Hormones: the birth of a concept and how it gained recognition

U3A Course, Spring Series 2017

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What I plan to talk about:

• First Session:
  History of hormones; concepts to chemicals
  Stories behind some key discovery milestones
  Technological help in advances

• Second Session:
  How hormones work
  Hormones’ role in digestion
  Gut hormones in excess (tumours)
What do you associate with the word ‘Hormone’

• Sex, Puberty, Menopause?

• Body building, Athletes?

• Maybe? Digestion
  Urine production
  Blood production and BP
  Brain function

• Regulates our entire metabolism
Early ‘application’ - Eunuchs

• Intentional castration

• Summerian city of Lagash in 21st C BCE Southern Mesopotamia (Iraq)

• Applications: Guardians of rulers or women
  Singers
  Courtiers and domestics
Why did this happen?

FIRST EXPERIMENTAL PROOF OF INTERNAL SECRETION

JOHN HUNTER (1728 – 1793) - 1792

ARNOLD ADOLPH BERTHOLD (1803-1861) - 1849

- Castration of cock caused atrophy of comb but this could be prevented if the testis were transplanted to another part of the body
Albrecht von Haller (1708 – 77)

- Swiss poet, naturalist, theologian, anatomist, physiologist
- “Father of experimental physiology”
- Body ‘emanations’: Bile digests fat
  Body a reactive organism
  Salivary gland duct a blood vessel (MD)
Theophile de Bordeu (1722 – 76)

• French poet, philosopher, physician

• Organs specific sensibilities

• Each organ of the body produced a specific ‘emanation’ (humour) which it secreted into the bloodstream
Claude Bernard (1813 – 78)
Claude Bernard

- Vaudeville comedy to medicine
  Med School in Paris 1834; physiology

- Father of "Experimental medicine"
  Vivisection

- ‘Milieu interieur’
Walter Bradford Cannon (1871 – 1945)

- American physiologist at Harvard

- Worked in lab of Henry Bowditch, a pupil of Bernard

- Enlarged Bernard’s concept to ‘homeostasis’ in 1920s; from ‘why’ to ‘how’ with ‘fight or flight’ response (BP, glucose)
Thomas Addison (1793 – 1860)

- Physician at Guy’s

- 1849 Presentation to South London Med Soc on anaemia, adrenal failure

- 1855 Monograph on suprarenal gland disease
  Some previous cases but not linked
  Brown-Sequard animal experiments

- Melancholia, depression; suicide
George Oliver (1841 – 1915)

- MB 1865; MD 1873 at UCL under Sharpey

- 1893 Arteriometer; effect of adrenals on blood vessels

- Links with UCL: took his idea to Schafer in 1893
Edward Albert Schafer (1850 – 1935)

• Student of Sharpey at UCL

• FRS 1878

• Prof of Physiology at UCL 1883 – 99

• Approached by Oliver 1893

• Coined term ‘endocrine’
Adrenaline raises BP
Adrenaline

• Variable versions of history

• Effect 1894 Oliver and Schafer

• Purifled 1901: Takamine

• Commercial potential

• Ineffective in Addison’s
Corticosteroids from Adrenal cortex

- Gluco- and mineralocorticoids isolated 1944
- Nobel prize 1950
  - Tadeusz Reichstein: Pole/Swiss
  - Edward C Kendall: Mayo
  - Philip S Hench: Mayo
Thyroid Disease

- Graves Disease 1835
  Goitre + exophthalmos

- Caleb Parry
  Observed 1786, published 1825

- Sayid Ismail al-Jurani
  Persian physician, 12th Century

- Adams and Purves Dunedin 1956, LATS
• Sir William Gull 1816 – 90; Guy’s Myxoedema
  Iodine deficiency

• Emil Kocher 1841–1917; Bern, Nobel 1909
  Myxoedema, goitre, thyroidectomy

• Moritz Schiff 1823 – 96; German in Bern
  “Something released into blood”
Ivan Petrovich Pavlov (1849 – 1936)

• Russian physiologist

• Nerve control of digestion fame for dog conditioned nerve reflexes

• Extensive studies on stomach secretion

• Believed pancreas and stomach were entirely under nerve controlled (vagus nerve)
Conditioned Reflexes?

