

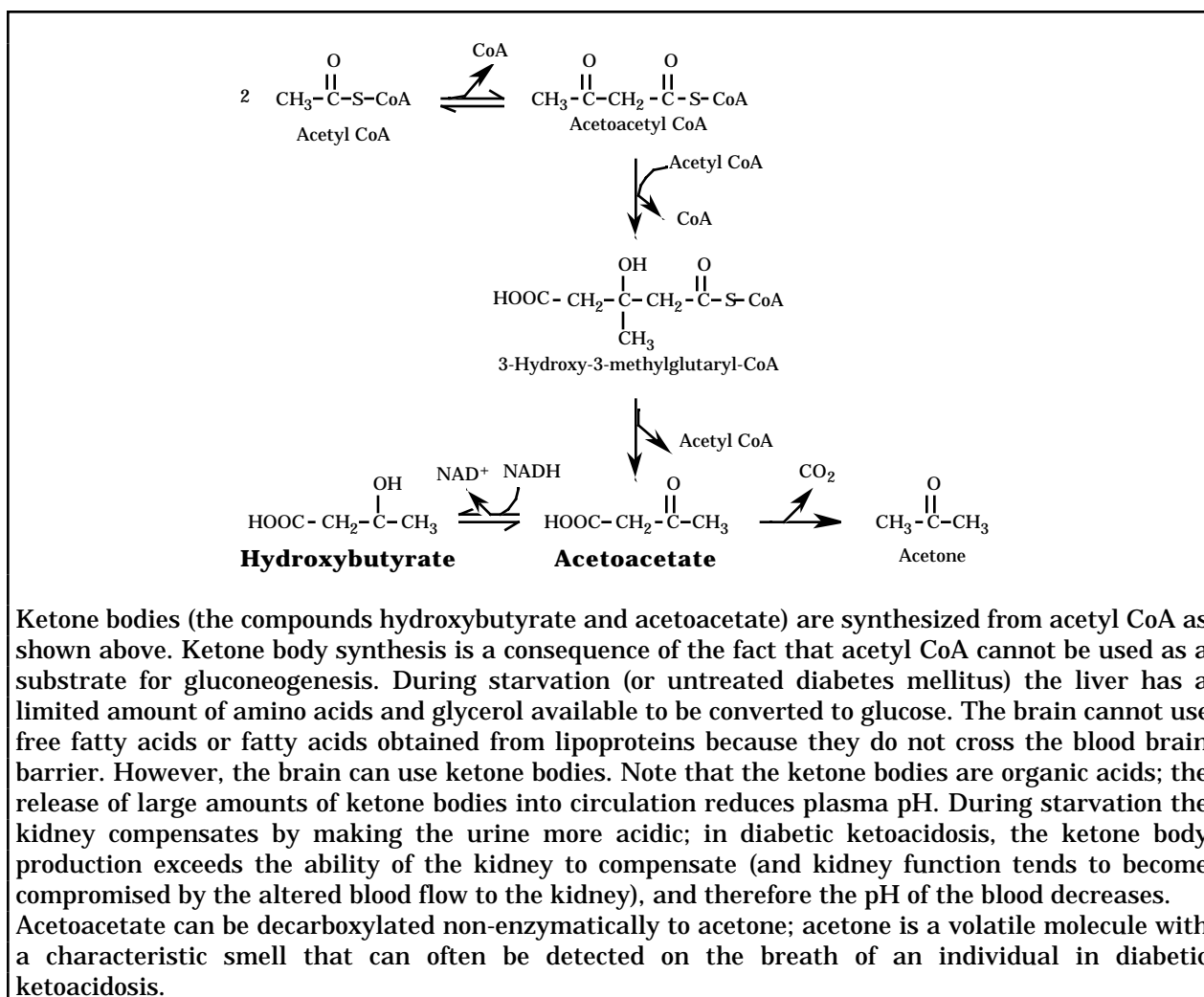
## Chapter 6

### Starvation and Diabetes Mellitus

#### Starvation

Glucose and glycogen stores are sufficient for about one day in the absence of food intake. In conditions of food deprivation lasting longer than one day a variety of metabolic changes take place. Insulin levels decrease and glucagon levels increase due to falling plasma glucose. The result of these changes is an increase in liver gluconeogenesis and a sharp decrease in glucose uptake by the muscle and adipose tissue. In prolonged starvation the kidney begins significant gluconeogenesis, eventually achieving levels nearly equivalent to those of the liver.

Over a period of several days the brain switches from glucose as the primary fuel to a mixture of glucose and ketone bodies; eventually ketone bodies may provide 65% of the total fuel requirements of the brain. Ketone body production by the liver is dependent on the insulin:glucagon ratio; when this ratio is reduced for several days, ketone body production rises markedly.



Ketone bodies (the compounds hydroxybutyrate and acetoacetate) are synthesized from acetyl CoA as shown above. Ketone body synthesis is a consequence of the fact that acetyl CoA cannot be used as a substrate for gluconeogenesis. During starvation (or untreated diabetes mellitus) the liver has a limited amount of amino acids and glycerol available to be converted to glucose. The brain cannot use free fatty acids or fatty acids obtained from lipoproteins because they do not cross the blood brain barrier. However, the brain can use ketone bodies. Note that the ketone bodies are organic acids; the release of large amounts of ketone bodies into circulation reduces plasma pH. During starvation the kidney compensates by making the urine more acidic; in diabetic ketoacidosis, the ketone body production exceeds the ability of the kidney to compensate (and kidney function tends to become compromised by the altered blood flow to the kidney), and therefore the pH of the blood decreases.

Acetoacetate can be decarboxylated non-enzymatically to acetone; acetone is a volatile molecule with a characteristic smell that can often be detected on the breath of an individual in diabetic ketoacidosis.

Some blood cells (especially erythrocytes) require glucose, and are essentially incapable of using other fuel sources. After a few days of starvation, only the blood cells and the brain use significant amounts of glucose, with the other tissues deriving their energy from other sources.

Insulin remains detectable but at significantly reduced levels during prolonged fasting. In addition, the pancreas becomes somewhat refractory, and upon refeeding an individual may become glucose intolerant for several days until normal insulin secretion responses are restored.

During starvation, growth hormone levels rise, although response to growth hormone appears to decrease, and IGF-I levels decrease in spite of the elevation in growth hormone. However, some growth hormone effects, such as enhanced lipolysis are elevated.

Glucocorticoid levels change relatively little in starvation; however, normal levels are required for survival of prolonged fasting. In contrast, although catecholamine levels rise somewhat in response to the initial hypoglycemia during fasting, lack of catecholamine action (*e.g.*, in adrenal medullary insufficiency) does not have detectable deleterious effects.

