Diabetes: a rising tide.

Christopher Whitty
Gresham College 2017.
Diabetes has been described since Egyptian texts in 1552 BC (Hesy-Ra).

- Others noticed ants attracted to the urine of sufferers.
- ‘The melting of flesh into urine’ (Arateus, 150 AD).
- Early diagnosis involved tasting urine.
- Link with exercise and diet was made early.

*Constantine the African examines urine.*
A recognition there were two types of patients with diabetes.

- From around the 1770s there was a recognition there were at least two types of diabetic patients.
- One group often died within weeks. This is what we would call Type 1 diabetes.
- For the second, survival was much longer and diet might help. This is what we call Type 2 diabetes.
Important scientific milestones: the pancreas.

- In 1869 Paul Langerhans, a doctoral student, describes clusters of clear cells in the pancreas. ‘Islets of Langerhans’.
- 1889 von Mering and Minkowski show that removing the pancreas from dogs causes diabetes.
The breakthrough was the isolation of insulin, and giving it to patients.

- The Canadian team of Banting, Best, MacLeod and Collip extracted and purified insulin.
- Given to Leonard Thompson, aged 14, in 1922, drifting in an out of coma. Thompson went on to live another 13 years.
- Banting and MacLeod were awarded the Nobel Prize.
Diabetes is common.

- An estimated 4.3 million people in the UK living with diabetes.
- Around 3.5m diagnosed.
- Around 415m globally.
- In all walks of life.
Diabetes has risen since 1990 as a proportion of morbidity. *Global Burden of Disease study 2017*
Physiology of diabetes and glucose control.

- .... is complicated.
- But the essence of it is simple.
- The body needs to keep glucose in a narrow range. Either too much or too little is a problem.
- The pancreas β cells produces insulin in response to high glucose.
- Other cells respond to this by storing energy.

*Cryer PE et al 2006*
Type 1 diabetes - around 10%

• The pancreas Islets of Langerhans produce insulin from β cells.
• These die off - an autoimmune disease.
• Without insulin the body cannot regulate glucose and energy.
• Eventually there is almost no insulin.
• The body usually responds to insulin normally.
Type 2 diabetes.

- The pancreas produces insulin in response to glucose.
- The body responds abnormally to this insulin, not reducing glucose as much as it should.
- Or too little insulin is produced.
- The effect is glucose goes up.
Age structure of Type 1 and Type 2 diabetes are very different.  UK National Diabetes Audit 2017
Gestational diabetes.

• Around 5% of pregnancies.
• Occurs in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimesters.
• Usually resolves after child born.
• But 7x increased risk of subsequently developing Type 2 diabetes.
• Pregestational diabetes rising in pregnancy.

Genetic inheritance and diabetes.

- **Type 1**: 85% have no first degree relatives affected, but
- The risk is about 15x higher if you do.
- 2-3% risk with mother, 6-9% risk with father, 30% if both. 30-70% for identical twins.

- **Type 2**: clusters in families, but a complex relationship. 2-6x more likely if a family member has it.
Ethnicity and diabetes.

• Children of Asian origin around 8.9x more likely to have Type 2 diabetes than their White counterparts, children of African heritage were 5.8 times more likely.

• South Asian and African heritage 2-4x more likely to develop Type 2 diabetes. Middle East heritage also high risk.

• Also higher risk of gestational diabetes.
The major risk for Type 2 diabetes is being overweight.

• 80-85% of Type 2 diabetes is accounted for by people being overweight or obese.

• An increase with deprivation (cf Type 1).

• Where people with Type 2 diabetes lose weight diabetes may go away.

Diabetes.co.uk
Trends in diabetes in the US over time. Most of the increase in those with BMI > 30.

(Menke et al, JAMA 2015)
Prevalence of Type 2 diabetes rose very rapidly from the 1960s to 2010.

- Three possible drivers:
  - Rising obesity.
  - Changes in diagnosis and medical practice.
  - Better survival.

- Data from 2009 Diabetes UK report.
Obesity in the UK. Over 2 decades from 15%-26%. Broadly stable last few years.

Percentage obese (BMI>30) by year. Health Survey for England.
Prevalence rates diabetes rising (R), but incidence probably stable or falling (L). Data for UK males. Zghebi S et al 2017
Data from Scotland- slightly reducing incidence in men (a) and women (b) varying by deprivation group. Read S et al 2016
A recent study of GP practice data. Similar findings in other industrialised countries.  
Zghebi S et al. 2017

• Annual mortality rates are falling for Type 2 diabetes.
• Prevalence rose from 3.2% to 5.3% from 2004-2014.
• Incidence around 44/10,000 PYR in 2004, to 37 in 2014.
• Mortality rates fell from 319/10,000 PYR to 216 over the same period.
Untreated diabetes.

The symptoms of untreated diabetes include:

• Going to pass urine frequently, with thirst.
• Tiredness.
• Weight loss.
• Skin infections, thrush and delayed wound healing.
Diabetic ketoacidosis (DKA) and hyperosmolar states (HHS/HHNS). Medical emergencies.

• Usually in undiagnosed Type 1 diabetes, or when people have not taken their insulin.
• Blood glucose goes very high, ketones build up, blood becomes acidic.
• Eventually lapse into coma.

• In hyperosmolar hyperglycaemic state (HHS or HHNS) diabetics with either Type 2 or Type 1 have life-threateningly high glucose without ketones. Usually illness or infection triggers it.
Insulin treatment.

• The first, and most important drug was insulin.

• The key to making a normal life possible was developing long-acting as well as short-acting insulin.

• Insulin can be given by injection, or pump.

• Beware hypoglycaemia.

