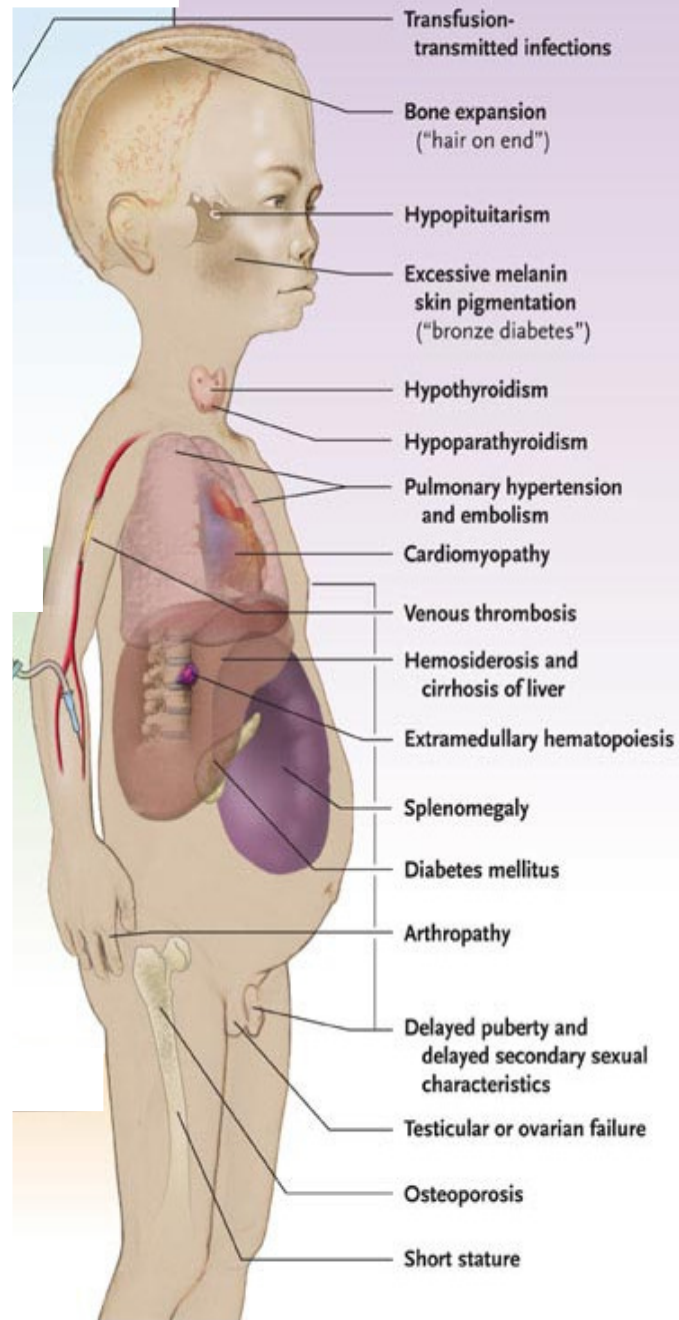


**COMPONENTS FOR SETTING UP LARGE
THALASSEMIA PREVENTION PROGRAMS**
The paradigm of Greece

Dimitris Loukopoulos
Biomedical Research Foundation, Academy of Athens

**The 12th International Conference on Thalassemia
and the Hemoglobinopathies, Antalya 2011**

Complications



Supportive therapy

Transfusion

Leukoreduction
Viral testing

Iron overload

Deferoxamine
Deferiprone
Deferasirox

Endocrinopathies

Hormone replacement

Osteoporosis

Osteoclast replacement
Vitamin D

Curative therapy

Hematopoietic stem-cell transplantation

Bone marrow
Cord blood?
Unrelated donor?
Nonmyeloablative?

Experimental therapy

Erythropoietin
Fetal hemoglobin modifiers
(hydroxyurea, butyrate)
Antioxidants

Future therapy

Gene therapy

Complications

Transfusion-transmitted infections

Bone expansion
("hair on end")

Hypopituitarism

Excessive melanin skin pigmentation
("bronze diabetes")

