

Newborn Thyroid Screening Development and History

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Features of Sporadic Congenital Hypothyroidism – Pre-screening

- ❑ Prevalence 1 in 5,000 to 1 in 10,000 births
- ❑ Delayed diagnosis – 3-6 months in most infants
- ❑ Retarded growth
- ❑ Delayed bone maturation
- ❑ Progressive reduction in IQ
- ❑ Neurologic dysfunction
- ❑ Metabolic dysfunction

Characterization of Fetal-Perinatal Thyroid Function

1950s – 1960's

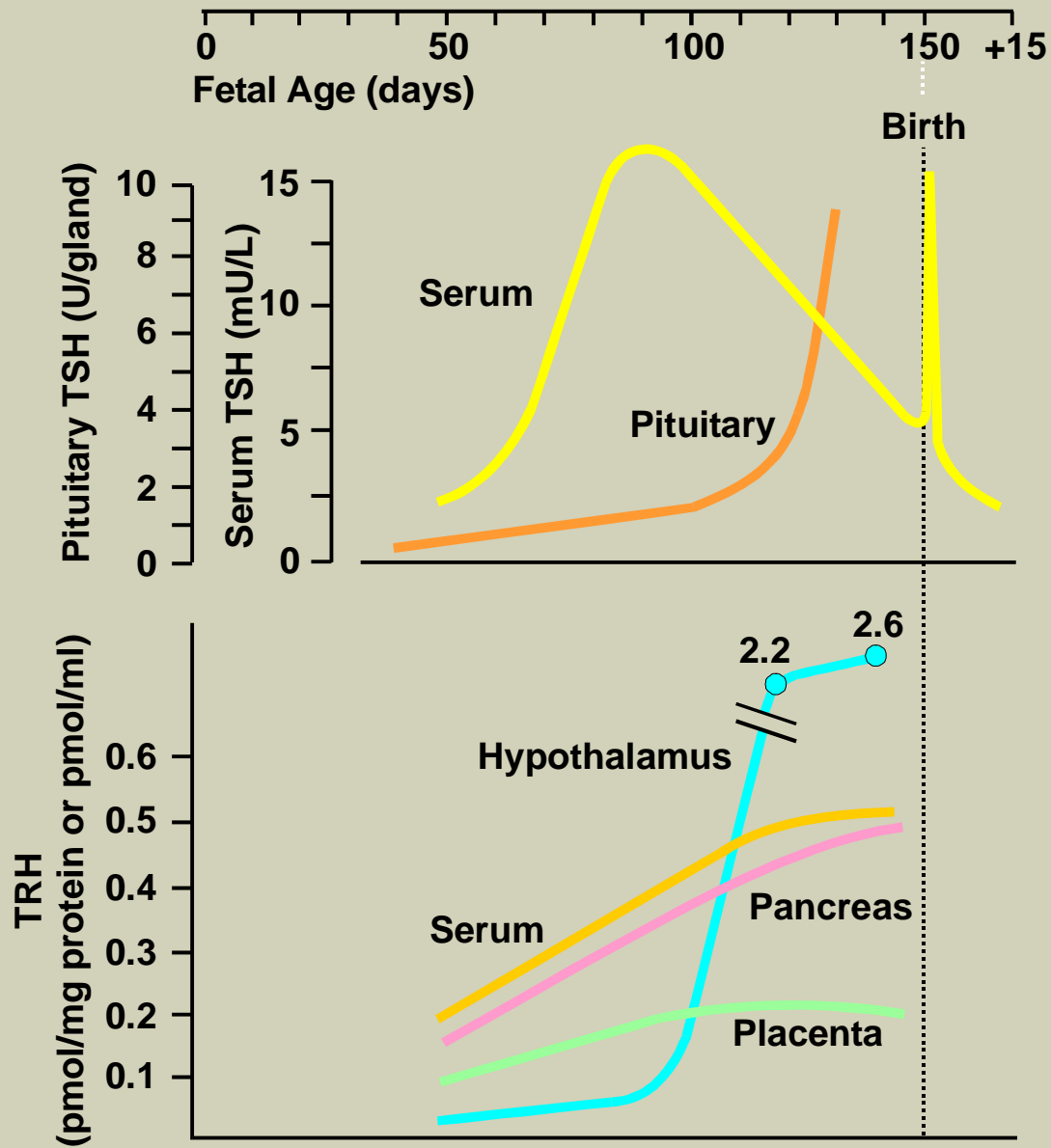
- ❑ Limited maternal to fetal T4 transfer
- ❑ Neonatal hyperthyroid state
 - High newborn thyroid RAI uptake
 - High PBI, BEI levels
 - Duration 2-4 weeks

