Hesy-Ra notes a disease causing frequent urination that is attractive to ants (A).

Thomas Willis adds mellitus ('like honey') (C).

Apollinaire Bouchardat notes less glucose in the urine resulting from war rations leading to fad diets (F).

Primary structure of insulin characterized by Frederick Sanger (first protein sequenced). Nobel prize in Chemistry awarded in 1958 (J).

Estimated 415 million people living with diabetes (~50% undiagnosed).

 estimated increase to 642 million people affected.

1552 BC
1425
150 AD
1674
1794
1700s
1869
1870
1916
1955
1970
2018

1963
2040

1889
1920

2018

1889
1920
1955
1970
2018

2040

2040

2040

2040

2040

2040

2040

2040

2040

2040
Leading causes of death in 2015 (WHO global estimates in millions)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>8.76</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>6.24</td>
</tr>
<tr>
<td>COPD</td>
<td>3.19</td>
</tr>
<tr>
<td>Lung disease/cancer</td>
<td>3.17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.69</td>
</tr>
<tr>
<td>Alzheimer's/dementia</td>
<td>1.59</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>1.54</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.39</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.37</td>
</tr>
<tr>
<td>Road injury</td>
<td>1.34</td>
</tr>
</tbody>
</table>

30 million cases of diabetes cost the US public more than $245 billion annually.

**Diabetes insipidus**

**Definition:** Set of incurable hormone deficiencies

**Incidence:** 3 in 100,000

**Symptoms:** Excess urination (polyuria up to 20L a day) and thirst (polydipsia), no effect on the glucose levels

**Complications:** Dehydration, seizures etc.

**Types:** Four main including central DI results from insufficient production of the antidiuretic hormone vasopressin

**Treatment of CDI:** Desmospressin (tablet, longer half-life)

**Vasopressin:** R = NH₂

**Desmopressin:** R = H

1955 Nobel prize in Chemistry awarded to Vincent du Vigneaud for synthesis of polypeptide hormones (including vasopressin)

**Diabetes mellitus**

**Definition:** Set of incurable metabolic disorders characterized by hyperglycemia (excessive glucose in the blood)

**Incidence:** 770 in 100,000

**Symptoms:** polyuria + polydipsia + polyphagia (the hyperglycemic triad), headache, fatigue, blurred vision, poor wound healing

**Acute complications:** hyperglycemic emergencies result in diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

**Chronic complications:** risk of cardiovascular disease (fatty acid deposits more build up quickly), stroke, kidney disease, nerve damage, foot ulcers, eye damage, sexual dysfunction

**Types:** Multiple

**Glucose digestion and cellular uptake**

- Mechanical/chemical digestion begins
- Conversion of fructose and galactose to glucose in the liver and storage of glycogen
- Pancreas secretes digestive enzymes and emits insulin
- Further digestion and absorption of glucose into the blood in the small intestine
Treatment of Diabetes

**Insulin**
- TFs PDX1, NeuroD1, MafA promote expression upon high glucose levels
- Stored as a hexamer in pancreatic β-cells, active as a monomer ($t_{1/2} = 5\text{ min}$)
- Increases glucose uptake + fat storage (deactivates glycogen synthase kinase)
- 51 amino acids, 5808 Da, A-chain and B-chain dimer linked by disulfide bonds
- Sequenced in 1955 by Sanger, X-ray in 1969 by Dorothy Hodgkin
- Varies between species (three AA difference in bovine, one in porcine)
- Since 2006 all insulin distributed in US is recombinant human

**Acute complication: Diabetic ketoacidosis**
- Lack of insulin promotes ketogenesis resulting in ketoacidosis (decreased pH in the blood)
- Symptoms include weakness, abdominal pain, nausea, vomiting, hyperventilation (respiratory alkalosis removes CO$_2$ to lower blood H$_2$CO$_3$)
- Simultaneous osmotic diuresis results in polyuria, polydipsia, cramps, vision trouble, altered level of consciousness
- Can lead to cerebral edema and death
- Treat with IV, potassium replacement and insulin therapy
- 135,000 hospital admissions annually in the US due to DKA

**Type 1 DM (‘insulin-dependent’, ‘juvenile’)**
- An autoimmune disease limits insulin production, (TT-cell mediated attack on β-cells, cause unknown although genetic and viral factors)
- 6% of DM usually developing in children, teenagers.
- Rapid development of symptoms (DKA likely)
- Diagnose by fasting blood glucose level, monitor via HbA$_1C$
- 20 year decrease in life expectancy

**Insulin therapy**
- Goal is tight blood-sugar control to prevent DKA
- Many dosing regimes to cover basal (background; food, exercise, health) and bolus (carbohydrate coverage) insulin replacement
- Side effect = weight gain, risk of hypo/hyperglycaemia if not managed
- Aim for 70-130 mg/dL before meals and <180 mg/dL 1-2 h after meals
- Subcutaneous injection and inhalation available, oral under massive investigation
- Analogues offer different ADME profiles (mainly single residue modifications)

**Insulin Delivery Devices**
- Insulin syringe
- Insulin pen
- Jet injector
- Insulin pump
**Type 2 DM (‘non-insulin-dependent’, ‘adult-onset’)**
- Cells fail to respond to insulin correctly due to resistance
- Reduction in insulin production possible (pancreatic β-cell amyloid buildup)
- 90% of DM, later onset than type 1
- Risk factors incl. genetic and physiological (including overweight, inactive lifestyle, smoking, vit D deficiency)
- Type 1 symptoms observed + weight gain (insulin effect)
- Same method of diagnosis as type 1 (check blood sugar and HbA1C)
- Insulin/IGF1 play a role in neural stem cell differentiation via the PI3K/AKT pathway. Overloading via excessive glucose ingestion causes the body to desensitize insulin receptors (as observed in pregnancy)
- 10 year decrease in life expectancy (CV, stroke, kidney failure etc.)

