A (Brief) Growth Hormone History in Canada

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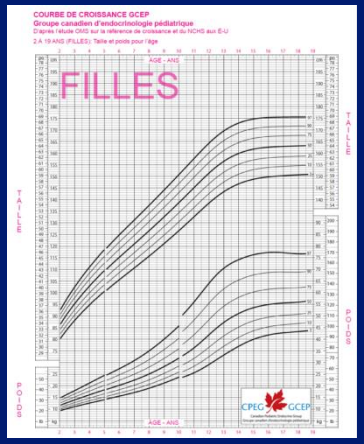

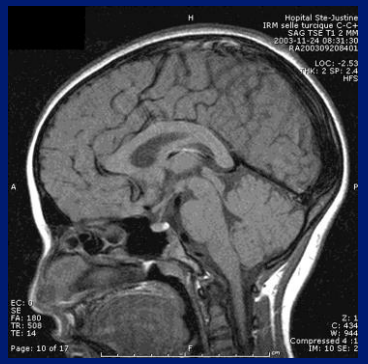

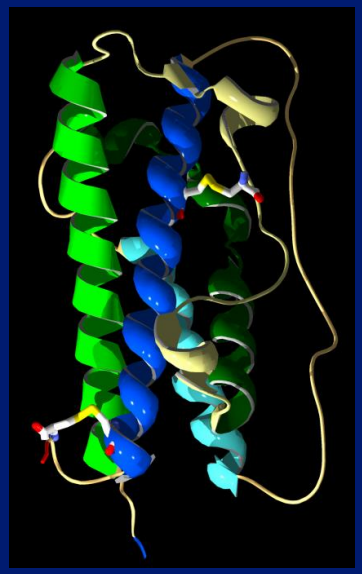

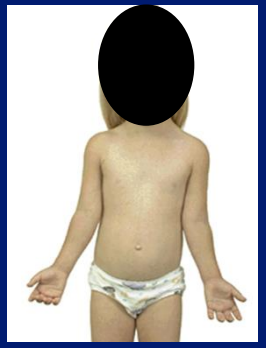

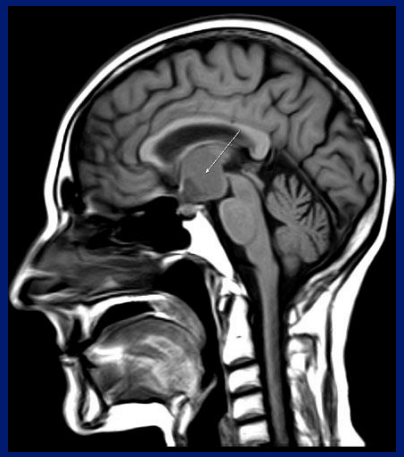

Disclosures

- I have served on the GeNeSIS International Advisory Board (Lilly), and served as an ad hoc consultant for Lilly, EMD Serono/Merck, Hoffman LaRoche, Sandoz, Pfizer, Versartis, OPKO

- I have been an invited lecturer for Lilly, EMD Serono/Merck, Hoffman LaRoche, Sandoz, Pfizer, Novo-Nordisk

- I have done contract research and received research and/or CME grants from Lilly, EMD Serono , Hoffman LaRoche, Pfizer, Sandoz

All of what I present today is from my own review of the topic and does not represent the opinions of any of the above companies

Objectives

- To explore the scientific beginnings and the contribution of Canadians to the rhGH era
- To remember the Canadian Growth Hormone Advisory Council and its enormous contribution to GH history in Canada and internationally
- To trace the origins of CPEG
- To set the stage for our two speakers who will present the GeNeSIS data!

Why Bother About GH History in Canada?

