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Biomedical
Science

Alchemy to Chemistry



A Taste of Honey

- Polyuria, a common, but not specific symptom of diabetes, recorded in Egyptian papyrus dated 1552 BCE and may represent earliest record of diabetes.
- Archaeological claims changes in human skeleton from Egypt (2055-1650 BCE) indicative of type 2 diabetes.
- **Sushruta** (c 500 BCE) Indian physician, described sweet taste of diabetic urine he termed 'madhumeha' or honey urine, common practice to taste urine if diabetes suspected. Also observed ants attracted to urine of diabetics, may still be used for diagnosis in Africa. He described two different forms of presentation, younger thinner patients and older and more obese patients who lived longer.



Why Diabetes Mellitus?

- **Aretaeus (130-200 CE)** gave more detailed description of symptoms, notably excessive thirst, weight loss as a 'melting down of flesh and limbs' into urine. He named diabetes from Greek 'siphon' and 'flowing out'.
- In 1778 **William Cullen (1710-1790)** added **mellitus** (Greek for honey) for sweetness of urine of diabetics.



Searching for the Cause

- Polyuria with glycosuria key features of diabetes in early 19th century, the cause remained elusive. Claude Bernard (1813-1878) in 1846 showed sugar absorbed from intestine converted to glycogen in liver for release into blood as required. Various theories raised that diabetes was due to infection or originated in the liver, brain or nervous system.

Claude Bernard (1813-1878)

**A History of Diabetes Mellitus:
From Tasting to Testing**
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Physick examining matula

Tasting and Testing (500CE until 17thC)

- Urine collected into special glass flask, a matula, examined by 'physick' for volume, colour, clarity, sediment, odour and taste for predictive 'diagnosis' of wide range of diseases.
- The sweetness of the urine of diabetics recognised in India, China, Africa and Persia, but not recorded in Europe until the 17th century. **Paracelsus (1493-1541)** suggested chemical analysis of urine and obtained white residue on evaporation he believed salt and proposed the cause of diabetes was deposition of salt affecting kidneys and stomach.
- British physician **Thomas Willis (1621-1675)** regarded diabetes as the 'pissing evil' and wrote treatise on urinalysis, his observations on diabetes recorded in 'Pharmaceutice rationalis' (1674). He described the urine as 'exceedingly sweet' and 'wonderfully sweet like sugar or honey'!
- 1772 **Matthew Dobson (1735-1784)** showed sugar like substance present in urine and blood of a diabetic patient. He found that evaporation of urine left a residue which tasted like brown sugar and serum also tasted sweet.
- 1780 **Francis Home (1719-1813)** demonstrated that urine containing sugar undergoes fermentation with yeast.
- 1815 **Michel-Eugene Chevreul (1786-1889)** French organic chemist demonstrated sugar present identical to grape sugar (glucose).
- 1862 **William Roberts (1830-1899)** adapted fermentation test using urinometer to measure the change in specific gravity on fermentation which related to concentration of urine glucose. Used by physicians, notably Frederick Pavy (1829-1911) of Guy's Hospital, to study effect of dietary variation.

Copper Reduction

- Many sugars, including glucose, have reducing properties, exploited by progressive colour changes during reduction of blue copper sulphate solutions to green, yellow to brown/red with increasing amounts of sugar.
- 1841 **Karl Trommer (1806-1879)**, German chemist first devised a copper reduction test, more stable copper sulphate reagent by **Hermann von Fehling (1812-1885)** in 1850.
- Sensitive copper reagent described in 1908 by **Stanley Benedict (1884-1936)** with further modification two years mainstay of urine monitoring of diabetes for over fifty years. 1945 Ames developed Clinitest, a more convenient solid tablet form of copper reduction and Clinistix, a dip and read specific reagent strip for urine glucose developed by Ames research team led by **Albert & Helen Free** in 1957.

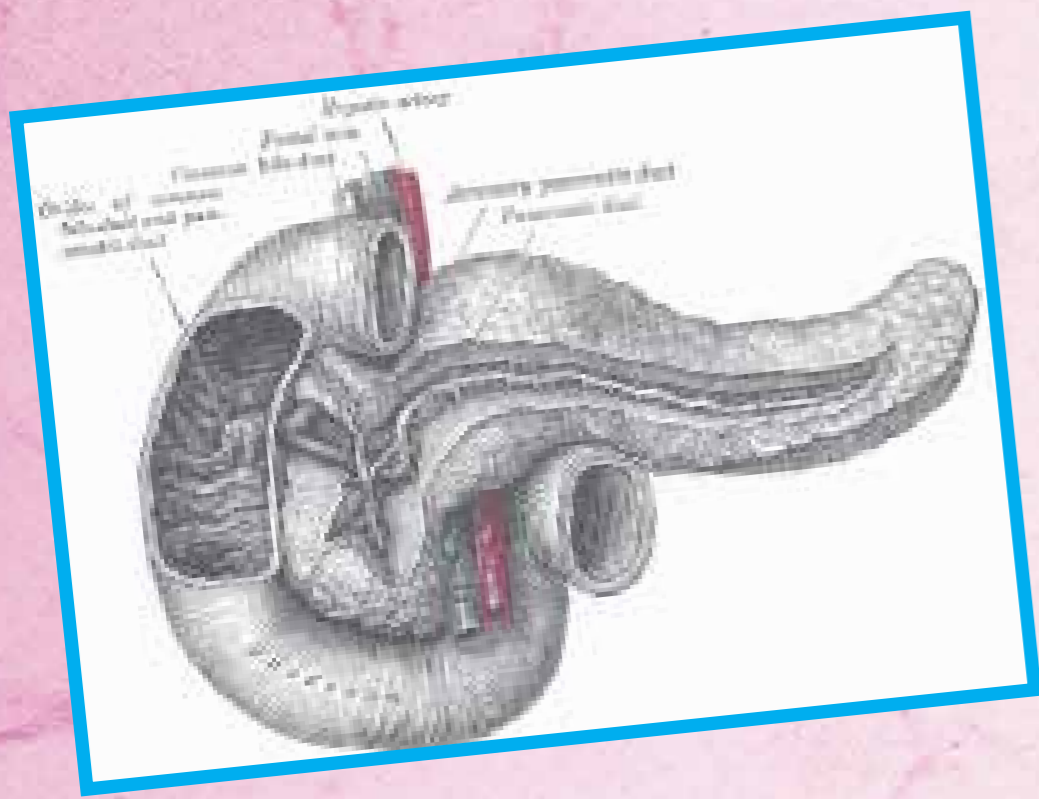
Helen Free

Stanley Benedict (1884-1936)