Hypothyroidism

Hypoparathyroidism

Pulmonary hypertension and embolism

Cardiomyopathy

Venous thrombosis

Hemosiderosis and cirrhosis of liver

Extramedullary hematopoiesis

Splenomegaly

Diabetes mellitus

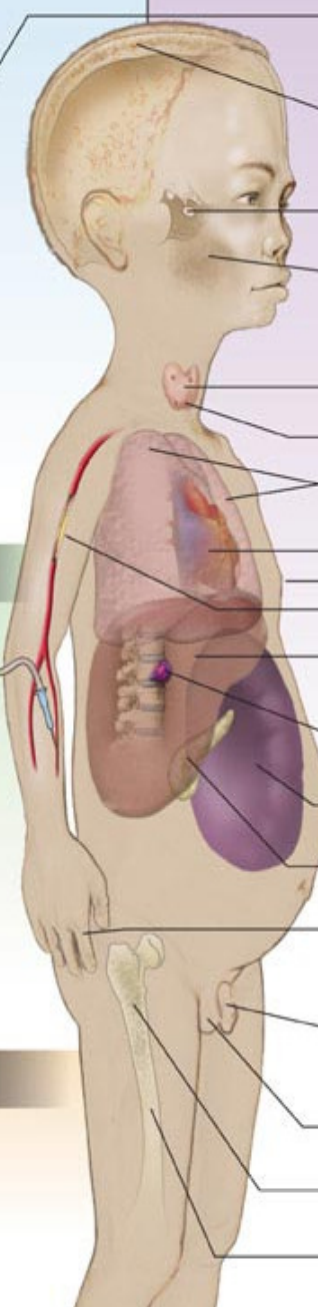
Arthropathy

Delayed puberty and delayed secondary sexual characteristics

Testicular or ovarian failure

Osteoporosis

Short stature



Category	Minimum treatment		Full treatment			
<i>Costs other than iron chelation</i>						
Day transfusion: hotel and nursing	375			375		
12 transfusions/year	1,088	(600	1,575)	2,250	(1,390	3,150)
Investigations	135	(135	435)	278	(278	870)
Occasional costs (such as operations)	150			645		
Staff salaries	300			620		
Total if no desferrioxamine therapy	2,048	(1,560	2,835)	n.a.		n.a.
Desferrioxamine therapy (iron chelation)	3,080	(1,440	4,725)	6,165	(2,880	9,450)
Total with desferrioxamine therapy	5,128	(3,000	7,560)	10,333	(6,190	15,110)

Source: [Alwan and Modell 1997](#).

Note: n.a. = not applicable. The figures in parentheses show the range of costs for a two-year-old and an adult; where no range is shown, the cost is independent of age. Both minimum and full treatment include transfusion and chelation. *Full treatment* means more frequent transfusion and consultations, more laboratory work, and more surgery.

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

- Probabilities of cure through genetic engineering are still minimal, while cure by bone marrow transplantation is feasible but not applicable at large for various reasons.
- The miserable and difficult life of the patients and their families along with the ever increasing cost make prevention of the disease absolutely necessary. Through this,
 - families at risk may have the possibility to give birth to non-thalassemic children, while
 - the Public Health System can face more effectively the ever increasing number of new patients along with the cost of therapy, which, under present conditions, cannot be less than optimal.

Prevention can be offered ● Retrospectively

● Prospectively

G U I D E L I N E S FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

- A program of prevention becomes a national priority when other causes of infant mortality are successfully controlled, and when the continuously improving care of the patients allows their long survival, i.e., increases the cost !
- Then, the National Health Authorities must be convinced to provide the necessary conditions and funds in order to cover not a few fortunate families but the entire population at risk.
- This step is of primary importance because, once such a large scale program of prevention is launched, this must proceed smoothly at all levels; gaps in the procedure are not allowed; restarting will be extremely more difficult. There are no excuses for inadequacies or errors.

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

CONVINCING THE AUTHORITIES. I

Assessment of the quality of life of the patients and of the available resources

- Census of patients
- Assessment of available and functioning hospitals and attached day care Units
- Assessment of the quality of life of the patients
Patients cannot be fully effective; often absent from school or work.
- Families are equally involved and waste lots of time (hence, lose day-pays) in order to take care or transfer the sick children to hospital etc.

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

CONVINCING THE AUTHORITIES. II

Financial aspects

- Assessment of the frequency of heterozygotes; evaluation of expected yearly births of thalassemic patients
- Evaluation of present cost and Projection of cost in the years to come
- Analysis of the cost of a large scale prevention scheme and projection of the benefit vs. cost in the years to come **if a prevention program were implemented**

The contribution of high level Health Authorities (WHO, Unesco, ONU etc)

- Has been instrumental for the start in countries where such programs were initiated. It is of utmost value for countries where such programs must be initiated. **Publications, Decisions, recommendations, pressure to local governments**

*The WHO committee for inherited hemoglobin disorders.
Drs. Anver **Kuliev**, Bernadette **Modell**, Antonio **Cao** and others*

THALASSEMIA AND THE SICKLE CELL SYNDROMES IN GREECE

Population (approximately) 10.000.000

Mean frequency of carriers

β -thalassemia 7.0%

Hemoglobin S 1.0%

Distribution of both traits extremely heterogeneous

Annual Number of births (approximately) 100,000

Expected number of new cases

β -thalassemia 110-120

sickle cell syndromes 20

Patients surviving to-date approximately 4.000

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

SENSITIZATION, INFORMATION AND EDUCATION OF THE POPULATION AT RISK

- The role of the Authorities
- The role of the Associations of parents and patients
- The role of Mass Media
- The role of the Church
- The role of the School
- In immigrant groups of ethnic minorities : The role of social workers talking the national language

Sensitization was broader in the past because patients with marked bone deformities were difficult to miss in public life and their problems were more known to the Society. AT THIS TIME, sensitization is weak because of improved treatment and decrease of the number of new patients.