- “If you don't know history, then you don't know anything. You are a leaf that doesn't know it is part of a tree. ”

  — Michael Crichton (1942-2008)

- It makes an interesting story, with many lessons

- Lilly has played a major role in this story, not only in GH research, but also in helping foster the pan-Canadian collaborations we share through CPEG

hGH Treatment – A Brief History of the First Era (1887 – 1985)

- 1887 The existence of GH was suspected (Minkowsky)
- 1916 Patients with GH deficiency described (Erdheim)
- 1956 Preparation/properties of human/monkey pituitary GH (Li and Papkoff, *Science*)
- 1957 Preparation of GH from human/monkey pituitary glands (Raben, *Science*)
- 1958 Treatment of first hypopituitary patient with GH (Raben, *J Clin Endocrinol Metab*)
- 1960's Purification procedure for extraction of pituitary GH scaled up by the Raben lab (New England Medical Center, Boston) for distribution in the US and Canada
- 1965 Cohort study (35 U.S. patients, mixed diagnoses) (Soyka et al, *NEJM*)
- 1967 Clinical GH trial in 18 European hypopituitary patients treated for up to 8 years (Prader, *Acta Endocrinol (Copenh)*)

Frasier, *J Pediatr* 1997; 131:S1-4; Blizzard Indian J Pediatr 2012; 79:87;

hGH – The Canadian Story

- 1957 Beck and McGarray (McGill) defined effects of human and monkey GH in man (*Science*, 1957)
- 1960-66 Canadian Investigators collected human pituitary glands, sent to Dr. Raben for GH extraction – product then returned to Canada
- 1965-66 MRC encouraged the development of a clinical research program for GH in Canada – under the chair of Friesen
- 1967 Canadian GH Purification Program (Friesen)
  MRC-funded National Registry of GH-treated patients
  Growth Hormone Advisory Committee established

- 1975 Clinical Trial of GH deficiency in children (Guyda)
- *1981 Canadian results extended in US: Treatment (2-15 y) of 35 GH-deficient children (Burns)*

Dean and Friesen, *CMAJ* 1986; 135:297

Medical Research Council of Canada therapeutic trial of human growth hormone: first 5 years of therapy

H. GUYDA,* MD, FRCP[C]; H. FRIESEN,† MD, FRCP[C]; J.D. BAILEY,‡ MD, FRCP[C]; G. LEBOEUF,§ MD; J.C. BECK,¶ MD, FRCP[C]

CMA JOURNAL/JUNE 7, 1975/VOL. 112 1301

Summary: The Medical Research Council of Canada has initiated human growth hormone (hGH) therapy in 151 patients with documented complete hGH deficiency that was idiopathic in 76% of cases, secondary to craniopharyngioma (organic) in 17% and of varied cause in 7%. Approximately 50% of the patients with idiopathic disease had isolated hGH deficiency; during therapy thyroid deficiency developed in five patients and cortisol deficiency in three.

A similar increase in mean height velocity occurred in the first treatment phase for patients less than 12 years old (0.93 ± 0.30 cm/mo) and those 12 years and older (0.86 ± 0.29 cm/mo). Although subsequent courses of hGH therapy yielded significantly diminished response in both age groups, this diminution was not progressive: the height velocity of the younger patients returned to 0.82 ± 0.26 cm/mo in the fifth therapy phase. The mean height velocity attained at the optimal dosage (0.20 to 0.29 units/kg three times per week) for each age group did not differ significantly. Despite therapy being carried out for only 6 months of the year, normal increment ratios for height age and bone age against chronologic age were observed in the patients with idiopathic disease. In only four patients did treatment failure occur, and three of these were more than 20 years old.

