Overcoming Diabetes

Living Well in the Twenty First Century

Summary

The term diabetes (mellitus) covers a spectrum of diseases that to varying degrees have both genetic and environmental causes. They all involve problems with blood sugar control resulting from an innate or acquired insensitivity to the pancreatic hormone insulin and/or an inability to produce it in sufficient amounts.

Raised blood sugar levels can directly harm body tissues, including the linings of both large and small blood vessels and peripheral nerves. Untreated or poorly controlled diabetes can result in complications such as potentially life threatening kidney disease, retinal damage leading to blindness, erectile dysfunction in men and diabetic foot disease. The latter may ultimately require amputations. Diabetes alone or in combination with other problems such as raised blood pressure and smoking also causes heart attacks and strokes.

The biological mechanisms underlying the two main forms of diabetes have recently become better understood. Type 1 disease – which often first occurs in children and younger adults – is due to autoimmune responses which kill the pancreatic beta cells that make insulin. It may be caused by agents such as Coxsackie B viruses amongst individuals who have genetic vulnerabilities and/or are exposed to infection at a particular (relatively late) point in their immune systems' development.

Type 2 disease typically occurs in middle and later life. It is caused by genetic vulnerabilities and being overweight, which is a function of living in an obesogenic environment. Building up fat deposits in the liver, pancreas and other body tissues is

associated with processes which cause insulin insensitivity (resistance). In response the pancreas initially produces more insulin. However, despite this, increases in blood sugar levels occur. Later in the disease pancreatic beta cells may be 'switched off' or killed as a result of ongoing adiposity related insulin resistance and chronic exposure to above normal glucose levels, causing harmful insulin shortages. It is also now known that significant weight loss (typically 10-15 kilogrammes) can lead to beta cell reactivation, and the recovery of normal glucose control.

Diabetes in its various forms has become more prevalent in countries such as Britain and the US in recent decades. There are presently approaching 4 million people in the UK with diagnosed diabetes, and an estimated 500,000 living with undiagnosed disease. There are in addition another 5 million plus people living with very early stage 'pre-diabetes', many of whom are unaware of their condition.

Lifestyle changes coupled with the effective use of available treatments significantly reduce the disease burden caused by diabetes. But many people have been unable to change their dietary, drinking and other habits sufficiently to protect themselves, and therapy is not always optimally prescribed or taken. This has led to fears that increased rates of diabetes coupled with other obesity related problems will in time (over and above the impacts of health, social care and welfare service funding restraints) further reduce life expectancy in Britain and could threaten the long-term viability of the NHS.

However, diabetes and its attendant problems could be effectively overcome as a major public health hazard by the 2050s if governments, health

care providers and the public have the confidence and political will required to keep investing in public health measures such as taxing sugary drinks and using effective treatments in an optimal manner. Key elements of the programmes needed to deliver this goal include:

1. Sharing knowledge about the nature and genetic and environmental causes of diabetes in ways that make it possible for everyone to act on it. It is particularly important to spread awareness of how building up fat/increasing adiposity causes Type 2 disease, and how losing weight may lead to remissions along with other health benefits.

2. Combatting obesity in ways that communicate respect for those affected, and address its social determinants alongside the medical and other personal needs of overweight individuals. The multiple interventions needed include moderating alcohol use via fiscal and other measures and placing more emphasis on programmes aimed at promoting responses to the early signs of developing weight (pre-obesity) related health issues amongst young and middle aged adults.

3. Building on initiatives like the NHS Diabetes Prevention Programme to enable increased numbers of people to know when they have pre/early stage diabetes, as well as further reducing the population living with undiagnosed problems. This could in future involve innovative forms of risk testing that combine measures of variables like waist sizes with genetic and epigenetic factors, and more systematic blood glucose monitoring in populations at risk of developing Type 2 disease. It will also require an open minded, public interest focused, approach to inquiring about when using medicines for the primary prevention of Type 2 diabetes is a valuable complement to lifestyle change, as well as continuing efforts to eliminate tobacco smoking.

4. Being assertively committed to taking up opportunities for the primary prevention or cure of Type 1 diabetes, as and when technologies such as suitable forms of enterovirus vaccination or stem cell based therapies become available.

5. Enabling everyone seeking to reverse their Type 2 diabetes to take part in a suitable programme, and where necessary be supported in maintaining disease remissions. Recent steps towards providing 5,000 places on rapid weight reduction courses are a welcome development, but fall a long way short of establishing a full scale 'diabetes remission service.' Further progress in this area should take place alongside providing access to bariatric surgery for obese people able to benefit from it.

6. Optimising the treatment of established diabetes amongst individuals with different forms of the condition, including varying sub-types of Type 2 disease. This may in time involve using Artificial Intelligence powered diagnostic and treatment selection aids in primary care and self-care support, coupled with good access to innovative pharmaceutical treatments. To maintain public confidence in care quality and help build individual patient self efficacy, the NHS should fund the use of modern devices for monitoring blood glucose levels and delivering insulin or other beneficial medicines/substances to an extent accepted as fair and by informed service users. Similar points will apply to the introduction of specialist technologies such as pancreatic cell transplantation, if and when they are sufficiently developed.

When the NHS was first formed it faced profoundly different tasks from those of today's health service, politically, medically and socially. Some observers claim that the health service has been slow to shift away from concentrating on infection control to preventing and treating non-communicable conditions of later life that are in large part behaviourally determined. But there is evidence that the UK health services are now working relatively well to limit the burdens imposed by diabetes and allied problems. In future the NHS could do even more to overcome the challenge of diabetes, if policy makers and health professionals understand the opportunities available and are sufficiently motivated to improve both public and individual health.

However, in the final analysis better outcomes in areas such as diabetes prevention and treatment cannot be achieved by health service changes and technological innovations alone. Health improvement will ultimately rest on those at risk being able to choose to live well and use treatments like medicines effectively, and on entire societies evolving the shared behavioural norms needed for achieving longer healthy life expectancies.

Introduction

Diabetes in its most severe manifestations was recognised long ago in ancient Egypt and other early societies, including those of India, China and Greece. Yet until the second half of the twentieth century diagnostic criteria for the condition were ill-defined and it was not seen as a major public health challenge, as distinct from a threat to the survival of a relatively small number of individuals. Distinctions between Type 1 (autoimmune response caused) and Type 2 (obesity and ageing linked) diabetes did not begin to be made until the 1930s (see Box 1), and even in the US in the 1950s the proportion of the adult population living with diagnosed diabetes was still under one per cent.

However, since then the incidence and prevalence of the disorders collectively known as diabetes has risen dramatically. This is so not only in the most economically developed nations, but also in poorer regions of the world (Forouhi and Wareham, 2014; NCD Risk Factor Collaboration, 2016). In the UK the number of people living with diagnosed diabetes is now about 4 million, twice the number recorded twenty years ago (Diabetes UK, 2018a). Another half a million or so individuals are living with undiagnosed diabetes. In total approaching 7 per cent of the adult British population now has a form of the disorder. In addition, a further one in every ten UK adults (5 million plus) in Britain are living with 'pre-diabetes'/very early stage disease. Their blood sugar levels have become raised to a level at which, unless corrective action is taken, it is probable they will go on to develop Type 2 diabetes and the vascular and other disease risks associated with it.

In this country almost a tenth of all health and social care outlays are related to meeting diabetes linked needs. Such figures, coupled with continuing increases in adult obesity, have led some commentators to fear that in future life expectancy will fall, and/or that health service costs will become unsustainable. For example, in the summer of 2018 the British Heart Foundation released an analysis

Box 1. Types of Diabetes

The modern distinction between Type 1 – once referred to as 'insulin dependent' – and Type 2 – obesity and aging related – diabetes mellitus is commonly attributed to the work of Sir Harold Himsworth. He read medicine in University College London Hospital in the 1920s and published a ground-breaking study of the disease in 1936. However, physicians working in settings such as ancient India had recognised the difference between the two basic forms of diabetes some 2,000 years before Himsworth offered his observations.

Type 1 diabetes is today known to be caused by auto-immune responses which destroy pancreatic beta cells responsible for making insulin. Its onset is typically – but not always – rapid, and often takes place early in life. Type 2 disease, which accounts for approaching 90 per cent of all cases, has a more insidious onset. It normally first becomes apparent in middle and later life and initially involves insulin resistance, followed by a gradual decline in pancreatic insulin production. Individuals with the disorder may eventually require insulin injections, but this by no means inevitable.

Until relatively recently Type 2 diabetes was not clearly defined. The WHO currently takes an Haemoglobin A1c (HbA1c) level of 48mmol/mol (6.5 per cent) as the cut off point for diagnosing the condition, subject to the results of other tests. Diabetes may also be indicated by a random venous glucose concentration of over 11 mmol/litre or a fasting blood glucose concentration of 7 or more mmol/litre. However, in the public understanding of diabetes context the meaning of these measures can be difficult for people to comprehend as compared to, say, figures relating to height, weight and waist size. For this reason it may be best to encourage people simply to know their HbA1c number.

The evidence available shows that males tend to be more at risk of both Type 1 and Type 2 diabetes than females, although women are more likely to die of kidney complications than men. Other forms of the condition include:

- **Gestational diabetes.** This term refers to increases in blood sugar that are most likely to occur in the second half of pregnancy and which usually resolve after birth. Gestational diabetes affects up to 5 per cent of all pregnancies, with the prevalence varying with the degree to which prospective mothers are overweight. The extent to which experiencing gestational diabetes is an indicator that (over and above variables like their Body Mass Index) women are at raised subsequent risk of diabetes is debateable, but from a precautionary standpoint it may flag a need for life-long monitoring.

- **Neonatal Diabetes Mellitus (NDM).** NDM is a very rare form of Type 2 diabetes (under one in every 100,000 births is affected) which can be mistaken for Type 1 disease. It is due to genetic variations which impede insulin production after birth. It normally resolves during the first 6 months, although those affected are likely to be at raised risk of diabetes later in their lives

- **Latent Autoimmune Diabetes of Adulthood (LADA).** This is a form of the Type 1 disease which has a relatively slow and late onset pattern, and is typically first identified amongst in individuals aged between their twenties and their fifties. It may account for 1-2 per cent of all diabetes cases, and can be mistaken for Type 2 diabetes.