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Islets to Insulin



The Pancreas: A Hidden Organ

- 100 AD **Repos**, Greek anatomist, named pancreas (*pan* all, *kreas* flesh) little known of function; believed protective 'cushion' for major blood vessels and nerves.
- 1689 **Johann Brunner (1653-1727)** induced temporary symptoms of extreme thirst and polyuria in dogs without pancreas.
- 1788 **Thomas Cawley** observed pancreatic tissue damage in autopsy of patient with diabetes, suggested an association.
- However, most attention given to exocrine role of pancreas in **digestion** until 19th century

The 'Active' Principle

- Concept of internal secretion by glands **Charles Edouard Brown Sequard (1817-1893)** applied to diabetes by **Edward Sharpey-Shaffer (1850-1935)** in 1895.
- Exactly 200 years after Brunner studies, **Oskar Minkowski (1858-1931)** and **Josef von Mering (1849-1908)** induced severe diabetes after removing pancreas in dogs and **Gustave Laguesse (1861-1927)** suggested in 1893 that 'internal secretion' produced by islets of irregular polygonal cells first described by **Paul Langerhans (1847-1888)** in 1869.
- 1901 **Eugene Opie (1873-1971)** proposed anti diabetic substance present in islet cells altered in diabetes. In next year **Ernest Starling (1866-1927)** and **William Bayliss (1860-1924)** introduced concept of hormones as chemical messengers transmitted by blood in seminal studies of secretin and pancreatic secretion.

Dietary Control & Quack Remedies For Diabetes

- 1792-96 British army surgeon **John Rollo (d 1809)** reduced glycosuria with high meat, low grains and bread diet. Bran muffins and almond biscuits were given as bread substitutes in 19th century. Fad diets early 20th century include potato, oatmeal cure and quack remedies eg vin urane pesqui, Dills diabetic mixture contained bromides, opium, arsenic, uranium nitrate often in alcohol.
- 1912 **Frederick Allen (1876-1964)** completed studies of glycosuria and diabetes to introduce calorie controlled diet, commonly called a 'starvation' diet. However, despite prolonging life expectancy, patients dangerously underweight, physically weak and often regressed into coma.
- **Elliot Joslin (1869-1962)** specialist in diabetes became pioneer in promoting glucose regulation, patient self management and education. Today there are Joslin Diabetes Centres across USA and Canada.

Pancreatic Extracts

- Treatment with thyroid extract in myxoedema in 1891 by English physician **George Murray (1865-1939)** raised potential of pancreatic extracts in diabetes. Potential difficulties purity of beta cells of islets which constitute only 1% of the pancreas, minimising digestive enzyme action.
- 1899 **Leonid Sobolev (1876-1919)** suggested ligation of pancreatic duct isolates islet cells to provide extract suitable for treatment. Between 1900 & 1921 at least 5 research groups attempted unsuccessfully to obtain safe and effective extract. Impurities caused severe side effects and variation in 'batch' potency could produce extreme hypoglycaemic episodes.



**Charles Herbert Best (1899-1978)
& Frederick Banting (1891-1941)**

Insulin: A Medical Miracle

- 1920 **Frederick Grant Banting (1891-1941)**, began research work at University of Toronto under **John JR Macleod (1876-1935)**. Banting realised from earlier observations of **Sobolev** and **Moses Barron** in 1919 that prolonged ligation of pancreatic duct would destroy acinar cells but not affect islet cells believed to contain pancreatic hormone 'insuline' (Latin-insula-island), as named by **Sharpey-Shaffer** in 1916.
- Banting and **Charles Herbert Best (1899-1978)** using laboratory dogs, excised pancreas and prepared extracts injected into depancreatised dogs. Best skilled in blood sugar micromethod developed by **RC Lewis** and **Stanley Benedict** in 1913 only required 0.2ml blood, found extracts lowered blood sugar and urine was sugar free with physical and clinical improvement. Similar results obtained from extracts of fresh foetal calf and adult beef pancreas.
- **James Bertram Collip (1892-1965)** joined research in late 1921 to help improve quality and purity of extracts, assessment of potency with measurement of blood sugar of rabbits. Also found that daily administration of extract could extend the life of diabetic dogs.
- First recorded use of insulin on humans January 1922; a pancreatic extract prepared by Best given to a 14-year-old boy with severe diabetes, with a fall in blood sugar. Repeated 12 days later with extract prepared by Collip with even more significant reduction in blood sugar.



**Elliot Joslin
(1869-1962)**

Frederick Allen (1876 -1964)



Frederick Banting (1891-1941)

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Insulin - A Therapeutic Miracle

Early Experience

- 1922 Large scale production of high quality insulin with collaboration of Eli Lilly
- 1923 British medical research council accepts patent rights and with drug companies insulin available in UK hospitals
- 1926 **John Abel (1857-1938)** prepared crystalline insulin, 10, 20, 40 units/ml available worldwide

Living on the Edge

- Variation in insulin quality, personal requirements and poor assessment of treatment with sustained periods of uncertainty, fearful of hypoglycaemia and hyperglycaemia. Only effective by injection and required lifelong in severe cases.
- Life expectancy of severe diabetics extended but greater awareness of complications and less emphasis on strict diets.
- 1934 British Diabetic Association founded, two years later **Harold Himsworth (1905-1993)** British physician confirmed earlier work of **Wilhelm Falta (1875-1950)** to identify two forms of diabetes-insulin sensitive or those insensitive or resistant.

Different Types of Insulin from 1936

- To avoid injections pre meals and during the night, longer acting insulin developed at Nordisk laboratories, Copenhagen under direction of **Hans Christian Hagedorn (1888-1971)**.
- 1936 Insulin combined with protamine to release insulin over 6-8 hours. Protamine Zinc Insulin (PZI) developed at Toronto University in same year, effective for 24 hours but tendency to hypoglycaemia.
- 1940 Neutral Protamine Hagedorn (NPH) or Isophane available and Lente series developed by Novo Labs 1952.

Structure of Insulin

- 1951 Amino acid sequence of insulin by British biochemist **Frederick Sanger (b1918)** polypeptide of 51 amino acids in two chains linked by disulphide bonds. 1969 British chemist **Dorothy Hodgkin (1910-1994)** determined spatial conformation by x ray diffraction.

Developments in Insulin Therapy from 1952

- Single injection of PZI or twice daily soluble insulin and NPH. To reduce infection risks disposable syringe/needle introduced 1961 by Becton Dickinson, needle free delivery devices by Derata 1979 and popular 'penjet', combined syringe and insulin vial as single unit designed by Glasgow physician **John Ireland (1932-1987)** in 1981 marketed by Novo 1985.
- 1964 Insulin pumps by **Dr Arnold Kadish** in Los Angeles but heavy, 1972 **Dean Kamer** designed lightweight form worn on body. 1978 studies by **John Pickup** and **Harry Keen** at Guy's with continuous subcutaneous insulin infusion in short pulses from battery operated pump improved glycaemic control. 2003 Medtronic/Becton Dickinson combined minipump/glucose monitor worn discreetly. Pumps improved personal freedom but were expensive.