Therefore, more efforts are necessary

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

SENSITIZATION, INFORMATION AND EDUCATION OF THE POPULATION AT RISK

The Associations of parents and patients

May also exert a significant influence on the policy makers the main supporting argument being that effective prevention of the birth of new patients, will allow use of the available resources towards improving management of their own surviving children

... ήρθε η στιγμή
ν' αποκτήσετε παιδί!

**εξετασθήκατε για
Μεσογειακή αναιμία;**



Κάντε δοκιμασία
στην ειδική εξέταση αίματος
**ΜΟΝΑΔΙΚΗ ΠΡΟΑΓΩΓΗΣ
ΜΕΘΟΔΙΑΚΗΣ ΑΝΑΙΜΙΑΣ**

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ & ΠΡΟΝΟΙΑΣ

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ ΚΑΙ ΠΡΟΦΥΛΑΞΗΣ
ΚΕΝΤΡΟ ΜΕΣΟΓΕΙΑΚΗΣ ΑΝΑΙΜΙΑΣ

Μεσογειακή αναιμία Δρεπανοκυτταρική αναιμία



ΟΡΓΑΝΙΣΜΟΣ ΣΥΛΛΟΓΩΝ ΣΥΛΛΕΓΙΜΩΝ ΟΙΚΟΓΕΝΕΩΝ
Αθηνών



ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ ΚΑΙ ΠΡΟΦΥΛΑΞΗΣ
ΚΕΝΤΡΟ ΜΕΣΟΓΕΙΑΚΗΣ ΑΝΑΙΜΙΑΣ
Αθήνα, 1997

Το Κέντρο Μεσογειακής Αναιμίας και Δρεπανοκυτταρικής Αναιμίας (Κ.Μ.Α.Α.) είναι ένα από τα τμήματα του Κέντρου Μεσογειακής Αναιμίας και Δρεπανοκυτταρικής Αναιμίας (Κ.Μ.Α.Α.) του Υπουργείου Υγείας και Πρόφυλαξης. Το Κ.Μ.Α.Α. είναι ένα από τα τμήματα του Κέντρου Μεσογειακής Αναιμίας και Δρεπανοκυτταρικής Αναιμίας (Κ.Μ.Α.Α.) του Υπουργείου Υγείας και Πρόφυλαξης. Το Κ.Μ.Α.Α. είναι ένα από τα τμήματα του Κέντρου Μεσογειακής Αναιμίας και Δρεπανοκυτταρικής Αναιμίας (Κ.Μ.Α.Α.) του Υπουργείου Υγείας και Πρόφυλαξης.

ΥΠΟΥΡΓΕΙΟ ΥΓΕΙΑΣ ΚΑΙ ΠΡΟΦΥΛΑΞΗΣ
ΚΕΝΤΡΟ ΜΕΣΟΓΕΙΑΚΗΣ ΑΝΑΙΜΙΑΣ
ΜΟΝΑΔΑ ΠΡΟΦΥΛΑΞΗΣ ΜΕΣΟΓΕΙΑΚΗΣ ΑΝΑΙΜΙΑΣ
Αθήνα

για τους γονείς
τους μελλοντικούς
τους νέους



αποφύγετε
τη γέννηση παιδιών
με
Μεσογειακή Αναιμία

FORMAL POSITION OF THE CHURCH AND THE LAW TOWARDS PREVENTION OF INHERITABLE DISEASE

An important but delicate matter.

The information below is not a recommendation.

Religion/Authorities	Attitude towards Prevention	Attitude towards Prenatal Diagnosis
Christian Orthodox.		
The Church	favorable* in the sense that this may avoid children or change partner	negative, but does not interfere
The Law	favorable;* cannot impose it	allowed before 24 th week
Christian Catholic		
The Church	favorable*	negative, but does not interfere
The Law	favorable* cannot impose it	allowed before 24 th week
Islam		
The Church and the Law	favorable*	fully negative in past years
The Law		now accepted in some countries, ignored or prohibited in others

* then, birth control?