- **Maturity Onset Diabetes of the Young (MODY).** MODY comprises a set of rare monogenic conditions caused by single gene variations, the most common type of which responds well to treatment with sulphonylurea containing medicines. In total there are only 20,000-40,000 MODY cases in the UK, which is under 1 per cent of the present diabetes total. MODY's rarity means that there is again a risk of misdiagnosis, in this instance because of its being mistaken for Type 1 disease.

indicating that because of increasing diabetes rates the number of people suffering heart attacks and strokes in this country may rise by over a quarter by 2035, adding major new elements to the NHS's workload (Rudd, 2018). More recently, Diabetes UK published data highlighting the fact that there are now about 7,000 individuals aged 25 and under with Type 2 disease in England alone, some 200 of whom are aged below 16.

The rising overall prevalence of diabetes – coupled with ongoing problems associated with smoking, becoming overweight and having inadequately controlled blood pressure – undoubtedly constitutes a serious threat to the public's health, nationally and globally. Yet there is also a danger that exaggerated projections of the future harm likely to result could prove counter-productive. In part via the generation of a sense of 'false hopelessness', they could draw attention away from the fact that, given adequate investment in services and the constructive use of new technologies, increasing opportunities are emerging for preventing and treating all forms of diabetes.

In fact, in age standardised terms the burden of diabetes linked morbidity and mortality has recently been relatively stable in north western European nations. So too (although the base rates are high) are associated problems such as child obesity in higher income countries such as the UK and the US (NCD Risk Factor Collaboration, 2017). In Britain the rising prevalence of Type 2 diabetes in the young is certainly a matter of concern. Nevertheless, the absolute number of individuals affected is still modest compared to the extent of the disease burden in middle and later life, and has to a degree been influenced by the changing ethnic composition of the UK population. For instance, people of south Asian origin tend to have high levels of adipose fat at birth, predisposing them to Type 2 disease at a relatively young age (Shah and Kanaya, 2014).

Examples of areas of progress range from the development of life style change programmes and rapid weight loss centred care strategies aimed at reversing, or at least halting or slowing, the progression of 'pre-diabetes' and Type 2 disease, through to the possible introduction of vaccines capable of preventing Type 1 diabetes in children and adults. Further advances could also take place in areas such as the co-ordinated use of genetic, epigenetic and phenotypical (observable physical characteristic based) tests capable of targeting preventive and treatment approaches, and using enhanced glucose monitoring and 'artificial pancreas' based methods of optimising the benefits of insulins and other medicines.

Even for those for whom prevention fails, high quality modern care should permit a reduced incidence of hyperglycaemia (raised blood sugar) and vascular disease linked kidney disease, sight loss and other complaints, including neurological complications. It ought also to permit freedom from problems like life threatening ketoacidosis (resulting from having too little insulin) or treatment engendered hypoglycaemia (caused by too much insulin).

Against this background the objective of this brief UCL School of Pharmacy report is to provide an overview of diabetes prevention and treatment at the start of the twenty first century and the range of health and social care improvements that should take place in the 2020s[1], given adequate investment and appropriate policy making. There is already sufficient biomedical knowledge available to limit significantly the extent to which diabetes is life threatening or disabling, were individuals and communities able to adopt protective life styles and use today's medicines and other therapies as effectively as possible. Key challenges for the next decade include not only developing more effective biomedical interventions but also service formats and the social science based professional skills and human insight needed to optimise health outcomes in care settings like general medical practice and community pharmacy.

In the short term, providing information about life-style related illnesses risks is by itself rarely an effective way of facilitating health protecting behavioural changes at the population level. Nevertheless, improving community wide understanding of how diseases are caused and can be avoided or controlled may over time promote better public health, through driving a multiplicity of complementary environmental adaptations and personal responses. Perhaps most notably, the popularisation of the germ theory of disease in the nineteenth and twentieth centuries helped to decrease infection rates amongst infants, children and adults via changed ways of living. Alongside this, it also opened the way to progressively more effective vaccine and medicine supply and use. Similar points can be made in relation to birth control.

Comparable social progress is now needed in the fields of diabetes and obesity control. One of the most important health challenges is to generate universally accessible understandings of the relationship between becoming overweight and suffering diabetes and its consequences, and how losing sufficient weight can reverse some forms of the condition and check others. Overcoming diabetes will require good use of both biomedical and social development opportunities, from changing collective ways of life to employing new diagnostic and biological monitoring technologies and enabling more people increase their diabetes control related sense of self-efficacy (see below) in order to take control of their health and maximise the value of the therapies available to them.

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1   This UCL School of Pharmacy report is intended to be an accompaniment to the 2019 Royal Pharmaceutical Society/UCL School of Pharmacy new year lecture to be given by Dr Elizabeth Robertson of Diabetes UK at the Royal Society on Thursday January 10th 2019
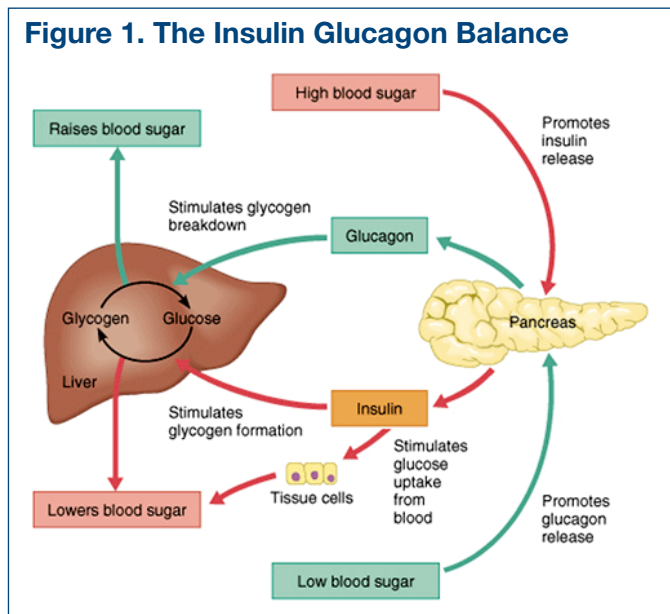
The Nature of Diabetes

Humans evolved in Africa as nomadic omnivorous hunters, capable when needs be of pursuing, exhausting and ultimately killing prey over prolonged periods, while also gathering and eating plant based foods whenever available. Until recently it was not 'natural and normal', even for people living in settings like Victorian England, to be assured of three meals a day. Hunger was commonplace before the modern era of food plenty. Biologically fit individuals needed – and still need – to be able to transport and store energy in the form of substances such as triglycerides[2] when chances arose, and to draw on the reserves held in organs such as their livers and adipose tissues when necessary.

The biological system required to achieve this involves the secretion of the hormones insulin and glucagon (Figure 1). Insulin is generated by beta cells in the pancreas. Its causes

2 Triglycerides are a form of fat (lipid) that is ingested or made in the liver, transported via the blood and stored around the body. Circulating triglyceride levels are typically inversely related to protective high density (HDL) cholesterol levels and are hence linked to the risk of conditions such as atheroma and coronary heart disease, regardless of the extent to which they might (or might not) themselves be directly harmful or indicative of 'over-eating' – see text.

blood sugar levels to fall, and energy to be stored in molecular form in fat and muscle cells and the liver. Glucagon has an opposite effect. It is synthesised by pancreatic alpha cells and causes the release of glucose.

Figure 1. The Insulin Glucagon Balance

Box 2. Communicating about Type 2 Diabetes

'Diabetes' encompasses a range of conditions with varying genetic, environmentally and behaviourally linked co-causes. Even within the Type 2 diabetes category a range of sub-types exists. However, from a health communications perspective it can be useful to highlight the fact that beneath such complexities the initial stages of Type 2 disease develop slowly, and stem from the gradual build-up of an increased waist size and fat deposits (that is, adipocity) in the liver, pancreas and other parts of the body. Acquiring a 'middle-aged spread' should not be regarded as a natural part of aging or a purely personal problem. It is to a large extent a consequence of living in a time of food abundance in which chronic over-eating and over-drinking reflect established social norms.

Increasing adipocity results in the release of messenger molecules called adipokines from 'fat cells'. These have a range of inflammatory and allied effects, including reducing the sensitivity of muscle and other cells to insulin after it has bound to the insulin receptors on their surfaces. This so-called 'insulin resistance' threatens to drive up blood sugar levels, as well as reducing the energy available to muscle and other cells.

In response to this challenge, overweight individuals and others at raised risk of developing Type 2 diabetes because of their genetic make-ups produce – unless they have a pre-existing pancreatic deficiency – more insulin, perhaps for as long as a decade or more. This allows them to function more or less well, albeit that their average blood sugars are likely to be somewhat above normal levels while still being below the formal diabetes threshold. This is what is meant by 'pre-diabetes'. In the light of today's knowledge a better term might be very early stage diabetes.

Eventually, the combined effects of continued over-eating and drinking, insulin resistance and relatively low-level glucose toxicity (see main text) can have a markedly deleterious effect on pancreatic beta cells. A tipping point may come at which, often relatively quickly, insulin production levels fall off and individuals' blood sugars rise above the threshold levels used for diagnosing Type 2 diabetes.

In the past 'pre-diabetes' was seen as a potentially reversible condition, while Type 2 disease was regarded as an irreversible disease. But this distinction is now known to be fallacious. Some people who develop lifestyle/obesity linked diabetes and have genetic vulnerabilities permanently lose their capacity to produce insulin, to the extent that they need insulin injections. Yet in most people with Type 2 disease the condition does not progress that far. Further, recent research funded by Diabetes UK shows that amongst a proportion of those who have developed the disease a loss of weight sufficient to markedly reduce the fat burdens in their livers and pancreases can restore both insulin sensitivity and insulin production.

If more people with either very early Type 2 disease or diagnosed diabetes understand the hazards affecting them and can, when they wish, take part in 'diabetes reversal' programmes the future harm burden should be reduced. The appropriate use of protective medicines alongside weight loss and fitness promoting interventions could further improve health outcomes at the border line between the primary and secondary prevention of diabetes – see main text. However, even if this proves to be the case there will still be large numbers of patients in need of effective pharmaceutical care to protect them from the consequences of established diabetes.

In diabetes[3] there is either a lack of capacity to produce adequate amounts of insulin, as in Type 1 disease and well established Type 2 disorders (Box 2), or there are (innate or acquired) failings in the ways the internal machinery of cells responds to insulin after it has bound to receptors on their surfaces. Such signalling malfunctions are termed insulin resistance. The latter typically results from genetically determined vulnerabilities coupled with the gradual impacts of raised blood sugar levels caused by 'over-nutrition'. However, in some instances genetic factors alone can be responsible for insulin resistance.