Experimental Treatment-Transplantation

- 1916 pancreatic graft by English surgeon **Frederick Pybus (1883-1975)**, first pancreatic transplant as treatment 1966 by **Richard Lillelei (1927-1981)** professor of surgery, Minnissota University. Improved islet cell isolation by **Paul Lacy (1924-2005)** allowed their transplantation. Relatively few transplants due to technical problems and limited success (10%) for insulin independence. Islet cell transplant improved 2000 by Canadian team led by **James Shapiro** using 'Edmonton' protocol and more effective immunosuppression.



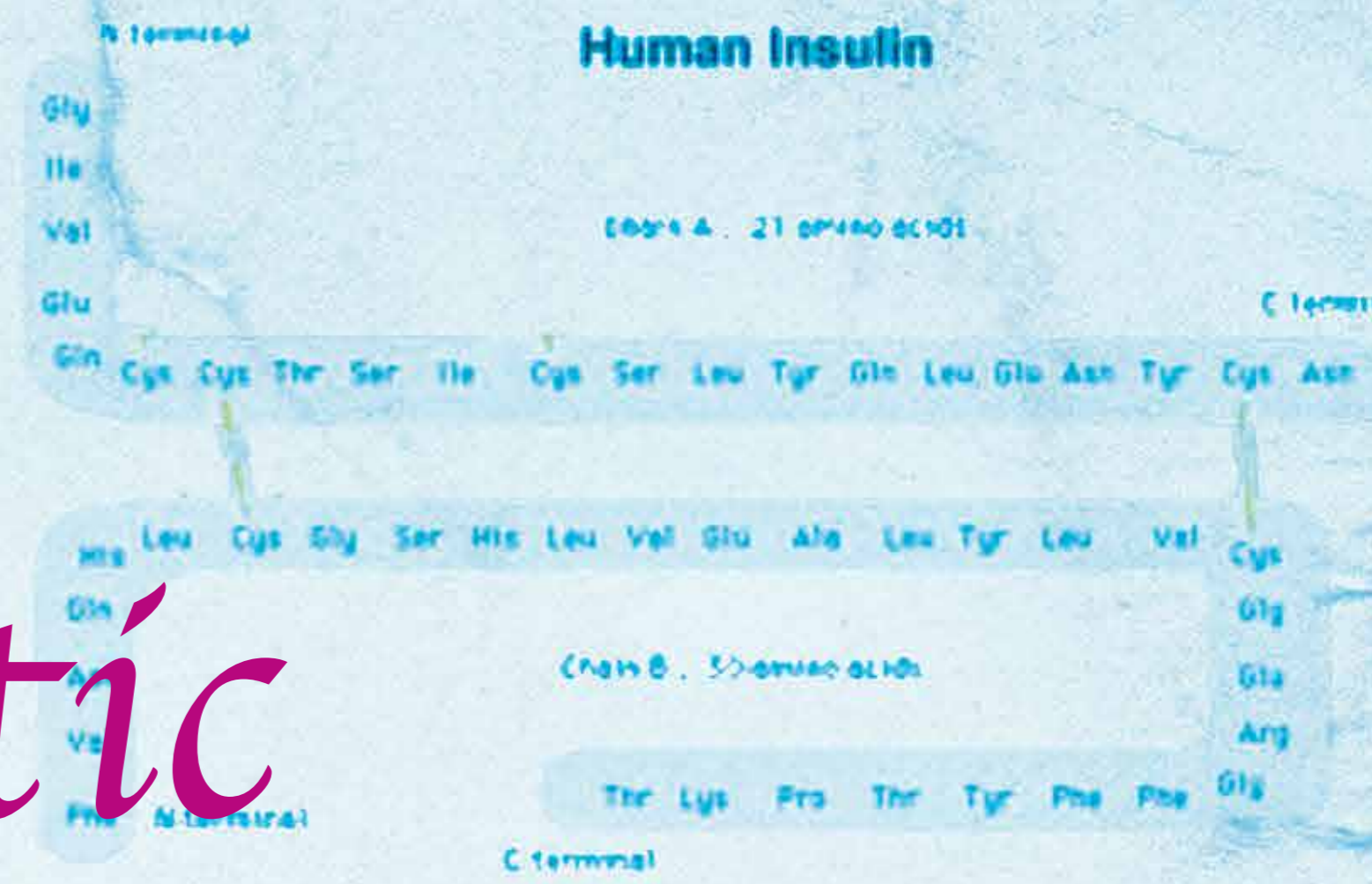
Human Insulin

- 1974 by Ciba Geigy expensive with allergic side effects. 1981 genetic engineering project by Genentech and Eli Lilly used gene insertion into E.Coli. During 1990's many UK patients transferred to biosynthetic insulin. Minor alterations in insulin amino acid structure gave insulin analogues such as Lispro (Humalog) by Eli Lilly in 1996 with fast short acting properties to cover meals. Combination with regular insulin eg Humulin R, NPH (Novolin N) and Lente (Humulin L) now available.

A Brief History of Oral Hypoglycaemic Agents (OHA) in Type 2 Diabetes

- 1942 oral sulphonamide found to lower blood glucose but serious toxic effects. 1955 carbutamine, a sulphonylurea, effective in older non insulin dependent diabetics stimulating beta cells to produce more insulin. Other safer first generation sulphonylureas include tolbutamide (1956), and chlorpropamide (1958) and second generation glycopyramide (1965), glybenclamide (1965) and gliclazide (1985). Metformin, biguanide introduced 1958 increased sensitivity to insulin, suppressing digestion and glucose absorption used alone or with second generation sulphonylurea. More recent OHA include alpha glucosidase inhibitors eg Bayer acarbose decrease glucose absorption and thiazolidinediones eg pioglitazone increase insulin sensitivity.