The Push for Biosynthetic hGH…

- hGH supply from human pituitaries limited
  - Pituitary GH (1-2 mg IM t.i.w. for 6 months per year); height cap of 5’
  - By 1980, all pre-pubertal patients received treatment for 10 m/y; pubertal patients received it continuously
  - In Canada, distribution was through the MRC task force (Friesen, Guyda, Bailey, Leboeuf, Beck), expanded to the Growth Hormone Advisory Committee, lead by Dean as of 1980
  - While ‘commercialised’ by Calbiochem (‘76) → Hoechst (‘77) → Serono (‘78), KABI (‘79), bulk of pituitary GH in the US produced through pituitary gland donations with GH distribution in the US through the National Pituitary Association (NPA), subsidized by the NIH.
- Gene Splicing and Recombinant DNA technology
  - Applied to making insulin in the 1970’s
  - Humulin® developed by Genentech and marketed by Lilly in 1982
- Orphan Drug Act 1983: a stimulus for drug development

Orphan Drug Act 1983

- Orphan Drug Act passed in 1983 *in the U.S.* to stimulate drug development for rare diseases

- Provides: 7-year marketing exclusivity a tax credit of 50 percent of the cost of conducting human clinical testing, research grants for clinical testing of new therapies to treat orphan diseases

- Administered by the FDA

- Amended by Congress:
  - → 1984 to define a rare disease (affects fewer than 200,000 people in the U.S. = 63 per 10,000 or a little less than 1 in 200)
  - → 1985 to extend marketing exclusivity to patentable as well as unpatentable drugs
  - → 1988 to require sponsors to apply for orphan designation before submitting an application for marketing approval.

THE ORPHAN DRUG ACT IMPLEMENTATION AND IMPACT. Dept Health and Human Services, May 2001. OEI-09-00-00380; http://www.dhhs.gov/progorg/oei

Unintended Consequences of Pituitary GH

- 4 case of Creutzfeld-Jacob disease reported in 1985
  - UK: Powell-Jackson J et al, *Lancet*;
  - USA: Gibbs et al *NEJM*; Kock et al *NEJM*; Brown et al *NEJM*)

- Many people involved in the decision to stop distribution of pituitary GH that year; about 400 children in Canada affected by decision

- NO cases of CJD have been described in Canadian patients treated with the pituitary GH purified by Friesen, likely due to an additional chromatographic filtration step which would have eliminated prions (personal communication, Harvey Guyda)

- The Result: FDA approval of rhGH in 1985 for the treatment of GHD patients and clinical trials got underway

Hintz, *J Clin Endocrinol Metab* 1995; 80:2298

hGH Treatment – The Second Era

- Replacement of Pituitary GH with Recombinant GH (Genentech/Lilly) 1986
  - 1987 Protropin ® (Somatrem, Genetech, Inc): Orphan Drug Status granted
    - ✓192 aa GH, manufactured in *E. coli*
    - ✓additional methionine on the N-terminal end of the GH protein
  - 1987 Humatrope ® (Somatotropin, Eli Lilly, Inc): Orphan Drug Status the same year
    - ✓difference in the molecular structure (191 aa, identical to human growth hormone)
- 1987 MRC Therapeutic Trials Committee negotiated with companies manufacturing rhGH to begin trials in Canada
- Lilly proposal accepted: Identical timelines to be met as per Somatrem, patients currently on treatment would benefit from a Compassionate Use Study (n=370), clinical trial of rhGH dosing started in Canada (3 versus 6 injections), promise to supply rhGH until approval

hGH Treatment – The Second Era
(cont.)

- 1986 Somatrem rhGH (+/- oxandrolone) randomised control trial
  1 y treatment of girls with TS (Rosenfeld *J Peds*)

- 1986 Lilly and Growth Hormone Advisory Committee discussed randomised, control Turner trial *to final height;*
  FIRST HUMATROPE INVESTIGATORS MEETING
- 1988 Rosenfeld trial extended to 3 years with loss of control arm (*J Peds*)
- 1988 Somatotrem Approved for Turner Syndrome in Canada just before study start but withdrawn by sponsor
- 1988 FIRST PATIENT ENROLLED IN CANADIAN TURNER TRIAL (GDCT)
- 1990s Pressure from North American Endocrine Community to approve rhGH for Turner Syndrome; Canadian Turner Trial (GDCT) defended successfully

Does growth-hormone supplementation affect adult height in Turner's syndrome? *Lancet* 1996; **348**: 25–27

Shayne P Taback, Robert Collu, Cheri L Deal, Harvey J Guyda, Sonia Salisbury, Heather J Dean, Guy Van Vliet

- Retrospective cohort study, 17 treated, 14 untreated
- Contingency table analysis of attained versus projected height showed significantly higher values in treated patients
- Only 4 of 17 had final heights of 5 cm or more over projection
- Multiple confounders

Editorial, same issue….