Late 1960's - 1970's (Harbor-UCLA Medical Center, Torrance, CA)

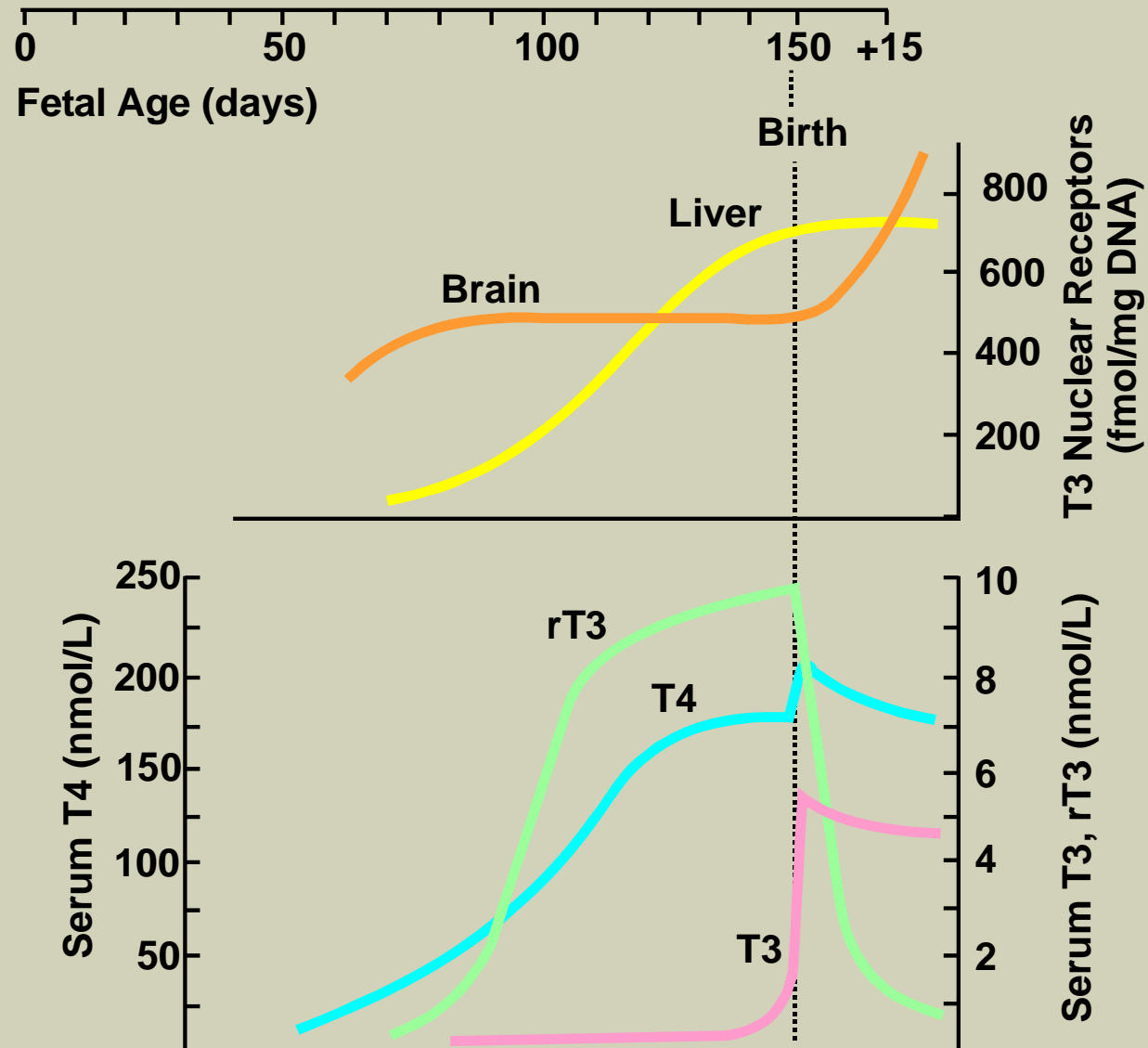
(Drs. Delbert Fisher, Calvin Hobel, Thomas Oddie, Jean Dussault, Inder Chopra, Allen Erenberg, Jossi Sack)