It would be beyond the scope of this report to explore the causes and mechanisms of diabetes in depth. But key points to emphasise include:

- **Most forms of diabetes have both genetic and environmental/behavioural causes**[4]**.** These can be linked – for instance, some populations accustomed over many generations to living in cold conditions may be more at risk of developing Type 1 diabetes than others. In the case of this autoimmune disorder a child is more likely to develop the illness if her or his father has it than when the mother is affected. If both parents have Type 1 diabetes their children have a roughly 30 per cent chance of contracting it. When an identical twin has the disorder his or her sibling has a 40 per cent lifetime risk[5].

In the case of Type 2 diabetes the equivalent inheritability figures are higher, at 75 per cent and 90 per cent respectively (Diabetes UK, 2018b). Yet no single gene has more than a small impact on its occurrence rate. This suggests a combination of vulnerabilities linked to multiple genes and a commonly encountered environmental co-cause, like the degree to which an environment is obesogenic. Genes associated with type 2 diabetes influence a variety of discrete variables like appetite, metabolic efficiency, propensity to insulin resistance and pancreatic beta cell resilience (see Prasad and Groop, 2015). In future detailed genetic testing coupled with phenotype analysis may facilitate more personalised prevention and treatment strategies in primary care and other settings, albeit that at present genetic testing is of

limited value compared to physical measures such as waist size and Body Mass Index (BMI).
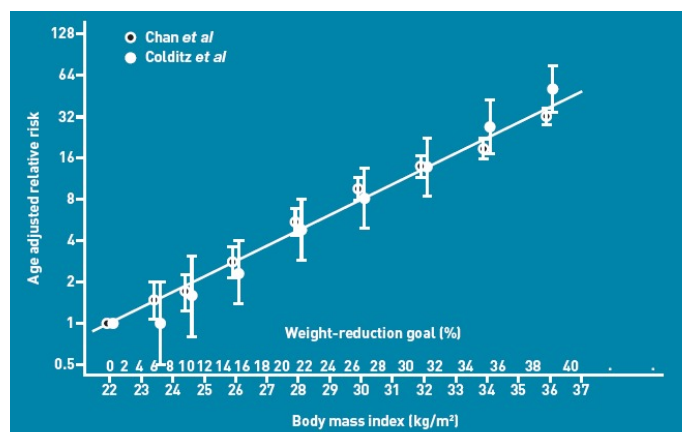
- **Developing an increased waist size and putting on weight are indicators that individuals' energy storage systems are being overloaded.** Just as force-fed geese develop fatty livers, so humans living in settings that promote 'over-nutrition' are in danger of building up harmful levels of fat in their livers and pancreases (Taylor, 2013). This is now known to be a central cause of Type 2 diabetes. 'Pre-obesity', in which individuals in their 20s, 30s and 40s begin to build fat round their stomachs and key organs and develop BMIs in the 25-30 range, is therefore a powerful Type 2 diabetes risk warning signal. It can be concluded that health promoting programmes and cultures should focus more on supporting younger adults in the early stages of becoming overweight than has historically been the case. Figures 2 and 3 illustrate recent weight related trends in England, and the relationship between BMI and Type 2 diabetes incidence.

Figure 2 Adult Obesity in the England, 1993-2016

Source: House of Commons Library, 2018

Figure 3. The Relationship Between BMI and the Relative Risk of Developing Type 2 Diabetes

Source: Wald et al, 2012

Note: the weight reduction goal shows the percentage of body weight that at any given BMI point the authors calculated would need to be lost to reduce the relative of diabetes to 1. In practice the weight loss needed to reverse diabetes may be lower

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3   This is true of diabetes mellitus (literally, 'sweet urine'.) Diabetes insipidus is a relatively rare conditions associated with problems caused by failures to produce or respond to the antidiuretic hormone vasopressin.

4   As indicated in Box 2, the main exceptions to this are neonatal diabetes mellitus (NDM – which can be mistaken for Type 1 disease) and maturity-onset diabetes of the young (MODY). MODY is more common than NDM, although even so it only accounts for about 2 per cent of all diabetes cases. Onset usually occurs in adolescence or early adulthood. Hence it is sometimes mistaken for Type 2 diabetes

5   These relatively low inheritability estimates imply the existence of an environmental co-cause to which not everyone in the same family or community is exposed, like having an infection at a vulnerable age. Most of the genes linked to Type 1 diabetes govern immune responses. However, some 15 per cent of those with this diagnosis have a condition called autoimmune polyglandular syndrome (APS) type 2. In addition to diabetes, they also have thyroid disease and poorly working adrenal glands. In this instance there is a 1 in 2 chance of a parent passing their form of Type 1 diabetes on to their child (American Diabetes Association, 2018).

- **High blood glucose levels directly harm blood vessels and nerves.** Regardless of how initially promoted, once raised blood sugar levels have become established 'glucose toxicity' is a key cause of problems such as, for example, diabetic foot pain and ulcers. Through a variety of mechanisms (including impacting on nitrous oxide production) chronically high glucose levels damage the linings of both large and small blood vessels and promote both macro- and micro- vascular disease. Glucose toxicity also affects pancreatic cells, so adding to insulin production problems, and is a cause of nerve damage. Neurones in the peripheral nervous system are especially vulnerable because they lack protective myelin sheaths.

- **The term 'metabolic syndrome' was coined in the 1980s: as a concept it highlights the fact that environments which promote frequent carbohydrate rich food and drink consumption and provide little incentive for keeping weight constant or taking exercise are – notwithstanding the pleasure they may offer – harmful.** The metabolic syndrome idea was founded on the observation that factors such as raised blood pressure, high triglyceride and LDL cholesterol levels, low HDL cholesterol, obesity and diabetes cluster together, along with events like kidney failure, strokes and heart attacks. At one stage some commentators may have hoped that a discrete biological driver of 'metabolic illness' would be discovered. However, modern social scientific and medical knowledge indicates that the metabolic syndrome is a phenomenon resulting from the overlapping juxtaposition of multiple discrete environmentally and genetically linked disease causes.

- **Type 2 diabetes is more diverse than has until recently been appreciated by health professionals and the wider public.** Some observers now say that there are tens or even hundreds of different disease forms. From a theoretical personalised medicine perspective there is some truth in such claims. Yet the practical value of such a radical shift away from a unitary view of Type 2 diabetes is doubtful. Alongside work undertaken by others (Kahn, 2018) the findings of Ahlqvist et al (2018) represent a step towards a more refined classification of the disease that could more easily translate into improved – better tailored – clinical care.

  The cluster analysis these authors conducted identified five diabetes sub-types (Box 3). In particular, their work highlights the fact that Type 2 patients with unusually high levels of insulin resistance are often treated in a similar manner to others, but are at special risk of kidney disease. By contrast, those stratified into a group characterised by high levels of insulin deficiency had the highest rates of diabetic retinopathy.

- **Type 2 diabetes is more reversible than has been traditionally understood**. It has commonly been thought that once diagnosed Type 2 disease is an inevitably progressive chronic compliant with individuals set to need increasingly powerful therapies, leading ultimately to insulin treatment like that required by people with Type 1 diabetes. But from the 1990s onwards, with the advent of new forms of bariatric surgery for people suffering from severe obesity and diabetes, it became apparent that in a significant number of cases people who radically reduced their food consumption rapidly regain normal blood sugar control, even after years of illness.

Box 3. Diabetes sub-Types

Research led by Professor Leif Groop of the Lund University Diabetes Centre in Sweden and the Institute for Molecular Medicine Finland in Helsinki has produced a refined classification of diabetes mellitus (Alqvist et al, 2018). Alongside other commentators, the authors of this Lancet article highlighted the heterogeneity of Type 2 diabetes. They were seeking better ways of identifying people at high risk of diabetes complications, who could benefit from intensified treatment before the disease causes serious harm.

These investigators studied the records of 14,775 adults from Sweden and Finland. The data they analysed included figures on Body Mass Indices (BMIs); age at diagnosis; HbA1c levels; beta cell functioning; insulin resistance; and the presence of diabetes-related autoantibodies. They also undertook gene testing and assessed patterns of disease progression and treatment. The five forms of diabetes they identified are:

1. Severe autoimmune diabetes (currently called type 1 diabetes), characterised by insulin deficiency and the presence of autoantibodies. This was identified in 6 – 15 per cent of subjects.

2. Severe insulin-deficient diabetes, characterized by younger age, insulin deficiency, and poor metabolic control but without autoantibodies. This was identified in 9 – 20 per cent of subjects.

3. Severe insulin-resistant diabetes, characterized by severe insulin resistance and a significantly raised risk of kidney disease. This was identified in 11 – 17 per cent of subjects.

4. Mild obesity-related diabetes. This affected 18 – 23 per cent of subjects.

5. Mild age-related diabetes. This affected 39 – 47 per cent of subjects.

These five diabetes types were found to be genetically distinct, in that there were no genetic mutations shared across all five clusters. Amongst the additional observations they reported was the fact that even in the advanced Scandinavian setting just 42 per cent of Type 1 patients and 29 per cent of those with a sub-type 2 diagnosis received insulin therapy from the point of disease onset, despite this being the most appropriate treatment. Treating the 40 per cent of individuals with sub-types 1,2 and 3 diabetes in an as early and effective manner as possible will deliver increased health gain, provided that prioritising them does not lead to the needs of the remaining 60 per cent of people with diabetes being neglected.

Building on such observations, Professors Roy Taylor and Michael Lean and colleagues in Newcastle, Glasgow and elsewhere have now shown that through interventions deliverable in primary care even well-established Type 2 diabetes is reversible in around 50 per cent of instances, depending on the individuals involved and the amounts of weight lost (Lean et al, 2018). Provided reduced weight levels can be maintained diabetes will stay in remission for indefinite periods. This shift towards understanding the disease as an ongoing acute response to a high food intake as distinct from a permanent disability has vital implications for health in the twenty first century.

In countries such as the UK and the US Type 2 diabetes is most prevalent in, and inflicts most harm amongst, less advantaged social groups. Relevant factors include being a member of a marginalised or isolated ethnic or social group; having a low income and/or working in multiple insecure and low status roles; and being at raised risk of mental ill-health. In addition to the reality that some forms of antipsychotic medicine are diabetogenic, living with problems like depression can impair individuals' efforts to maintain their health. At the same time living with any chronic illness can cause anxiety and depression.

Although it began as a 'rich man's' habit cigarette, smoking is now the clearest modern example of social and economic disadvantage being linked to a harmful behavioural response. Non-adherence in medicine taking is also associated with poor diabetes outcomes.