Finally, decreased thyroid hormone production, and in particular, decreased conversion of T<sub>4</sub> to T<sub>3</sub> in peripheral tissues result in decreased basal metabolic rate. This results in an increased efficiency of fuel utilization and in reduced protein breakdown during caloric restriction and starvation. However, decreases in thyroid hormone levels require several days to have significant effects.

Early in starvation the muscle acts as a source of free amino acids for gluconeogenesis. Over time muscle protein degradation decreases, probably as a result of decreased thyroid hormone and increased growth hormone levels. Lipolysis of triacylglycerol stores in adipose tissue provides the majority of the fuel required for survival. The lifetime of an individual in the absence of food varies, depending on the size of the fat stores.

### **Fuel Reserves**

The body stores three types of fuel: carbohydrate, protein, and fat. Table I summarizes the distribution of this fuel among the tissues of the body.

The carbohydrate stores, predominately glycogen with small amounts of circulating glucose, contain sufficient energy to support metabolism for about one day. In principle, the various protein stores could provide fuel for a prolonged fast; in practice, most of the protein has a functional role (in the form of enzymes, contractile proteins, and structural molecules). However, some protein degradation is often necessary to support gluconeogenesis, since fatty acids cannot be used as substrate for glucose synthesis. (Note that the brain and blood do not contain “degradable protein”; these tissues obviously contain protein, but in general this protein is exempt from degradation for fuel.) The major energy reservoir is provided by the fat stores of adipose tissue.

**Table I.**  
**Fuel reserves of “typical” 70 kg individual**

Organ	Available energy (kcal)		
	Glucose/glycogen	Triacylglycerols	Degradable Protein
Brain	8	0	0
Blood	60	45	0
Liver	400	450	400
Muscle	1200	450	24,000
Adipose tissue	80	135,000	40

(modified from Stryer (1995) *Biochemistry*, 4th Ed.)

Triacylglycerol has a much higher energy density than protein or carbohydrate. There are two reasons for this: metabolism of pure fat releases about 9 kcal/g, while protein and carbohydrate contain about 4 kcal/g. These figures are slightly misleading; *in vivo*, metabolism of protein or carbohydrate yields only about 1 kcal/g of stored substrate due to the large amount of water associated with these compounds. In contrast, triacylglycerol is hydrophobic, and therefore little water is associated with fat stores; metabolism of the fat stored in adipose tissue yields nearly the full 9 kcal/g. This is good news for individuals attempting to carry their energy stores with them -- the weight of glycogen equivalent in energy to the normal fat stores of a 70 kg man would be about 100 kg! On the other hand, in contemplating weight loss, each kilogram corresponds to 8000 kcal, enough energy to maintain normal metabolism for several days.

### Effects of Exercise on Glucose Homeostasis

Fatty acid oxidation is a relatively slow process. As a result, although resting skeletal muscle uses fatty acid oxidation as its primary energy source, it mainly uses glycolysis to generate the energy required for repetitive contractions. The muscle obtains glucose from breakdown of its glycogen stores (stimulated by epinephrine and by  $\text{Ca}^{2+}$  released during muscle contraction) and from circulation to provide substrate for glycolysis. During prolonged heavy activity pyruvate generation by glycolysis in the muscle often exceeds the capacity of the muscle mitochondria to process the pyruvate to  $\text{CO}_2$  and ATP. The muscle therefore converts the excess pyruvate to lactate (in order to regenerate the oxidized nicotinamide cofactor required for additional glycolysis) and exports the lactate. The liver uses the lactate as a substrate for gluconeogenesis; the glucose thus synthesized then travels to the muscle to support further activity. This exchange between the muscle and liver is called the Cori cycle.

High levels of insulin would interfere with a number of the metabolic changes necessary to support the Cori cycle. However, the muscle requires the ability to

import glucose from the circulation, which is a largely insulin-dependent process. In order to reconcile these conflicting aims, the muscle increases its sensitivity to insulin, and therefore maintains its ability to transport glucose in spite of the fact that insulin levels tend to fall during exercise (primarily as a result of inhibition of insulin release by catecholamines).

The liver response to exercise is similar to that observed in early starvation: the liver dramatically increases its glucose output by increasing its rate of gluconeogenesis and glycogen breakdown. These effects are stimulated by catecholamine action, both directly in the liver, and indirectly, by catecholamine stimulation of pancreatic glucagon release. However, during exercise the primary gluconeogenic substrate is lactate, not the alanine derived from muscle breakdown used during food deprivation.

This increased sensitivity of the muscle to insulin is one reason for the beneficial effects of exercise in Type II diabetics. There is also some evidence that decreased glycogen stores in muscle resulting from exercise directly stimulates glucose uptake.

### **Diabetes Mellitus: Type I**

Diabetes was originally described as a disorder of excessive urination; the descriptive mellitus (meaning sweet, and referring to the presence of large amounts of glucose in the urine) was added to differentiate it from diabetes insipidus (an unrelated disorder resulting from lack of anti-diuretic hormone action).

Type I diabetes is also known as Insulin-Dependent Diabetes Mellitus (IDDM) and juvenile-onset diabetes. Most new cases are diagnosed during childhood or early adulthood; however, onset has been observed from infancy to about 45 years of age. It is a moderately common disorder, affecting about 1 in 250 of the general population in the United States.

Type I diabetes is the result of a destructive autoimmune attack specific to the  $\beta$ -cells. There is clearly a genetic component mediating predisposition to Type I diabetes, but a monozygotic twin of a Type I diabetic has only ~40-50% of becoming diabetic. Interestingly, risk of developing Type I diabetes is higher in offspring when the father, rather than the mother, has diabetes. Predisposition for Type I diabetes is associated with certain HLA types (especially DR3 and some DR4 types); other genetic factors are probably also involved.

The onset of Type I diabetes generally follows an infection or ingestion of a  $\beta$ -cell toxin. These events are thought to trigger the autoimmune attack on the  $\beta$ -cells that results in their destruction. Suspects considered as possible viral triggers include rubella (since about 30% of children exposed to rubella during fetal life develop diabetes) and coxsackie virus. Antibodies against glutamic acid decarboxylase (GAD), insulin, and several other islet antigens are commonly observed in Type I diabetes, and detection of antibodies against these antigens has been used to predict development of diabetes. Earlier diagnosis would assist in preventing deaths from diabetic ketoacidosis, and might allow prevention of  $\beta$ -cell destruction before irreversible deficits have occurred.

