The Future Ain’t What It Used To Be*

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Oregon Health Sciences University

*Yogi Berra
“A CRETIN”
Age 4 years
Ht 25 in wt 16 lb
From:
Holt’s Textbook of Pediatrics 1896
Inverse Relationship Between Age at Clinical Diagnosis and IQ Outcome*

<table>
<thead>
<tr>
<th>Age Rx</th>
<th>IQ (mean)</th>
<th>IQ (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 mo</td>
<td>89</td>
<td>64-107</td>
</tr>
<tr>
<td>3-6 mo</td>
<td>71</td>
<td>35-96</td>
</tr>
<tr>
<td>&gt;6 mo</td>
<td>34</td>
<td>25-80</td>
</tr>
</tbody>
</table>

Newborn Screening for Congenital Hypothyroidism: A History

- **1973** - Quebec: T4 RIA on filter paper PKU specimens (Dussault, et al.)
- **1974** - Pittsburgh: Cord blood TSH screening (Foley, et al.)
- **1975** - Oregon: Filter paper T4 with TSH on infants with T4 <10% (Murphey, et al.); developed a multistate regional program
- **1975** - Screening for CH added to existing programs in NA, Europe, Japan, & Australia, NZ
- **1980-90** - under development in Latin & South America, Eastern Europe, Asia & Africa
Newborn Screening for Congenital Hypothyroidism: Current Status 4/00

• 2000 - U.S.: All 50 states screen
  – 4 million births/ year
  – 1,000 infants detected/year

• Worldwide:
  – Estimated 24 million births screened/year
  – 6,000 infants detected/year
# NW Regional Screening Program

## Congenital Hypothyroidism: 1975-2000

<table>
<thead>
<tr>
<th>State</th>
<th>Number Screened</th>
<th>Number Hypothyroid</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oregon</td>
<td>1,039,777</td>
<td>299</td>
<td>1:3478</td>
</tr>
<tr>
<td>Idaho</td>
<td>446,030</td>
<td>99</td>
<td>1:4505</td>
</tr>
<tr>
<td>Montana*</td>
<td>143,010</td>
<td>20</td>
<td>1:7150</td>
</tr>
<tr>
<td>Nevada</td>
<td>405,290</td>
<td>106</td>
<td>1:3823</td>
</tr>
<tr>
<td>Alaska</td>
<td>199,072</td>
<td>70</td>
<td>1:2484</td>
</tr>
<tr>
<td>Hawaii</td>
<td>46,000</td>
<td>14</td>
<td>1:3286</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>2,279,179</strong></td>
<td><strong>608</strong></td>
<td><strong>1:3749</strong></td>
</tr>
</tbody>
</table>

*Withdrew from NWRSP in 10/85*
Congenital Hypothyroidism: Etiologies, Sex Ratio, Ethnicity

- Thyroid dysgenesis 0.84
  - Aplasia (~1/3)
  - Ectopic gland (~2/3)
- Inborn error of T4 synthesis 0.12
- Maternal antibody-mediated CH 0.04
- Female:male = 2:1
- Ethnicity: - Caucasian 1:4,000
  - Hispanic 1:2,000
  - African-American 1:32,000
# Congenital Hypothyroidism: Etiologies and Sex Ratio

<table>
<thead>
<tr>
<th>Tc99m scan*</th>
<th>Total</th>
<th>Female</th>
<th>% female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgenesis</td>
<td>178</td>
<td>126</td>
<td>71%</td>
</tr>
<tr>
<td>– Agenesis</td>
<td>37</td>
<td>-22</td>
<td>-58%</td>
</tr>
<tr>
<td>– Ectopic</td>
<td>141</td>
<td>-104</td>
<td>-74%</td>
</tr>
<tr>
<td>Goiter</td>
<td>42</td>
<td>18</td>
<td>43%</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>totals</td>
<td>230</td>
<td>147</td>
<td>64%</td>
</tr>
</tbody>
</table>

Devos, et al. JCEM 84:2502, 1999
CH: Etiologies

Thyroid Dysgenesis

Role of transcription factors TTF-1, TTF-2, and PAX-8

[Important for thyroid morphogenesis & differentiation; transcription factors bind to promoters of Tg & TPO and regulate thyroid hormone production]