Epidemiological Trends

The rise in Type 2 disease prevalence seen in recent decades, which in Britain includes an approximate doubling in case numbers from 2 million to 4 million in the twenty years since the end of the 1990s, has in part been a function of population ageing and increased rates of diagnosis in older people with less severe late onset disease. The importance of the latter is highlighted by the fact that the overall rate of diabetes in people aged around 60 is roughly double that amongst those aged 50, but only half that in men and women in their 70s and early 80s.

But in age standardised terms main the driver of increased rates diabetes has been obesity. Weight related factors on occasions make Type 1 diabetes more difficult to manage (Mottalib et al, 2017). However, as an autoimmune condition that typically starts in childhood or early adulthood, Type 1 diabetes is not caused by people being overweight. The most likely driver of the gradually rising incidence rate observed since around the 1950s in this country and other nations is that (as with poliomyelitis at the time the NHS was first established) exposures to an infection or infections once universally experienced early in life are being delayed because of environmental changes associated with smaller family sizes and raised hygiene standards. It is posited that later ages of first infection expose vulnerable individuals to an increased risk of aberrant immune responses that kill pancreatic beta cells.

Changed patterns of enterovirus infection have for some time been thought to be implicated in rising Type 1 disease rates. There is now strong epidemiological evidence from Finland (which has amongst the highest rates of Type 1 diabetes in the world) and elsewhere that this is the case, particularly in respect of Coxsackie virus infections (Richardson and Morgan, 2018).

Efforts are currently being made to develop a Coxsackie virus vaccine capable of protecting children and adults from Type 1 diabetes (see, for instance, Drescher et al, 2015; Stone at al, 2017). This is an important public health opportunity, albeit it would be premature to suggest that a safe and effective product will soon be available. Even if a suitable vaccine is eventually produced, it would also be wrong to assume that it will be 100 per cent effective. One possibility is that additional viral contributors to Type 1 diabetes occurrence exist. For instance, some research evidence links Epstein-Bar Virus infection to the risk of autoimmune disease based diabetes (Harley et al, 2018).

Opportunities for diabetes prevention are discussed below. Before that, however, it is worth noting that despite concerns about increased rates of obesity and Type 2 diabetes in recent decades, life expectancy in this country grew – baring the direct and indirect impacts of wars – consistently during and for a century before the period between the start of the 1950s and 2010.

This progress, which was to a significant extent due to declines in age standardised vascular disease mortality, has recently stalled in the UK. In some less advantaged British communities life expectancy is now falling. But in overall terms the obesity and diabetes 'pandemic' of recent decades has coincided with marked declines in death rates from causes like strokes and heart attacks. In the latter instance age standardised mortality from myocardial infarctions in Britain rose between the 1940s and the middle 1980s. But it has since dropped markedly, despite the 'take off' in reported obesity and diabetes rates.

The reasons for such seemingly paradoxical trends may in part relate to definitional shifts, and failings to adequately age standardise some data sets. Growing numbers of new diabetes cases in people aged 70 and over will not be associated with the volume of vascular disease harm that similar increases in diabetes amongst people in their 30s, 40s or 50s would generate.

However, for the purposes of this brief report the most important conclusion to stress is that since the 1950s advances in pharmaceutical care have, alongside reductions in tobacco smoking, done much to moderate the impact that increased rates of obesity and diabetes would otherwise have inflicted. In primary care in particular the mass prescribing, dispensing and consumption of anti-hypertensive medicines from the 1970s and statins from the middle to late 1990s onwards have reduced macro-vascular disease mortality and morbidity and hence offset 'metabolic syndrome' linked harm.

Better, more extensive, use of medicines like metformin (see below) and more recently introduced treatments for Type 2 disease has also generated outcome related benefits, as has the capacity of insulin based products and delivery systems to enhance the wellbeing of people with Type 1 diabetes and other forms of severe insulin deficiency.

It is to be hoped that in the 2020s, in addition to being able to further the primary prevention of diabetes and its consequences via 'public health' interventions and where appropriate evidence based medicine use, NHS and other health service providers will be able to support ongoing improvements in access to and the effective use of existing and new treatments for established diabetes.

Preventing Diabetes

Preventive health and social care has a variety of objectives. Conventional approaches differentiate between primary prevention, involving social, pharmaceutical (including vaccine based) and other interventions designed to stop illnesses occurring; secondary prevention, that seeks to treat or cure illnesses at an early stage, before they cause significant harm; and tertiary prevention, which aims to help people live in as fulfilling a way as possible with established diseases and disabilities. To be optimally effective all forms of prevention often require social and environmental changes as well as biomedical inputs and individual actions.

Efforts to curb the incidence of and minimise the harm caused by diabetes can be described within the framework provided by this basic model. However, improved understandings of the reversibility of Type 2 diabetes suggest that in this instance some caution should be applied in differentiating between primary and secondary prevention. In as much as the condition is reversible if levels of liver and pancreatic fat can be cut sufficiently the dividing line between primary and secondary prevention (along with that between 'pre-diabetes' and diagnosed Type 2 diabetes) is blurred, if not made redundant. For the purposes of this brief report the most important points to make about diabetes prevention are:

- **Population-wide changes in community-wide lifestyle norms that reduce average weight levels, curb collective and individual consumption of items like alcoholic drinks and sugar-containing beverages, increase vegetable intake, lower average LDL and blood pressure levels, eliminate tobacco smoking and encourage physical fitness amongst people of all ages and both genders would together significantly reduce the health and economic burdens imposed by Type 2 diabetes.** Cumulative experience across the world indicates that such progress will be both possible and necessary if the UK is to achieve goals such as increasing healthy life expectancy by five years within coming decades. Some public health specialists may believe that the only acceptable means of achieving population wide shifts in 'metabolic syndrome' risks will be via behavioural change. Yet there is evidence that some preventive forms of medicines use in middle and later life (Box 4) could be beneficial in primary

Box 4. Using Medicines for Primary Prevention

It is now over 15 years since Wald and Law (2003) first proposed using polypills containing low doses of three antihypertensive medicines with complementary modes of action and a statin for the primary prevention of cardiovascular disease amongst healthy individuals aged 50 and over. Their calculations indicate that in time up to 80 per cent of unwanted events such as strokes or heart attacks could be prevented amongst those taking such a medicine for preventive purposes, as compared to their continuing with their lives normally. There is also long standing evidence that taking such medicine combinations benefits everyone living with diabetes. (See, for instance, Gaede et al, 2008.)

Part of the logic of the original polypill proposal and subsequent work rests on the fact that age is the dominant risk factor for vascular disease. This means that entire populations of a suitable age can benefit from taking it for preventive purposes. In today's conditions many unwanted cardiovascular and cerebrovascular events occur amongst individuals conventionally classified as being at relatively low risk.

There are powerful arguments in favour of using medicines like combined anti-hypertensives (which have relatively low side effect to health gain ratios) in primary prevention programmes. But against this some commentators warn against diluting awareness of the need for conventional public health approaches based on lifestyle change alone. There have been suggestions that taking 'protection pills' may lead people to think that seeking a healthy lifestyle is no longer necessary. It may also be feared that giving healthy people medicines for preventing disease would 'flood GP surgeries with the worried well', or open the way to the medical profession losing its control over public access to therapeutic drugs.

In fact there is no evidence that taking blood pressure or lipid lowering medicines automatically discourages people with, or at risk of, conditions such as diabetes from seeking lifestyle changes. Both the latter and medicines use have important health contributions to offer. In the case of pharmaceuticals such as metformin (or in future drugs with shared modes of action but perhaps fewer gastric or other side effects) there could again be public health advantages to be derived from its more widespread (elective) use in population groups that are either at risk of diabetes, or are living with very early stage disease.

It might, for example, be that the efficacy of weight loss centred disease remission courses could be cost effectively augmented by supplementary forms preventive medicines use. However, from a policy perspective such ideas can appear inherently challenging, not least because they could face opposition from sections of the medical and wider public health communities. Even so, they deserve balanced evaluation and rational consideration.

Questions relating to whether or not current 'evidence based' regulatory requirements make it prohibitively costly and time consuming for medicines established as disease treatments to be licensed for use in primary prevention programmes demand attention. There are similar concerns that ill-informed approaches to evidence based (as opposed to probability based) policy making can harmfully delay the introduction of beneficial innovations in the fields of public health and disease or disease risk screening.

prevention terms, should public and professional opinion be prepared to accept the effective de-medicalisation of pharmaceutical interventions like those needed to reduce community-wide blood pressure levels.

- **Targeted attempts to reduce diabetes and vascular disease related risks might, in addition to society-wide developments, reduce health inequalities and improve mortality and morbidity in specific sections of the population**. The NHS England/Public Health England/Diabetes UK Diabetes Prevention Programme (DPP) launched in 2015, which is aimed at helping people with 'pre-diabetes' reduce their blood sugar levels before they develop frank diabetes, is an example of an important attempt to reduce the incidence of the disease at a population scale. This initiative builds on developments in the US and elsewhere (including Scotland – see Scottish Government, 2018).

However, there remain – despite recently announced plans to increase the number of placements to 200,000 per annum – questions about the adequacy of the DPP's resourcing, given the scale of the tasks involved. It is also of note that the evidence currently available about the capacity of lifestyle change promotion alone to optimise the health of people known to be at relatively high risk of diabetes is limited. This means that the complementary use of drugs such as metformin should also be considered in this context. Another caveat is that targeting by definition narrows communication and can impose costs additional to those of population-wide health promotion. This may be taken to indicate that interventions like the DPP should be additional to, rather than a substitute for, adequately funded community-wide obesity reduction and diabetes harm minimisation programmes.

- **Type 1 diabetes and related conditions such as LADA (Latent Autoimmune Diabetes of Adulthood), along with the various forms of MODY (monogenic Maturity Onset Diabetes of the Young), are not as yet amenable to primary prevention.** During the 2020s the introduction of new vaccines might change this situation, as could in the coming one to two decades the advent of innovative gene therapies. Yet for the present care will need to focus on early disease detection and the provision of effective treatments, centred on assuring the supply of insulins or when appropriate medicines in ways that as far as possible normalise blood sugar levels and minimise the risks of both hypo- and hyper-glycaemia.

To date, the English NHS's track record in providing drugs and allied pharmaceutical products has been relatively good as compared to its providing access to devices such as insulin pumps and, recently, sophisticated methods of insulin level monitoring. It is to hoped that as 'artificial pancreas' type technologies continue to improve the UK market for such devices will not be permitted to become a backwater, into which companies are slow to introduce innovative products.