- ❑ Development of RIA Systems for T4, T3, rT3, TRH, human and ovine TSH
- ❑ Development of Sheep Model for Study of Fetal Thyroid System Ontogenesis
- ❑ Characterization of Human Perinatal Thyroid Function

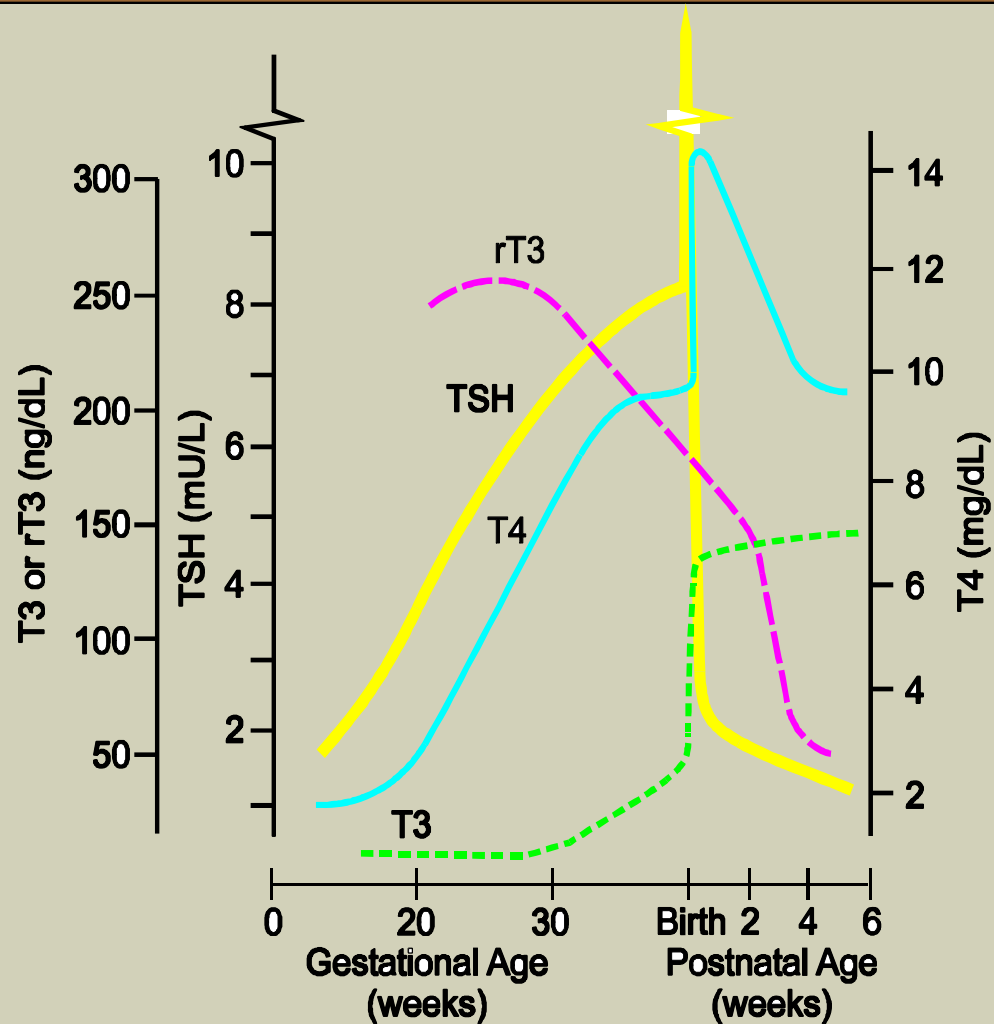
Ovine Fetal-Perinatal Thyroid Physiology



Ovine Fetal-Perinatal Thyroid Physiology



Human Perinatal Thyroid Physiology



Characterization of Fetal-Perinatal Thyroid Function in Early 1970s

- ❑ Limited M-F placental thyroid hormone transfer
- ❑ Maturation of HPT function between 20-40 weeks gestation
- ❑ Low T3, high rT3 production in the fetus
- ❑ Neonatal TSH surge in response to extrauterine cooling
- ❑ Transient neonatal hyperthyroid state
- ❑ Transition to high T3, low rT3 postnatal state during neonatal period

