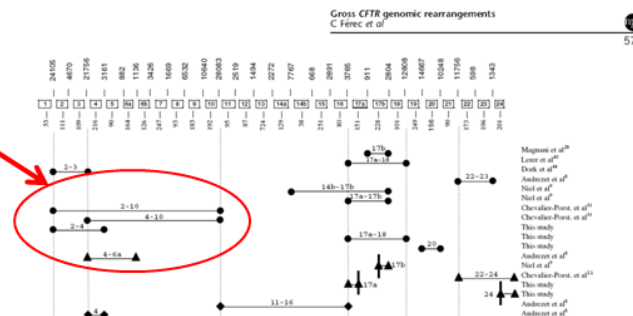


Alice Krebsová

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	1525-1G>A	
F508del	743	S1196X	1
CFTRdels2.9/21kb	59	E585X	1
G551D	32	G178E	1
N1303K	29	185+1G>A	1
G542X	19	1249-1G>A	
3849+108bC>T	15	I1396N	
1898+1G>A	12	3944delGT	
R347P	11	R1969C	
3271-28A>G	10	3238delA	
2143delTT	9	296+1G>A	
W1292X	8	G27R	
2789+5G>A	8	3823+1G>A	
R552X	6	delc2TFS1-1811_IVS24	
4374-1G>T	5	R73X	
1717-1G>A	4	S1118P	
S841L	4	M95I	
Y122X	4	Q372X	
R336K	4	R1155X	
821+1G>T	3	S42F	
2184insA	3	2184delA	
W57G	3	711+1G>T	
3141del9	3	1507del	
R1162X	2	L1324P	
R117H	2	2837delG	
G55E	2	L1335P	
E92X	2	2721del11	
574delA	2	1811+1G>C	
IVS21-78-IVS23+577del1532pb	2	delece 2. exonu	
D1192H	2	3434T>G	
1898+1G>C	1	R831X	1
R334W	1	3840delT	1
2183delAAA>G	1	L1335F	1
3659delC	1	711+3A>G	1
3600+2insT	1	F508del/delece v oblasti 58 kb před genem <i>CFTR</i>	
711+5G>A	1	v jeho promotorové oblasti, včetně exonů 1-10	1

N - počet nalezených mutací





# Biochemical studies

Helena Tomášová

## Protease-antiprotease activity

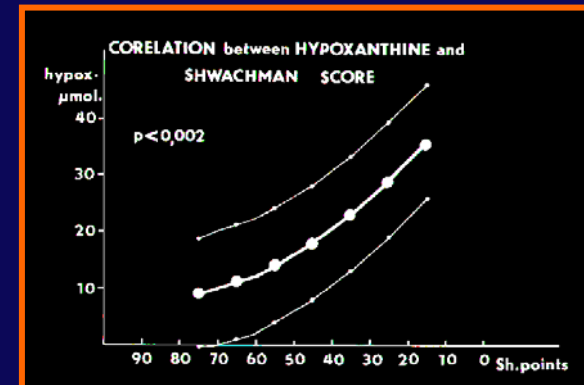
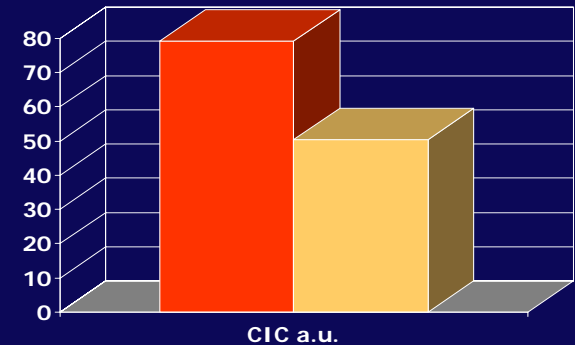
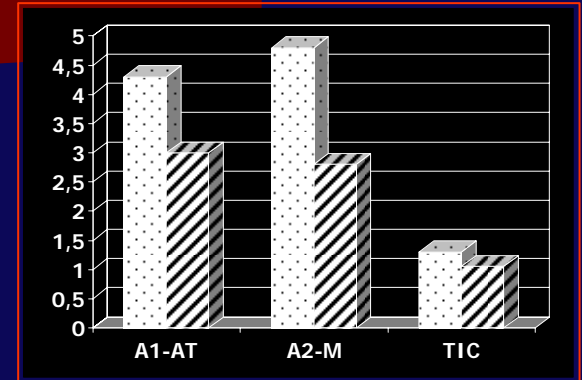
Proteases were 3x more elevated in CF, while antiproteases (A1AT, A2M, TIC), also elevated, could not compensate their effect.