Human Insulin

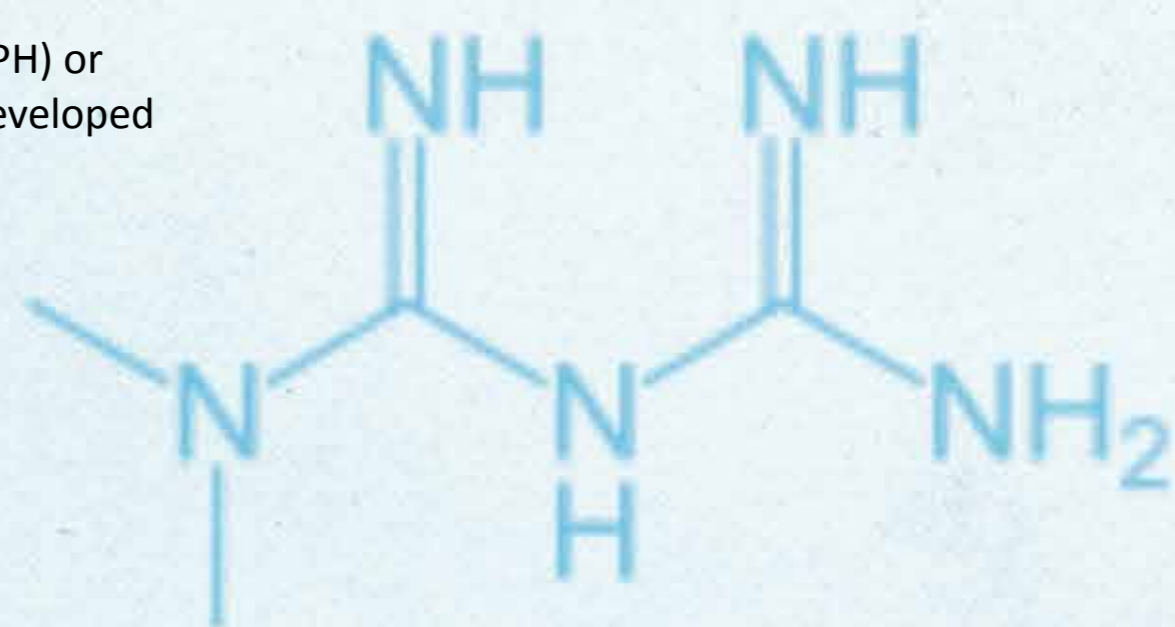
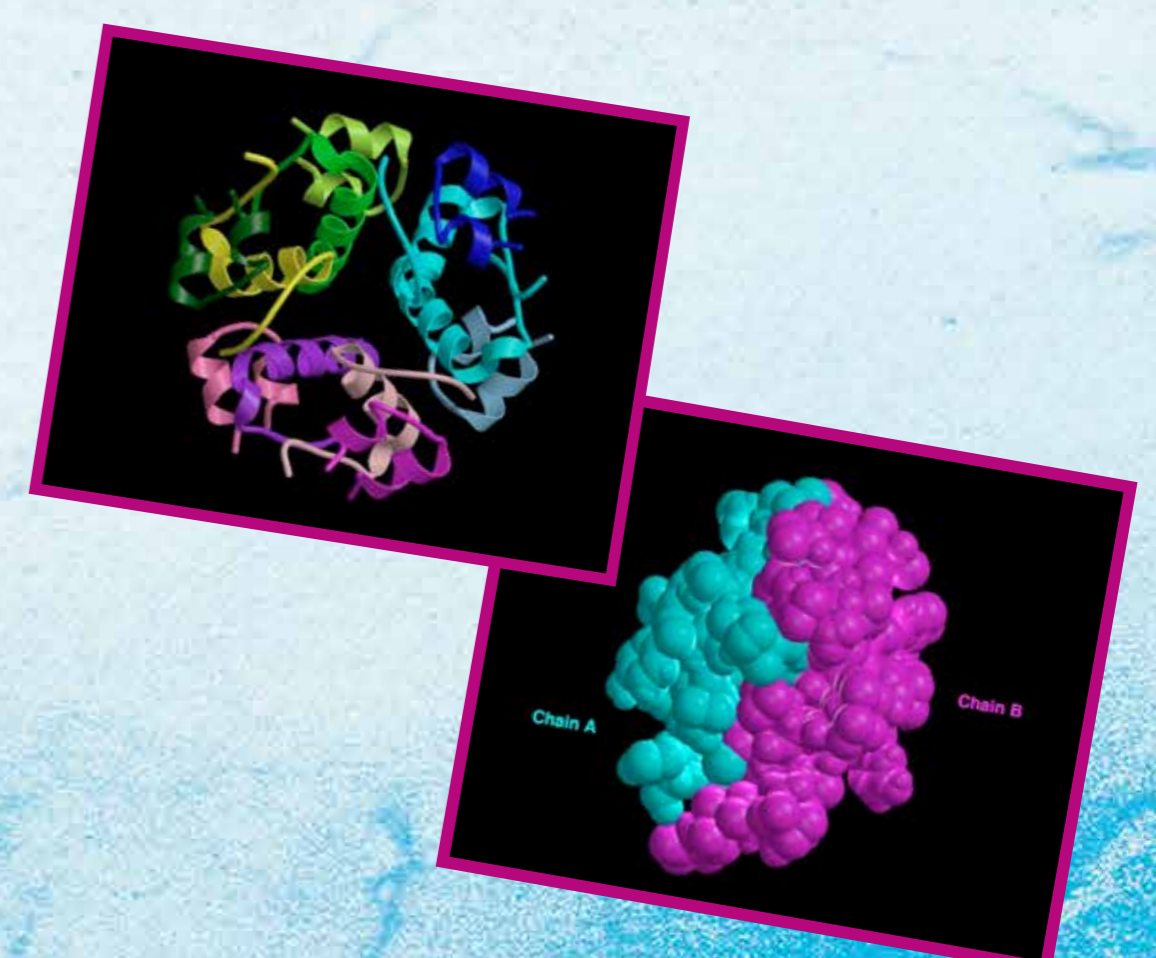


Type 1 Diabetes is an Autoimmune Disorder

- Pioneer work by **Solomon Berson (1919-1972)** and **Rosalyn Yalow (1921-2011)** developed an insulin radioimmunoassay which showed an insulin binding globulin in serum of insulin treated diabetics and measureable insulin concentrations in type 2 but low concentrations in type 1. 1965 Belgian pathologist **Willy Gepts (1922-1991)** reported a high frequency of insulinitis, lymphocyte infiltration of islet cells, in type 1 patients dying within six months of diagnosis suggesting an 'immunological' cause. Islet cell auto antibodies described 1974 by **D Doniach (1912-2004)** and **GF Bottazzo** at Middlesex Hospital associated with specific HLA types in juvenile or insulin dependent diabetes. Comparison with other autoimmune disorders and studies by notably, **Jon Nerup** and colleagues in 1975 confirmed HLA link to B8 & B15, and the concept that genes transmit a tendency to develop diabetes. However, the 'trigger' for autoimmune response has not been established but viral causes have been proposed..