Diabetes.co.uk
Insulin naturally varies during the day. Ideally artificial insulin mimics this.
Oral hypoglycaemic drugs operate by several mechanisms

Include:

- Stimulate insulin production from the pancreas directly (eg sulfonylureas, repaglinide).
- Decrease liver glucose production (eg metformin).
- Inhibit breakdown of gut enzymes GLP-1 and GIP which reduce glucose and stimulate the pancreas (eg DPP-4i).
Metformin.

- French lilac used in traditional medicine. Contains guanidine.
- Derivatives found to reduce sugar levels in rabbits.
- From this eventually biguanides— the most important is metformin. Used in diabetes from 1957.

*Galega officinalis / French lilac / goats rue.*
Sulfonylureas.

• Discovered by chance by Marcel Janbon (1942) when testing sulfonylurea antibiotic against typhoid.

• Include drugs such as glibenclamide, gliclazide.

Dr. T Rao
Dipeptidyl peptidase-4 inhibitors (DPP-4i).

• Several drugs in this class, more being developed.
• First, sitagliptin, was licenced in 2006.
• Work indirectly by preventing the breakdown of the gut enzyme incretins.
For both Type 1 and Type 2 diabetes, without very good glucose control there are several major risks. These include:

- Heart disease and heart attacks.
- Stroke.
- Eye disease and blindness.
- Skin infections, peripheral vascular disease and nerve damage leading to ulcers and limb loss.
- Kidney disease and renal failure.
- Serious infections.
There has been a substantial reduction in complications from diabetes (US data).

Gregg E et al NEJM 2014
Diabetic retinopathy. Moderate (L) and severe.
Controlling blood sugar more effectively substantially reduces retinopathy.

Percentage with retinal change progressions. DCCT. *NEJM, 1993.*

And this is sustained for severe retinopathy (OR 69%). EDIC. *NEJM 2000.*
The difficulty is the balancing act on control of blood sugar. Short term risk of hypos v long term gain.

DCCT group, NEJM, 1993
Retinopathy treatment: laser therapy and anti-VEGF injections.
Foot ulcers in diabetes.  

- Around 60,000 people with diabetes have foot ulcers at any time in UK. Bad prognostic sign.
- Cost around £1Bn a year.
- Around 7000 amputations a year in UK. Only half survive >2 years.

Laborde M, Podiatry Today
Good glycaemic control reduces amputations in Type 2 diabetes. Risk ratio 0.65 on meta-analysis.

Hasan R et al 2016
Considerable variation across the country on amputations in diabetes.

Pathways may include:

• Delayed diagnosis of diabetes.
• Less good glycaemic control.
• Less good foot care.
• Delayed presentation with foot problems.
• Less effective non-invasive treatment.
• Local surgical practice.

_PHE data._
Renal disease

• Diabetes is one of the leading causes of renal failure.

• Tight glucose control delays onset of kidney disease, but probably not progression.

• Controlling blood pressure, especially with an ACE inhibitor drugs delays onset.
Significantly increased risk of infections. Include skin, urinary tract, influenza complications.

Cardiovascular disease mortality: heart disease and stroke. Type 1 (L) and Type 2.

Rawshani et al 2017 NEJM; Swedish data.

36,869 patients, 42% reduction mortality

457,473 patients, 46% reduction
Heart disease advances.

There is no clear evidence that tight glycaemic (glucose) control significantly reduces cardiovascular disease. Reductions similar to non-diabetics including:

- Smoking going down
- Blood pressure control
- Cholesterol lowering
- ACE inhibitor drugs
- ß-blockers
- Aspirin
- Exercise
- Coronary stents

Banchory Group Practice
By attention to detail and incremental scientific advance diabetes mortality is falling.

**Type 1 diabetes - all cause mortality - 29% reduction.**

**Type 2 diabetes - 21% reduction over 15 years.**

*Rawshani et al 2017*
Gastric surgery (bariatric surgery).

- In people with severe obesity bariatric surgery leads to weight loss.
- If they have Type 2 diabetes this often resolves, and the reduction in blood sugar is maintained.

Schauer et al, NEJM 2017

Note: For mapping purposes, the map shows identical values for Sudan and South Sudan. These values concern the former Sudan as it existed prior to July 2011.
Prevalence of raised fasting blood glucose (age 18+, female).  WHO 2016.
Wealthy country trends and projections in obesity. *OECD 2017*
Global overweight- children and adolescents.

WHO 2017.
We, the public, need to engage with the food industry on this. Pleasure, profits and health are not mutually incompatible. But it needs a different approach.

My local supermarket, last weekend.
Don’t get all your diabetes advice from newspaper headlines... and they will often warn of dire consequences from state intervention.
Ladder of state intervention.

- Ban.
- Tax heavily.
- Regulate.
- ‘Nudge’ tax or intervention.
- Mass voluntary programme.
- Engage with industry.
- Inform.
- Leave up to individuals.
We will need multiple interventions, all with a modest but incremental impact. We do not yet know the optimal mix.

Examples of possible state interventions include:

- Sugar tax on fizzy drinks
- Traffic light labelling of foods
- Restricting direct advertising to children
- Restricting fast food outlets near schools

Source: Instituto Nacional de Estadística y Geografía
*12-month moving average

Economist.com

Economist
The aim should be not to reduce enjoyment, but to reduce unnecessary energy intake.

0g fat

8.5g fat
New directions in science for treatment and prevention are occurring all the time.

Examples include:

• Islet cell transplants.
• Pancreatic transplant.
• Artificial pancreas.
• Immunotherapy in early Type 1 diabetes.
• Low calorie diets to put Type 2 diabetes into remission.