Possible Newborn Screening Options

- ❑ Cord blood testing T4, TSH or both
- ❑ Measurement of peak T4 at 2-3 days
- ❑ Measurement of TSH at 3-7 days
- ❑ Measurement of TSH, T4 or both at 3-7 days
- ❑ Measurement of rT3 at 3-7 days

Early History of Newborn Screening

- 1970's
 - PKU screening expanded to Europe, South America, Japan, Australia
- 1973
 - 43 US states mandated PKU screening

Newborn Thyroid Screening (1971-1974)

- ❑ Dr. Dussault adapted T4 RIA to filter paper blood spot specimens
- ❑ Pilot screening for CH using established Quebec PKU screening program.
- ❑ Measured T4 in heel stick samples at 3-5 days
- ❑ Detected 7 CH infants among 47,000 infants screened (1 in 6,714 births)*
- ❑ Instituted early oral T4 therapy

**Dussault et al, J Pediatr 86:670, 1975*

Kroc Foundation Symposium (44 participants)

Perinatal Thyroid Physiology and Disease*

*(Delbert A. Fisher, Gerard N. Burrow - Editors)
Raven Press, NY, 1975*

- ❑ Maternal Fetal Thyroid Physiology
- ❑ Effects of Thyroid Hormones on Development
- ❑ Thyroid disease in Pregnancy and the Newborn
- ❑ Newborn Screening for Hypothyroidism

**Funded by Kroc Foundation and National Foundation –
March of Dimes*

Kroc Foundation Symposium, 1975

Newborn Screening Topics

- ❑ Possible Approaches to Screening (Fisher, Sack)
- ❑ Quebec Experience (Dussault)
- ❑ Improved Filter paper T4 Method (Larsen, Broskin)
- ❑ Toronto – Comparison of Cord Blood and Filter Paper T4 Approaches (Walfish)
- ❑ Comparison of Cord Blood TSH plus T4, and Cord blood TSH Approaches (Walfish)
- ❑ Cord Blood TSH Screening (Foley et al)

ATA Newborn Thyroid Screening Committee

Established 1974

DA Fisher - Chair

*GN Burrow, JH Dussault, DR Hollingsworth,
PR Larsen, EB Man, PG Walfish*

3 pilot programs monitored through 1975

ATA Screening Committee (Pilot Screening Programs)

Quebec – filter paper T4 with < -2 SD recall
n = 100,000; 15 CH detected

Pittsburgh – cord serum TSH with >60 mU/L recall
n = 15,000; 4 CH detected

Toronto – cord serum T4, $<10\%$ to TSH assay
n = 6,000; 2 CH detected (cord serum)

21 CH infants detected for 121,000 infants screened
CH prevalence 1 in 5,760 births

ATA Screening Committee Recommendations

- ❑ Establish and expand preliminary screening programs
- ❑ Combine CH screening with existing newborn Genetic screening programs
- ❑ Further develop of TSH measurement for filter paper samples
- ❑ Consider rT3 measurement

**Fisher et al, J Pediatrics 89:692, 1976*



1976

- Highly sensitive TSH RIA developed for newborn CH screening (Grajwer LA, Lam RW, Bruce VA, Parlow AF, Fisher DA, Clin Res 24:192A, 1976)

Development of CH Screening Programs (1976-1977)

- ❑ United States
 - Northeast Regional – MA, CT, ME, NH, RI
 - Northwest Regional – OR, AK, ID, MT, NE
 - Pittsburgh
 - Toronto
- ❑ Europe – 12 countries
- ❑ Australia
- ❑ New Zealand
- ❑ Japan
- ❑ Israel



Screening for CH: Results of Screening One Million North American Infants

*Fisher DA, Dussault JH, Foley TP Jr., Klein AH,
La Franchi S, Larsen PR, Mitchell ML,
Murphy WM, Walfish PG*

J Pediatrics 94:700-705, 1979

Screening for CH: Results of Screening One Million North American Infants

Program	Method	Recall Rate
Quebec	FPT4 + TSH	1.1%
New England Regional	FPT4 + TSH	0.40%
Oregon Regional	FPT4 + TSH	0.30%
Pittsburgh	Cord TSH (moved to FPTSH)	0.17%
Toronto	Cord T4 + TSH	0.15%

Screening for CH: Results of Screening One Million North American Infants

1,046,362 infants screened

284 CH infants detected*

Prevalence 1 in 3,684 births

■ Diagnoses

■ Primary CH	246	1 in 4,254 births
■ Central CH	10	1 in 68,200 births
■ Transient CH	28	1 in 37,370 births
■ TBG deficiency	12	1 in 8,913 births

- Only 8 infants suspected clinically before screening results reported.

