Supporting notes, Diabetes presentation (not all slides have notes attached).

Slide number	Notes
1	Title page
2	Numerous studies have shown that there is a rising incidence of diabetes and it's complications in all age groups, both in the UK and worldwide. In 1997, Amos estimated that 124 million people worldwide have diabetes, 97% NIDDM and that by 2010 the total number with diabetes is projected to reach 221 million. In 2000, Sorensen reported that the World Health Organisation has recognised that there is a "global epidemic of obesity" and the prevalence of type 2 diabetes is rising in parallel. In 2001, Boyle estimated the number of Americans with diagnosed diabetes is projected to increase from prevalence of 4.0% in 2000 to a prevalence of 7.2% in 2050. A diabetes clinical information system in Tayside, Scotland, showed a doubling in incidence and prevalence of type 2 diabetes between 1993 and 2004, with statistically significant increasing trends of 6.3 and 6.7% per year respectively. Evans, 2007.
6	Ketosis - a state in metabolism occurring when the liver converts fat into fatty acids and ketone bodies which can be used by the body for energy. Adipose tissue consists of highly specialized cells which store energy in the form of a triglyceride and release it upon hydrolysis in a process known as **lipolysis**, yielding three fatty acids and one glycerol molecule. These ketone bodies are a by-product of the lipid metabolic pathway after the fat is converted to energy. Ketoacidosis, by contrast, is the accumulation of excessive keto acids in the blood stream (specifically acetoacetate and beta-hydroxy butyrate).
7	What symptoms might you expect to see in a patient with undiagnosed or poorly controlled diabetes ? Thirst Increased frequency Toilet visits during night Fatigue Thrush Boils In children, vomiting, stomach pain Glucose excreted in the urine leads to an increase in the concentration gradient. Water follows the glucose, and therefore more glucose is lost

	in the urine.
8	What is the OTT ? The patient should have been fasting for the previous 8-14 hours (water is allowed). Usually the OGTT is scheduled to begin in the morning (0700-0800) as glucose tolerance exhibits a diurnal rhythm with a significant decrease in the afternoon. A zero time (baseline) blood sample is drawn. The patient is then given a glucose solution to drink. The standard dose since the late 1970s has been 1.75 grams of glucose per kilogram of body weight, to a maximum dose of 75 g. It should be drunk within 5 minutes. Blood is drawn at intervals for measurement of glucose, and sometimes insulin levels. The intervals and number of samples vary according to the purpose of the test. For simple diabetes screening, the most important sample is the 2 hour sample and the 0 and 2 hour samples may be the only ones collected. In research settings, samples may be taken on many different time schedules. If renal glycosuria (sugar excreted in the urine despite normal levels in the blood), then urine samples may also be collected for testing along with the fasting and 2 hour blood tests.
11	**Pima indians** - a group of American Indians living in an area consisting of what is now central and southern Arizona and Sonora in Mexico. The name means "river people". The name "Pima" apparently comes from a phrase that means "I don't know", used repeatedly in their initial meeting with Europeans. The USA group have the highest prevalence of type 2 diabetes on Earth, much more than is observed in other U.S. populations. The Pima people have been the subject of intensive study of diabetes, in part because they form a homogeneous group. The general increased diabetes prevalence among Native Americans has been hypothesized as the result of the interaction of genetic predisposition (the thrifty phenotype, suggested by anthropologist Robert Ferrell in 1984) and a sudden shift in diet from traditional agricultural goods towards processed foods in the past century. For comparison, genetically similar Pimas in Mexico have virtually no type 2 diabetes. It has been suggested that in poor nutritional conditions, a pregnant female can modify the development of her unborn child such that it will be prepared for survival in an environment in which resources are likely to be short, resulting in a **thrifty phenotype**. Individuals with a thrifty phenotype will have a smaller body size, a lowered metabolic rate and a reduced level of behavioural activity… adaptations to an environment that is chronically short of food. Those with a thrifty phenotype who actually develop in an affluent environment may be more prone to metabolic disorders, such as obesity and type II diabetes, whereas those who have received a positive maternal