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

CARRIER IDENTIFICATION

- **Select optimal methodology;**
- **Consider cost;** in areas with relatively low incidence (2-3%) consider initial screening by simple methods locally and sending "suspect" samples to centralized laboratories for confirmation.
 - MCH and MCV have an acceptable diagnostic power
 - the one tube osmotic fragility testing (an pre-prepared ampule containing a 0.45% NaCl solution can identify suspect carriers in large areas with low frequency of heterozygotes.
 - Sickling or solubility tests for HbS detection.
 - Complete blood counts plus Fe/ferritin determinations may offer additional useful information.
 - Confirmation with hemoglobin electrophoresis or high pressure liquid chromatography.
- **Avoid purchasing sophisticated apparatuses;** when they break down or lack some basic reagents, it will be difficult to bring back the people reported during the inactive days. Besides, the various additional parameters they offer are meaningless for carrier identification.

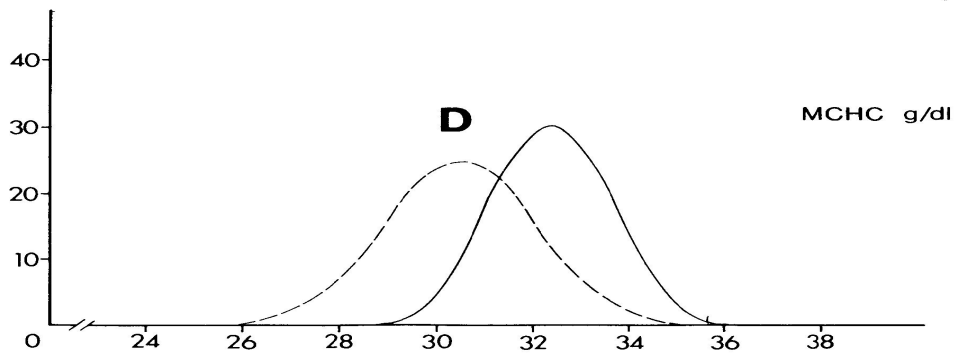
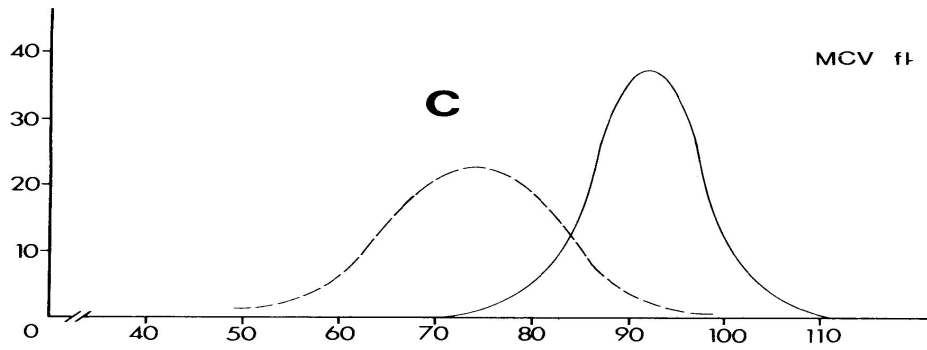
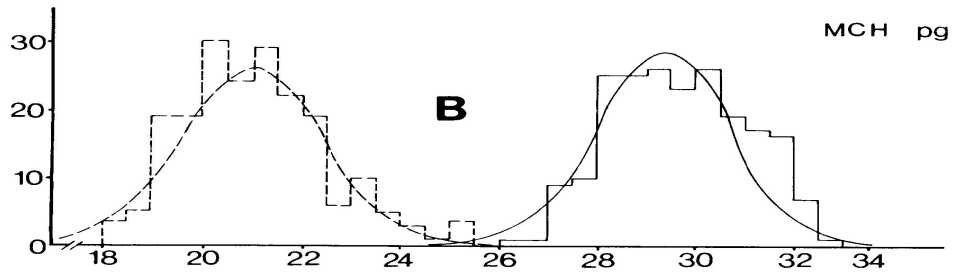
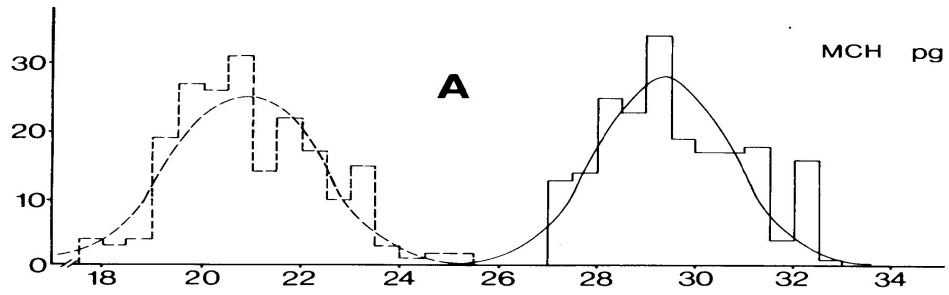