**Including 7 cases missed in screening programs*

Screening for CH: Results of Screening One Million North American Infants

- ❑ 127 infants with primary hypothyroidism adequately studied
 - 63% aplastic or hypoplastic glands
 - 23% ectopic thyroid tissue
 - 14% normal or enlarged glands
- ❑ Average time to treatment in the 5 programs
 - Quebec 25 days
 - Oregon 38 days
 - New England 23 days
 - Pittsburgh 18 days
 - Toronto 22 days

Organizing Committee, Intl. Conf. on Newborn Thyroid Screening (1977)

□ Members

■ North America

- G. Burrow, J. Dussault, D. Fisher

■ Europe

- F. DeLange, G. Morreale de Escobar

■ Japan

- M. Irie, H. Naruse

■ Australia

- JF Connelly

First Intl. Conf. on Neonatal Thyroid Screening (Quebec, Canada - 1979)*

105 thyroidologists, pediatricians, internists, geneticists, and government health officials from 16 countries

Reviewed

- ❑ Background physiology
- ❑ Screening experience to date
- ❑ Optimal methods and recall procedures
- ❑ Diagnosis and management
- ❑ Recommendations

**Burrow GN, Dussault JH; Newborn Thyroid Screening, Raven Press, NY, 1980, pp 1-322*

Progress Report on Neonatal Screening for CH in Europe (1979)*

Newborn Committee of the ETA

*(F Delange, C Beckers, R Hofer, MP Konig,
F Monaco, S Varone)*

Survey covering 1,276,307 infants
50 centers in 15 countries

**In Burrow GN, Dussault JH. Neonatal Thyroid Screening,
Raven Press, NY, 1980, pp 107-131*

European Progress Report 1979*

Method	No. Centers	Recall Rate (%)
TSH alone	22	0.03-0.85
T4 + TSH (all)	15	0.03-5.0
T4 + TSH (suppl)	6	0.07-2.8
T4 alone	5	1.4-5.2
TSH or T4 + rT3	2	0.26-3.6

**National programs in Austria, Denmark, France, Israel, Luxembourg, Norway, Switzerland*

European Progress Report (1979)

- ❑ 1,276,307 infants screened
- ❑ 321 CH infants detected (permanent)
 - Prevalence 1 in 3,976 births
- ❑ 135 transient CH detected
 - Prevalence 1 in 9,454 births