WATCH WHAT I CAN MAKE PAVLOV DO. AS SOON AS I DROOL, HE'LL SMILE AND WRITE IN HIS LITTLE BOOK.
William Maddock Bayliss 1860 - 1924

- Medicine at Univ Coll
  Physiology Oxford

- 1890 Met Starling; married his sister in 1893

- 1899 Starling joined Bayliss in Univ Coll faculty
Ernest Henry Starling 1866 - 1927

- 1889 MD Guy’s Hospital; Physiology

- Starling’s Law - peristalsis

- 1902 Collaboration with Bayliss on gut research

- Leuret and Lassaigne (Paris, 1825) Vinegar in duodenum - pancreatic secretion (?chyme)

Dolinski (1894) Duodenal acid; thesis with Pavlov
Discovery of Secretin

• Acid in duodenum (nerves intact) -> pancreatic secretion

• Loop of jejunum: *Denervated*
  Acid in loop -> pancreatic secretion
  Concluded: “It must be chemical”

• Jejunal extract IV - -> pancreatic secretion
The original experiment

“The crucial experiment” (Ofwel: met blijdschap geven wij kennis van de geboorte van een nieuw vakgebied; de endocrinology)

Fig. 2. Effect of injecting acid extract of jejunal mucous membrane into vein. Explanation as Fig. 1. The steps on the drop-tracing are due to a gradual accumulation of secretion on the lever of the drop-recorder, which fluid falls off at intervals. Blood-pressure zero = level of drop recorder.

(uit: Bayliss WM, Starling EH (1902) J. Physiol. 28: 325-353)

- Intraveneuse toediening van een extract uit de mucosa van de dunne darm (jejunum).
- Ca. 70 seconden (!) na injectie start de secretie van pancreassap.
- “We have already suggested the name ‘secretin’ for this body...”
‘Hormones’ are born

• William Hardy, biologist, invited Starling to dinner at Caius College

• W T Vesseus, classical scholar, consulted for advice during dinner

• Suggested Greek word for ‘excite’ or ‘arouse’ ‘ormao’ or hormone in English; next appeared in Croonian Lecture

Quoted in Joseph Needham’s book, 1936
The Croonian Lectures

ON

THE CHEMICAL CORRELATION OF THE FUNCTIONS OF THE BODY.

Delivered before the Royal College of Physicians of London on June 20th, 22nd, 27th, and 29th, 1905,

BY ERNEST HENRY STARLING, M.D. LOND., F.R.S.,
FELLOW OF THE COLLEGE; JODRELL PROFESSOR OF PHYSIOLOGY,
UNIVERSITY COLLEGE, LONDON.

LECTURE I.

Delivered on June 20th.

THE CHEMICAL CONTROL OF THE FUNCTIONS OF THE BODY.

MR. PRESIDENT AND GENTLEMEN,—From the remotest ages the existence of a profession of medicine, the practice of its art and its acceptance as a necessary part of every community have been founded on a tacit assumption that the functions of the body, whether of growth or activity of organs, can be controlled by chemical means; and research by observation of accident or by experiment for such means has resulted in the huge array of drugs which form the pharmacopoeias of various civilised countries and the common armamentarium of the medical profession throughout the world.

These chemical messengers, however, or "hormones" (from ὑποδεικνύω, I excite or arouse), as we might call them, have to be carried from the organ where they are produced to the organ which they affect by means of the bloodstream and the continually recurring physiological needs of the organism must determine their repeated production and circulation through the body.
Pavlov corrected

• Pavlov repeated B & S study in Babkin’s lab
  “Of course they are right. It is clear that we did not take out an exclusive patent for the discovery of the truth”

• Nobel Prize 1904 for work on physiology of digestion
  B & S findings not acknowledged at Nobel award

• Pavlov stayed in Russia; survived denouncing Stalin
Gastrin

• John Edkins (St Barts) – 1905 Injected pyloric mucosa in cats: acid stimulated

• 1910 Histamine discovered; confusion

• 1938 S Komarov: isolated pure gastrin: peptide

• 1964 RA Gregory and HJ Tracy: aa structure
Diabetes mellitus

- Greek physician Aretaeus of Capadocia (81 – 138)

- ‘Diabetes’ – Greek syphon (polyuria)
  Mellitus – sweet

- Galen of Pergamum (129 – 216) Kidney problem

- Johann Brunner (1653 – 1727) Swiss. Removed pancreas and spleen in dogs; thirst and polyuria
Islets of Langerhans 1869

- Paul Langerhans  German (1847 – 88)

- Pancreatic clear cells; stained differently; rich nerve and blood supply
Gustave-Edouard Laguesse (1861 – 1927)

- Conclusion drawn: Secretion arose from Islets of Langerhans

- Link to diabetes?