Table 1
HEMATOLOGIC AND BIOCHEMICAL VALUES IN THE GREEK POPULATION

		Young adults with no evidence of thalassemia (Normal controls)		Young adults with heterozygous β-thalassemia	
		Males	Females	Males	Females
		200	200	111	159
Number of persons examined					
Hemoglobin	g/dℓ	15.40 ± 1.00	13.30 ± 0.7	13.30 ± 0.80	11.30 ± 1.10
Hematocrit	ℓ/ℓ	0.474 ± 0.032	0.412 ± 0.022	0.442 ± 0.037	0.375 ± 0.038
Red cell count	× 10 ¹² /ℓ	5.17 ± 0.39	4.49 ± 0.32	6.03 ± 0.40	5.23 ± 0.63
MCH	pg	29.90 ± 2.60	29.80 ± 1.20	22.40 ± 1.70	22.00 ± 2.78
MCV	fL	92.10 ± 5.10	92.10 ± 5.20	73.70 ± 8.50	72.70 ± 8.60
MCHC	%	32.40 ± 1.26	32.20 ± 1.26	30.50 ± 1.50	30.10 ± 1.50
HbA ₂	%	2.50 ± 0.50		5.00 ± 0.95	4.98 ± 0.95

Note: Mean values ± standard deviation.

HPLC Chromatograms

A

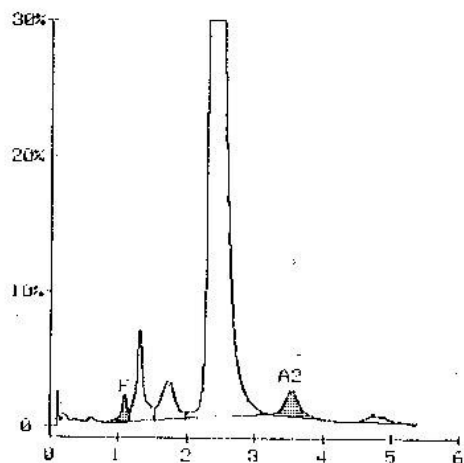
*****Beta Thal Short*****
 DATE:08/15/95 TIME:17:28:54

TECH ID# 2
 VIAL# 11 SAMPLE ID# 000000010

ANALYTE ID	%	TIME	AREA
F	1.2	1.09	22966
P2	5.0	1.30	98779
P3	4.1	1.73	81235
Ao	85.8	2.37	1708029
A2	2.9	3.53	57396
S-WINDOW	1.2	4.73	22962

TOTAL AREA 1991367

F 1.2% A2 2.9%



S

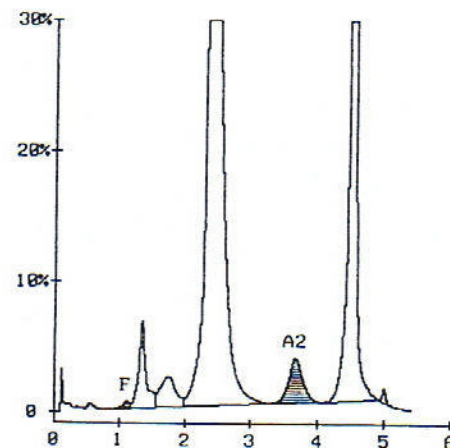
***** Beta Thal Short *****
 DATE:96/05/18 TIME:17:38:03

TECH ID# 0
 VIAL# 3C
 SAMPLE ID# 000000000000000000

ANALYTE ID	%	TIME	AREA
F	0.3	1.10	9530
P2	3.7	1.33	106286
P3	2.9	1.74	83002
Ao	57.4	2.35	1663792
A2	4.3	3.65	99173
S-WINDOW	31.4	4.50	910051

TOTAL AREA 2071034

F 0.3% A2 4.3%



GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

CARRIER IDENTIFICATION

- Establish local (national) normal values
- Offer carrier identification on free hours and free of charge
- Reply consistently to persons reporting for the tests.
Explain thoroughly and patiently !