Type 2 Diabetes and Genetic Vulnerability

- As early as 600 BCE observed that diabetes often ran in families but it was not until the 20th century genetic studies by **G Pincus (1903-1967)** in 1933 with further work in 1947 by **H Harris (1919-1994)** all with inconclusive results. The association between genetic predisposition, insulin resistance, central obesity and hypertension was proposed in 1988 by **Gerald Reaven (b1928)** and raised the current emphasis for lifestyle modification in diet and increased exercise.



Hans Christian Hagedorn (1888-1971)

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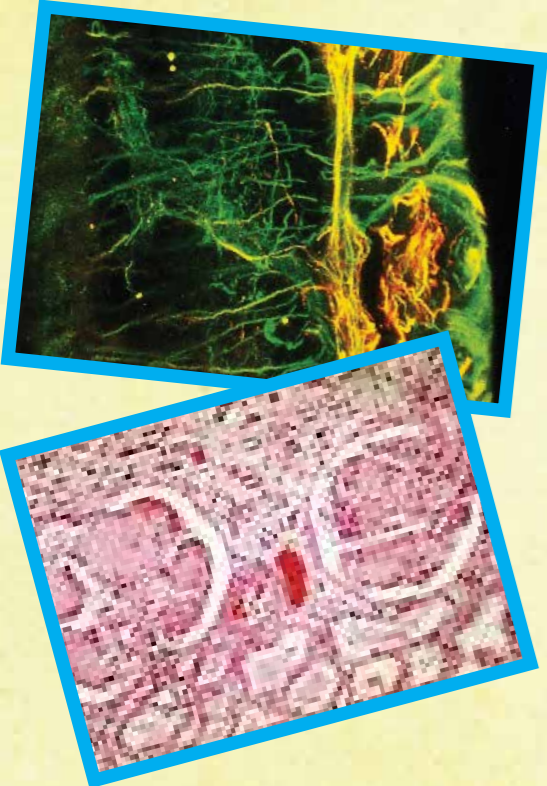
Complications, Control & Testing

Complications of Diabetes

Neonatal mortality

- 1937 increase highlighted by **Raymond Titus (1883-1949)**. At King's College caesarean section between 36th to 38th weeks of pregnancy introduced from 1942. In 1954 improved outcomes with blood glucose near normal during pregnancy reported by **Jorgen Pedersen (1914-1978)**.

Retinal scarring



Retinopathy

- 1934 Mayo Clinic studies showed repeated retinal haemorrhages cause of blindness in diabetes. Around 1950 laser photocoagulation first used and many laser variations followed. More recently specialised surgery introduced.

Diabetic Nodular Nephropathy

Nephropathy

- 1936 **Paul Kimmelsteil (1900-1970)** and **Clifford Wilson (1906-1997)** at Harvard demonstrated nodules within renal glomeruli which impaired renal function. Treated first by protein restriction, later renal dialysis and transplantation

Neuropathy

- Observed by **John Rollo** in 1798 and reported by **Frederick Pavy** in 1885 affecting sensory esp. hands, feet and the autonomic nervous systems. 1954 **William Oakley (1906-1998)** proposed diabetic nerve damage significant factor in perforating foot ulcers and gangrene.

Cardiovascular disease

- During the 20th century repeated reports of vascular lesions, early myocardial infarction and strokes more common in type 2 diabetes confirmed by 1950 Framingham heart study. Various pathological mechanisms proposed for increased risk of atherosclerosis. Blocked arteries to the lower limbs are common cause of gangrene affecting toes.

New Technology & the Complications Control Trials

- Impact of serious complications fuelled a global debate on need for blood glucose control led to two major trials. USA 1985-1993 for type 1 and UK 1977-1997 for type 2. New technologies were used to assess outcomes of more intensive treatment and maintaining blood glucose close to normal range and included glucose meters, HbA1c and urine microalbumin.

Glucose meters

- Further advances in reagent strip technology at Ames resulted in Dextrostix (1964) used to measure whole blood glucose. To improve precision and reliability Ames developed the Ames Reflectance Meter in 1970. Intense commercial developments have taken place during the last four decades and a wide variety of reagent strip meter systems are available to GP's, Clinics and significantly the patients themselves. Laboratory staff today play an important role in 'point of care testing' and management of glucose meters.

Glycated haemoglobin (HbA1c)

- HbA1c in blood haemolysates of diabetics first demonstrated by **Samuel Rahbar** in 1968. In 1976 it was shown by **A Cerami** and **Ronald Koenig** that % formed could be related to the average blood glucose over previous 4 months, the life cycle of red blood cell. This was a significant factor in the retrospective assessment of blood glucose control to target limits in the trials. HbA1c is now a high volume workload assay in all laboratories using methods such as affinity chromatography, HPLC or immunoassay.

Microalbumin

- More sensitive immunoassay for urine albumin was devised in 1963 by **Harry Keen** and used as an early indicator of impaired renal function. It has been replaced by automated renal function tests.