	forecast will be adapted to good conditions and therefore better able to cope with rich diets. This idea, which is also known as the **Barker hypothesis** is now widely (if not universally) accepted and is a source of grave concern for societies undergoing a transition from sparse to better nutrition.
12	BMI = weight in Kg, divided by height in metres squared.
14	The problem with diabetes is that we must maintain a balance between insulin production and blood glucose levels, as well as encouraging the correct action of insulin. In Type 2, insulin is being produced, but for some reason it's not working properly, and also it's being produced in smaller quantities, so the aim of many treatment regimes is to increase the production of insulin, and also make it more effective. The sulphonylureas are a family of drugs based on a common sulphonylurea core. These drugs act via augmentation of secretion of insulin from pancreatic beta-cells. Sulphonylureas may also cause a reduction in serum glucagon and potentiate the action of insulin at the extrapancreatic tissues. They vary in potency tremendously with first generation sulphonylureas such (e.g. tolbumatide, chlorpropamide) being less potent thant second generation sulphonylureas (e.g. glipizide, glimepiride). Sulphonylureas are metabolised by the liver to less active metabolites which are subsequently excreted by the kidneys. Care should therefore be taken in both renal and hepatic impairment. The duration of action and dosage frequencies of the some commonly used sulphonylureas are shown below: **Cautions include:** **Side Effects include:** haematological disorders associated with sulphonylureas are rare - possible adverse effects include leucopenia, thrombocytopenia, agranulocytosis, haemolytic anaemia, pancytopenia and aplastic anaemia. chlorpropamide is associated with more side-effects than other sulphonylureas, principally because of its very prolonged duration of action and the consequent hazard of hypoglycaemia and it should no longer be used.
15	Metformin is a biguanide oral hypoglycaemic which suppresses appetite. Metformin is first-line drug treatment for overweight patients with type 2 diabetes (1) in whom diet and exercise treatments have failed. The principle advantage of metformin treatment is that glycaemic control is improved but with significantly less weight gain than when sulphonylureas are used (2). It is unlikely to cause hypoglycaemia. Metformin is contraindicated if there is liver, kidney or heart failure,

	or in patients with a very high alcohol intake because of the perceived risk of serious lactic acidosis.
16	Work by acting on receptors inside the cell, affecting DNA activity, and bringing about a decrease in insulin resistance.
18	Type 1 diabetes is an autoimmune disease that results in the permanent destruction of beta cells. The cause of Type 1 is still not understood. Type 1 diabetes could be a virally induced autoimmune response. In the proposed scenario, pancreatic beta cells in the Islets of Langerhans are destroyed or damaged sufficiently to abolish endogenous insulin production. This aetiology makes type 1 distinct from type 2 diabetes mellitus. It should also be noted that the use of insulin in a patient's diabetes treatment protocol does *not* render them as having type 1 diabetes, the type of diabetes a patient has is determined only by disease aetiology. The autoimmune attack may be triggered by reaction to an infection, for example by one of the viruses of the Coxsackie virus family or German measles, although the evidence is inconclusive. This vulnerability is not shared by everyone, for not everyone infected by these organisms develops Type 1 diabetes. This has suggested a genetic vulnerability and there is indeed an observed inherited tendency to develop Type . It has been traced to particular HLA phenotypes, though the connection between them and the triggering of an auto-immune reaction is poorly understood. Some researchers believe that the autoimmune response is influenced by antibodies against cow's milk proteins. A large retrospective controlled study published in 2006 strongly suggests that infants who were never breast fed had twice the risk of developing Type 1 diabetes as infants who were breast fed for at least three months. The mechanism is not understood. No connection has been established between autoantibodies, antibodies to cow's milk proteins, and Type 1 diabetes. A subtype of Type 1 (identifiable by the presence of antibodies against beta cells) typically develops slowly and so is often confused with Type 2. In addition a small proportion of Type 1 cases have the hereditary condition maturity onset diabetes of the young (MODY) which can also be confused with Type 2. In December 2006, researchers from Toronto Hospital for Sick Children revealed research that shows a link between Type 1 diabetes and the immune and nervous systems. Using mice, the researchers discovered that a control circuit exists between insulin-producing cells and their associated sensory (pain-related) nerves. It's being suggested that faulty nerves in the pancreas could be a cause of Type 1 diabetes. Other pancreatic problems, including trauma, pancreatitis or tumors (either malignant or benign), can also lead to loss of insulin