## Circulating immune complexes

were elevated in *Pseudomonas aeruginosa* infected patients

## Hypoxanthine concentrations

correlated with the Shwachman score





# CF and immunity

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

Anna Šedivá

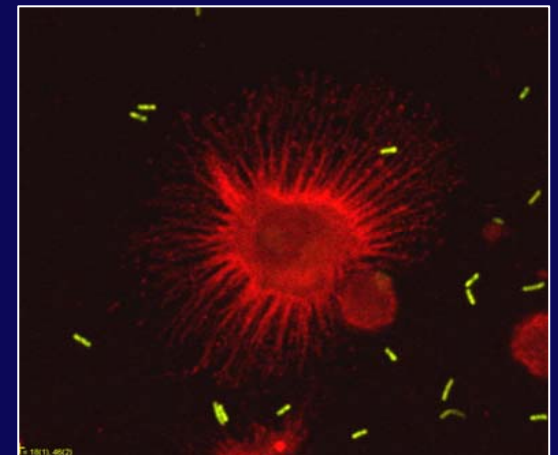
Autoantibodies C-ANCA positive in a subset of patients

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

Disbalance in cytokine production with negative influence on lung functions

TGF $\beta$ -1 as a disease modifying gene

Dendritic cells and infection with *P. aeruginosa*