• Study of 98 subjects with CH & dysgenesis:
  PAX-8 mutations in 2: 1 ectopy (stop codon)
  1 hypoplasia (single base change)

  Macchia et al Thyroid 7(suppl 1):S-6 1997

• Study of 61 subjects: no TTF-1 mutations
  Lapi et al Thyroid 7:383, 1997

• Case report: 2 sibs with thyroid agenesis and TTF-2 mutations (+cleft lip, choanal atresia)
CH: Etiologies
Thyroid Dysgenesis
Role of TSH receptor “loss of function” gene mutations [autosomal recessive]:
8 pedigrees reported up to 1998*
Apparent athyreosis:
   Tc99m scan: no uptake
   US: hypoplastic gland in normal location
   Serum Tg normal
TSH not critical for migration; necessary for growth & function

*Gagne JCEM 83:1771, 1998
Congenital Hypothyroidism

• Is screening a success story?
• What is the psychometric outcome of CH vs. controls?
• Hypothyroxinemia in preterm infants - ? Rx
• Maternal hypothyroxinemia - ? screen for
Congenital Hypothyroidism
Psychometric Outcome

Summary of 11 studies worldwide measuring IQ in >800 CH and control infants:

• 7 found no significant IQ difference
• 4 found a significant difference, with IQ ranging from 6 to 11 points lower in CH
• Even studies that find no global IQ difference may report learning problems:*
  – Vocabulary and reading comprehension
  – Arimethic
  – Memory  

*Rovet & Ehrlich Pediatrics 105:515, 2000
Congenital Hypothyroidism
Psychometric Outcome

Potential explanations for reduced IQ:

• Effects of fetal hypothyroidism, likely in more severe cases, where early Rx does not reverse damage

• Delayed onset of postnatal Rx, or delay in correction of hypothyrooxinemia

• Inadequate Rx in the first 2-3 years of life
Influence of Timing and Thyroxine Dose on IQ in CH**

<table>
<thead>
<tr>
<th>Free T4</th>
<th>Treatment Group</th>
<th>Severe CH MDI</th>
<th>Mild CH MDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.21 ng/dl</td>
<td>Early/high*</td>
<td>124*</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Early/low</td>
<td>103</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Late/high</td>
<td>99</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>Late/low</td>
<td>97</td>
<td>100*</td>
</tr>
</tbody>
</table>

*Early = < 13 days of age; high = T4 > 9.5 mcg/kg/d; p<.005

Thyroid Function in Preterm Infants: Summary

- Qualitatively similar, quantitatively lower
- Cord T4 and free T4 correlate with gestational age and birth weight
- T4 or free T4 may even fall after birth
- T4 and free T4 rise and meet term infant levels by 3 to 6 weeks of life
Thyroid Function in Preterm Infants: T4 and Free T4 < *in utero*

- Loss of maternal T4 contribution
- Iodine deficiency (if present)
- Immaturity of HPT axis:
  - ↓ hypothalamic TRH production
  - Immature thyroid response to TSH
  - Inefficient organification of thyroglobulin
  - ↓ T4 to T3 conversion
  - ↓ TBG production
- Complications of prematurity
- Non-thyroidal illness
Primary Hypothyroidism in Preterm Infants by Birthweight*

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Incidence</th>
<th>% Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2500 gm</td>
<td>1:3051</td>
<td>4%</td>
</tr>
<tr>
<td>1501-2499 gm</td>
<td>1:589</td>
<td>44%</td>
</tr>
<tr>
<td>&lt;1500 gm</td>
<td>1:153</td>
<td>91%</td>
</tr>
</tbody>
</table>

*Mandel, et al. Thyroid 7:S106, 1997*
Screening Preterm Infants for CH: Possible Changes in Screening Strategy

“Infants < 1500 gm should undergo repeat screening tests with measurement of T4 and TSH at 2, 6, and 10 weeks of age”

Mandel, et al.
Maternal Hypothyroidism: Impact on Neurodevelopmental Outcome of Offspring

Haddow et al. study:

• Study population:
  – 62 children born to mothers whose serum TSH >98% at 17 wks gestation; tested at age 8 yrs
  – 62 mothers out of 25,216 screened = 1:407
  – 124 matched control children and mothers