	production. The exact cause of Type I diabetes is not yet fully understood, and research on those mentioned, and others, continues.
21	Other treatment possibilities: **Pancreas transplantation -** Pancreas transplants are not generally recommended because introducing a new, functioning pancreas to a patient with diabetes can have negative effects on the patient's normally functioning kidney. However, they are highly recommended for patients who require a kidney transplant, and may also be wise in patients with extremely labile diabetes. **Islet cell transplantation -** Less invasive than a pancreas transplant, islet cell transplantation is currently the most highly used approach in humans to temporarily cure type 1 diabetes. In one variant of this procedure, islet cells are injected into the patient's liver, where they take up residence and begin to produce insulin. The liver is expected to be the most reasonable choice because it is more accessible than the pancreas, and the islet cells seem to produce insulin well in that environment. The patient's body, however, will treat the new cells just as it would any other introduction of foreign tissue. The immune system will attack the cells as it would a bacterial infection or a skin graft. Thus, the patient also needs to undergo treatment involving immunosuppressants, which reduce immune system activity. **Encapsulation approach** – encapsulation of transplanted islet cells in a protective coating has been developed to block the immune response to transplanted cells, which relieves the burden of immunosuppression and benefits the longevity of the transplant. Islet sheet with encapsulation research is pressing forward with large animal studies at the present, with plans for human clinical trials within a few years. **Stem cells approach -** Research is being done at several locations in which islete cells are developed from stem cells. In January 2006, a team of South Korean scientists had grown pancreatic beta cells, which can help treat diabetes, from stem cells taken from the umbilical cord blood of newborn babies. In April 2007, it was reported by the *Times Online* that 15 young Brazilian patients diagnosed with Type 1 diabetes were able to naturally produce insulin once again after undergoing mild chemotherapy to temporarily weaken their immune systems and then injection of their own stem cells. This allowed the pancreatic beta cells to produce insulin. Since white blood cells were blocking the pancreas from producing insulin, the team killed the immune cells, allowing the pancreas to secrete insulin once more. However, there were no control subjects, which means that all of the processes could have been completely or partially natural. Secondly, no theory for the mechanism of cure has been promoted. It is too early to say whether the results will be

	positive or negative in the long run. **Gene therapy approach** – Designing a viral vector to deliberately infect cells with DNA to carry on the viral production of insulin in response to the blood sugar levels. Technology for gene therapy is advancing rapidly such that there are multiple pathways possible to support endocrine function, with potential to practically cure diabetes. **Nanotechnology approach -** Under the nanotechnological approach to curing diabetes type 1, many 'nanobots' would be injected into the patient's bloodstream. These nanobots would be able to synthesise insulin, and to secrete it according to the level of glucose they would sense.
26	One of the biggest challenges facing diabetes management today, and one which is likely to increase.
29	The presence of amyloid prevents communication between alpha and beta cells.
32	Removal of insulin receptors due to high levels of intra-cellular glucose.
34	Glucagon-like peptide-1 part of the incretin family, gastrointestinal hormones. GLP-1 possesses several physiological properties that make it a subject of intensive investigation as a potential treatment of diabetes mellitus. The known physiological functions of GLP-1 include: • increases insulin secretion from the pancreas in a glucose-dependent manner. • decreases glucagon secretion from the pancreas. • increases beta cells mass and insulin gene expression. • inhibits acid secretion and gastric emptying in the stomach. • decreases food intake by increasing satiety.
35	Dipeptidyl peptidase-4 inhibitors can also increase the levels of GLP-1, which helps promote improved blood glucose control. **Inhibitors of Dipeptidyl peptidase 4** , also **DPP-4 inhibitors**, are a new class of oral hypoglycemics which block DPP-4. Their mechanism of action is thought to result from increased Incretins (such as GLP-1 levels), which, inhibit glucagon release (which increases the blood glucose) but more importantly increase insulin secretion and decrease gastric emptying. Drugs belonging to this class are vildagliptin, sitagliptin and saxagliptin.