GENETIC COUNCELLING

- Invite and advise in person carriers whose partner is also a carrier
- Avoid forcing couples at risk to decide. Instead, provide ample information.
- Explain thoroughly the possibilities and limitations of prenatal diagnosis

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

PRENATAL DIAGNOSIS

- Legal and Ethical Aspects
- Financial aspects; what can/must the insurance of patients cover
 - who pays for the test?
 - who pays if the test is not carried out ?
 - who pays if a misdiagnosis occurs?
- Follow-up and Psychologic support of mothers, especially in case of bad results
 - Fear
 - Feelings of being guilty, taking too much responsibility
 - Influence of family
 - Feelings of being guilty towards surviving affected child
- Technical aspects.
 - Competence of the obstetricians; safety.
 - Competence of the laboratory; identify "reference" laboratories

GUIDELINES FOR THE CONTROL OF THALASSEMIA AND SICKLE CELL DISEASE IN AREAS WITH HIGH FREQUENCY

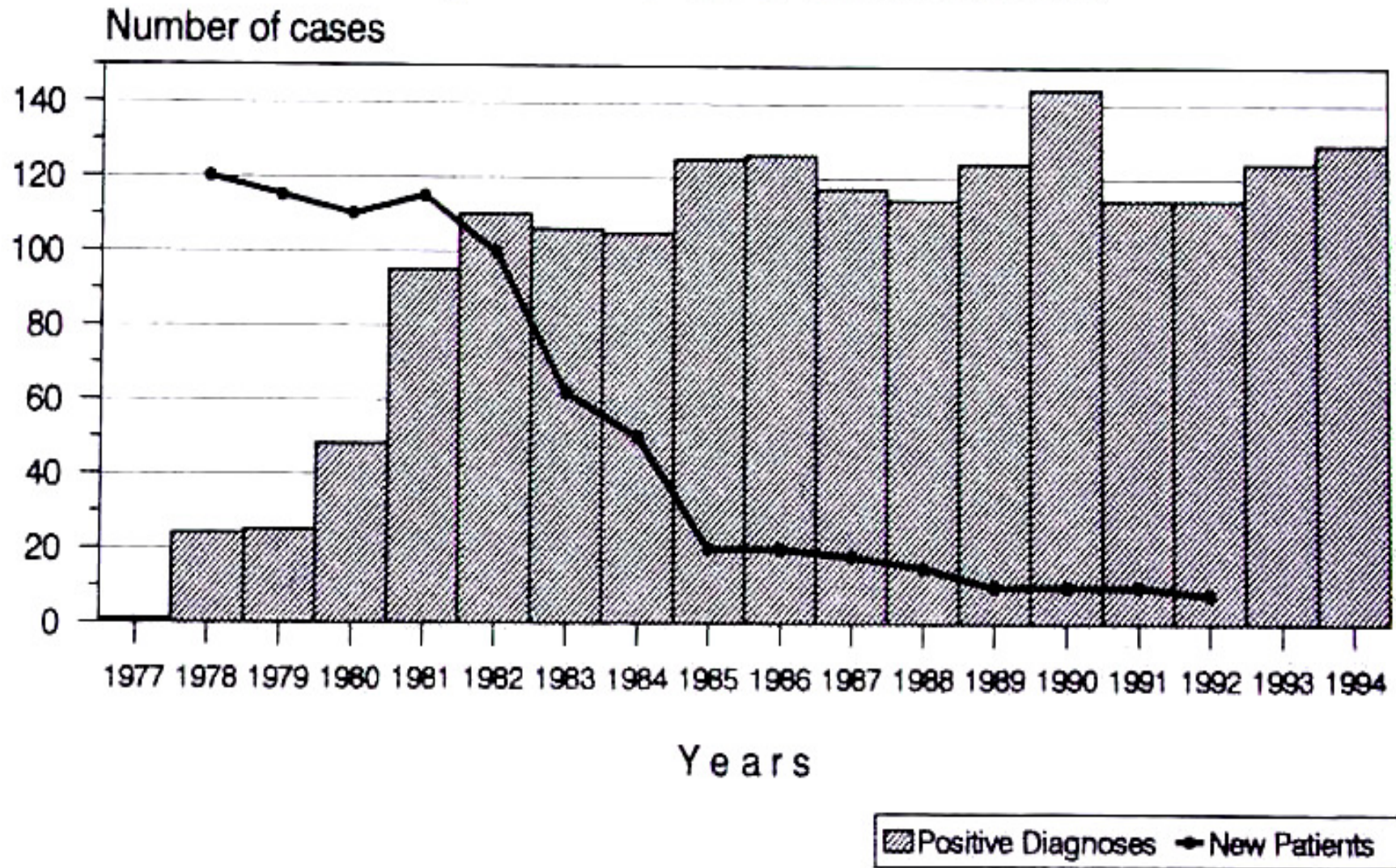
MONITORING; QUALITY CONTROL

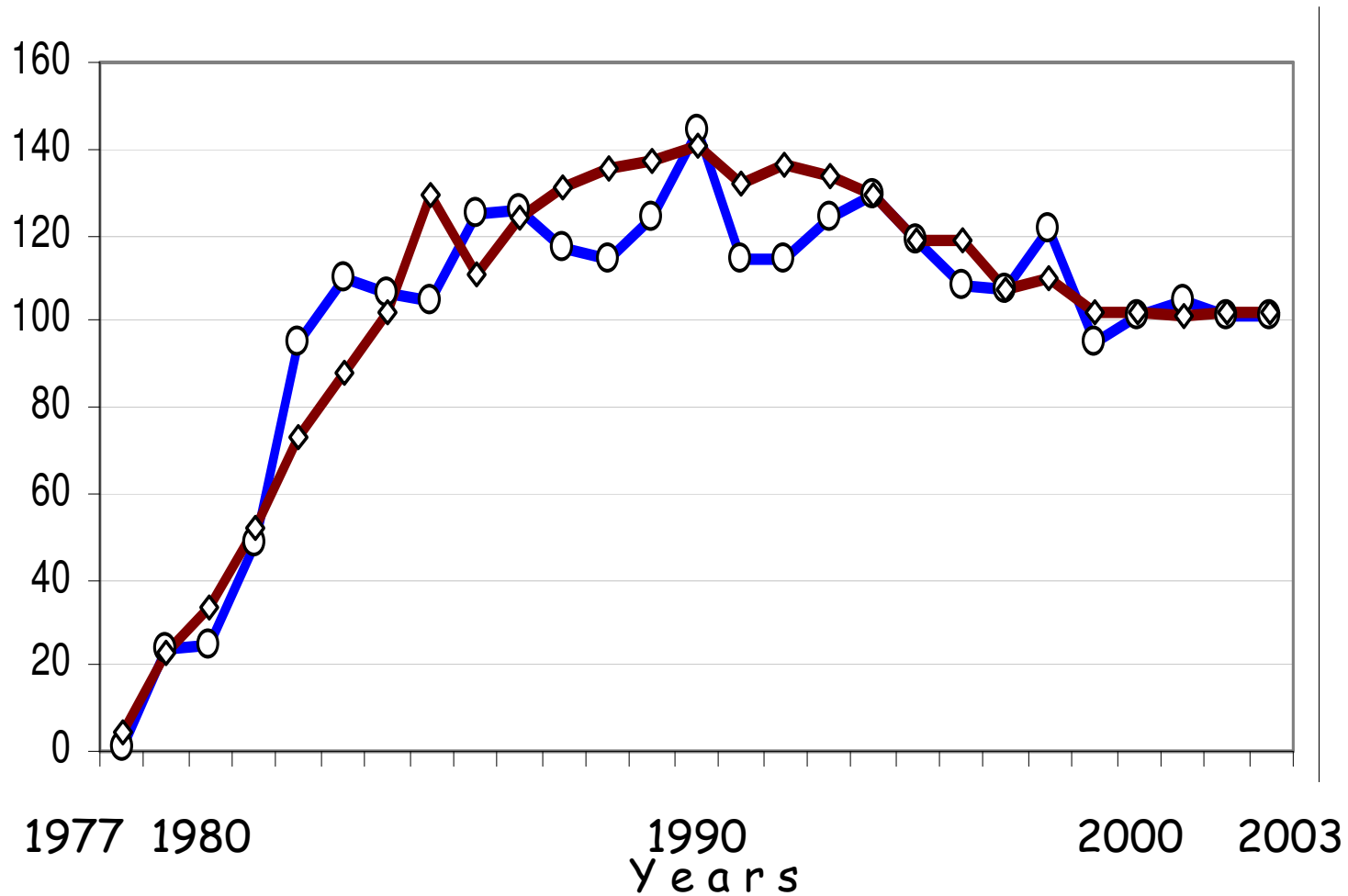
- Mandatory reporting of all new cases reporting to hospitals for vasoocclusive crises or in need for transfusion
- Internal control of techniques
- “External” quality control; private laboratories;
academic laboratories
- Frequent re-evaluation of cost; staff
automation
novel techniques

NO MISTAKES ALLOWED !