# Anthropometry and nutrition



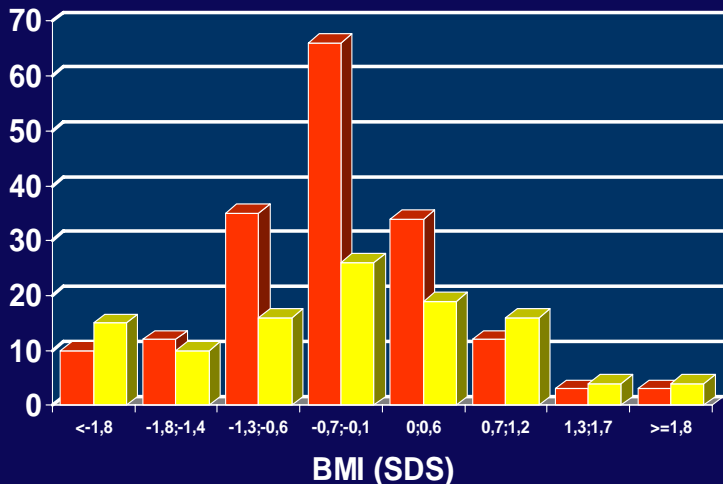
Daniela Zemková



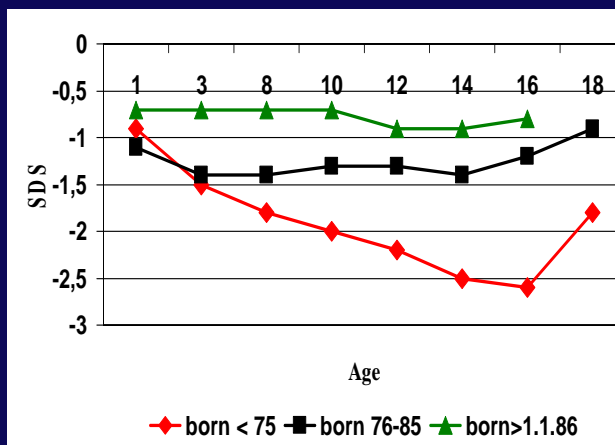
Božena Tomášková

Assessment of the nutritional status is performed at every clinical examination

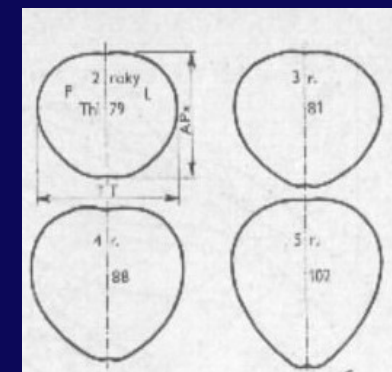
Longitudinal follow up of all patients



Mid arm circumference Improvement due to modern therapy



Marie Nováková  
Kyrthometry







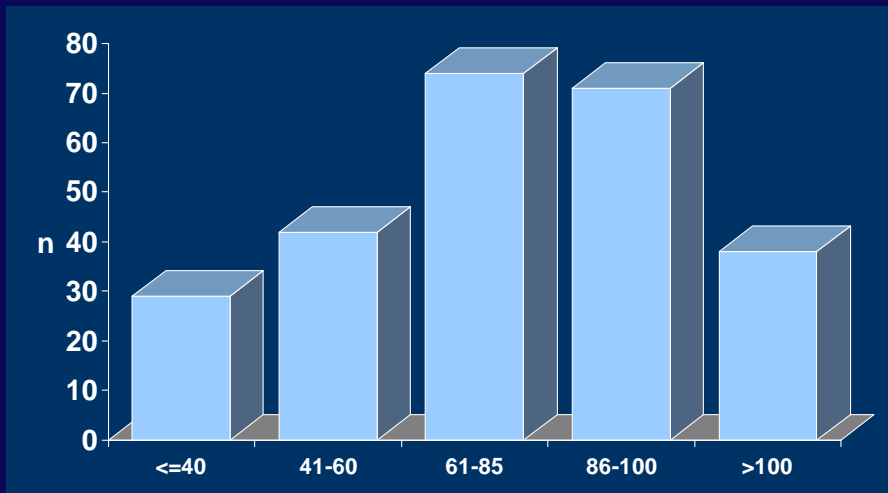
Alois Zapletal

# Lung function tests

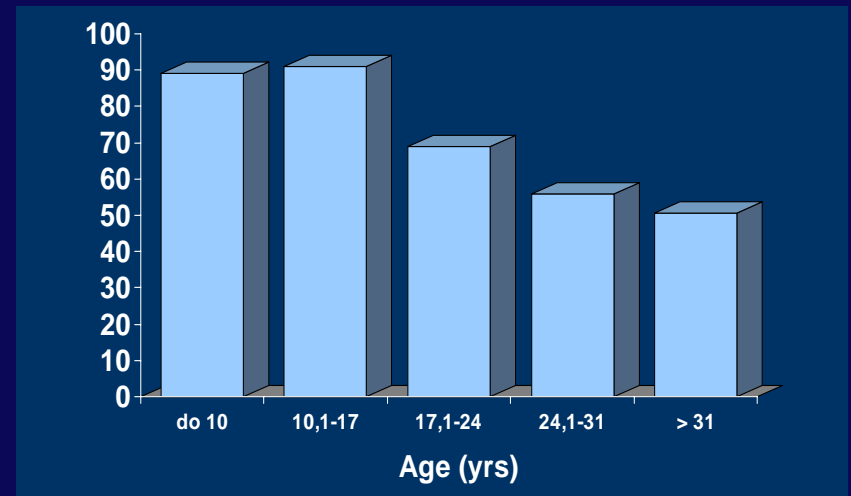
**Spirometry and oximetry is performed at every clinic**