	NB - Sitagliptin entered the Australian drug market in late 2007/early 2008 for the treatment of difficult to control diabetes mellitus type 2. Early results are encouraging enough to continue trials
36	Increased circulating levels of insulin are highly toxic to the endothelium.
39	This phenomenon was named after Dr. Michael Somogyi, a Hungarian-born professor of biochemistry who prepared the first insulin treatment given to a child with diabetes in the USA in October 1922. Somogyi showed that excessive insulin makes diabetes unstable, and first published his findings in 1938. However, there is controversy over whether this actually occurs or not. Occasionally, insufficient insulin delivery can result in hyperglycemia. The appropriate response is to deliver insulin to reduce the blood sugar level, and to consider adjusting the insulin regimen to deliver additional insulin in the future to prevent hyperglycemia. Conversly, excessive insulin delivery may result in hypoglycemia. The appropriate response is to treat the hypoglycemia and to consider adjusting the insulin regimen to reduce insulin in the future. Somogyi and others have proposed that if prolonged hypoglycemia is untreated, then stress due to low blood sugar can result in a high blood sugar level rebound. The physiological mechanisms driving the rebound are defensive. When the blood glucose level falls below normal, the body responds by releasing glucagon as well as the stress hormones adrenaline and cortisol. Glucagon facilitates release of glucose from the liver which raises the blood glucose immediately, and the stress hormones cause insulin resistance for several hours, sustaining the elevated blood sugar. Although an attractive theory which has gained a firm following among both clinicians and individuals with diabetes, there is little clinical evidence to support its existence. In fact most clinical studies indicate that a high fasting glucose is because the insulin given on the previous evening fails to last long enough. Although hypoglycemic episodes are common during the night the reason that they fail to waken people with diabetes is due to a failure of release of adrenaline during sleep. Thus, Somogyi's proposed explanation doesn't appear to operate during the night. Recent studies using continuous glucose monitoring show that a high glucose in the morning is not preceded by a low glucose during the night, powerful evidence refuting the Somogyi effect.
48	Also called the **sorbitol-aldose reductase pathway**, the polyol pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney and nerves.