Treatment of newly diagnosed Type I diabetics often (~30% of cases) results in a “honeymoon period” during which the patient regains essentially normal insulin secretion and glycemic control. This may be due to alleviation of the toxic effects of the metabolic changes (such as acidosis, electrolyte imbalance, and hyperlipidemia) observed in untreated diabetes allowing partial restoration of  $\beta$ -cell function. Immediately following the discovery of insulin it was thought that relief of the necessity to supply insulin might allow recovery of the  $\beta$ -cells, and cure the disorder. However, the autoimmune attack appears to continue until all of the  $\beta$ -cells have been destroyed. In addition, the  $\beta$ -cell appears to be a cell type particularly vulnerable to irreversible damage.

About 10% of Type I patients also develop other autoimmune disorders, particularly those involving the adrenal or thyroid.

## Diabetes Mellitus: Type II

Type II diabetes is also called Non-Insulin-Dependent Diabetes Mellitus (NIDDM) or adult-onset diabetes. It is about 10-fold more common than Type I, with more than 14 million cases in the United States. Type II is a much more heterogeneous disorder than Type I, with several possible underlying causes (Figure 1).

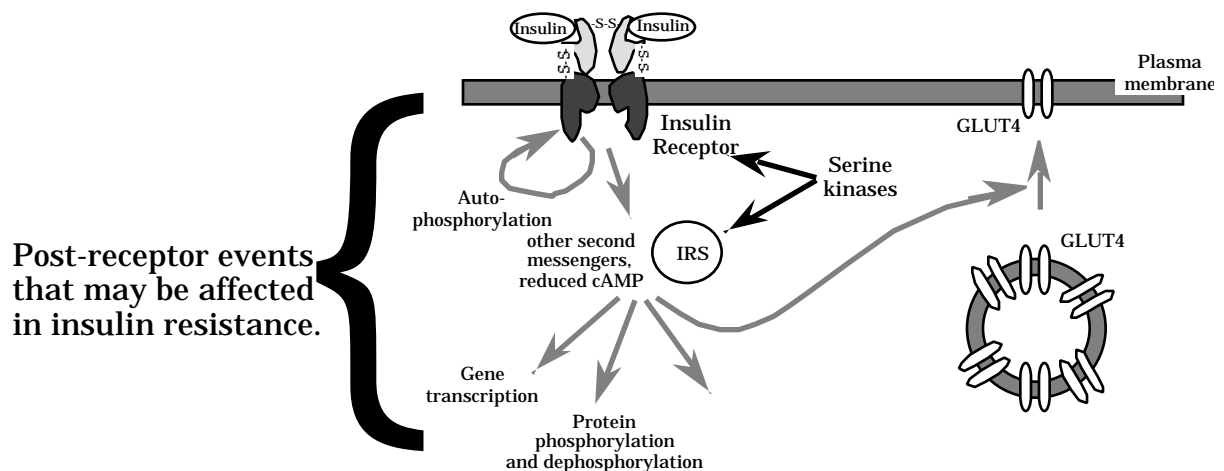


Figure 1. Impaired insulin responsiveness may be due to a reduction in tyrosine kinase activity of the insulin receptor, to decreased amounts of the insulin receptor kinase substrates, or to decreased response to the second messengers. Increased serine phosphorylation of the insulin receptor or of the IRS proteins inhibit the function of these proteins, and may be one mechanism involved in generating insulin resistance. (Grey arrows: potentially decreased activity; black arrows: increased.)

Type II diabetes is more strongly linked to genetics than Type I. While Type I diabetes is the result of a genetic predisposition combined with a triggering event, Type II appears to be entirely a result of genetics. Nearly 100% of monozygotic twins of Type II diabetics will develop the disorder.

The cause of the vast majority of Type II diabetes cases is resistance to insulin; in most cases the insulin receptor is normal, but the magnitude of post-receptor events

is lower at any given amount of insulin. Most individuals with Type II have elevated insulin levels. Obesity is associated with insulin resistance, and 80-85% of Type II patients are obese by some definition. The degree of resistance observed in Type II patients is often correlated with degree of obesity; however, insulin resistance is also observed in non-obese Type II. In addition to the insulin resistance, there is often a defect in glucose (but not amino acid) stimulation of insulin release. It is not clear whether this is a cause or a consequence of hyperglycemia (since prolonged hyperglycemia in normal individuals also results in decreased  $\beta$ -cell responsiveness to glucose).

Although at least 90% of the cases are thought to be the result of post-receptor defects, mutations in the insulin receptor probably account for some cases of Type II diabetes. In the relatively small number of patients known to have insulin receptor mutations, the disorder presents with a variety of developmental abnormalities in addition to insulin resistance; these abnormalities are thought to reflect the fact that extremely high insulin levels result in insulin binding to IGF-I and IGF-II receptors.

Several mutations have been observed in the insulin coding sequence. The known mutations that affect receptor binding cause extremely rare forms of Type II diabetes. Other mutations that inhibit proinsulin processing have been observed; these result in autosomal dominant hyperinsulinemia, but not diabetes. There is a single gene for insulin in humans and most other vertebrate species (rats and mice have two genes). The human gene is located on chromosome 11.

Other mutations associated with Type II include mutations in the glucokinase gene, in the IRS proteins, and in glucose transporters. MODY (= maturity onset diabetes of youth) is a form of Type II that typically develops between ages 15 and 25. It is often associated with mutations in the GLUT4 transporter or with aberrant glucokinase activity. However, the underlying genetic defect in most cases of Type II diabetes is not known.

Type II diabetes is strongly associated with obesity; 60-90% of Type II patients are obese, depending on the population. Plasma free fatty acid levels are elevated in obesity and in Type II diabetes, and have been associated with increased plasma glucose and induction of insulin resistance. A potential positive feedback loop therefore exists: increased adipocyte number results in increased free fatty acid release, which results in decreased insulin action, and consequently in additional increased free fatty acid release.

Leptin is a peptide hormone secreted by adipose tissue which is currently receiving a great deal of attention. Mice lacking leptin are obese, which, along with other data, suggests that leptin may play a role in regulating food intake. On the other hand, leptin released by adipose tissue from obese individuals may cause insulin resistance in some cell types, and therefore might exacerbate, or even play a role in causing, Type II diabetes.

Elevated VLDL and LDL, and reduced HDL levels are also commonly observed in Type II diabetes. Lipoprotein lipase activity is dependent on insulin, and is usually

reduced in Type II diabetics. In addition, elevated VLDL levels have been associated with increased insulin resistance. Finally, obesity is associated with increased levels of VLDL. These factors may interact to form another positive feedback loop that results in altered lipid profiles in Type II diabetics.