$FEV_1$



Median  $FEV_1$  in different age groups







Pavel Dřevínek

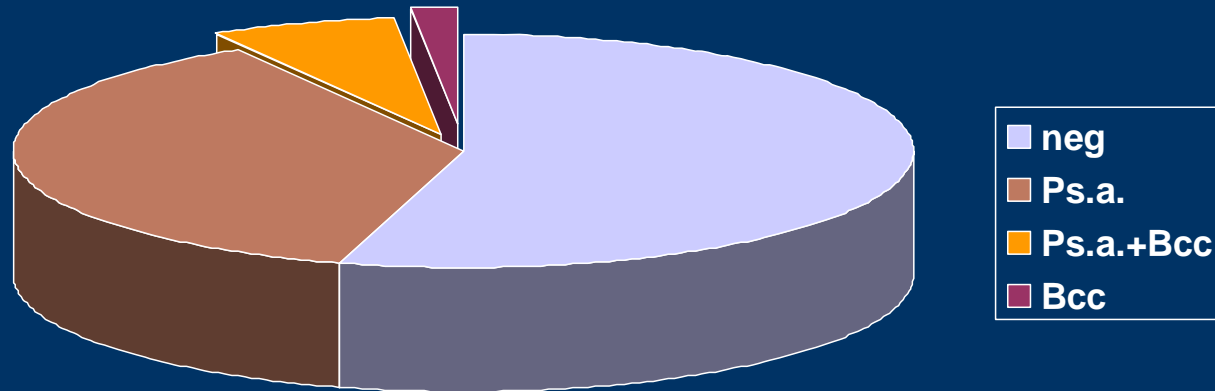
# Bacterial infection

*Pseudomonas aeruginosa*  
*Burkholderia cepacia* complex

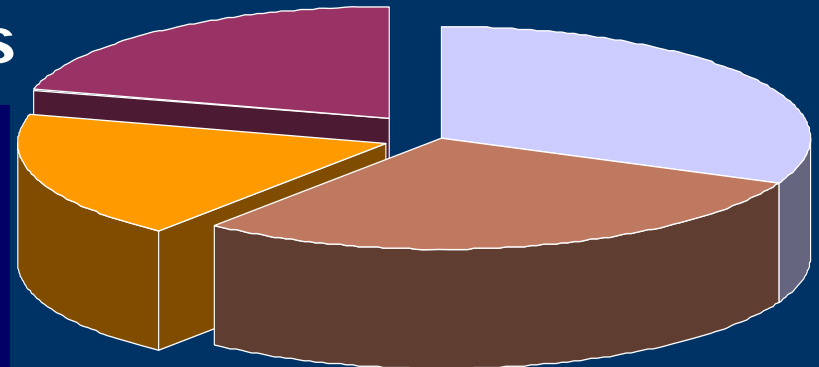


Šárka Vošahlíková

## Children



## Adults



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

PSEUDOMONADA

BOJ ANTIBIOTIKY



CEPACIE



STAFYLOK



BOJ INHALATOREM



A JE TO!





# Physiotherapy



Libuše Smolíková



## Respiratory handling



Jana Šimoničková



## Respiratory physiotherapy

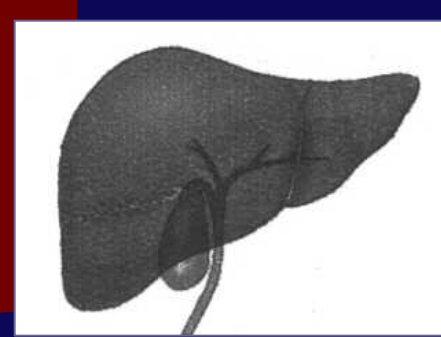
- Autogenic drainage
- Active cycle of breathing techniques
- PEP mask, Flutter
- Acapella choice
- Inhalation therapy
- Incentive spirometry
- Assisted AD, bouncing
- Physical exercise





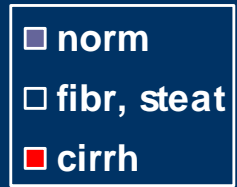
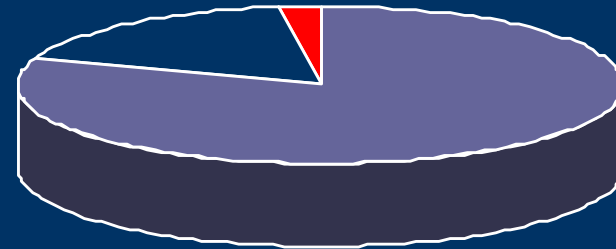
Radana  
Kotalová