	In cells unused glucose enters the polyol pathway when aldose reductase reduces it to sorbitol. This is then converted to fructose. This can be returned to the glycolysis pathway, but in uncontrolled diabetics who have high blood glucose - more than the glycolysis pathway can handle – there is increased production and accumulation of sorbitol. This affects the production of Myo-inositol, required for normal nerve function. Sorbitol may also glycate nitrogens on proteins, such as collagen, and the products of these glycations are referred-to as AGEs - advanced glycation endproducts. While most cells require the action of insulin for glucose to gain entry into the cell, the cells of the retina, kidney and nervous tissues are insulin independent, so glucose moves freely across the cell membrane, regardless of the action of insulin. The cells will use glucose for energy as normal, and any glucose not used for energy will enter and activate the polyol pathway. When sorbitol accumulates it cannot cross cell membranes, and it produces osmotic stresses on cells by drawing water in. Excessive activation of the polyol pathway increases intracellular and extracellular sorbitol concentrations, increased concentrations of reactive oxygen species and decreased concentrations of nitric oxide and glutathione. Each of these imbalances can damage cells; in diabetes there are several acting together. It has not been conclusively determined that activating the polyol pathway damages microvasculature. Nerve cell hypoxia is also caused by PVD, etc.
61	Lyrica – pregabalin – mimics action of gabapentin – neurotransmitter in brain. Capsaicin - The result appears to be that the chemical mimics a burning sensation, the nerves are overwhelmed by the influx, and are unable to report pain for an extended period of time. With chronic exposure to capsaicin, neurons are depleted of neurotransmitters and it leads to reduction in sensation of pain and blockade of neurogenic inflammation. If capsaicin is removed, the neurons recover
64	Jean-Martin Charcot (1825-1893) was the first to describe the disintegration of ligaments and joint surfaces (Charcot disease, or Charcot joint) caused by disease or injury. Charcot foot is the term given to neurogenic arthropathy that affects the joints in the foot. Neurogenic arthropathy is a rapidly progressive degenerative arthritis that results from neuropathy. In Charcot foot, pain perception and the ability to sense the position of the joints in the foot are severely impaired or lost, and muscles lose their ability to support the joint properly. Loss of these motor and sensory nerve functions allow minor traumas such as sprains and

	stress fractures to go undetected and untreated, leading to ligament laxity, joint dislocation, bone erosion, cartilage damage, and deformity of the foot. The bones most often affected are the metatarsals and the tarsals, located in the forefoot and mid foot, respectively. Risk Factors - Diabetes mellitus and pre-existing neuropathy are the primary risk factors. Causes - Chronic hyperglycemia is believed to trigger the development of neuropathy, which, over time, may proceed to Charcot foot. Symptoms - While peripheral neuropathy develops over decades, the progression of Charcot foot (ligament tears, small fractures, subluxation, dislocation, deformity) can occur in a matter of weeks or months. A minor trauma can initiate the process. Increased bone resorption makes the bones susceptible to small fractures. Because of the loss of pain perception and the loss of the sense of position of the foot, joints receive repeated injuries, such as tom ligaments and bone fractures. Early signs that may present soon after injury include the following: • Heat • Insensitivity in the foot • Redness • Strong pulse • Swelling of the foot and ankle The early stage of Charcot foot may manifest these symptoms: • Dislocation of the joint • Instability of the joint • Subluxation (misalignment of the bones that form a joint) • Swelling After an injury, the synovial fluid that leaks out of the joint capsule may produce swelling. Muscle weakness and slack ligaments caused by nerve damage cause instability of the joint and subsequent subluxation and/or dislocation. Subluxation initiates the process of degenerative joint disease (arthropathy). The ends of misaligned bones grind against each other and fragments of bone and cartilage fall into the joint and often produce audible crepitus, a coarse grating sound, when the joint is moved. Deformity of the foot that occurs in advanced disease is caused not

	only by joint displacement and/or dislocation but also by osteophytes and fractures. Large bony overgrowths, or osteophytes; develop as the body replaces lost bone with new bone and may protrude from the top of the foot. Fractures may cause the tarsal bones to collapse and outward bowing of the arch, or "rocker foot." Complications - Calluses and ulcers may form when bony protrusions rub inside the shoes. Infected pressure ulcers and osteomyelitis may develop. Septic arthritis may manifest with malaise and fever. Characteristics of septic arthritis include inflammation of synovial membranes and infected synovial fluid escaping from the joint capsule into the joint. Compression of blood vessels and nerves are caused by disorganisation of the joint and may not produce symptoms due to loss of feeling in the foot.
71	The renal vasculature is very prone to damage in diabetes. Renal tissues are independent of insulin, and therefore take in glucose without need of insulin.
73	Protein depletion occurs as protein is lost in the urine. Calcium homeostasis becomes a problem, hence the devilment of renal bone disease.
83	Estimated by 2010 150 – 250 million people will have been diagnosed.