Hyperglycemia, hyperinsulinemia, dyslipidemia, obesity, and hypertension are observed in large numbers of Type II patients. When found together, these symptoms are sometimes called Syndrome X. Syndrome X is probably merely a subset of Type II diabetes. However, the combination of these clinical features should serve as a reminder that any type of treatment should be considered in light of its results on all facets of the syndrome, since some drugs used to treat one of the symptoms (antihypertensives, in particular) will exacerbate other features of the disorder.

Onset of Type II is often very gradual, and may be asymptomatic. For poorly understood reasons perhaps related to the continued presence of insulin, Type II relatively rarely results in ketoacidosis. In severe cases, the disorder may present as a syndrome known as HONK (Hyperglycemic hyperOsmotic Non-Ketotic coma); more commonly the disorder is only diagnosed when secondary consequences of prolonged hyperglycemia (especially deteriorating peripheral neuronal function) become apparent.

In many cases of obese Type II diabetes a relatively minor degree of weight loss, particularly when as the result of increased exercise, results in restoration of normal insulin responsiveness. However, in many patients resolution of the hyperglycemia requires use of insulin, either directly or via use of sulfonylurea drugs (compounds that stimulate insulin release from  $\beta$ -cells). Non-insulin-dependent diabetes mellitus is therefore frequently a misnomer.

<p>Some researchers have proposed changing the names of the disorders to Immune-Dependent Diabetes Mellitus and Non-Immune-Dependent Diabetes Mellitus (which keep the same abbreviations). Even this change may not avoid ambiguity: some forms of Type II appear to be the result of auto-antibodies that inhibit insulin binding to the insulin receptor. Type II diabetes is a heterogeneous disorder; as more information becomes available, it may prove useful to sub-divide Type II into several additional types to reflect the true underlying cause (and probably preferred treatment) for the hyperglycemic state.</p>
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### Other Forms of Diabetes Mellitus

**Gestational diabetes:** Insulin requirements rise during pregnancy. At least in part as a result of this, some women without diabetic symptoms prior to becoming pregnant develop glucose intolerance during gestation. Untreated, the consequent poor glycemic control results in significant complications for both mother and fetus. These include both problems during pregnancy and labor, and long term effects on the offspring, including much higher than normal incidence of Type II diabetes. In most cases, maternal glucose tolerance is restored following delivery. However, individuals diagnosed with gestational diabetes are at significantly elevated risk for

later development of Type II diabetes.

**Secondary diabetes:** A variety of endocrine disorders can result in forms of Type II diabetes, including Cushing's syndrome (hypersecretion of cortisol or high level glucocorticoid therapy), catecholamine-producing pheochromocytoma, acromegaly, and pancreatic tumors that overproduce glucagon or somatostatin. In general, resolution of the underlying problem also restores glycemic control.

Women with polycystic ovary syndrome (PCOS) have a much higher risk of developing Type II diabetes, especially if obese, than do weight-matched controls. The reason for this is not yet known. The insulin resistance may be the result of the elevated androgen levels and anovulation characteristic of PCOS. Alternatively, high levels of insulin observed in Type II diabetes may alter ovarian function. It is also possible that PCOS and some forms of Type II diabetes may reflect a common genetic defect.

Surgical removal of the pancreas obviously results in diabetes similar in most respects to Type I, except that the incidence of hypoglycemic episodes is higher than in true Type I due to lack of glucagon.

Some drugs are associated with decreased insulin release from the  $\beta$ -cells or reduced insulin sensitivity (the latter includes most forms of oral contraceptive drugs). Most of these drugs do not cause diabetes, but may exacerbate the poor glycemic control in developing or pre-existing cases of diabetes.

Finally, the  $\beta$ -cells are sensitive to some environmental toxins that, in rare cases, may damage or destroy enough of the cells to result in a non-immune-mediated disorder symptomatically identical to Type I diabetes.

### Effects of Insulin Deprivation

In Type I diabetes (and in severe cases of Type II) a relatively sudden decrease in insulin action results in a variety of metabolic changes that, together, can be lethal: **diabetic ketoacidosis (DKA)**. A new case of Type I diabetes often presents with DKA; DKA may also be the result of an infection, serious stress (emotional or physical), a mechanical failure (for Type I patients on insulin pumps), denaturation of the insulin during storage, or failure to inject insulin at an appropriate time. In other words, DKA may be a result of lack of insulin, or of a condition that significantly decreases the systemic sensitivity to insulin of the diabetic individual.

Muscle protein breakdown is stimulated by the absence of insulin. This results in increased amino acid release into circulation, and therefore increased substrate for liver gluconeogenesis. Lipolysis is also stimulated by the unopposed effects of growth hormone and glucocorticoids. The liver responds to the lack of insulin by undergoing the adaptations of starvation: increased glycogen breakdown and increased gluconeogenesis (using the substrate released by the muscle and adipose tissue), and initiation of rapid ketone body synthesis. The muscle and adipose tissue markedly decrease their glucose uptake (which is largely an insulin-dependent



process). The combination of these effects is a massive increase in plasma glucose (often to 500-1500 mg/dL).

The kidney is unable to reabsorb this much glucose, and large amounts of glucose are lost to the urine, along with a great deal of water due to osmotic pressure. The loss of water results in dehydration. The high levels of ketone bodies often induce nausea and vomiting, exacerbating the dehydration. The dehydration results in increased plasma osmolarity and hypotension, peripheral circulatory failure, loss of consciousness, and, if untreated, death. The ketone bodies also result in decreased plasma pH, which exacerbates the other problems, as does the insulin resistance that occurs as a result of increased glucocorticoid levels responding to the failing circulation and reduced pH. The reduced pH results in hyperventilation (Kussmaul respiration) in an attempt to rid the blood of carbon dioxide. If pH falls below 7.0, the patient may experience a catastrophic loss of blood pressure as a result of vasodilation, and breathing may appear normal due to loss of the compensatory mechanism that stimulates Kussmaul respiration. These effects are summarized in Figures 2 and 3.