Finally, it is debateable as to whether or not enabling individuals with Type 2 diabetes to lose weight via going on very low calorie diets for periods of three months of more (see Box 5) in order to put their condition into remission should be classified as a form of primary or secondary prevention. Strictly speaking it is the latter. However, once remission has been achieved efforts to maintain it via ongoing dietary modifications and/or the use of (for example) incretin based or other medicines might better fit a primary prevention definition. A core point to make about the future of diabetes prevention and treatment is that as

Box 5. The DiRECT Trial Diabetes Remission Diet

Lean et al's (2017) recent study of the use of an ultra-low calorie diet based approach to reversing Type 2 diabetes involved 298 people aged up to 65 years drawn from 49 General Practices in Scotland and Tyneside. Building on the results of two previous projects it reported that approaching 90 per cent of those taking part who lost 15kg or more entered remission. By one year the average participant had lost 10kg and over 40 per cent of the 298 individuals involved were still in remission.

The liquid diet developed for this Diabetes UK funded research permitted those taking it in the order of 850 calories a day for a period of 3-5 months. It is consumed in the form of three drinks per day, with one taken at each meal time. It was reported that most trial participants did not experience significant hunger, and they were able to live relatively normally during the time they were losing weight. Such observations indicate that for many people losing weight via this intensive dieting strategy would be a much more viable, if not quite as efficacious, approach to reversing Type 2 diabetes than undergoing bariatric surgery. The latter is only suitable for people living with very severe obesity linked problems, not least because there is a limited but significant mortality risk.

The DiRECT trial's importance in part stems from the fact that, contrary to conventional wisdom, it demonstrated that intensive dieting can lead to more significant and sustainable weight losses than more gradual approaches. Key issues relate to how best individuals can be supported in maintaining disease remissions over time, and the scale of resources that may in future be needed to scale up NHS services to serve the entire UK population.

It was recently announced that the Diabetes Prevention Programme in England will eventually provide 200,000 places a year, and that 5,000 places on diabetes reversal courses will be funded. This ill generate more data on outcomes. If it emerges that much larger numbers of people should be provided with self-efficacy raising services in order to maintain their weight losses and related health gains, significantly more investment will be needed. One future option could be to provide funding for (level 2 or 3) 'Healthy Living Pharmacies' to ensure that suitable behavioural support can be offered, perhaps along the lines pioneered by The Chronic Disease Self-Management Programme (Lorig, 2014).

Box 6. Medicines for the Treatment of Type 2 Diabetes

Drug class	Mode of action
Biguanides	The only drug of this class now available is metformin: related products were withdrawn because of their potential to cause lactic acidosis. The mode of action is complex – see main text. Metformin reduces glucose production in the liver and to an extent mimics the effects of exercise via the activation of an enzyme called 5-adenosine monophosphate activated protein kinase (AMPK). It was first licensed in the 1950s and has since the 1990s become the most widely prescribed antidiabetic medicine throughout the world.
Sulphonylureas	The first of this large class of medicines was also licensed in the 1950s. Sulphonylureas are often prescribed with metformin. They act on pancreatic beta cells to increase insulin secretion, and are now known to be of particular value in, for instance, treating some forms of MODY. However, increased insulin production is associated with weight gain, and there have been concerns relating to the overall survival impacts of sulphonylurea therapy.
Alpha-glucosidase inhibitors	Drugs in this class inhibit the action of an enzyme involved in the digestion of carbohydrates in the same way that some natural products do. They can therefore help people with diabetes to maintain glycaemic control.
Meglinitides	Like sulphonylureas, these drugs increase insulin secretion. Also like sulphonylureas, they can cause weight gain and carry a risk of hypoglycaemia.
Thiazolidinediones	Also known as glitazones, drugs in this class were first introduced in the 1990s. They affect adipocyte (fat cell) differentiation and reduce insulin resistance. As with all medicines, there have been safety concerns. For example, some thiazolidinediones (now withdrawn) were associated with a raised hepatitis risk and all medicines in this group can exacerbate heart failure linked problems. However, used appropriately they offer important benefits.
Amylin analogues	The only drug available in this class was licensed in 2005. Like naturally occurring amylin produced in the healthy pancreas it assists in blood sugar control by curbing glucagon production during eating, slowing food emptying from the stomach and reducing appetite. Used as an injectable, this medicine can be of value to people with both Type 1 and Type 2 diabetes.
Incretin mimetics/ agonists	Incretins are metabolic hormones produced in the intestines and the pancreas that contribute to controlling blood glucose levels via a number of mechanisms which complement the actions of insulin. They also increase insulin production per se. The first drug in this class, which acts like naturally occurring glucagon-like peptide 1 (GLP-1), became available in 2006 – see main text.
DPP 4 inhibitors	These medicines prevent the breakdown of naturally produced GLP-1, so enhancing its availability. They were also initially marketed in 2006.
SGLT2 inhibitors	Drugs in this class, which have been available since 2013 and are also known as gliflozins, work by increasing the renal secretion of glucose. It has since been observed that in addition to this anti-glycaemic effect their use can significantly reduce heart failure mortality amongst people with diabetes.
Insulins	Insulin injections have been central to the treatment of Type 1 diabetes since the industrial production of animal sourced insulin began in 1923. Biosynthetic recombinant 'human' insulin was first marketed in 1982. Since then wide a range of short, rapid and long acting insulins has been introduced, with the aim of giving people with Type 1 disease and those with Type 2 who require insulin injections better control of their blood sugar levels. Research continues on developing orally active and/or inhaled insulins or insulin like products, and on the possibility of manufacturing 'smart insulins' that will reduce risks like those of hypoglycaemia.

and when more health professionals and members of the public come to fully understand the practical potential for reversing the pancreatic and other physiological changes characteristic of Type 2 disease its personal and social costs will in time fall.

Better Treatment and Care

Current approaches to treating Type 2 diabetes were shaped by two seminal studies conducted in the United States and the United Kingdom in the 1980s and 90s. The Diabetes Control and Complications Trial (DCCT) was published in 1993. It showed amongst US patients with Type 1 disease that intensive insulin therapy involving frequent doses (at that time the range of insulins available was not as extensive as it now is) adjusted for variations in eating and activity delayed the onset and progression of complications like retinopathies and kidney and other disorders. The UK Prospective Diabetes Study (UKPDS) was published in 1998. It confirmed the ability of treatments that lower blood sugar and blood pressure to slow or stop the emergence of micro- and macro- vascular disease amongst participants with Type 2 diabetes.

Diabetes care in the primary care setting remains primarily focused on blood sugar control and cardiovascular and

cerebrovascular disease prevention. In ideal settings, in which healthy lifestyles are the norm and high levels of concordance/compliance in medicines and insulin use are facilitated, existing therapies significantly reduce the harm caused by diabetes. However, in practice not all medicine taking reflects well informed prescriber intentions and not all the unwanted aspects of diabetes, such as its microvascular consequences, can be avoided by attempts to control blood sugar levels. Awareness of unmet needs has led to the ongoing pursuit of better treatments that modify underlying disease mechanisms, together with enhanced ways of monitoring patients' wellbeing and delivering precisely calibrated amounts of pharmacologically active substances.

In addition to today's wide range of short and long acting (and potentially 'smart acting'[6]) human insulin based products available for people with Type 1 and advanced Type 2 diabetes to use in ways which allow them and those around them as normal a life as possible, Box 6 offers a summary of the different types of Type 2 diabetes medicine. Examples of recent innovations include:

- **Incretin mimetics and analogues**. Incretins are hormones produced in the gut. They control blood sugar levels, in part via stimulatory actions on pancreatic beta cells. The first injectable medicine in this class became available in 2006. Since then drugs that have a simultaneous effect on the glucose-dependent insulinotropic polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor have been trialled.

- **DPP 4 inhibitors.** The initial dipeptidyl peptidase 4 inhibitor was also first put on sale in 2006. Medicines of this type confer benefits to people with Type 2 diabetes by preventing the breakdown of naturally produced GLP-1 and GIP, so increasing effective incretin concentrations.

- **SGLT 2 inhibitors/gliflozins.** This drug class was first marketed in 2013. The anti-hyperglcaemic action of these medicines stems from increasing the renal secretion of glucose. However, drugs of this type are in addition now known to reduce heart failure mortality amongst people with diabetes by up to a third (Zelniker et al, 2018), perhaps in part by affecting the pressure gradient existing between interstitial tissues and capillaries.

Pharmaceutical care proponents hope that the ongoing development of medicines like these will further reduce the unwanted consequences of diabetes and open the way to oral or injectable treatments that are as effective as bariatric surgery in controlling or curing Type 2 cases (Stumvoll and Tschöp, 2018). If this proves possible it could, perhaps via innovative medicine use alone or in combination with interventions like those employed the Diabetes Prevention Programme, generate fundamental changes in Type 2 disease outcomes. However, this is not to deny the fact that all medicines (like surgery and even psycho-social
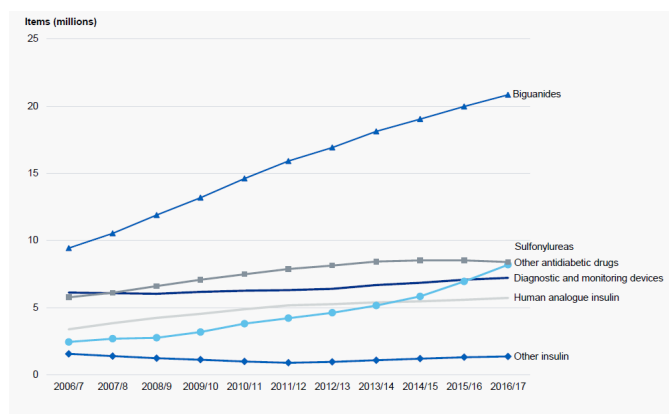
interventions) carry a risk of unwanted effects, or that older off-patent treatments may also still have significant unrealised potential.
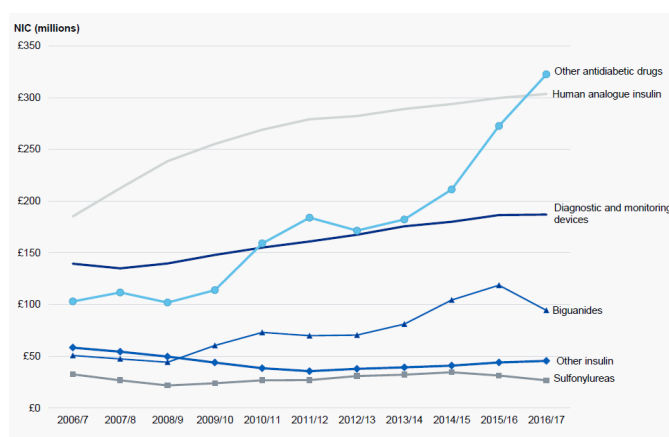
Metformin's role

Metformin is today's most widely used and lowest cost Type 2 diabetes treatment – see Figures 4a and 4b. It is now the only biguanide medicine available. This class of drugs was originally found through studies of herbal diabetes medicines derived in Europe from French Lilac. Metformin as a discrete molecular entity was identified during studies undertaken in France in the early 1920s, at the time Banting and Best and their Canadian colleagues first gave insulin to a human subject. But it was not introduced as a diabetes medicine there until the early 1950s. Metformin containing medicinal products were first marketed in the UK in 1958 and in the US in the mid-1990s.