# 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



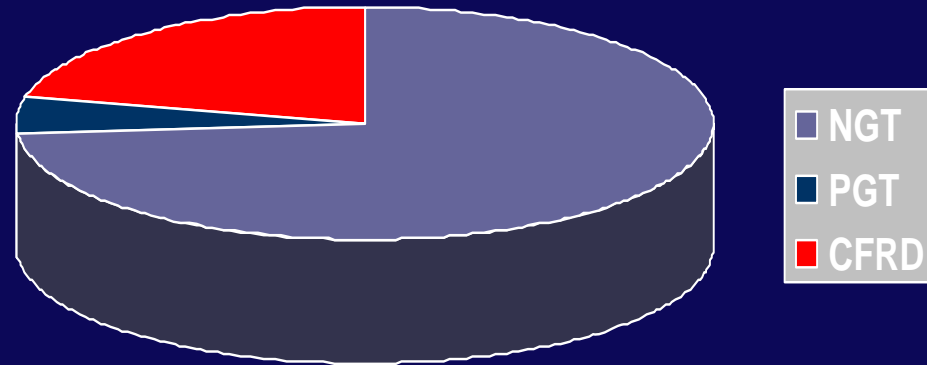
Stanislava  
Koloušková

## Complications (2)

### CFRD

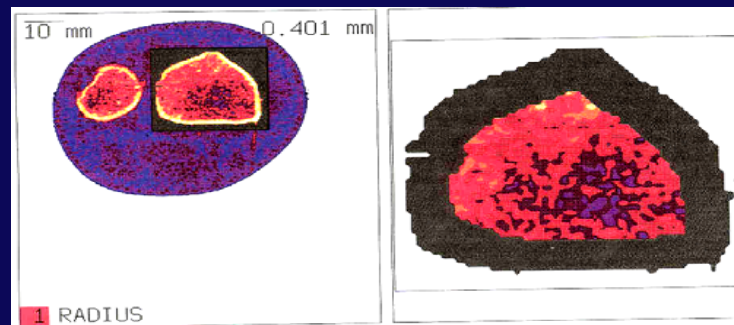
29.4% of adults

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



Kamila Šmídová



Tereza Tesařová



Helena Chladová



Alice Picková

“Marching with a Chick”:  
increasing awareness of CF

Auctions of patients’  
drawings

Summer camps (cancelled due to  
infection control)

Weekends with parents





Ondřej Cinek

5 CF centres:

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

# Czech CF Registry



## Český registr cystické fibrózy

[www.cfregistr.cz](http://www.cfregistr.cz)

## EU Projects



[www.eurocarecf.eu](http://www.eurocarecf.eu)

ecorn-cf.eu Rada odborníků

**Rada odborníka o cystické fibróze**

pacienti a lékařské týmy by měli mít snadný přístup k odborným znalostem a radám v oblasti cystické fibrózy.

- V tomto fóru je možné klást otázky anonymně. Pokud chcete položit otázku anonymně, ujistěte se, že nejste přihlášen.**
- Pokud se zaregistrujete a přihlásíte před položením dotazu, můžeme vás okamžitě e-mailem informovat, že byl váš dotaz zodpovězen.**
- Vaše osobní údaje jako jméno a e-mailová adresa jsou přístupná pouze našim expertům. Nevou dostupná veřejnosti ani nikomu dalšému.
- Před položením nové otázky: Přesvědčte se, zda již otázka nebyla zodpověna - využijte seznam témat a vyhledávání.**

• Český (Czech)  
• Německý (German)  
• Anglický  
• Litevskoska (Lithuanian)  
• Niederšlein (Dutch)  
• Polský (Polish)  
• Lisébe Románš (Romanian)

[www.ecorn-cf.eu](http://www.ecorn-cf.eu)

Příručka o cystické fibróze pro pacienty a jejich rodiče

[www.cfnetwork.be](http://www.cfnetwork.be)

Vychází s podporou AstraZeeva Česká Republika, s.r.o. AstraZeeva

Harmonizing genetic testing across Europe

**What is EuroGenet?**

EuroGenet is an EU-funded Network of Excellence (NoE) with 5 Units leading at all aspects of genetic testing: Quality Management, Information Systems, Public Health, New Technologies and Education. Through a series of activities, EuroGenet encourages the harmonization of standards and practices of these areas throughout the EU and beyond.

**What can EuroGenet offer you?**

- [Info for public](#)
- [Info for clinicians](#)
- [Info for industry](#)
- [Info for laboratories](#)
- [Info for research teams](#)

**Find a lab or test**

Find information on a test for a genetic disease or on a laboratory across Europe.

**How to register?**

Find out more about the world of Genetic Testing by registering! You'll get access to additional information if you [register here](#).

**Contact us**

If you have any questions, suggestions or wish to be involved in EuroGenet, please contact us at [info@eurogenet.eu](mailto:info@eurogenet.eu)

**News: EuroGenet - Newsletter**

**ESHG Conference 2008: 31 May - 03 Jun 2008**

**Guidelines on counselling**

The public understanding of the results and consequences of the test is a integral part of genetic testing. EuroGenet also aims at improving the quality of genetic counselling services associated with genetic testing across Europe. One of the goals is to establish recommendations for genetic counselling in connection with different testing situations.

**UKINCOAS**

The EuroGenet is a model for similar networks in Latin America.