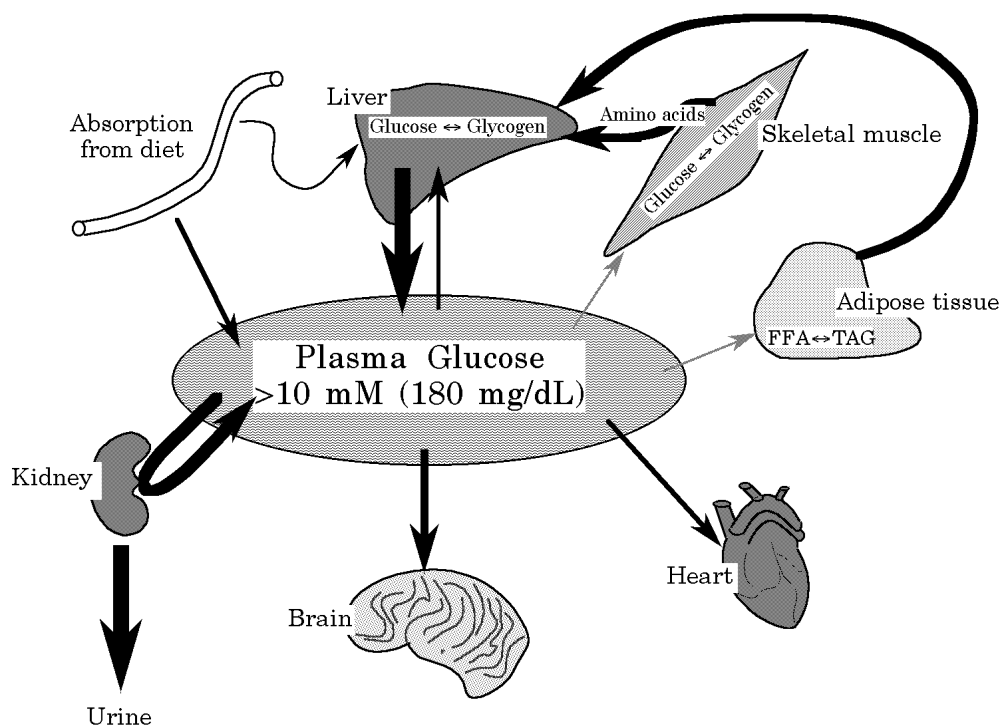


Figure 2. Glucose metabolism in the absence of insulin. (Compare to Figure 1 of Chapter 5.) Without insulin, glucose uptake into the muscle and adipose tissue is minimal, and these tissues are being actively broken down to provide substrate for liver gluconeogenesis and ketone body synthesis. The liver absorbs some glucose, but releases large amounts into circulation. The absorption of glucose in the gut, and utilization of glucose by the heart and brain are essentially normal (at least at first). As the plasma glucose levels exceed 180 mg/dL, much of the excess is lost to the urine. In untreated diabetes, urinary nutrient losses can result in significant weight loss in spite of increased food intake.

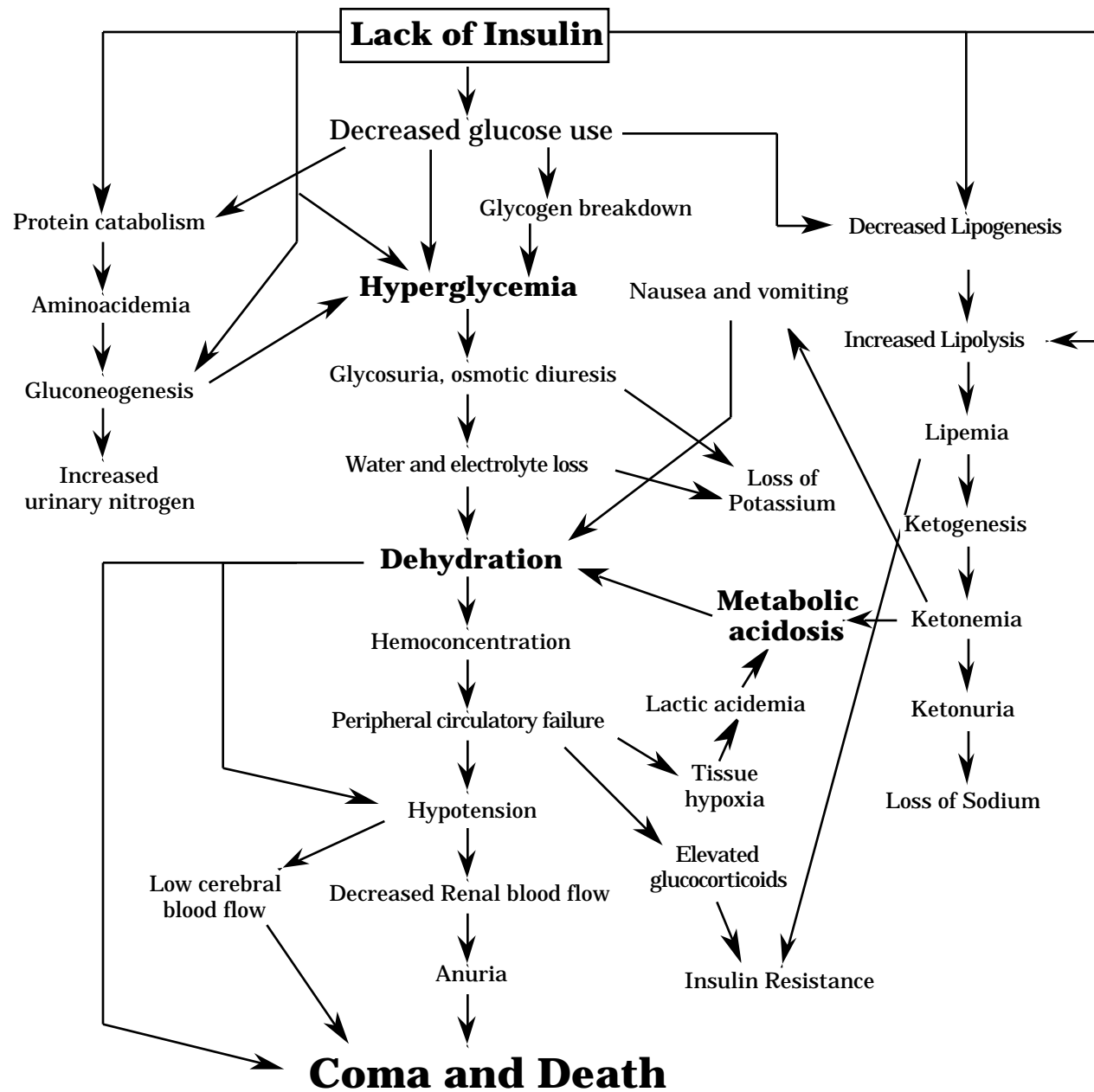


Figure 3. Summary of the effects of lack of insulin on physiological processes. (Note: some of the arrows reflect indirect effects.) Lack of insulin stimulates breakdown of protein, especially in muscle, and increased lipid breakdown, especially in adipose tissue. The free amino acids and fatty acids released in these processes are transported to the liver, where they serve as substrate for glucose and ketone body synthesis. Much of the excess glucose and ketone bodies are excreted in the urine, along with large amounts of water, sodium, and potassium. The stresses induced by lack of insulin raise glucocorticoid levels, which both worsen the hyperglycemia directly and induce resistance to the residual insulin. The severe dehydration and loss of essential ions, exacerbated by the anorectic effects of high concentrations of ketone bodies and the lowered plasma pH results in the shutting down of the kidney, brain, and circulatory system, and, if untreated, in death.