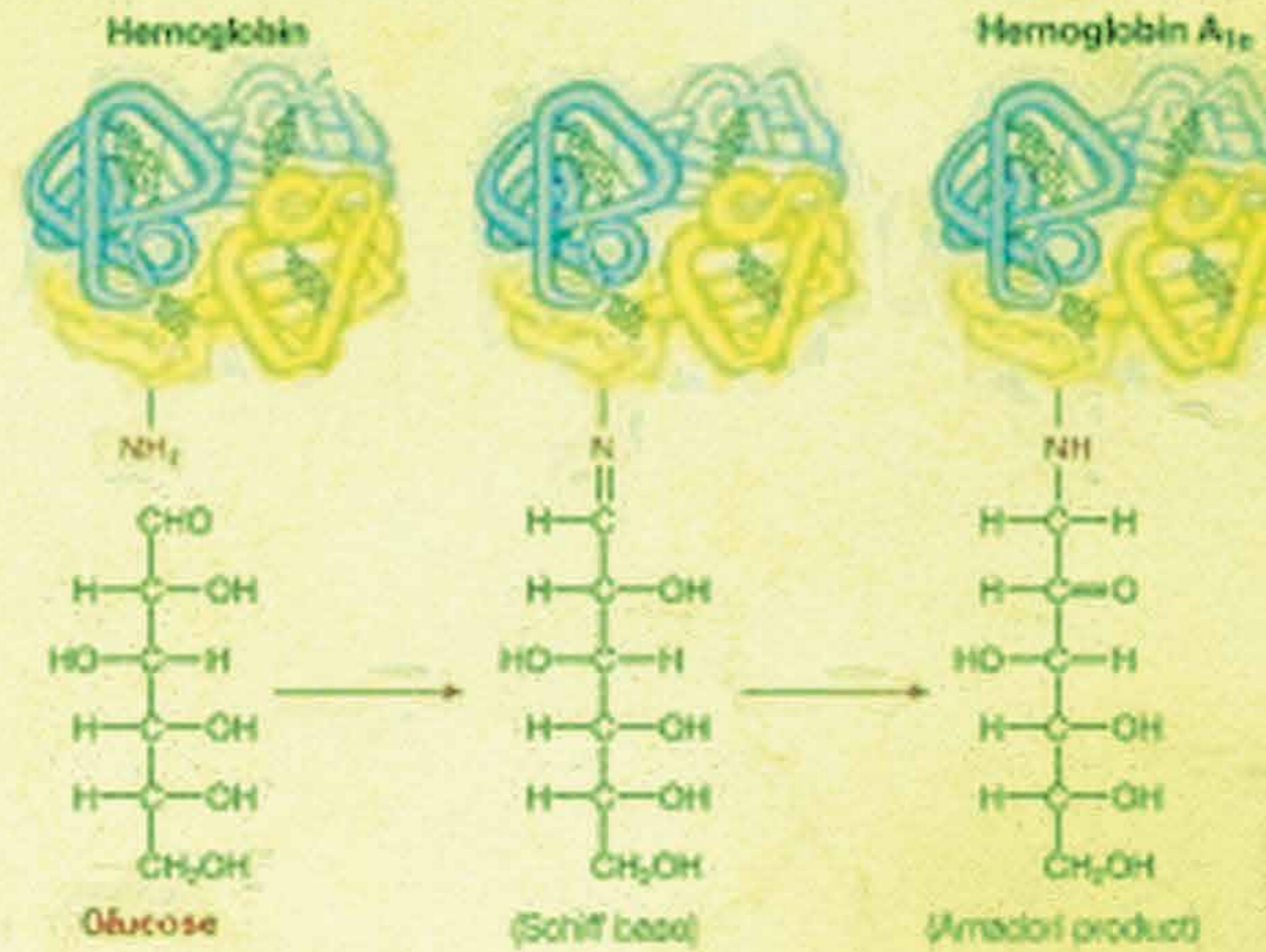
Results

DCCT (type 1 diabetes)

- Found significantly reduced risks of retinopathy, nephropathy and neuropathy. A higher risk of hypoglycaemia was reported and no reduction of risk of cardiovascular disease.

UKPDS (type 2 diabetes)

- Positive benefits were found for retinopathy and nephropathy by improved blood glucose and blood pressure control. Due to the mix of treatment eg insulin, sulphonylureas, metformin this was a longer trial and interpretation of results more complex.



**Ames Reflectance
Meter 1970**



**A Range of
Modern Meters**

DAILY NEWS

**'Read All About It':
Diabetes Makes the Headlines**

2000: DIABETES BECOMES EPIDEMIC
World Health Organisation estimated that 171 million in the World have diabetes and projected to 366 million in year 2030

2012: MOST NHS COSTS ON DIABETES ARE WASTEFUL (Diabetes UK)
80% of NHS costs in diabetes involve treatment of complications.

2012: 24,000 WITH DIABETES ARE DYING NEEDLESSLY (Diabetes UK)
Refers to the number of people failing to have 9 recommended tests for diabetes at GP annual review.

2013: DIABETES UK TOLL HITS 3 MILLION (Diabetes UK)
An increase from 2.2 million in 2006 and a further 850,000 may be undiagnosed type 2

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DEVELOPMENTS IN TESTS FOR GLUCOSE



DEPICTED IS THE LABORATORY AND EQUIPMENT IN THE UNIVERSITY OF TORONTO USED BY BANTING AND BEST. THE INSTRUMENT SHOWN IS A DUBOSCQ COLORIMETER

STANLEY ROSSITER BENEDICT (1884 – 1936)

IN 1907 HE INTRODUCED A TEST FOR DETECTING GLUCOSE IN URINE. A SAMPLE OF URINE IS BOILED WITH A COPPER SULPHATE SOLUTION AND THE PRESENCE OF GLUCOSE IS DETERMINED BY A CHANGE IN COLOUR FROM BLUE TO YELLOW/ORANGE.



HELEN M FREE (b. 1923) & ALFRED FREE (1913 – 2000)

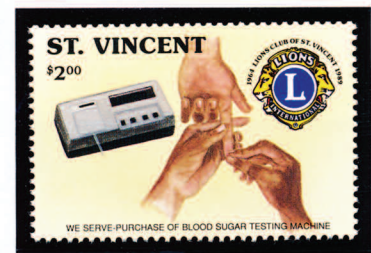
AMERICAN RESEARCH CHEMISTS WHO WORKED AT THE MILES LABORATORIES WERE SEEKING TO FIND A BETTER AND EASIER TEST FOR GLUCOSE AND KETONES THAN THE *CLINITEST TABLET* TOGETHER THEY DEVELOPED A CHEMICALLY COATED TEST STRIP WHICH DETECTED VARIOUS SUBSTANCES IN URINE. THIS RESULTED IN THE PRODUCTION IN 1957 OF THE *CLINISTIX* 'DIP AND READ TEST' FOR URINARY GLUCOSE. *MULTISTIX* FOLLOWED IN 1981



THIS STAMP ISSUED FOR THE NATIONAL DIABETES ASSOCIATION OF BRAZIL, DEPICTS A HUMMING BIRD WHICH LIVES ON NECTAR (SUGAR) AND ITS TAIL IS SHOWN AS A 'DIPSTICK' FOR GLUCOSE

ANTON H CLEMENS (1928 – 2011)

GERMAN/AMERICAN ENGINEER WORKING AT MILES LABORATORIES IN 1970 DEVELOPED THE FIRST BLOOD GLUCOSE METER – *THE AMES REFLECTANCE METER (ARM)* THIS LED TO THE DEVELOPMENT OF THE SELF MONITORING OF BLOOD GLUCOSE (SMBG) FOR DIABETIC PATIENTS MODERN MACHINES POWERED BY SMALL BATTERIES NOW HAVE DIGITAL DISPLAYS, MEMORY FEATURES AND COMPUTER DOWNLOAD FACILITIES



STRUCTURE AND MEASUREMENT OF INSULIN



JOHN JACOB ABEL (1857 – 1938)

AMERICAN BIOCHEMIST AND PROFESSOR OF PHARMACOLOGY AT THE JOHN HOPKINS UNIVERSITY. IN 1926 HE ISOLATED AND PURIFIED CRYSTALLINE INSULIN. THE RHOMBOHEDRAL CRYSTALS ARE SHOWN ON THE STAMP ISSUED FOR THE 15th INTERNATIONAL DIABETES FEDERATION CONGRESS HELD AT KOBE, JAPAN IN 1994.