- Labelled an endocrine secretion
  (as opposed to exocrine from the pancreatic acini)

- Endocrinology was defined more clearly
Studies on dog pancreas

- 1884 Arnozan and Vaillard: tying off pancreatic duct -> acinar (enzyme producing cells) atrophy, but not Islet atrophy

- 1890 von Mering and Minkowski: Pancreatectomy -> diabetes Prevented by re-implanting portion of pancreas
Frederick Banting (1891 – 1941)

• Banting, Canadian. Pancreatic extract ineffective in diabetes; ? effect of acinar enzymes

• JJR Macleod, Prof Physiology, Toronto. Lab, students Charles Best and Clark Noble, and biochemist James Collip

• Initially caused pancreatic acinar atrophy in dogs; crude extract ‘isletin’; lowered glucose in dogs; ‘Marjorie’ kept alive with crude extract
Purification of insulin

• Studies repeated with more dogs; foetal calf a better source of Islets

• ‘Isletin’ purified: diabetic patient (Leonard Thomson, 14) injected; bad allergic reaction

• Collip purified ‘isletin’ over 12 days; effective; they had produced insulin

• Eli Lilly commercialised process
Nobel Prize 1923

• Awarded to Banting (Age 32) and Macleod

• Upset that Best and Collip not named

• Prize money shared with Best and Collip

• Patent for insulin sold to University of Toronto for 50 cents; Eli Lilly gained commercial rights
Frederick Sanger (1918 – 2013)

- British biochemist: Quaker; Cambridge
- Structure of insulin 1951; bovine 3aa, porcine 1aa different from human
- 1st Nobel Prize 1958
- 2nd Nobel Prize 1980
Pituitary Gland

• Acromegaly: Egypt 1365 BCE; Goliath?

• Galen: Phlegm drain to nose

• 18 – 19th C: Acromegaly, Amenorrhoea, Diabetes insipidus, Reproduction

• Mid – late 20th C: Relationship to endocrine organs Links with brain (hypothalamus)
Radioimmunoassay (RIA)

- Solomon Berson (1918 – 72)
- Rosalyn Yalow (1921 – 2011)
- Insulin (1959) then gastrin
- Discrimination noted
- Nobel Prize for Yalow 1977
Karolinska Peptide ‘Factory’

• Erik Jorpes (1894 – 1973)
  Finland -> Sweden

• Viktor Mutt (1923 – 98)
  Estonia -> Sweden

• 1961 isolated secretin; barrels of pig gut

• Isolated over 50 naturally occurring peptides
Hormone cellular origin

- Nikolai Kulchitsky (1856 – 1925) 1897 Clear cells in gut
- M C Ciacco (1877 – 1956) 1906 Enterochromaffin, argentaffin cells
- Friederich Feyrter (1895 – 1973) 1938 Whole coordinated system
Linking Structure with Function (1970s)

- AGE Pearse, Julia Polak, Enrico Solcia

Antibodies linked to studies

![Diagram of Direct and Indirect methods with Antigen, Primary Antibody, Secondary Antibody, and Fluorophore markers.](image)
Bioactive Peptides in Nature

• Vittorio Erspamer (1909 – 99)

• Peptides in frog skin

• *Hyla caerulea* Caerulein

• *Bombina bombina* Bombesin
Morton I Grossman (1919 – 81)
How hormones work
Endo/ Para/Auto/ Neurocrine

- Secretory vesicles
- Endocrine cell
- Blood vessel
- Target cell
- Neuro-secretory cell
- Hormone molecules
- Nerve signal
- Neuro-transmitter molecules
- Nerve cell
Classifications of hormones:

- Hormones
  - Steroids
    - Adrenal Cortical hormones (Corticoids)
      - Female sex hormones
        - Estrogens (estrone esteradiol)
      - Male sex hormones
        - Androgens (e.g., Testosterone)
    - Sex hormones
  - Peptide hormones (Insulin and glycogen)
  - Amino acid derivatives (Thyroid hormones)
  - Miscellaneous (prostaglandins and cytokinins)
Steroid Hormone Response

1. Steroid hormone binds to the steroid receptor in the cytoplasm.
2. The steroid-receptor complex enters the nucleus.
3. The receptor binds to a regulatory sequence on DNA, initiating transcription.
4. mRNA is transcribed from the DNA.
5. The mRNA is translated into a new protein.

New protein

DNA

Regulatory sequence

mRNA
proteohormone (polypeptide hormone)

receptor

mRNA

protein

functional adaptation
What happens when we eat?