Patients in DKA may have normal or even elevated plasma potassium levels. This is misleading; during DKA, large amounts of potassium are lost in the urine, and these patients require potassium replacement to survive. The plasma levels observed reflect potassium lost from intracellular pools. The lowered plasma pH is the result of the release of large amounts of organic acids into circulation; the most important of these are the ketone bodies (see box at the beginning of this chapter). During DKA, acid production exceeds the ability of the kidney to excrete protons, resulting in acidosis. Lactic acidemia, due to tissue hypoxia caused by reduced peripheral circulation, may further reduce the pH.

DKA is usually associated with peripheral neuropathy as a result of the hyperglycemia affecting the nerves directly, and probably also as a result of altered circulation causing tissue hypoxia.

If the loss of insulin action is relatively slow (as often occurs in new cases of Type I diabetes), the individual usually experiences increased thirst (as a result of the dehydration) and loss of weight (due to the loss of calories in the urine and degradation of fat and protein stores) in spite of increased appetite.

As noted earlier, in Type II diabetes, the hyperglycemia may result in coma due to dehydration, although usually without the ketone body synthesis or acidosis.

The coma that results from DKA (or hyperglycemic hyperosmotic non-ketotic coma, in Type II diabetes) is lethal if untreated. Up to 10% of patients arriving at a hospital in DKA die as a direct result of the systemic failure that results from lack of insulin.

### Long Term Complications of Diabetes Mellitus

Glucose is essential for life. However, high levels of glucose are toxic. Diabetes is associated with a variety of long-term complications, especially retinopathy (diabetes is a leading cause of blindness), neuropathy (in particular both temporary and permanent impairment of peripheral sensory nerves), and nephropathy (renal failure is a major complication of diabetes). In addition, altered peripheral circulation results in significant risk for development of gangrene, especially of the feet. These pathologies are all thought to be due to the effects of long-term elevations in plasma glucose. Hyperglycemia may induce insulin resistance, even in Type I diabetics, exacerbating the disorder in these patients.

The DCCT (**Diabetes Control and Complications Trial**, a large scale clinical trial; the resulting paper is cited in the reference list for this chapter) showed that the severity of the long-term complications of diabetes is related to how well glucose is controlled. The basis for the toxicity of high levels of glucose is incompletely understood, but it is known that hyperglycemia increases the amount of glycated protein (non-enzymatic covalent modification of the protein by glucose).

Glucose toxicity is incompletely understood, but high plasma glucose clearly results in a non-enzymatic covalent modification of proteins. One such protein is hemoglobin; while glycated hemoglobin (also called hemoglobin A1c or Hb<sub>A1c</sub>) probably has similar activity to that of the

unmodified protein, it does act as a marker for glycemic control for the previous several weeks. Although there is considerable variation between laboratories performing the tests (these tests are being standardized, but the process is incomplete), normal individuals generally have glycosylated hemoglobin levels of 4 to 6%. A diabetic individual in good glycemic control would have an HbA<sub>1c</sub> of 6-8%, while poorly controlled glucose over a period of several weeks results in HbA<sub>1c</sub> of 10-15%.

Some recent studies have suggested that hyperglycemia indirectly increases the activity of the  $\alpha$  isoform of Protein Kinase C, and that increased activity of this protein is a major factor in the deleterious effects of hyperglycemia on the vascular system. Diabetic rats treated with an inhibitor of the enzyme exhibited fewer complications than controls.

Paradoxically, individuals with diabetes are also subject to **hypoglycemia**. Hypoglycemia in diabetics is the result of either insulin overdose, increased sensitivity to insulin, decreased counter-regulatory response, or increased insulin secretion (especially early in Type I diabetes before complete destruction of the  $\beta$  cells). Hypoglycemia can result in unconsciousness and permanent brain damage or death if untreated. About 10% of all diabetics suffer a hypoglycemic episode that requires medical assistance to survive each year. Direct effects of hypoglycemia are confusion, weakness, behavioral abnormalities, seizures, and loss of consciousness. Hypoglycemia is often associated with palpitations, tachycardia, blurred vision, sweating, and tremors, which are due to increased catecholamine release in response to the hypoglycemia. Since these autonomic symptoms occur at higher plasma glucose levels than the direct neurological effects, they can act as a warning of impending severe hypoglycemia.

**Hypoglycemic unawareness** is an apparent failure of the autonomic response, or failure of the individual to recognize the gross physiological effects of the autonomic response, and can result in loss of consciousness (and, if untreated, possibly death) without prior symptoms. Hypoglycemic unawareness occurs in about 25% of IDDM patients, and may be more common in patients who have previously frequently experienced hypoglycemia. Hypoglycemia tends to become more frequent in individuals attempting the tight control of plasma glucose recommended by the DCCT; this finding has resulted in recommendations that diabetic individuals maintain glucose levels at the upper end of the normal range (or slightly above) to reduce incidence of hypoglycemic episodes.

In Type I diabetics in particular, unexpected exercise can result in either hyperglycemia (as a result of increased epinephrine and other counter-regulatory hormones) or, more commonly, hypoglycemia (as a result of increased insulin sensitivity and increased muscle glucose uptake). Thus the individual must compensate for the expected deviation in plasma glucose as a result of the exercise. The compensation required exhibits a wide range of individual variation, and for each patient it is impossible to predict the exact effects of altered insulin doses without testing.

The risk of atherosclerosis (and therefore of heart disease and stroke) is greatly increased by obesity and hypertension, which are common in Type II diabetes. LDL uptake into cells is stimulated by insulin, and is usually decreased in insulin resistance. LDL uptake is also inhibited by glycation (non-enzymatic covalent modification by glucose) of ApoB (the protein component of LDL). These and other

changes in LDL composition are implicated in stimulation of foam cell formation and therefore in the development of atherosclerosis.

### Treating Diabetes Mellitus

In Type I diabetes mellitus, the disorder is a direct result of destruction of the  $\beta$ -cells, and therefore the individual requires exogenous insulin to survive. Until relatively recently insulin was purified from bovine or porcine pancreas. The insulin sequence from these sources has three (bovine) or one (porcine) amino acid differences from human insulin. Either as a result of these differences or as a result of impurities in the insulin preparations, many patients developed antibodies against the foreign insulin, which altered their responsiveness and therefore increased their insulin requirements. In the United States and other industrialized countries recombinant human insulin, which has fewer side effects, is available.