Figure 4a. Number of FPS Prescriptions for Drugs Used for Diabetes in England, 2006/7-2016/17

Source: Health and Social Care Information Centre, 2017

Figure 4b. Cost of FPS Prescriptions for Drugs Used for Diabetes in England, 2006/7-2016/17

Source: Health and Social Care Information Centre, 2017

In North America exaggerated fears about the safety of taking metformin almost certainly, because of its late introduction and the use of more hazardous alternative therapies, cost significant numbers of lives. Even so, the drug is not without unwanted side effects. The most commonly encountered adverse consequences are diarrhoea and other gut disturbances, although the use of introductory strategies

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6   It is envisaged that the action of 'smart' or self-regulating insulins will vary according to ambient blood sugar levels.

which minimise intestinal problems can enable most people to tolerate treatment. Metformin also impairs vitamin B12 absorption and increases homocysteine levels, indicating that best practice care should include B12 supplementation. It can be estimated that without this between one in ten and one in twenty people using metformin for ten or more years will develop an avoidable peripheral neuropathy.

There are also drug interactions involving metformin and medicines such as, say, the proton pump inhibitors cimetidine and ranitidine and the antibiotics trimethoprim and cephalexin. However, against this metformin is effective in reducing blood sugar levels, does not cause weight gain, and is in overall terms amongst the least hazardous of all prescribed antidiabetic medications.

Metformin is often used in combination with other antidiabetic treatments. It reduces glucose production in the liver, albeit the overall mode of action is – like that of many traditional medicines – complex. In addition to cutting the availability of glucagon it activates a key enzyme known as has AMPK[7], which can be described as a 'metabolic master switch' governing insulin and glucose production and fat synthesis and breakdown. The effects of AMPK activation reflect those of exercise and fasting. There is observational evidence that people taking metformin for Type 2 diabetes can enjoy longer lives than other similarly aged individuals (Bannister et al, 2014) and a number of research centres are presently exploring its potential in cancer prevention and slowing ageing.

As understanding of the differing causes and characteristics of Type 2 disease subtypes becomes more complete, and awareness of the full therapeutic potential of more recently introduced antidiabetic drugs continues to improve, dependence on metformin as a single first line treatment choice may in future decline. Yet for the present the evidence available supports its widespread use, along with lifestyle related interventions and the use antihypertensive and allied medicines. Indeed, there is a case for greater use of metformin in contexts like that of pre-diabetes (Aroda et al, 2017). Likewise, people being treated with – for instance – antipsychotic medicines could also benefit from the pro-active use of metformin, rather than being left to develop diabetes and subsequently be offered treatments as and when their iatrogenic illness is recognised.

Early diagnosis and the productive use of blood sugar monitors and other devices

Health care cannot be optimised in circumstances where disease risks are inadequately identified, or when conditions are undiagnosed. Knowledge of this highlights the need for pro-active diabetes case finding approaches. Where

established diabetes exists, achieving the best possible treatment outcomes can also require active blood sugar monitoring and the use of items such as insulin pumps and – as they become available – artificial pancreas devices which will deliver insulin and other biologically active substances in line with individuals' changing needs (Box 7).

In the case of Type 1 diabetes there were in 2018 reports that, despite high level endorsements, NHS patient access to 'flash' blood sugar monitoring devices has been particularly disappointing in England (Lacobucci, 2018). NHS England responded to claims that some CCGs were ignoring evidence and inappropriately restricting provision in order to cut costs by saying that more equitable and appropriate funding will in future be guaranteed. But the fact that such shortfalls in care quality were permitted to exist until independent advocates for good care quality intervened is indicative of cultural and allied problems in need of rectification.

The 'FreeStyle Libre affair' may be seen as reflecting other longer standing issues, from previous NHS failures to supply insulin pumps to British children with diabetes (JDRF, 2016) to apparent denials of the value of early disease detection and treatment. Despite initiatives such as the NHS Health Checks programme in England there are still in the order of half a million UK citizens with undiagnosed Type 2 diabetes. Undue reliance on *ad hoc* testing is difficult to defend. In mainstream primary care, for example, a significant proportion of General Practices do not pro-actively test patients' blood sugars in any way after they have reached their 40s unless they are classified as being at high risk of developing diabetes. Even if not NICE mandated, universal measures aimed at identifying pre-diabetes/early diabetes in the population aged 50 and over would in time improve public health.

In the case of Type 2 diabetes management it might be claimed that from a medical and cost effectiveness perspective there is little benefit to be gained from blood sugar testing, as opposed to relatively infrequent HbA1c testing. Yet from a broad bio-psycho-social standpoint access to rapid and accurate blood sugar measurement could be of substantive value, even to individuals with 'mild' forms of Type 2 diabetes. If the timely feed-back of blood glucose data were to help sustain desirable behavioural changes it might in practice prove more clinically effective than approaches to diabetes care that, even if evidence based in a narrowly defined sense, are delivered without an empathetic understanding of the psychological, social and economic realities in which people live.

Diabetes Related Policy Issues

A new long term plan for the NHS in England was originally due to be published in early December 2018, but was delayed. This timing may to an extent have reflected a desire to show, correctly or otherwise, that important domestic policy matters have not been ignored while the Government has been pre-occupied with the UK's negotiations about

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7   5-adenosine monophosphate activated protein kinase (AMPK). Using metformin in addition changes the microbiomes (gut bacteria) of those taking it, and probably affects incretin production. Metformin use also, via AMPK activation, inhibits the mTOR signalling pathway, which plays an extensive part in regulating cell metabolism, growth, proliferation and survival. This links to interest in metformin as a possible anticancer/anti-aging agent.

Box 7. Innovations in Diabetes Prevention, Treatment and Care

Innovations for preventing diabetes where possible, or improving outcomes when it must be lived with, are taking place in multiple spheres. They range from service developments like the extensions to the Diabetes Prevention Programme and the introduction of diabetes remission courses described in this report through to optimising the prescribing and use of existing and yet to be marketed medicines. New medical devices will also have important roles. The types of short, medium and longer term progress to be expected in the coming ten to twenty years can be summarised as:

'Self-care enhancers'

Along with educational and other initiatives aimed at strengthening public understanding of diabetes and related risks, these could include online psychological support services for individuals seeking to improve their chances of avoiding diabetes related harm and extending self-care access to medicines such as anti-hypertensives for use in the primary prevention of disease and disability

Technologies for supporting risk management and the timely diagnosis of very early stage and established diabetes in primary care

These will include AI powered record keeping and diagnostic and clinical decision support programmes for optimising the treatment of diabetes sub-types, together with the wider employment of genetic and phenotypical testing for disease risks. Service extensions in settings like community pharmacies could also help enable everyone seeking it to have 'walk in' access to professional support for IT led self-diagnosis and for managing weight, blood sugar and other diabetes and pre-diabetes related risk factors.

Providing good personal access to 'high performance' blood sugar monitoring devices

As blood sugar monitoring devices grow easier and less intrusive or painful to use while also being rapid and accurate, demand for them may well extend beyond the population living with Type 1 disease through to more people with Type 2 diabetes. Combined with increases in digital information storage and analysis capacities, this will further enhance the value of both home and professionally held health records and could promote greater self efficacy amongst people living with diabetes.

Delivering the 'artificial pancreas'

The concept of developing an artificial pancreas dates back to at least the 1960s. The advent of 'flash' glucose testing and related technologies has opened the way to single hormone closed-loop (ie autonomously functioning) devices being made available in the US. More sophisticated devices are in development which will in time be able to deliver not only insulin but other hormones of hormone-like products relevant to the management of blood glucose levels.

Developing protective vaccines and medicines, and other treatments with new modes of action

As noted in the main text, a vaccine against Coxsackie B virus infection that may prevent at least a proportion of Type 1 disease cases is already in development. There is also interest in developing immunotherapies which if delivered in a timely manner may stop the autoimmune reactions involved in pancreatic cell deaths. Other examples of research in progress range from Swedish work on finding a drug that will activate AMPK as or more effectively than metformin but with hopefully fewer side effects through to research on developing new (if possible orally active) incretin agonists and smart insulins, which will automatically respond to varying blood glucose levels. Further into the future, gene and/ or cell and related therapies should in time become available for correcting 'DNA level' vulnerabilities associated with diabetes. They may also be able to preserve or restore pancreatic cell functioning and/or combat insulin resistance.

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the country's European exit, and that health service funding is not suffering because of 'Brexit'. The comments and considerations below discuss key policy issues from a diabetes prevention and treatment related viewpoint.

Funding health and social care

In the summer of 2018 the government announced a decision to increase the annual funding of the health service in England by a little over £20 billion in real terms by 2023/24. From 2020 there should, subject to higher than expected inflation, be a 3.4 per cent annual growth in the NHS budget. This ought to relieve immediate financial pressures, although it will not compensate for relatively low rates of welfare service growth during the recent 'austerity' period. There in particular remain questions as to the resourcing of social care and allied provisions which impact on the lives of many people with long term conditions.

Total health spending across the UK as a whole represents some 10 per cent of GDP, of which in the order of 85 per cent is accounted for by NHS outlays. This is comparable to the EU average for overall health care, but is significantly below the spending recorded in the North West European nations such as France, the Netherlands and Germany. In comparison with countries such as Sweden the resourcing gap widens if welfare service disparities that affect wellbeing beyond the context of conventionally defined health and health related social care are included.