1. Cephalic phase of acid secretion

Conditioned reflexes:
- taste
- smell
- chewing
- swallowing
- hypoglycemia
## Secretions into the G-I Tract

<table>
<thead>
<tr>
<th>Source</th>
<th>Volume (ml/d)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>1 000</td>
<td>6–7</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 500</td>
<td>1–3</td>
</tr>
<tr>
<td>Brunner’s GI</td>
<td>200</td>
<td>8–9</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 500</td>
<td>8–8.3</td>
</tr>
<tr>
<td>Bile</td>
<td>1 000</td>
<td>7.8</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 800</td>
<td>7.5–8</td>
</tr>
<tr>
<td>Colon</td>
<td>200</td>
<td>7.5–8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>7 200</strong></td>
<td></td>
</tr>
</tbody>
</table>
2. Food in stomach – Gastric phase
Gastrin subtypes

- Preprogastrin
- Progastrin
- Gastrin-34
- Gastrin-17
- Gastrin-14
Gastrin Family

NH₂ - VSORTDGESRAHLGAL
CCK-58

CCK-33
CCK-39

MSVRGSPAKRAQOIY

CCK-8
SO₃H

SLDPSPHRISDRDYMGWMDF

CCK-8

G-17s

(SO₃H)
3. Food exits stomach – pyloric valve

- “Pylorus not just a pretty hole!” It is very clever!
- Precise regulator of what enters gut
4. Food enters duodenum

Acid stimulates secretin
Protein and fat stimulate CCK

Small intestine (duodenum)

Fats, peptides, amino acids

CCK secretion

Liver

Gallbladder

Pancreas
5. Food is absorbed: Sugar
Insulin is released
Blood sugar after oral glucose
Blood glucose control: other factors

• Adrenaline: Fight or flight

• Corticosteroids: Stress response

• GIP: Gastric inhibitory polypeptide
  Glucose-dependant insulinotropic peptide

• Others
CONTROL OF FOOD INTAKE

- Leptin
- Ghrelin
- Insulin

Adipose tissue, Pancreas, Stomach

Energy balance: Expenditure, Intake
Ghrelin – Hunger hormone

Stomach Empty

- $\uparrow$ Ghrelin $\Rightarrow$ $\uparrow$ Appetite
- $\downarrow$ CCK, GLP-1, PYY – all $\downarrow$

Stomach Full

- $\downarrow$ Ghrelin $\Rightarrow$ $\downarrow$ Appetite
- $\uparrow$ CCK, GLP-1, PYY – all $\uparrow$
Leptin – Satiety hormone

1. We Eat

2. Fat Gets Stored

3. Fat Cells Secrete More Leptin

4. Brain "sees" Increased Leptin

Increased leptin is a signal to stop eating.
CONTROL OF FOOD INTAKE

- Adipose tissue
- Pancreas
- Stomach
- Leptin
- Ghrelin
- Insulin

Energy balance: Expenditure vs. Intake
Endocrine Tumours: 1. Insulinoma

- First described 1924 (Harris)
- Produces insulin
  - Unregulated
  - Minority spread
- Symptoms: hypoglycaemia
- Treatment: Surgery (first 1929)
Endocrine tumours: 2. Carcinoid

- Often small and slow growing
  - Often “incidentaloma”
  - Whole gut, most small bowel

- Can produce serotonin

- Carcinoid syndrome: <10%, and only when liver involved
Carcinoid Syndrome

- Flushing, diarrhoea, wheezing, cramps, right sided heart valve disease

- Treatment: Surgery, Radionuclide, Somatostatin
Endocrine Tumours: 3. Gastrinoma (ZES)

- Duodenum and pancreas: Gastrin 50% malignant, 25% MEN I
- Acid secretion, large stomach
  Often 3 – 5 x normal acid
- Severe complicated peptic ulcers + Diarrhoea
- Treatment: Surgery, acid suppression
Endocrine Tumours: 4. VIPoma (Pancreatic cholera, WDHA)
VIPoma

- Pancreatic cholera; WDHA Syndrome; Werner (Watery Diarrhoea, Hypokalaemia, Achlorhydra)
- Flushing, low BP, High blood Ca and glucose

- 90% Pancreatic
- 1/3 spread by time diagnosed

- Treatment: Surgery, Octreotide, Radionucleotides
Vasoactive Intestinal Peptide

- Sami Said (1928 – 2013)
  Cairo; USA; Sweden 1971 (J&M)

- Stimulates G-I secretion

- Control: -27microL/min
  Jejunum: 510
  Ileum: 153

Barbezat and Grossman: Science 1971
Endocrine Tumours: 5. MEN 1

- Criteria: Age <40, Family history, >1 or recurrent tumours, >1 organ system

- Parathyroid 90%+, Pancreas 65%, Pituitary 18%
  Nil to many hormones eg insulin, gastrin, other

- Only 1 parent need be affected; often benign with non-secreting incidental adenoma
KEEP CALM AND CONTROL YOUR HORMONES
“The excitement of learning separates youth from old age. As long as you’re learning you’re not old”

Rosalyn Yalow