The importance of monitoring

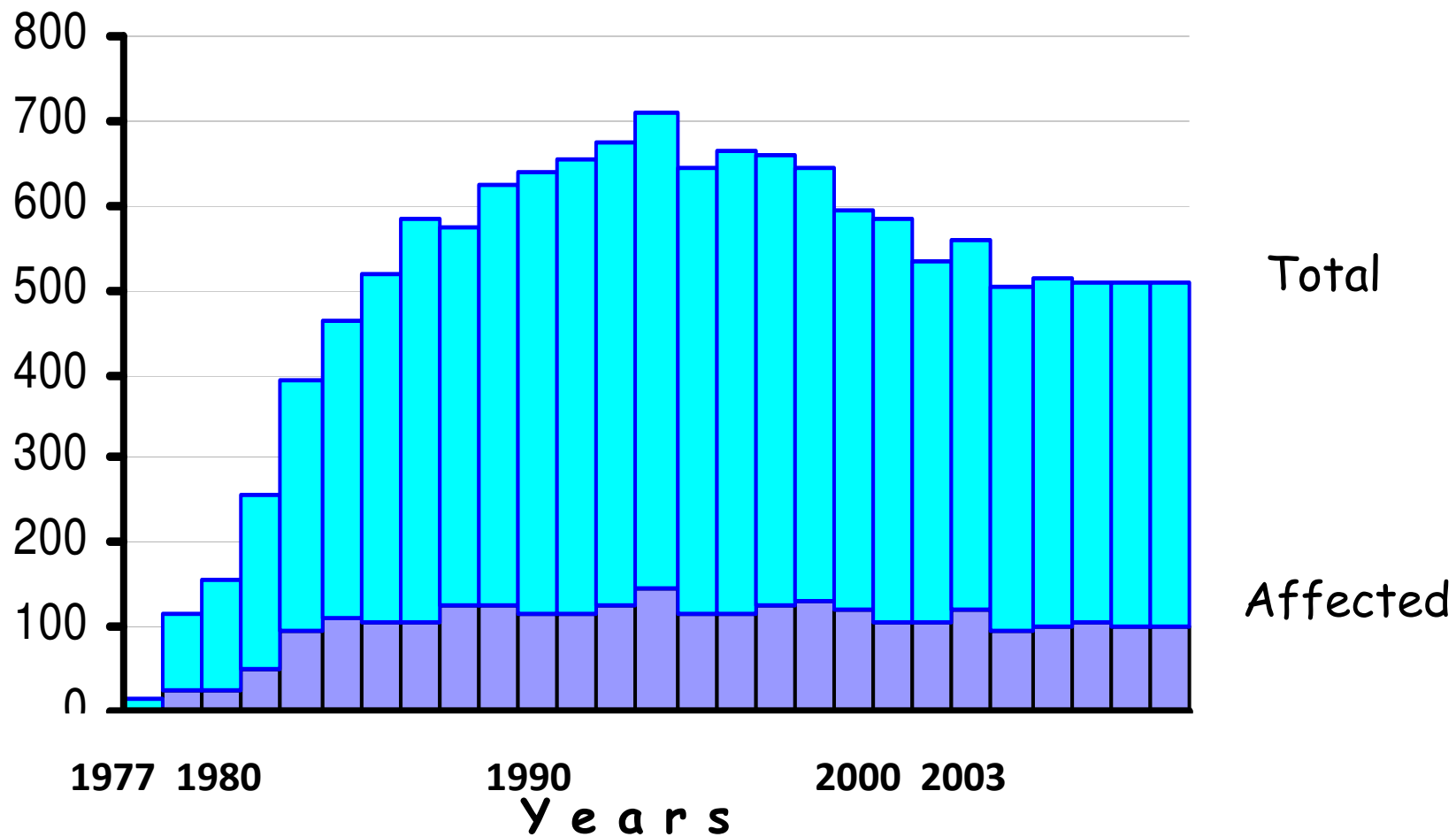
B. Impact on birthrate of affected children





Comparison between expected and diagnosed thalassemia cases

(Loutradi, 2003)



Activity of the Athens Center from 1977 to 2003

Decrease due to other (University and Private Institutions coming into play) and to general decrease of birth rate in Greece.

Comparison of positive versus expected diagnoses does not disclose any significant deviations.

(Loutradi, 2003)

Reported Births of newborns with thalassemia over the years 1990-2010

Approximately 200 new patients

- Personal reasons
- Lack of information; **Immigrant workers**. **Gypsies**. **Greeks**
- Negligence

- Errors in *in vitro* fertilization; missed diagnosis of donor or recipient !!!
- Error in pre-implantation technology

- Missed diagnosis of mother
Missed diagnosis (private laboratory)

Conclusion :

- **Prevention of thalassemia and HbS** now running on a regular basis in almost all Mediterranean countries, in most cases coupled with prenatal diagnosis. Over the years these programs have allowed birth of several thousands of non-thalassemic children to many couples at risk.
- **For the time being**, the only realistic solution to face the problem of thalassemia and sickle cell disease in countries with high incidence.
- **The future** : Pre-implantation diagnosis is a possibility and can give excellent results; however, it is not yet applicable at large because of prohibitive complexity and cost