It is presently uncertain as to how much the UK economy will grow in the decade ahead. From a diabetes care perspective this means that, given that it is currently estimated that meeting diabetes related needs accounts for 9-10 per cent of overall NHS costs, there will be continuing pressures to limit spending. Yet on the other hand policy makers have expressed a wish to extend healthy life

expectancy relative to overall survival. Tackling the obesity/diabetes/vascular disease/cancer nexus must be central to any such programme.

A strategy involving increased spending on primary and secondary diabetes prevention would be desirable from such a perspective. However, a skewed approach to implementing such a policy could restrict the access of people with advanced, on occasions life threatening, forms of diabetes to effective but – in the short term at least – relatively costly technological innovations and intensive forms of personal care.

This could well be seen as unfair and so undermine trust in the NHS. It could at the same time weaken the UK's position as a global bioscience and life-sciences industry leader. For national health policies to be successful they should therefore seek to achieve a robust balance between providing sophisticated medical treatments and health technologies on the one hand, and delivering optimally (cost) effective prevention and routine disease management on the other. This will demand policies based on wider criteria than those presently used in disciplines such as health economics.

Eliminating tobacco smoking

Tobacco smoking remains the single most significant avoidable cause of morbidity and mortality in this and many other countries. It represents a special threat to people with diabetes because of its vascular consequences. Smoking rates are continuing to fall and government policies in all the UK countries are focused on maintaining this trend via stopping people from becoming addicted to the habit wherever possible, and supporting cessation when necessary. The introduction of vaping is seen by most UK smoking policy specialists as a valuable means of promoting the latter, and of reducing the harm associated with nicotine use (West, 2018).

However, there are concerns that in England the shift of previously ring fenced NHS public health budgets to local government has been associated with reductions in the availability of specialised smoking cessation services. As smoking is increasingly confined to limited numbers of less advantaged people there is some risk that political motivation to seek its elimination will decline to the point that the pursuit of this goal is *de facto* abandoned.

It is important that everyone at raised risk of, or who is living with, diabetes should not smoke, and that those who are smokers should have good access to effective cessation support in both community and hospital settings. (At any one time about a sixth of all hospital beds are occupied by individuals who have diabetes – Wright, 2018). This is an example of a problem for which high quality services offered in community pharmacy/'healthy living centre' settings can offer an effective solution for a significant section of the population. There is an opportunity for professional groups and third sector (charitable and patient group) organisations to work together to monitor smoking amongst people with diabetes and act as advocates for maintaining and when needs be extending appropriate service provision.

Obesity prevention in populations and individuals

Preventing and/or managing and minimising the harm associated with child and adult obesity is now central to government health policy agendas in many parts of the world. This represents welcome progress. Establishing a broad public understanding of the nature of diabetes and its relation with obesity is a major twenty first century public health task, along with that of equipping young, middle aged and older adults with the ability to recognise and respond to 'pre-obesity' (that, is overweight defined as having a BMI in the range 25-30) as well as obesity *per se*, and to be aware of how diabetes can in some instances be reversed and problems like, for instance, erectile dysfunction in males be avoided or moderated.

However, enthusiasm for reducing the burden of diabetes and other diseases (from arthritic conditions to cancers, including a raised risk of pancreatic cancer) associated with 'fatness' (that is, morbid adiposity) should be tempered by an awareness of the challenges involved in combating obesity in a fair and effective manner. Relevant points include:

- More than is so in 'unipolar' areas like reducing smoking rates or alcohol use, modifying individuals' and communities' diets without going back to a situation where less advantaged people are at risk of hunger and malnutrition related disease is a complex task. Achieving desired outcomes will require multiple carefully crafted policy interventions and action at many levels in society. There is data from the US (see, for instance, Gregg, 2016) and elsewhere showing that positive progress towards limiting or reducing obesity rates is possible. Yet delivering tangible gains in terms of reduced disease burdens or health service costs will take much longer than any one (five year) Parliamentary term.

- Simplistic attempts to control obesity often involve blaming those who 'choose to be fat' or can be labelled as failing to control their eating. At worst, populist politicians blame the parents of obese children. Such strategies can serve to deflect criticism away from social policy failings, and avoid challenging the eating and alcohol use habits of other groups of voters whose possible electoral responses are more feared. Unfair blaming can stigmatise individuals and families whose weight related problems are due to much more than a lack of personal effort. Studies conducted by London University and other researchers show that it is easy to over-estimate the degree of agency individuals acting alone have in combating being overweight, and that it is often unfair and counter-productive to blame parents for child obesity (Selzam et al, 2018).

A key conclusion to draw is again that individuals such as patients' advocates and organisations like health charities have a responsibility to check and monitor politically driven policies and their social impacts. This includes seeking to ensure that they effectively protect those about whom 'voter-volume' driven decision-makers are least likely to care.

Proactive medicines use for the primary prevention of diabetes and vascular disease

As previously discussed, there is evidence indicating that, alongside lifestyle modification, medicines such as metformin together with statins and anti-hypertensives can – whether as employed as single agents or in 'polypill' combinations – contribute to the primary prevention Type 2 diabetes.

Some medical and allied commentators warn against undue medicalisation. They may point to side effect risks and imply, albeit questionably, that encouraging the use of protective drugs promotes unhealthy lifestyles. However, seen from an alternative perspective it can be argued that avoidable deaths and disabilities linked to diabetes and related conditions are taking place because policy makers have been unduly influenced by suggestions that if doctors were to spend more time on helping healthy people to stay disease free through increasing their use of protective medicines their surgeries would be 'swamped', and they would have less time for people who are already ill.

One way of defending public interests in this area might be to 'de-medicalise' the supply of drugs with antidiabetic and vascular health promoting actions, when (like vaccines) they are provided for preventive as opposed to treatment purposes. Suitably regulated community pharmacy or internet supply could deliver support for their appropriate use. For policies of this type to succeed more effort will be required to communicate their public health benefits. Sufficiently informed leadership will also need to be in place to counter pressures from sectional professional, regulatory or commercial interests that may have little genuine interest in making health information more obtainable or low cost health-maintaining products more easily accessible.

Fostering the early detection of diabetes and delivering better diabetes treatment in primary care – an extended role for community pharmacy?

Initiatives such as NHS Health Checks and the NHS Diabetes Prevention Programme in England, together with other pro-active approaches to pre-empting, diagnosing and effectively treating diabetes elsewhere in the UK, represents significant progress. So does the use of QOF[8] and other payments to drive GP performance, and the employment of (limited numbers of) clinical/primary care pharmacists with expertise in the field of diabetes in General Practices.

The NHS Long Term plan also promotes primary and community care capacity increases aimed at helping patients with disease exacerbations to avoid unplanned hospital admissions in ways that will benefit people with conditions such as diabetes. However, this is by no means an original concept. For instance, some thirty years ago the *Peterborough Hospital at Home Project* demonstrated the ability of well-designed community/primary care services to reduce NHS hospital admission rates and improve patient outcomes (Taylor, 1989).

Pilot schemes and allied developments can generate evidence regarding the effectiveness of innovative services. Recently announced plans to provide 5,000 places on 'diabetes remission courses' in England fall into this category. Yet in the medium term the NHS needs to incorporate new ways of providing care into its mainstream structures and procedures if they are to give optimum nationwide value. The ultimate test of the remission course pilots will be the extent to which they open the way to much larger scale changes in NHS care, or failing that the supply of privately purchasable services aimed at public health improvement.

Similar concerns exist in areas ranging from the introduction of mhealth and other internet/computer facilitated options (including Artificial Intelligence – AI – supported diagnostic systems and related innovations such as the wearable monitoring technologies the NHS DPP is currently seeking to foster – see King's Health Partners, 2018) through to enabling community pharmacies to act more effectively as centres which both supply pharmaceuticals and provide easy access to clinical care.

AI driven applications will (coupled with developments in areas such as 'near patient' genetic, epigenetic and proteomic testing) be increasingly able to assist in case finding and achieving better health outcomes. Used to good effect, they should help both individuals seeking to manage their own health well and professionals to identify illnesses more accurately, and to choose between increasingly refined personal treatment options in well-informed ways. The introduction of voice responsive programmes and complementary developments such as visual image based analytical capacities should, as Ministers and experts like Erik Topol (2018) have highlighted, progressively enhance the potential of IT to add health sector value.

Nevertheless, this is not to say that advances in areas such as mhealth will resolve shortages of GPs or nurses, or automatically improve care quality. Indeed, it might be argued that to date using computer based records and allied systems has, rather than personalising interactions, often contributed to the anonymisation of primary health care encounters and reductions in the quality of the therapeutic relationships formed. It is also evident that, in ways parallel to the working of the 'inverse care law', those most at risk of sub-optimal therapy and unwanted disease consequences

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8   In England the Quality and Outcomes Framework offers GPs and their colleagues financial incentives to keep a register of diagnosed diabetes patients and to ensure regular monitoring of their condition. But it does not provide comparable payments for offering pre-emptive care such as testing blood sugar levels amongst older people at 'normal' risk of undiagnosed diabetes.

in contexts such as diabetes care may also be less able than others with fewer problems in life to use IT applications of any sort to their advantage, unless empathetic professional help is available to them.

For many NHS users GPs and practice nurses are, and will remain, their most important source of advice, guidance and care. But recognising this should not negate awareness of the fact that continuing shortfalls in GP numbers and ongoing trends towards increased practice sizes, coupled with changing service preferences in parts of the community, mean that extending the parts played by community pharmacists and local pharmacy based health services in diabetes prevention and treatment deserves serious attention.

Experience with forming Healthy Living Pharmacies and initiatives like the North East London Self-care Pharmacy scheme (Patel, 2018) has demonstrated that enhancing primary care capacity via community pharmacy developments can yield improvements in diabetes care (Wright, 2018). Pharmacies could also in future offer accessible settings for people to receive professionally informed help with using computer based diagnostic and treatment advice systems. Important barriers to the full scale national realisation of such promises relate to the need for committed leadership, and complementary General Practice and wider community health and social care changes aimed at enabling the overall primary and social care system to work in a well-coordinated manner.

Facilitating Type 2 diabetes remissions and making them last

Recent Diabetes UK supported work on the role of fat deposition in the liver and pancreas in causing the insulin resistance and insulin secretion reductions characteristic of Type 2 diabetes, and the extent to which rapid weight loss can sustainably reverse this disease process, has transformational potential. As more health professionals and people living with diabetes come to understand its full implications there may well be major increases in the numbers of people willing and wanting to take part in programmes aimed at promoting the re-normalisation of their blood glucose control.

Establishing the capacity required to meet initial demands has to be an immediate key priority. But at the same time providing support for maintaining, with or without ongoing drug use, diabetes remissions for indefinite periods is also an important and in some ways more difficult task.

