ENDOCRINOLOGY
OF PCM

From Undernutrition to Type 1 Diabetes
PROGRESS IN MEDICINE

- TEACHERS AND MENTORS
- REMEMBER HISTORY
- BUILD ON THE PAST
Mentors

- Prof. Thomas Bothwell
- Prof. Robert McDonald
- Prof. Bernard Pimstone
- Prof. Allan Drash

Role models all
Shaped me by challenging me
Depended on me to keep up and produce
Gave me rope
Befriended me
An analysis of the life and career of the late Bernard Pimstone is relevant for those wishing to pursue a challenging career in the field of clinical research. Dedication, perceptiveness and a sense of humanity and of humour are closely linked to creative endeavour. Commitments to both patient care and teaching can be successfully integrated and play an essential role in the life of the clinical investigator.
SPECTRUM OF PROTEIN-CALORIE MALNUTRITION

Nutritional

Kwashiorkor

Marasmic

Marasmus

Kwashiorkor

Short

Stature
WHY DO CHILDREN WITH PCM NOT GROW?

WHAT IS THE HORMONAL MECHANISM?

WHAT TREATMENT WILL MAKE THEM GROW?
WHY DO CHILDREN WITH PCM NOT GROW?

WHAT IS THE HORMONAL MECHANISM?
LOW GH LEVELS

WHAT TREATMENT WILL MAKE THEM GROW?
GROWTH HORMONE?
First Results

- BASAL GH LEVELS HIGH—NOT LOW
First Results

- **BASAL GH LEVELS HIGH—not low**
- Inverse correlation with serum albumin levels
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  - Decreased after only 3 days of protein re-feeding
  - However, carbohydrate feeding had no effect
  - IV albumin had no effect
  - Growth hormone Rx had no effect
OGTT

Pre-Treatment

After Feeding

H.S.

40

30

20

10

H.G.H.

mug/ml

B.G.

mg/100 ml

H.G.H.

mug/ml

B.G.

mg/100 ml

MINUTES

0 30 60 90 120 150

0 30 60 90 120 150

BG

x---x

hGH

---•---
IVGTT
IVGTT
Arginine Stimulation Test

![Graph showing HGH levels before and after arginine stimulation with time points at admission and 3 weeks.](image)
DYNAMICS OF GH SECRETION

- High (acromegaloïd) levels --- not suppressible by oral or IV glucose

- If low --- no response to arginine stimulation

- Often decreased by day 3 and no response to stimulation
Growth Hormone - Somatomedin (IGF-I) Axis

- Hypothalamus
- Anterior Pituitary
- Negative Feedback
- GRF (+) Somatostatin (-)
- Growth Hormone
- Tissues
- Somatomedins
- Protein Synthesis
- Cell Proliferation
- Growth
Summary 3

- Somatomedin (IGF1) was low in the face of high GH levels

- Somatomedin increased with refeeding

- Somatomedin could not be increased by administering IV growth hormone

Did this have any connection to the insulin deficiency of PCM??
Why is GH Not Suppressible??

Pituitary over secretion??

Normally suppressed by somatostatin infusion
WHY DO GH LEVELS NOT SUPPRESS?

WHAT IS THE NORMAL MECHANISM?

Suppression by somatostatin?
Insulin response to glucose?

WHY DO LOW LEVELS NOT INCREASE?

Adaptation or Detrimental Consequence?
Summary 2

- Children with PCM have frequent glucose intolerance – especially if hypo-albuminemic.

- This is associated with insulin deficiency – especially first phase during both Oral and IV glucose tolerance tests.

- Insulin responses to glucose increase during recovery.

- Apparent insulin resistance during refeeding.

- Are these abnormal consequences or adaptive phenomena??
GH deficiency

GH deficiency

GH Resistance

IGF-1 Resistance

Anterior Pituitary

Growth Hormone

GH

↓

IGF-1

↓

Resp. Infections

STAT5b Defect ?

IUGR

IGF-1 Gene Defect ?
Post-binding events in GH action

GHR

GHR associated protein kinase

protein kinase substrates

Phosphorylation
Short Stature Due to IGF-1 Deficiency

Growth Hormone Secretion

Growth Hormone Receptor Activation

Post-Receptor GH Signaling

IGF-1 Gene Expression

1º IGFD

2º IGFD
Hormonal Abnormalities in PCM

**High**
- Growth Hormone
- TSH response to TRH
- Reverse T3
- 11 hydroxy corticoids

**Low**
- Somatomedin-IGF 1
- Prolactin response to TRH
- T3
- LH
- FSH
- Insulin response to glucose
- Growth hormone receptor
Hormonal Abnormalities in T1DM
(a disorder of intracellular starvation)

**High**
- Growth Hormone
- TSH
- Reverse T3
- Cortisol

**Low**
- Somatomedin-IGF 1
- T3
- LH
- FSH
- Insulin response to glucose
- Growth hormone receptor
Are these hormonal changes adaptation or a detrimental consequence of malnutrition or T1DM??
Conclusion 1

ADAPTATION

PCM is the commonest cause of short stature, growth failure and IGF1 deficiency in the world

Poverty
Malabsorption
Psychogenic
Insulin deficiency
Conclusion 2

- **History** --- Remember the work of the last century. Despite being old, it was usually correct.

- **Therapy.** If an abnormality is an adaptation, overriding it may not be the best therapy. It is not likely to be effective and may be harmful.

- **Mentors.** We stand on their shoulders and the next generations should be able to stand on ours.