Jury still out on growth hormone for normal short stature and Turner's syndrome

M D C Donaldson
Royal Hospital for Sick Children, Glasgow G3 8SJ

See pages 13, 25

The two papers in this week's issue on the therapeutic use of growth hormone exemplify the difficulty of determining the impact of growth-promoting treatment on final height, whether in short normal children or in children with a growth disorder such as Turner's syndrome.

In conclusion, more data must be thoroughly analyzed to better understand the patient and treatment variables underlying the heterogeneous response to GH supplementation. This will be best achieved through a combination of complete sets of observational studies and of randomized trials (in both cases with "intent-to-treat" analysis, ie, attempting to record the adult height attained by those patients who did not continue GH to adult height). Although we concur with Chu et al[2] that it would be a retrograde step to deny all patients with Turner's syndrome the option of GH supplementation, we think that counseling to avoid unrealistic adult height expectations remains of paramount importance.

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The Evolution of CPEG – Role of the GDCT Pan Canadian Turner Trial

- Humatrope Investigator Meetings held yearly, in February, as of 1996
- The Growth Hormone Advisory Committee members transitioned to the Canadian Pediatric Endocrine Group (https://home.cc.umanitoba.ca/~hdean/)
- First CPEG meeting, with agenda and minutes, held March 2, 1996 (Toronto)
  - Terms of reference: Status as subsection of CSEM
  - Representation on the Drugs and Therapeutics Committee of LWPES/PES
- Subsequently, CPEG held biannual meetings in conjunction with
  - the CDA-CSEM Annual meeting in October
  - the Humatrope Investigator Meeting in February
- As of 2006, CPEG officially adopted bylaws: now an independent organisation

GH Safety and the Canadian Growth Hormone Advisory Committee

- Compulsory Canadian registry from 1967-1987, voluntary thereafter

Mortality in Canadian Children with Growth Hormone (GH) Deficiency Receiving GH Therapy 1967–1992*

J Clin Endocrinol Metab 81: 1693-6; 1996

SHAYNE P. TABACK†, HEATHER J. DEAN, AND MEMBERS OF THE CANADIAN GROWTH HORMONE ADVISORY COMMITTEE‡

- 1366 children treated for GHD in the 25 years up to Dec 31, 1992. Individual cases reviewed for circumstances before death and autopsy information

- 37 deaths: 11 from tumor recurrence

  9 caused by the preventable endocrine complications: adrenal crisis and hypoglycemia

GH Treatment and the Canadian Growth Hormone Advisory Committee

- 2005 Completion of Pan Canadian Study: GH Treatment to Final Height in 150 Girls with Turner Syndrome

- 2005 Last Humatrope Meeting, Montreal

- 2005 – 2014 Additional studies and publications from Lilly trials/Lilly sponsored research with the Pediatric Endocrine community/GeNeSIS

Impact of Growth Hormone Supplementation on Adult Height in Turner Syndrome: Results of the Canadian Randomized Controlled Trial

J Clin Endocrinol Metab, June 2005, 90(6):3360–3366

The Canadian Growth Hormone Advisory Committee*

Health-related quality of life of young adults with Turner syndrome following a long-term randomized controlled trial of recombinant human growth hormone

BMC Pediatrics 2011, **11**:49

Shayne P Taback[1,3*] and Guy Van Vliet[2,3]

Genomic Imprinting in Turner Syndrome: Effects on Response to Growth Hormone and on Risk of Sensorineural Hearing Loss

J Clin Endocrinol Metab, August 2006, 91(8):3002–3010

Catherine E. Hamelin, Greg Anglin, Charmian A. Quigley, and Cheri L. Deal, on behalf of the Canadian Growth Hormone Advisory Committee