Additional research is urgently needed to provide more evidence as to the most effective ways of making Type 2 disease remissions last to the point when they can reasonably be classed as cures. It could be that – given professional commitment to improving public health and appropriate public and/or private funding – pharmacy based high street clinics will for significant numbers of people offer a convenient future setting for them to receive

help in maintaining freedom from Type 2 diabetes. But the overall scale, complexity and resources that may be needed to execute this remission maintenance task well should not be underestimated.

The value of biomedical innovation

It would be outside the scope of this analysis to enter into a detailed discussion of the value of diabetes related biomedical innovations. Nor can the strengths and weaknesses of the health technology assessment (HTA) methods used by NICE and similar bodies to determine the prices purchasers are willing pay for them be explored in depth. However, there have recently been concerns about the fact that in England alone primary care supplied drugs and linked items now cost £1 billion a year. This is a little in excess of a tenth of all Family Practitioner Service – FPS – pharmaceutical spending.

The overall cost of drugs and allied items used by the entire UK NHS for the care of people with diabetes in the community and in hospitals can also be estimated to be approaching 10 per cent of all pharmaceutical spending. The latter, in net terms, in turn represents 12-13 per cent of present health service outlays[9].

Some commentators fear that such levels of expenditure are excessive and potentially unsustainable, at least for a tax funded health service. However, points worth emphasising in response to such claims include:

- **Total spending on health care in the UK is, when expressed as a percentage of GDP, modest in comparable international terms: the proportion allocated to pharmaceuticals is also no more than average.** There is in addition evidence that resourcing universal health care via a tax funded approach is, at least from an equity oriented standpoint, more efficient and effective than using non-mandatory insurance or user fee based options, provided services are well managed. In part because many voters tend to prefer low direct taxes, the NHS has been less well funded (and so under more financial pressure) than some health systems based on social insurance or the more fragmented 'private plus public' US model. But this should not be taken to mean that it is unaffordable, or that NHS medicine costs in general or those specifically relating to diabetes are out of control.

- **On average a prescription written for the treatment of diabetes costs about twice the current average.** There are several reasons for this. Some relate to the fact that because of unmet needs and the fact that the scientific understanding of diabetes is developing in ways that are allowing new therapies to be introduced, the total cost of patented and similarly protected anti-diabetes treatments is temporarily high compared with that of the generic medicines being prescribed.

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9 Author's estimates based on various published sources.

- **Innovative medicines are for a limited period more expensive than longer established products.** This is because public policies are in place to encourage further investment in research and development via the returns made on new medicines. However, as intellectual property terms expire and competition increases pharmaceutical prices fall closer to the marginal costs of production. Over time this makes them increasingly cost effective. Labour intensive forms of health and social care, by contrast, tend to become more costly over time, as and when societies become more prosperous and wage rates rise.

Failures to understand this dynamic, and the fact that only fundamentally new treatments can ever hope to eradicate diseases like Type 1 diabetes or, when prevention fails, guarantee the effective and affordable management of conditions like Type 2 disease, can lead to ill-founded fears about pharmaceutical care cost escalations. In total, NHS medicine and allied spending expressed as a proportion of health service outlays has remained at around 10 per cent for the last half century. Seeking reasonable economy is sensible in any sphere. Yet as far as innovative and increasingly effective NHS diabetes medicines and device costs are concerned budget holders' desires to save money should be balanced by an awareness of the fact that, as in all other areas, undue downward pressures risk harming patient outcomes and so driving up overall care costs. They also risk undermining future investment in research and development and manufacturing.

Integrating care

NHS and other plans highlight the need to integrate services in ways which permit better health and health linked social care outcomes. From the perspective of an individual living with, or at risk of, diabetes and her or his family it is common sense to say that preventive and treatment approaches should be well co-ordinated, and that when needs be general practice and other forms of primary health care provision in the community should work in ways that link robustly with specialised hospital and community based services. Likewise, social care and mental and physical health care should from a consumer stand point be seamlessly joined. In the diabetes arena this is important in not only managing psychoses and more transient forms of anxiety and depression, but also in contexts such as that of gestational diabetes.

Because of the advantages of good service co-ordination there has been recurrent interest in forming organisations which bridge across traditional NHS and local government divides. Presently in England the development of the Greater Manchester Health and Social Care Partnership is attracting considerable attention from what is commonly termed an integration perspective. Building on the groundwork undertaken during the preparation of sustainability and transformation plans (STPs), similar Partnership bodies are now forming elsewhere.

This is for good reason. Yet from a diabetes prevention, treatment and care advocacy position it is worth underlining the point that large scale organisational changes are no substitute for the actual delivery of good quality services to individuals in need. The latter often depends on the strength of highly localised relationship networks, the degree to which the cultures in which individuals find themselves promote commitment to improving the health and wellbeing of people who do not share the social positioning of high level policy makers, and the extent to which personal financial and allied incentives are aligned with patient-centred values and objectives.

It is of course desirable to try to remove counter-productive institutional rivalries and dysfunctional barriers to joint working. But if diabetes in its various forms is to be effectively overcome via better health care and well-informed individual and community action during the 2020s and beyond it would be helpful for those seeking to foster desirable progress to keep the possibility of unintended consequences of interventions such as simply forming larger organisations in mind. As the evidence discussed in Box 8 indicates, reforms aimed at delivering 'service integration' might perversely undermine, or at least fail to improve, health outcomes when they impose cultures which impair the personal relationships needed for high quality primary care delivery and inhibit the development of self-efficacy based competencies amongst people with long term conditions.

Conclusions and Recommendations

Diabetes is today recognised as a set of insulin production and response related conditions which threaten the health and wellbeing of people of all ages. It affects the entire community, although those living in less advantaged circumstances are most likely to be experience severe harm. There are fears that diabetes, together with other obesity associated health challenges, will cause many people who are presently alive to have shorter lives than their parents.

Warnings about the health impacts of the rising prevalence of diabetes demand serious attention, not least because of recent falls in life expectancy in Britain after over a hundred and fifty years of uninterrupted progress. However, undue pessimism should be avoided. Looked at from an alternative perspective there is now – both nationally and internationally – more opportunity to prevent or treat diabetes and other non-communicable diseases than ever before. If appropriate policies are pursued it should in overall terms be possible to at least halve existing premature death and disease related disability rates within the next few decades (Peto, 2012).

The conclusion offered here is that communities like that of the UK are in fact closer to being able to in age standardised terms radically reduce the burdens imposed by diabetes than is commonly realised. At the scientific level vital steps towards understanding the causes of all forms of the disease have been made, and in favourable settings it is already possible to avoid much of the harm which untreated diabetes would generate. Prevention and cure are both becoming increasingly realistic goals, and further advances in areas ranging from risk testing to the use Artificial Intelligence powered diagnostic and therapeutic guidance programmes are emerging. So too are long sought after developments such as the introduction of effective and (at least in affluent countries) affordable 'artificial pancreas' devices.

Timely progress is not, of course, inevitable. It will require political will, good policy making and sustained practical effort to overcome diabetes. But if governments, health care providers and the wider public maintain the confidence and integrity of purpose required to keep investing in public health measures and effective new treatments, and to act on the evidence available about the societal and personal actions needed to protect health, diabetes and its consequences will not be major causes of death or disability by 2050s. The key elements of the health service and wider social programmes needed to deliver this endpoint include:

1. Sharing knowledge about the nature and genetic and environmental causes of diabetes in ways that make it available to everyone, and enable those at risk to act. It is particularly important to spread awareness of how building up fat in the liver, pancreas and other organs and tissues first causes resistance to insulin and subsequently reduces its production, and how losing sufficient weight can lead to Type 2 diabetes remissions as well as other health benefits.

2. Combatting obesity in ways that communicate respect for those affected, and address its social determinants alongside the specific medical and other personal needs of overweight individuals. Illustrations of the multiple interventions that will need to sustained over long periods encompass moderating alcohol use via fiscal and other measures and programmes aimed at promoting responsiveness to the early signs of weight gain related health issues amongst young and middle aged adults.

3. Building further on initiatives like the NHS Diabetes Prevention Programme to enable significantly increased numbers of people to know when they have 'pre-diabetes' and to protect themselves, as well as further reducing the population living with undiagnosed diabetes. This could in future involve innovative forms of risk testing that combine measures of variables like waist sizes with genetic and epigenetic factors, coupled with more systematic blood glucose monitoring in the entire population aged 50 years and over. It will also require an open minded and public interest focused approach to exploring questions about when using medicines for the primary prevention of Type 2 diabetes is a valuable complement to lifestyle change, and continuing efforts to ensure that tobacco smoking is eliminated.

4. Being assertively committed to taking up opportunities for the primary prevention or cure of Type 1 diabetes, as and when technologies such as suitable enterovirus vaccines or cell based therapies become available.

5. Moving to provide services that will enable everyone wishing to try to reverse their Type 2 diabetes to take part in a suitable programme, and as necessary be supported in maintaining disease remissions. Progress in this area should take place alongside providing access to bariatric surgery for obese people able to benefit.

6. Optimising the treatment of established diabetes amongst individuals with different forms of the condition, and varying sub-types of Type 2 disease. This will in future involve using AI based diagnostic and treatment selection aids in primary care and self-care support, together with innovative pharmaceutical treatments when there is evidence of benefit. To maintain public confidence, the NHS will need to be able to fund the use of modern devices for monitoring blood glucose levels and delivering insulin or other beneficial medicines/substances to an extent accepted as fair and reasonable by patients and the wider public. Similar points will apply to the introduction of specialist technologies such as pancreatic cell transplantation, if and when they are sufficiently developed.

When the NHS was first formed it faced very different tasks from those confronting it today, politically and socially as well as medically. Some observers claim that it has been slow to shift away from concentrating on problems such as controlling infections like tuberculosis and polio to preventing and treating the non-communicable conditions of later life. But there is evidence that the UK health services are now working relatively well to limit the burdens imposed by diabetes and allied causes of illness. In future the NHS will be able to do even more to reduce disease burdens and in time overcome the challenge of diabetes, if policy makers and health professionals understand the opportunities available and give sufficient priority to improving public health.

However, in the final analysis achieving optimal results in areas such as diabetes prevention and treatment will not be possible simply by enhancing health services and providing more sophisticated medical technologies. Such improvement will ultimately rest on those at risk of disease being in a position to choose to live well and use products like medicines effectively, and on entire societies evolving behavioural norms that will contribute to achieving longer healthy life expectancies.

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