**Acute complication: Hyperosmolar hyperglycemic state**
- Osmotic diuresis without significant ketogenesis (due to sufficient insulin in the blood)
- Complications may include seizures, blood clots, mesenteric ischemia and rhabdomyolysis
- Usually preceded by infection
- Treat with IV, low mw heparin, potassium replacement, antibiotics
- Common especially in elderly (exact frequency unknown)

**Treatment: Diet and exercise**
- Excess body fat associated with 30% (Chinese), 60-80% (European/African) and 100% (Pacific Islanders) of cases
- Vigorous exercise once per week found to reduce risk of type 2 by 30%
- Glycemic index rates foods by how much and how quickly they raise blood glucose
- Weight loss surgery is effective for patients unable to control blood sugar
Treatment of Diabetes

Cian Kingston, 2018

Treatment: Medications

**Metformin**

**Overview:** First-line, oral delivery, generic: $5-$25 per month, $t_{1/2} = 6h$ in plasma

**History:** Introduced 1957 France, 1995 US, WHO LEM

**Action:** Suppress gluconeogenesis in liver (not well understood) and increases insulin sensitivity (stimulates GLUT4)

**Possible side effects:** Diarrhea, nausea, abdominal pain, lactic acidosis

**Contraindications:** Any risk of LA (kidney disorder, liver/lung disease)

**Sulfonylureas**

- Acetohexamide (1st gen)
- Carbutamide (1st)
- Chlorpropamide (1st)
- Metahexamide (1st)
- Tolazamide (1st)
- Tolbutamide (1st)
- Glyburide (2nd) - Roche
- Glibornuride (2nd) - MEDA
- Glipizide (2nd) - Pfizer
- Gliclazide (2nd)
- Glipizide (3rd) - Sanofi-Aventis
- Glycopyramide (2nd)

**Overview:** Oral delivery, generally disfavored due to weight gain

**History:** Discovered 1942

**Action:** Stimulates insulin secretion, evidence of increased sensitivity and decreased lipolysis

**Possible side effects:** Risk of hypoglycemia, weight gain, gastrointestinal, headache, CV

**Contraindications:** Liver/kidney impairment (hypoglycemia risk)

**Meglitinides**

- Repaglinide - Novo Nordisk
- Nateglinide - Novartis

**Overview:** Similar to sulfonylureas but milder

**History:** Main branded drug is repaglinide which gained FDA approval in 1997
Treatment of Diabetes

**Thiazolidinediones**

*Rosiglitazone - GSK*
(released 1999, $2.5 bn in 2006, linked to heart attack in 2007, EMA suspension 2010)

*Piglitazone - Takeda*
($2.4 bn in US in 2008)

*Troglitazone - Parke-Davis then Pfizer*
(FDA approval against recommendation in 1997, hepatotoxicity discovered, Pfizer have resolved claims to cost of $750 million)

**Overview:** Disfavored due to numerous side effects
**History:** Multiple controversies, withdrawals
**Action:** increase storage of fatty acids in the liver
**Possible side effects:** Various including bladder cancer, CV

**Dipeptidyl peptidase-4 inhibitors**

*Sitagliptin - Merck*

*Vildagliptin - Novartis*

**Overview:** Lower risk of hypoglycemia, subcutaneous delivery
**History:** New class, four drugs FDA approved since 2014
**Action:** increase insulin secretion
**Possible side effects:** weight loss, unclear risk of pancreatic cancer
Treatment of Diabetes

Sodium-glucose transport protein 2 inhibitors/gliflozin drugs

Canagliflozin - Janssen

Dapagliflozin - BMS/AstraZeneca

Overview: Low chance of DDI, oral delivery, administered w/o regard for meals

History: Newest class of drugs on the market

Action: Blocks renal glucose reabsorption thereby dramatically lowering blood sugar levels independent of insulin secretion (state of β-cells has no effect)

Possible side effects: weight loss, CV benefit, ketoacidosis, UTI, hypoglycemia

Other types of diabetes mellitus

Prediabetes: leads to type 2

Gestational: 2-5% of pregnant women affected, hormones interfere with insulin. Usually disappears but greater risk of type 2 in future

Type 3c (pancreatogenic): Possibly 5-10% of all diabetic cases. 80% of cases result from chronic pancreatitis

CF-related: Mucus causes scarring of the pancreas

Mitochondrial: Gradual pancreatic beta-cell dysfunction upon aging

LADA: Latent version of type 1

MODY: hereditary, 11 types

Neonatal DM: Monogenic, occurs in first 6 months

‘Type 3’: Alzheimer’s

Future therapeutics: Advanced glycation end-products (AGE)

- Glycation (non-enzymatic glycosylation) is the addition of a sugar to a protein (usually via lysine) or lipid
- Implicated in age-related diseases e.g. Alzheimers, CV, cancer, blindness, stroke, kidney failure etc
- Particularly bad in long lived cells incl. pancreatic β-cells
- Glucose usually has a low rate of glycation (10 times less than fructose), but accelerated due to higher concentration with DM
- Multiple (unknown) deleterious pathways and potential therapies

Canagliflozin

Dapagliflozin

Degradation of asparagine:

\[ A + \text{HO}_2\text{C-}_{\text{NH}_2} \rightleftharpoons \text{HO}_2\text{C}\text{NH}_2 + \text{NH}_3 + \text{CO}_2 \]