Some studies have suggested that incidence of hypoglycemic unawareness is greater in patients treated with human insulin than in patients treated with bovine or porcine hormone. Whether this is a direct consequence of the use of the human insulin, or of more frequent hypoglycemic episodes (as a side-effect of the DCCT recommendations), or is due to greater effective potency of the human insulin and therefore lower margin for error in dosage (due to lack of anti-human insulin antibodies), or is an artifact is not yet established.

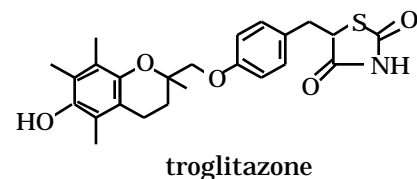
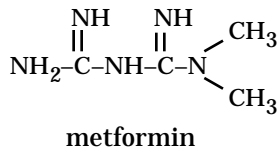
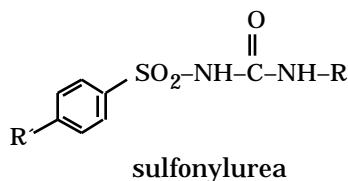
Insulin can be administered either sub-cutaneously or intravenously. Sub-cutaneously administered insulin has a fairly long period of action (3 to 15 hours depending on the formulation); treatment generally involves a relatively small number of injections (2 to 5 per day). This procedure is obviously a poor mimic of the pancreas, which has the ability to continuously monitor blood glucose and respond within seconds to changes in glucose concentration. In addition, exercise or other factors may alter the rate of absorption of the injected insulin or the sensitivity of the system to the insulin resulting in unwanted (and potentially dangerous) changes in the effectiveness of the administered dosage. Because the much more rapid onset of insulin action induced by intravenous injection increases the risk of hypoglycemia, intravenous administration of insulin is primarily used in hospitals as part of the procedure for reversing the effects of diabetic ketoacidosis.

Type II is more complicated; the ideal treatment for obese Type II is a revised diet, along with sufficient weight loss and exercise to restore normal insulin responsiveness, but this may be difficult or impossible to maintain. Non-obese Type II and obese Type II unable to maintain normoglycemic control on diet and exercise alone may require insulin or oral hypoglycemic drugs.

Oral hypoglycemic drugs fall into three classes: 1) sulfonylurea drugs, which stimulate release of insulin from  $\beta$ -cells; 2) biguanide drugs which inhibit glucose uptake in the intestine and increase GLUT4 on the cell surface of insulin target tissues by an unknown mechanism; and 3) the new thiazolidinedione drugs, which increase insulin sensitivity of target tissues by a poorly understood mechanism. In established Type I diabetes sulfonylurea drugs have no effect and biguanides are

rarely useful. The sulfonylurea drugs tend to cause weight gain in Type II, which may exacerbate the underlying disorder. The thiazolidinedione drugs appear to have little effect in Type I diabetes, suggesting that they may be actually reversing insulin resistance (*i.e.* counteracting the molecular defect that causes most forms of Type II diabetes).

The hypoglycemic drugs derive their names from their chemical structures. The sulfonylurea drugs have the general structure shown at left; adding the appropriate R and R' modifications yield tolbutamide and the newer glipizide and glyburide (which are ~100-fold more potent). Metformin (center) is the only biguanide available in the United States, although at least one other is used in Europe. Troglitazone (recently approved under the trade name Rezulin) is the only clinically available thiazolidinedione. Troglitazone seems very promising, but must be used with some caution because only a limited number of patients have been treated with this drug.



Improvements in these drugs has been hampered by lack of understanding of their mechanism of action. This is especially true of the thiazolidinedione drugs, which are the newest class of oral hypoglycemic drug. Recent studies have suggested that the thiazolidinedione compounds work through the one or more of the PPAR (the peroxisome-proliferator activated receptors, orphan members of the steroid receptor family). Studies testing this hypothesis may lead to more effective drugs for treating Type II diabetes.

A major feature of treating an individual with diabetes is education of the patient. The patient must accept the fact of the disorder, and the fact that they will be living with it and its consequences for the remainder of their life. They must also learn how to monitor blood glucose, and understand the consequences of poor control. They must be aware of the effects of diet and exercise on blood glucose levels.

Different foods have different effects on plasma glucose levels. This is due primarily to differences in absorption of the glucose content from different foods. As an example, sucrose (table sugar, a disaccharide of glucose and fructose) usually has a smaller effect on plasma glucose levels than does white bread or potatoes. The **glycemic index** of a food is a measure of the change in plasma glucose caused by a given food relative to that of a standard (usually white bread). However, the usefulness of the glycemic index is compromised somewhat by individual variation and by the interactive effects on glucose absorption of different foods consumed together.

The physiological response to insulin and the counter-regulatory hormones varies during the day. This is true in normal individuals, but the timing is somewhat different, and the effects potentially far more important, in diabetes. In normal individuals, insulin sensitivity peaks in the morning, and falls somewhat during the day. In diabetic patients, in contrast, insulin sensitivity is usually lowest in the morning.

One aspect of this variability in sensitivity to insulin is known as the **dawn phenomenon**; plasma glucose levels of individuals with diabetes are often markedly elevated in the morning. The mechanism for this is not completely understood. The dawn phenomenon may be due to elevated

counter-regulatory hormones (especially cortisol, which is normally highest in the morning; see Chapter 2), to insufficient insulin remaining from the most recent injection, to altered insulin sensitivity, or to some combination of these factors.

### Prevention of Type I Diabetes Mellitus

Injection of insulin is necessary for survival of Type I diabetes. However, this procedure is capable of only gross control of plasma glucose. In addition, the administered insulin enters the general circulation directly instead of traveling first to the liver; in a normal individual the liver experiences a higher insulin concentration than the rest of the body due to the direction of blood flow and to the fact that the liver inactivates much of the insulin prior to allowing it to reach the general circulation. The result of these inadequacies of current treatment is a significant incidence of complications in all forms of diabetes mellitus.

In principle, it should be possible to use immunosuppression to prevent autoimmune destruction of the  $\beta$ -cells. Thus far, however, the results of these attempts have been disappointing, due to either ineffectiveness or toxicity of the immunosuppressant used. It is possible that the treatment trials have all been initiated after losses of  $\beta$ -cell function were already too great to be reversed, suggesting that earlier intervention may be more successful. In this regard, it has been shown in both animal models and in humans that antibodies against islet antigens are detectable long before overt glucose intolerance. Screening of susceptible individuals for these antibodies may allow earlier, and potentially more successful, immunosuppressant treatment.