Second International Conference on Neonatal Thyroid Screening

Tokyo, Japan 1982*

400 participants from 35 countries

Programs

Part 1: Neonatal Thyroid Screening

Part 2: Neonatal Screening for Inborn Errors of Metabolism

**Naruse H, Irie M. Neonatal screening, Excerpta Medica Intern. Congr Series 606, Amsterdam, 1983, pp 1-519*

Third Intl. Meeting, Belgium, 1988 15th Anniversary of CH Screening*

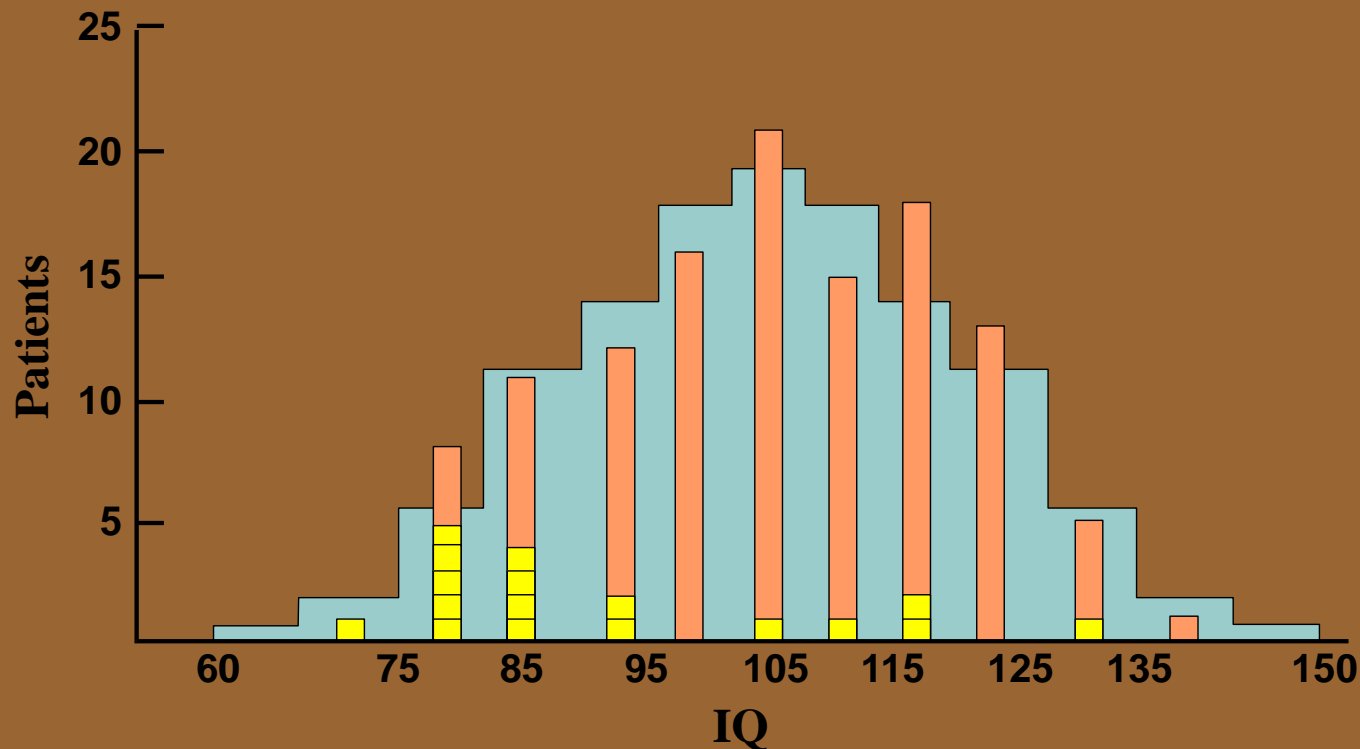
(100 participants – 25 speakers - 221 authors)

□ Program

- Physiopathology
- Etiology
- Diagnosis
- Therapy
- Neurointellectual Development

**Delange F, Fisher DA, Glinoeer D, Research in Congenital Hypothyroidism, Plenum Press, New York, 1989, pp 1-367*

Stanford Binet IQ for 118 Treated CH Patients at 3-5 Years (T4 10 µg/kg/day)*



*New England Congenital Hypothyroidism Collaborative – In Delange, Fisher, Glinooer, Eds., *Research in Congenital Hypothyroidism NATO ASI Series*, Plenum Press, NY, 1989, pp 291-297

Background normal range: yellow squares = inadequately treated (Repeated T4 < 8 µg/dL with TSH > 15 mU/L year 1; mean IQ 90)

Neuropsychological development of early treated congenital hypothyroidism: Analysis of literature data

Meta analysis, 7 publications
675 CH patients, 570 controls

- ❑ 6.3 IQ point deficit in CH patients
- ❑ Most important independent risk factor – severity of CH (bone age retardation at birth)

* *Derksen-Lubsen G, Verkerk PH. Pediatr Res 39:561.1996*

Developmental Outcome and Treatment Variables

Review of 16 Studies of T4 Treatment Variables vs. DQ or IQ 1984-2002

Variable	Range of Mean Values	DQ or IQ Association Number of Studies	
		YES	NO
Age Rx onset	13-28 days	2	9
Initial T4 dose	6 - 9.3 $\mu\text{g}/\text{kg}/\text{d}$	6	4
Inadequate Rx	1mo – 6yr	7	7

**Heyerdahl S, Oerbeck B, Thyroid 13:1029-1038,2003*

- Factors influencing mental development in CH children detected by newborn screening
 - Severity of CH
 - T4 treatment dose
 - Time of treatment onset
 - Treatment compliance
 - Social class

- Persisting CNS dysfunction
 - Disordered coordination and fine manipulation
 - Learning disabilities
 - Behavioral problems

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Summary

Dedication

Jean Dussault, 1941-2003

Francois Delange, 1935-2007