FREDERICK SANGER (b.1918)

BRITISH BIOCHEMIST WORKING AT CAMBRIDGE UNIVERSITY DISCOVERED THE COMPLETE AMINO-ACID SEQUENCE OF A PROTEIN. USING HIS NEW METHODS FOR AMINO-ACID SEQUENCING. HE DETERMINED THAT THE INSULIN MOLECULE WAS COMPOSED OF TWO DIFFERENT AMINO-ACID CHAINS LINKED BY TWO BRIDGES OF SULPHUR ATOMS. HE WAS AWARDED THE **1958 NOBEL PRIZE** FOR CHEMISTRY FOR THIS WORK.



DOROTHY MARY CROWFOOT HODGKIN (1910 – 1994)

BRITISH CHEMIST AND CRYSTALLOGRAPHER. DURING HER TIME AT SOMERVILLE COLLEGE OXFORD, SHE USED X-RAY CRYSTALLOGRAPHY TO DETERMINE THE STRUCTURE OF VARIOUS SUBSTANCES INCLUDING INSULIN. HODGKIN WAS AWARDED THE **1964 NOBEL PRIZE** IN CHEMISTRY FOR HER WORK ON THE STRUCTURE OF BIOCHEMICAL COMPOUNDS, SPECIFICALLY FOR DEFINING THE MOLECULAR STRUCTURE OF VITAMIN B12

ROSALYN SUSSMAN YALOW (1921 – 2011)

AMERICAN BIO-PHYSICIST WHO DEVELOPED RADIOIMMUNOASSAY (RIA) FOR THE QUANTITATIVE MEASUREMENT OF LOW LEVEL CONCENTRATIONS OF PEPTIDE HORMONES. IN THE MID 1950s **YALOW AND BERSON** FOUND THAT PEOPLE RECEIVING INJECTIONS OF ANIMAL INSULIN PRODUCED ANTIBODIES. IN 1961 THEY USED A RIA TECHNIQUE TO MEASURE INSULIN CIRCULATING IN THE BLOOD YALOW WAS AWARDED THE **1977 NOBEL PRIZE** FOR MEDICINE FOR THE DISCOVERY AND DEVELOPMENT OF RADIOIMMUNOASSAY OF PEPTIDE HORMONES



SEARCHING FOR A TREATMENT



FREDERICK BANTING (1891 – 1941)

CANADIAN PHYSICIAN APPROACHED **JOHN MACLEOD**, PROFESSOR OF PHYSIOLOGY, UNIVERSITY OF TORONTO, FOR RESEARCH FACILITIES IN HIS LABORATORY. MACLEOD ASSIGNED STUDENT **CHARLES BEST (1899–1978)** AND BIOCHEMIST, **JAMES COLLIP (1892–1965)** TO ASSIST. TOGETHER THEY SET OUT TO OBTAIN A PANCREATIC EXTRACT. IN 1921 BANTING AND BEST REPORTED THEY HAD ADMINISTERED MORE THAN 75 DOSES OF '**ISLETIN**' THEIR PANCREATIC EXTRACT TO 10 DOGS WITH SURGICALLY INDUCED DIABETES, RESULTING IN A REDUCTION IN BLOOD AND URINARY SUGAR. THEY PUBLISHED THE RESULTS OF THEIR FIRST HUMAN CLINICAL TRIAL IN MARCH 1922. BANTING AND MACLEOD WERE AWARDED THE **1923 NOBEL PRIZE** FOR MEDICINE.

NICOLAE PAULESCU (1869 – 1931)

ROMANIAN PHYSIOLOGIST IN 1916 DEVELOPED AN AQUEOUS PANCREATIC EXTRACT WHICH WHEN INJECTED, LOWERED THE BLOOD SUGAR LEVEL OF A SURGICALLY INDUCED DIABETIC DOG. HE PUBLISHED THREE PAPERS ON THE EFFECTS OF INJECTING PANCREATIC EXTRACTS INTRAVENOUSLY INTO NORMAL AND DIABETIC DOGS DURING APRIL TO JUNE 1921. PAULESCU NAMED HIS EXTRACT '**PANCREINE**' AND SECURED PATENT RIGHTS FOR ITS MANUFACTURE ON 10th APRIL 1922



AUGUST STEENBERG KROGH (1874 – 1949)

DANISH PHYSIOLOGIST ON A VISIT TO AMERICA IN 1922 TO PRESENT A PAPER AT YALE UNIVERSITY, DECIDED TO VISIT BANTING AND MACLEOD IN TORONTO. HE WAS FAMILIAR WITH THEIR WORK ON INSULIN AS HIS WIFE WAS A DIABETIC. KROGH SECURED THEIR PERMISSION TO PRODUCE INSULIN IN SCANDINAVIA.

KROGH AND HANS CHRISTIAN HAGEDORN (1888 – 1971)

KROGH AND FELLOW DANISH PHYSICIAN, HAGEDORN BEGAN THE PRODUCTION OF INSULIN DERIVED FROM PIG PANCREAS AT THE LEO LABORATORIES IN DENMARK.

IN MARCH 1923, THE FIRST PATIENTS WERE TREATED WITH **INSULIN LEO**. THEY ESTABLISHED **NORDISK INSULIN LABORATORIES** AS AN INDEPENDENT NOT PROFIT INSTITUTION IN 1924. A SECOND COMPANY **NOVO TERAPEUTISK** WAS FOUNDED IN 1925 AND DENMARK BECAME THE WORLD LEADING PRODUCER OF INSULIN. IN 1936 THE FIRST SLOW RELEASE INSULIN WAS PRODUCED. THE TWO COMPANIES COMBINED IN 1989 TO FORM **NOVO NORDISK**



UNRAVELLING

THE ROLE OF THE PANCREAS AND THE LIVER

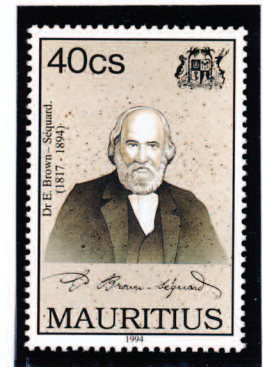


CLAUDE BERNARD (1813 – 1878)

A FRENCH PHYSIOLOGIST AND PHYSICIAN WHO FOUND HIGHER CONCENTRATIONS OF SUGAR IN THE HEPATIC VEIN COMPARED TO THE PORTAL VEIN AND SUMMISED THAT THE LIVER MUST BE SECRETING SUGAR. THE LIVER CONTAINS A STARCH LIKE SUBSTANCE WHICH HE CALLED **GLYCOGEN** (SUGAR FORMING)

CHARLES EDOUARD BROWN – SEQUARD (1817 – 1893)