Haddow et al. NEJM 341:549, 1999
Maternal Hypothyroidism: Haddow, et al. Study
Thyroid function in women during pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypothyroid Mothers</th>
<th>Control Mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>13.2 ± 0.3*</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>T4</td>
<td>7.4 ± 0.1*</td>
<td>10.6 ± 0.1</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.71 ± 0.1*</td>
<td>0.97 ± 0.07</td>
</tr>
<tr>
<td>↑TPO Ab (%)</td>
<td>77*</td>
<td>14</td>
</tr>
</tbody>
</table>

* p<.001

Haddow et al. NEJM 341:549, 1999
Maternal Hypothyroidism: Haddow, et al. Study

Psychometric testing at 7-9 years of age:

<table>
<thead>
<tr>
<th></th>
<th>Total (n=62)</th>
<th>Rx (n=14)</th>
<th>UnRx (n=48)</th>
<th>Control (n=124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>103</td>
<td>111</td>
<td>100*</td>
<td>107</td>
</tr>
<tr>
<td>13 other</td>
<td>2</td>
<td></td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

tests p<.05 v. control

- Attention
- language
- reading recognition
- Visual-motor performance
- non-dominant hand

Haddow et al. NEJM 341:549, 1999
Maternal Hypothyroidism: Pop, et al. Study

- Study population: 220 Dutch infants and mothers
- Maternal fT4 measured at 12 weeks and 32 weeks gestation
- Psychometric testing carried out at 10 months of age
- Subgrouped by maternal fT4 <5%, <10%

Pop et al. Clin Endocrinol 50:149, 1999
Maternal Hypothyroidism: Pop, et al. Study

• Study population: 11 infants born to mothers with fT4 <5% (<0.76 ng/dl) at 12 wks gestation

<table>
<thead>
<tr>
<th></th>
<th>maternal ft4 &lt;5% (n=11)</th>
<th>fT4&gt;5% (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor DI</td>
<td>86*</td>
<td>100</td>
</tr>
<tr>
<td>Mental DI</td>
<td>105</td>
<td>112</td>
</tr>
</tbody>
</table>

• No differences were seen when comparisons were made at 32 weeks

*Stat significant

Pop et al. Clin Endocrinol 50:149, 1999
Maternal Hypothyroidism: Pop, et al. Study

- Study population: 22 infants born to mothers with fT4 <10% (<0.81 ng/dl) at 12 wks gestation

  maternal ft4 <10% (n=22) fT4>10% (n=198)

  Psychomotor DI 92* 99
  Mental DI 112 114

- No differences were seen when comparisons were made at 32 weeks

*Stat significant

Pop et al. Clin Endocrinol 50:149, 1999
Maternal Hypothyroidism: Impact on Offspring Neurodevelopment

• Maternal hypothyroidism in the first trimester, prior to onset of significant fetal thyroid production, is likely a risk factor for impaired infant neurodevelopment

• The impact on IQ is less than congenital hypothyroidism

• Maternal hypothyroidism is more common (1:400) than CH (1:3,000-1:4,000)

• Screening for thyroid deficiency early in pregnancy (?before) should be studied
Screening Newborns with Hyperthyroxinemia

Pilot Screening Program in Oregon 7/97-6/98

• Enrollment criteria: screening T4 >99.5%
• 101 subjects participated/326 eligible out of 65,200 total newborns
• Serum measurement of:
  • fT4, T4
  • fT3, T3
  • TSH
## Screening for Hyperthyroxinemia

**Pilot Program Summary**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Estimated Incidence per 65,200</th>
<th># detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Graves</td>
<td>1:12,500</td>
<td>0</td>
</tr>
<tr>
<td>TSH receptor act mutation</td>
<td>?1:100,000</td>
<td>0</td>
</tr>
<tr>
<td>α subunit G protein act mutation</td>
<td>?1:100,000</td>
<td>0</td>
</tr>
<tr>
<td>THR</td>
<td>?1:100,000</td>
<td>2</td>
</tr>
<tr>
<td>TBG excess</td>
<td>1:25,000</td>
<td>10</td>
</tr>
<tr>
<td>Other BP excess</td>
<td>?1:25,000</td>
<td>5</td>
</tr>
</tbody>
</table>
### Thyroid Hormone Resistance Case Study