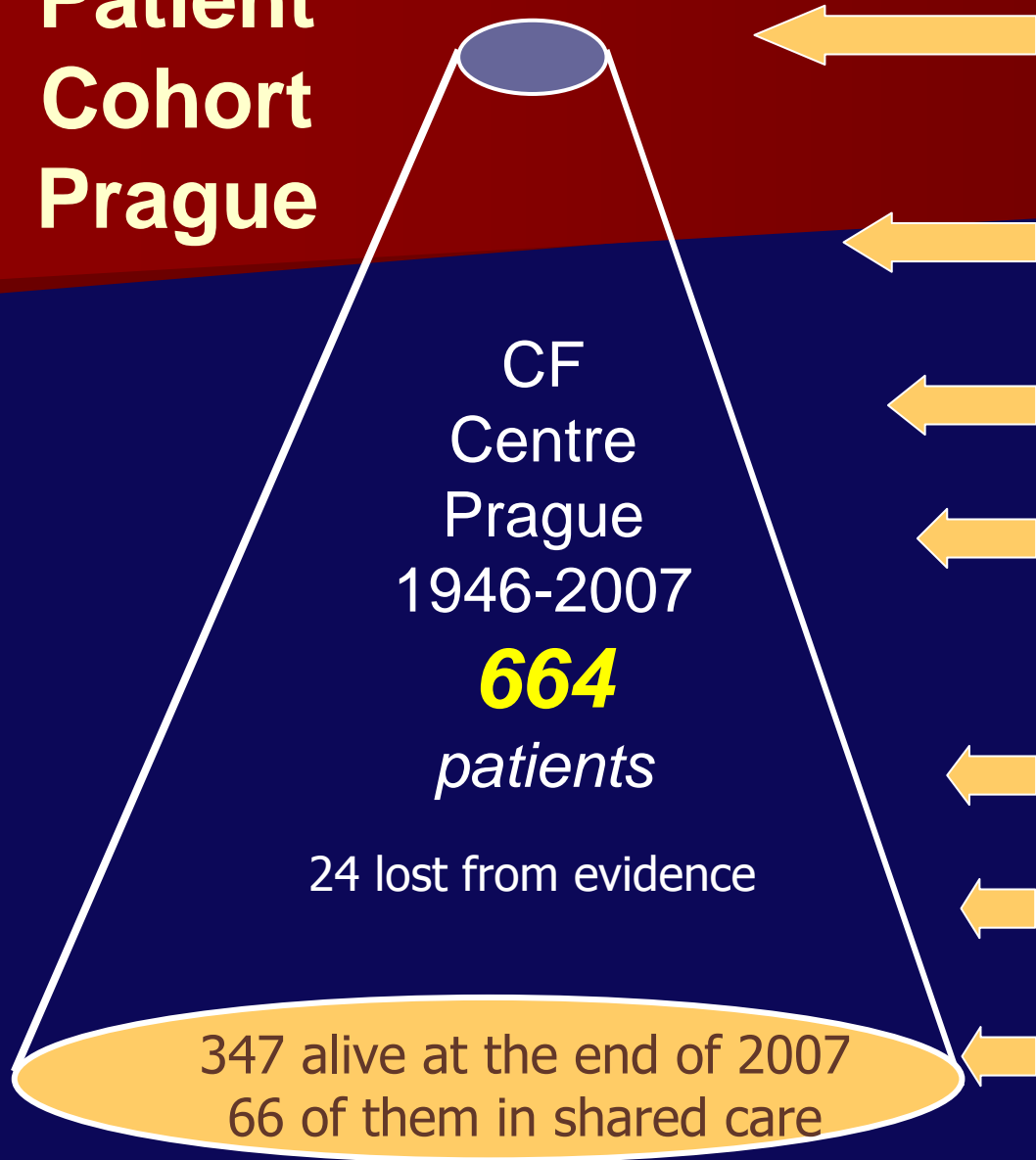
**New European Network of Genetic Nurses and Counsellors**

While there are a growing number of non-medical genetic practitioners in clinical practice in Europe, there has not been an organization established to the needs of these professionals.