A MAURITIAN PHYSICIAN INVESTIGATING THE ADRENAL GLAND IN 1869 POSTULATED THE INTERNAL-SECRETION THEORY. HE SUGGESTED THAT ALL GLANDS WITH DUCTS (EXOCRINE) OR WITHOUT DUCTS (ENDOCRINE) SUPPLY USEFUL OR ESSENTIAL SUBSTANCES TO THE BLOOD. LACK OF THESE SUBSTANCES MAY PRODUCE PHYSIOLOGICAL SIGNS



OSKAR MINKOWSKI (1858 – 1931)

A LITHUANIAN PHYSICIAN AND SURGEON WORKING WITH JOSEPH VON MERING IN 1889 REMOVED THE PANCREAS OF A DOG WHICH DEVELOPED THE SYMPTOMS OF DIABETES, CAUSING EXCESSIVE HUNGER, ABNORMAL THIRST AND MARKED POLYURIA. DURING FURTHER EXPERIMENTS THEY FOUND SUGAR IN THE URINE (DEXTROSE) AND PHYSICAL DETERIORATION, LEADING TO COMA AND DEATH. THIS WAS ONE OF THE MOST SIGNIFICANT DISCOVERIES IN THE UNDERSTANDING OF DIABETES

GERTY THERESA RADNITZ CORI (1896 – 1957)

CARL FERDINAND CORI (1896 – 1984)

CZECHOSLOVAKIAN BIOCHEMISTS WORKING IN AMERICA DURING 1930's AND 1940's CLARIFIED THE BIOCHEMICAL REACTIONS INVOLVED IN THE GLUCOSE-GLYCOGEN INTERCONVERSION NOW KNOWN AS THE **CORI CYCLE**. THEY ISOLATED THE ENZYME **GLYCOGEN PHOSPHORYLASE** WHICH IS INTEGRAL TO THE PROCESS. IN 1947 THEY WERE AWARDED THE **NOBEL PRIZE** FOR MEDICINE



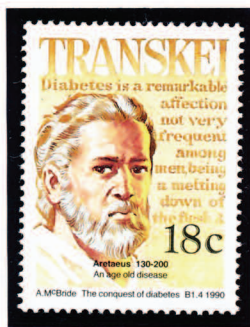
THE PISSING EVIL



THE EBERS PAPYRUS (1552 BCE) DISCOVERED NEAR THEBES BY GEORGE EBERS A GERMAN EGYPTOLOGIST IS THE EARLIEST WRITTEN DESCRIPTION OF DIABETES, CONTAINING REMEDIES FOR *'THE ELIMINATION OF URINE WHICH IS TOO PLENTIFUL'*

HIPPOCRATES (460 – 377 BCE)

GREEK PHYSICIAN REGARDED AS THE 'FATHER OF MEDICINE' REFERRED TO EXCESSIVE URINARY FLOW WITH WASTING OF THE BODY HE STATED *'THE AMOUNT OF URINE PASSED WAS NOT PROPORTIONATE TO THE AMOUNT DRUNK BUT IN CONSIDERABLE EXCESS'*



ARETAEUS OF CAPPADOCIA (130 -200 CE)

PROVIDED THE FIRST ACCURATE DESCRIPTION OF THE SYMPTOMS, IN HIS TREATISE 'ON THE CAUSES AND SYMPTOMS OF CHRONIC DISEASES' HE NOTED THAT. PATIENTS *'NEVER STOPPED MAKING WATER AND THE FLOW IS INCESSANT'*. HE NAMED THE DISEASE **DIABETES** FROM THE GREEK WORD FOR SYPHON.

CLAUDIUS GALEN (130 – 201 CE)

GREEK PHYSICIAN AND SCHOLAR DISCUSSED DIABETES IN SEVERAL OF HIS WORKS REFERRING TO THE AILMENT AS *'DROPSY INTO THE POT'* OR *'DIARRHOEA OF THE URINE'* AND *'THE THIRSTY DISEASE'*. HE BELIEVED IT TO BE A DISEASE OF THE KIDNEYS. THIS CONCEPT WAS ACCEPTED THROUGHOUT EUROPE INTO THE 19TH CENTURY



MOSES MAIMONIDES (1135 – 1204 CE)

JEWISH PHYSICIAN AND PHILOSOPHER SPOKE OF A DISEASE WITH EXCESSIVE THIRST (POLYDIPSIA) AND THE PASSING OF LARGE VOLUMES OF URINE (POLYURIA). HE AGREED WITH GALEN THAT THIS ILLNESS IS THE SAME AS DIABETES (INSIPIDUS). PATIENTS WITH THIS ILLNESS DRINK LARGE QUANTITIES OF FLUID AND RAPIDLY URINATE MORE THAN THEY DRINK.

WATER – CASTERS AND TASTERS

ERSTTAG



„HARNBESCHAU“, EINE MINIATUR AUS DEM CANONE DI AVICENNA (980–1037)



5. KONGRESS DER EUROPÄISCHEN VEREINIGUNG FÜR UROLOGIE IN WIEN, 12.–15. MAI 1982



UROSCOPY - EXAMINATION OF URINE BY SIGHT (WATER-CASTING), SMELL AND TASTE TO DIAGNOSE DISEASE. URINE WAS COLLECTED IN A **MATULA**, A BULBOUS GLASS VESSEL SHAPED LIKE A URINARY BLADDER. TRAVELLING UROSCOPISTS INCLUDING PHYSICIANS, ‘WATER-DOCTORS’ AND CHARLATANS SET UP STALL IN TOWNS AND VILLAGES HANDING OUT MATULAS IN WICKER BASKETS. CUSTOMERS THEN RETURNED WITH THEIR SAMPLES WHICH WERE EXAMINED AND MEDICATION PRESCRIBED



PARACELSUS (1493 – 1541)

SWISS PHYSICIAN WHO RIDICULED THE ‘PISS GAZERS AND PROPHETS’ AND SUGGESTED THAT THE WAY FORWARD WAS BY CHEMICAL ANALYSIS. HE EVAPORATED URINE FROM DIABETICS AND OBTAINED A WHITE RESIDUE WHICH HE MISTOOK FOR SALT



IBN-SINA AVICENNA (980 – 1037)

PERSIAN PHYSICIAN, PHILOSOPHER AND ASTRONOMER WHO WROTE ‘CANON OF MEDICINE’ A FIVE VOLUME ENCYCLOPAEDIA. IN THIS HE DESCRIBED DIABETES AS A PROGRESSIVE DISEASE WITH EXCESSIVE WATER FLOW, SWEET TASTING URINE, WASTING OF THE BODY, AND NON- HEALING WOUNDS.