An additional, or possibly complementary approach is the use of injected insulin in individuals exhibiting autoimmune attacks (e.g., antibodies against islet antigens), but retaining full glycemic control. Preliminary studies suggest that injected insulin may both act to decrease the severity of the autoimmune attack and allow the  $\beta$ -cells to “rest” and recover from damage inflicted. A large clinical trial testing this concept is in progress.

Alternatively, it may be possible to prevent the autoimmune attack from beginning. For poorly understood reasons, individuals who were breast fed as infants have reduced incidence of Type I diabetes. In animal models, the BCG vaccine (a vaccine against tuberculosis) appears to decrease the initiation of the autoimmune attack. Another potentially useful therapy is oral administration of insulin to individuals at risk for development of Type I diabetes; this treatment has been used with some success in some, but not all, rodent models of Type I diabetes. The orally administered insulin is, of course, degraded to small peptides during digestion, but a poorly understood process called oral tolerization (in which compounds are rendered no longer immunogenic after oral administration) sometimes results, and may prevent the autoimmune attack.

Finally, it may become possible to cure cases of established Type I diabetes. Although transplantation of whole pancreas has been performed successfully, because of the toxicity of immunosuppressants this procedure is most frequently

performed in cases where another organ (especially a kidney) is also being transplanted. For poorly understood reasons, some types of diabetic complications may persist in pancreatic transplant patients. In addition, even with immunosuppression, destructive autoimmune attack on the new pancreas has been observed. Other possibilities with greater likelihood of general applicability are implantation of  $\beta$ -cells encased in a membrane permeable to glucose and insulin but not antibodies, or transplantation of  $\beta$ -cells genetically modified to avoid induction of an immune response. These techniques will require significant research before they become generally available.

### In Their Own Words

Through the wonders of modern technology (*i.e.* the Internet and the newsgroup **misc.health.diabetes**) I asked a number of people with diabetes what they would like their physicians to know. Here are a few of their responses:

*“I would go into the depression that goes along with a chronic disease such as diabetes. When I feel good about myself I find myself under good regulation and when I am depressed I have bad regulation. I would also tell them that some of us with diabetes have done some intensive studies and are quite knowledgeable, while others are ignorant about what is going on. The doctor has to understand people with chronic diseases and take time to listen to their patients. I am still looking for a good doctor.”*

*“Tell your students that all people are different and that although there may be guidelines for treating and managing diabetes the specifics may vary by individual. It would be helpful if physicians would tell patients this about diabetes, as well as medications, instead of teaching what they know as “gospel” and having patients worry because they don't fit into this “norm”. It would also be helpful if diabetes care professionals would keep up with the latest research and treatment options by reading . . . the journals.”*

*“To understand what it's like to have diabetes, I would like people to stop thinking that the injections themselves are the bad part. The shots are nothing at all for me and others I've talked with. What's horrific is the loss of freedom. Having to test my blood every few hours and carry around with me ALL my paraphernalia for the tests and the shots is a HUGE burden. You get a day off from work now and then but a diabetic NEVER gets a day off! Having to be aware of what I've eaten and how much insulin is on board and what to do about what's gonna happen next is a full time job. I'd like some sensitive discussion about the psyche of it all . . . the drill is easy to learn (though a nightmare).”*

*“Make sure they understand three things: 1) We know when we are not taking the best care of ourselves. We do not need a lecture, just some gentle persuasion and encouragement. 2) We know this disease, each and every feature of this faceless beast.*



*Do not talk down to us about something you treat and we live with. 3) This is a condition we spend every waking and some sleeping hours trying to combat. It is our best friend and worst enemy. If we do not acknowledge, accept and nurture it, it will kill us. Not going off on MD's in general, just letting you know some things about some of the mile long line of specialists I have been to that really turned me off."*

*">For example, instead of admitting the possibility that your epidural could have >raised your bg, they would rather seem confident and say "no way". Hope this is >helpful and not too discouraging.*

*"This holds for everything from vitamin A to Zinc. :-) How many of them even know about the glycemic index? I see dozens of postings about the dangers of sugar; for most people (you might be an exception) bread or cereal is worse at short-term rise in bg, and fats are a problem in the long-term rise.*

*"To teach others, one must be knowledgeable. To teach about complicated biological entities such as people, one must be aware of not only one's lack of knowledge, but the lack of knowledge of mankind."*

*">When I was diagnosed, I tried to get answers to so many questions and got only >the clinical, textbook answer, nothing practical like I've learned here. The other >thing I've learned is that often times practitioners refuse to tell us that we are all >different and may respond differently to different stimuli.*

*"This is a major failure of all medical education, and occurs in far too many other fields. As I tell my colleagues when they become parents, the children have not read the books on how to behave. A major cause of the failure of our public schools is the refusal to believe that children should not all be taught the same way.*

*"I can tell you that the so-called "normal" values for the results of various medical tests are usually based on saying that the middle 95% of people are normal. This would not be bad if they realized this, but the attitude that test results which fall in this range must be good, and those which do not are likely to be bad, is unsound worship of statistics.*

*"It is YOU who should be treated, not the normal person; as a diabetic, you are already not normal. "*

## References

Gerich *et al.* (1991) "Hypoglycemic unawareness." *Endocr. Rev.* **12**: 356-371.

Marks & Skyler (1991) "Immunotherapy of Type I diabetes mellitus." *J. Clin. Endo. Metab.* **72**: 3-9.

Diabetes Control and Complications Trial Research Group (1993) "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus." *N. Engl. J. Med.* **329**: 977-986.

Howard & Howard (1994) "Dyslipidemia in non-insulin-dependent diabetes mellitus." *Endocr. Rev.* **15**: 263-274.

Bach (1994) "Insulin-dependent diabetes mellitus as an autoimmune disease." *Endocr. Rev.* **15**: 516-542.

Kahn (1995) "Causes of insulin resistance." *Nature* **373**: 384-385.

Porte & Schwartz (1996) "Diabetes complications: why is glucose potentially toxic?" *Science* **272**: 699-700.

Taylor *et al.* (1996) "Does leptin contribute to diabetes caused by obesity?" *Science* **274**: 1151-1152.

Slover & Eisenbarth (1997) "Prevention of Type I diabetes and recurrent  $\beta$ -cell destruction of transplanted islets." *Endocr. Rev.* **18**: 241-258.

Mitanchez *et al.* (1997) "Glucose-stimulated genes and prospects of gene therapy for Type I diabetes." *Endocr. Rev.* **18**: 520-540.

Dunaif (1997) "Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis." *Endocr. Rev.* **18**: 774-800.