[www.eurogentest.org](http://www.eurogentest.org)



# Patient Cohort Prague



CF  
Centre  
Prague  
1946-2007

**664**

*patients*

24 lost from evidence

347 alive at the end of 2007  
66 of them in shared care

1946 – 1959

**26** infants diagnosed

1960: **Sweat testing**

1978: **i.v. ATB** treatment

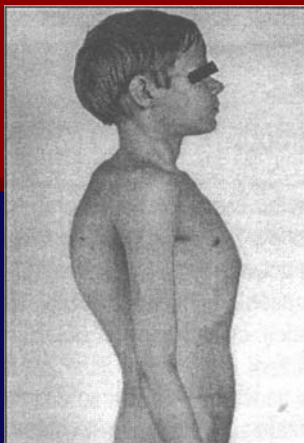
1989: **CFTR** gene ->  
DNA diagnostics

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

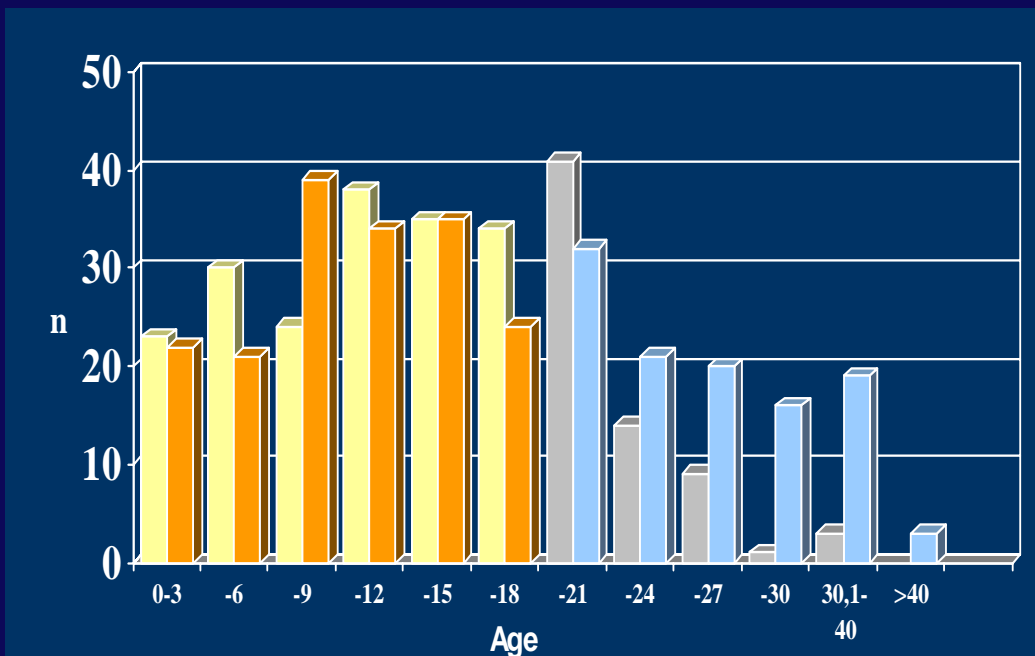


Libor Fila

**1998 vs 2007**

**Children**  
**183 vs 184**

**Adults**  
**68 vs.93**

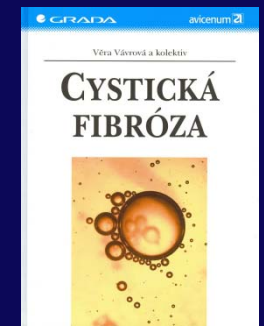