<table>
<thead>
<tr>
<th>Age</th>
<th>T4</th>
<th>fT4</th>
<th>T3</th>
<th>Ft3</th>
<th>TSH</th>
<th>TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 d</td>
<td>23.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 d</td>
<td>32.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 d</td>
<td>23.3</td>
<td>4.6</td>
<td>364</td>
<td>968</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>203 d</td>
<td>29.5</td>
<td>4.0</td>
<td>341</td>
<td>776</td>
<td>2.73</td>
<td>2.9</td>
</tr>
<tr>
<td>Mother</td>
<td>7.0</td>
<td>1.2</td>
<td>116</td>
<td>248</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>7.9</td>
<td>1.1</td>
<td>158</td>
<td>332</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>
LWPES Mission Statement

“To promote the acquisition and dissemination of knowledge of endocrine and metabolic disorders from conception through adolescence.”
LWPES Membership

- US and Canadian members = 743

<table>
<thead>
<tr>
<th>Category</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Academic</td>
<td>313</td>
<td>145</td>
<td>458</td>
<td>62%</td>
</tr>
<tr>
<td>- PhD only</td>
<td>7</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>- Pvt practice</td>
<td>170</td>
<td>80</td>
<td>250</td>
<td>34%</td>
</tr>
<tr>
<td>- Industry</td>
<td>13</td>
<td>8</td>
<td>21</td>
<td>3%</td>
</tr>
<tr>
<td>- NIH (gov’t)</td>
<td>8</td>
<td>6</td>
<td>14</td>
<td>2%</td>
</tr>
<tr>
<td>[emeritus]</td>
<td>48</td>
<td>9</td>
<td>57</td>
<td></td>
</tr>
</tbody>
</table>

total = 743
“Those who can, do. 
Those who can’t, teach.”

George Bernard Shaw
Pediatric Endocrine Trainees: Tracking over 3 years

<table>
<thead>
<tr>
<th></th>
<th>95-96</th>
<th>96-97</th>
<th>97-98</th>
<th>98-99</th>
<th>99-00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yr 1</td>
<td>45</td>
<td>37</td>
<td>33</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Yr 2</td>
<td>-</td>
<td>34</td>
<td>30</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Yr 3</td>
<td>-</td>
<td>-</td>
<td>33</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Totals</td>
<td>96</td>
<td>96</td>
<td>115</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pediatric Endocrinology
Job Openings

• Total per LWPES Web Site Ads = 51
  – Academic = 37
  – Private Practive = 14
Pediatric Endocrinologist: Job Description

“Pediatric endocrinology is sometimes frustrating, because you are sitting in consultation clinic and explaining to everybody why they really do not need you and what they really need is to accept what they are. It is a clinic that all the unhappy people come to. The short that want to be tall, the tall that want to be shorter, the fat that want to be thin and the thin that want to be fat.”

D. Levine279@aol.com
Dear Dr. LaFranchi,

“Heather was the first case you discovered through the newborn screening program in Oregon. I thought that you might be interested to know that Heather is now almost 24, has graduated from college, and beginning in September she will be teaching 5th through 8th grade bands in Ridgefield, Washington. She was valedictorian of her high school class and graduated summa cum laude this past June from Central Washington University.”
Dear Dr. LaFranchi,

“I want to personally thank you and your staff for my involvement with the growth hormone project all those years ago. I hope that the important work you do continues to go well, and that you are encouraged at the positive difference you make in kid’s lives.

I graduated from Seattle Pacific University in June with a bachelor of arts degree in religious studies (minor in journalism) and am currently on the staff in the internet group at Big Idea Production, a Chicago-based media company that produces the computer-animated “VeggieTales” children’s video series. I am getting married in Olympia on July 17. By the way, I am 6’1” (or so). Thank you again, and blessings to you in Christ.

Your fan, Darren
Newborn Screening: The Future (Again)

- Adding new technologies, e.g. tandem mass spectrometry
- State-enabled screening vs. private enterprises
- Resolution: “Hospitals and physicians should be permitted to choose among qualified providers of newborn screening services as they currently do for all other clinical laboratory services.” [ALEC]
- Application of microchip arrays to newborn screening in the future?