Growth Hormone Is Effective in Treatment of Short Stature Associated with Short Stature Homeobox-Containing Gene Deficiency: Two-Year Results of a Randomized, Controlled, Multicenter Trial

J Clin Endocrinol Metab, January 2007, 92(1):219–228

Werner F. Blum, Brenda J. Crowe, Charmian A. Quigley, Heike Jung, Dachuang Cao, Judith L. Ross, LeeAnn Braun, and Gudrun Rappold, for the SHOX Study Group

GH Treatment to Final Height Produces Similar Height Gains in Patients With SHOX Deficiency and Turner Syndrome: Results of a Multicenter Trial

Werner F. Blum, Judith L. Ross, Alan G. Zimmermann, Charmian A. Quigley, Christopher J. Child, Gabriel Kalifa, Cheri Deal, Stenvert L. S. Drop, Gudrun Rappold, and Gordon B. Cutler, Jr

GH Safety, the Canadian Growth Hormone Advisory Committee, CPEG and GeNeSIS

- Funding for database maintenance became a major issue in the 1990's
- As a result, CPEG encouraged enrolment of all GH-treated patients in ongoing Phase 4 post-marketing research databases available in Canada in order to monitor safety
- GeNeSIS born: 1999 (→ 2015) : Most detailed CRF database to date
- International scientific advisory board presided by Pierre Sizonenko and later, by John Parks
- Eli Lilly 'important people'
  - Werner Blum
  - Charmian Quigley
  - Chris Child
  - Many, many others

Health Canada Approval of rhGH in Canada

	Humatrope	Genotropin	Saizen	Nutropin	Norditropin	Omnitropin*
Pediatric and Adult GHD	✓	✓	✓	✓	✓ (Ped)	✓ (Ped) (✓ Adult)
Turner Syndrome	✓	✓	✓	✓		(✓)
IUGR-SGA	✓	✓	✓		✓	(✓)
Idiopathic Short Stature	✓	✓				(✓)
Chronic Renal Failure			✓	✓		
Prader-Willi Syndrome						
SHOX Deficiency	✓					

* Biosimilar approval process differed for indications (✓)

Indications where GH approved but not widely used in Canada

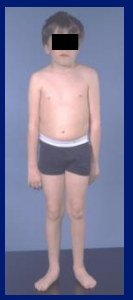
- GH deficient children with Prader-Willi syndrome (if no OSA, T2D, psychiatric issues),

  although center-dependent (0-100%l)



- Children born small for their gestational age (SGA). A very heterogeneous group. Includes Silver-Russell syndrome, and other forms of

  in utero growth delay)



- Children with ‘idiopathic’, non-GH deficient short stature (height of -2.25 SD, or the shortest 1.2% of children), but again, *center-dependent*

More Advances: Adherence and The Science of Gadgeterie

Who Pays??

- For GH Deficiency – Government funded for almost 30 years; Pediatric/Adult Endocrinologists play different roles in the treatment decision depending upon the province and center (particularly with regards to ‘GH inadequacy/GH insufficiency’)

- For Turner Syndrome and Renal Failure – government funded in some provinces

- For other indications (SGA with no catch-up growth, ISS, SHOX deficiency, PWS particularly if GHD not demonstrated): insurance companies

- For all indications except non-GHD PWS, special programs exist (compassionate use, co-pay)

Why Post-Marketing Surveys?

- Safety, Safety, Safety, Safety
- Treatment outcome in a real-life setting (effectiveness as opposed to efficacy)
- Snapshot of practice patterns of participating centers/physicians
- A look at how Canada compares to other countries

So Without Further Ado…

And with Special Thanks To:

- Harvey Guyda
- Heather Dean
- Ron Fehst
- Susan Kirsch
- Chris Child and all my GeNeSIS colleagues

Merci!

For Fellowship Opportunities Contact:

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