**Kateřina Austová**  
(Pediatric nurse)

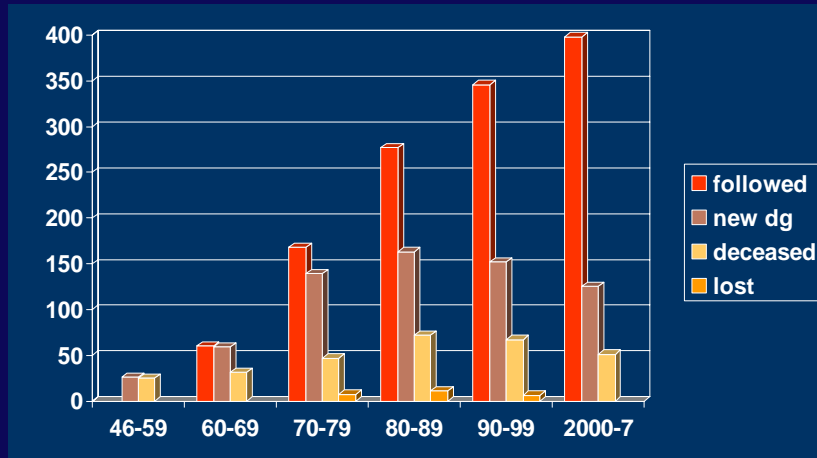


**Božena Mottlová**  
(Adult nurse)

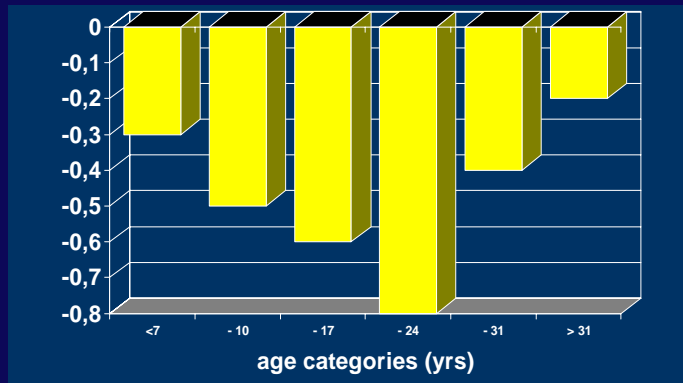
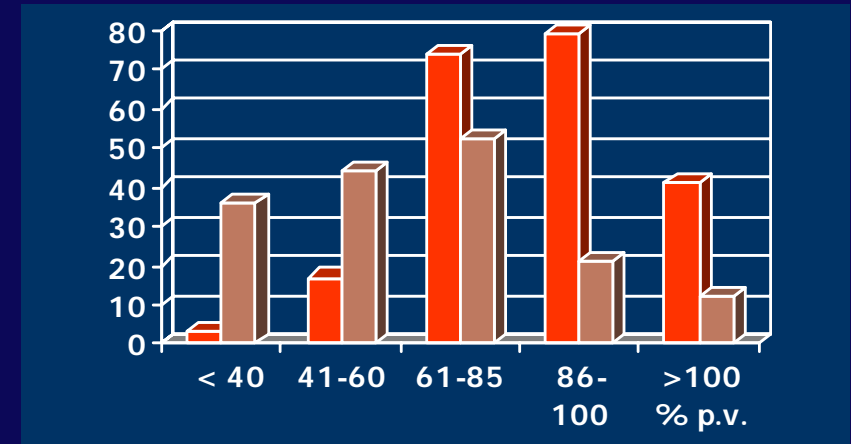
# Results of implementation of modern treatment schemes after 1990



Number of newly diagnosed patients and their survival steadily increases



Lung function (FEV<sub>1</sub>)



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

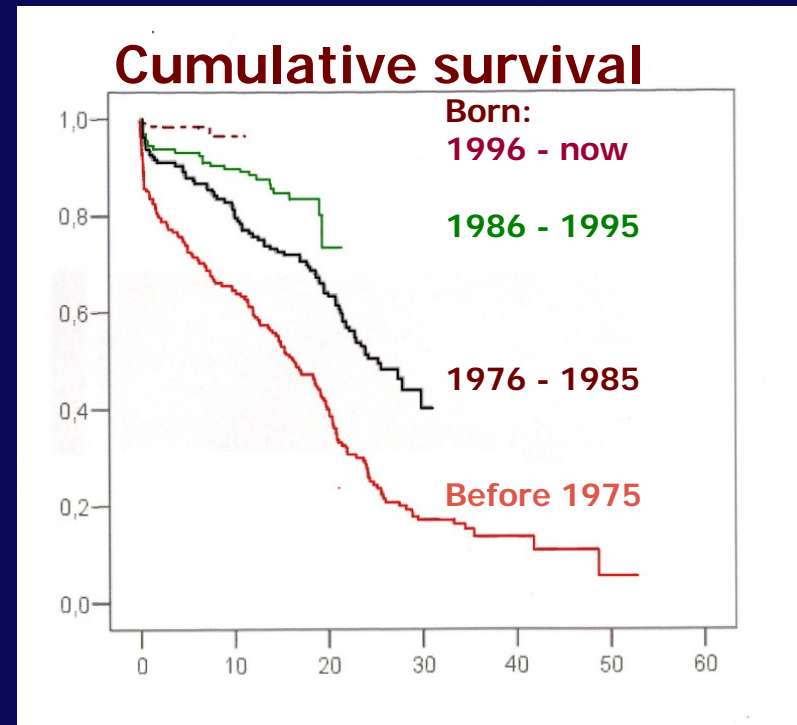
Due to political and socio-economic restrictions optimal treatment was **not accessible** to us prior to **1990**.

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"

