Kirk-Othmer Encyclopedia of Chemical Technology.

INSULIN AND OTHER ANTIDIABETIC AGENTS

Diabetes mellitus is a pathologic condition characterized by chronic hyperglycemia (elevated blood glucose) and additional disturbances of carbohydrate, fat, and protein metabolism. In general terms, diabetes mellitus results from too little insulin production or a failure of insulin to function. Normally, blood glucose levels are tightly maintained in the fasting state between 3.6 and 5.3 mmol/L (65 – 95 mg/dL) and up to 7.3 mmol/L (130 mg/dL) following a meal. Following guidelines from the World Health Organization and the American Diabetes Association, the diagnosis of diabetes mellitus should be considered when blood glucose levels are ≥6.7 mmol/L (120 mg/dL) following an overnight fast and ≥10 mmol/L (180 mg/dL) following meals or an orally ingested glucose [50-99-7], $C_6H_{12}O_6$, challenge (1, 2).

There are multiple causes of diabetes. Whereas the molecular bases of some forms of diabetes are well understood, in many cases etiologies are unknown. It is customary to divide diabetes into two main forms: insulin-dependent diabetes mellitus (IDDM), also referred to as Type I or juvenile-onset diabetes, and noninsulin-dependent diabetes mellitus (NIDDM), also called Type II or maturity-onset diabetes (3).

IDDM is the more common form of diabetes in children and young adults. This form of the disease is defined by the presence of such classical diabetes symptoms as extreme thirst, excessive urination, and weight loss in the presence of hyperglycemia. Patients with IDDM are also prone to developing an acute condition called diabetic ketoacidosis; in many cases the diagnosis of IDDM is first made when a patient arrives at the emergency room in this condition. Hyperglycemia and ketoacidosis result directly from the body's inability to utilize circulating glucose and free fatty acids in the absence of insulin. Therefore, dehydration related to hyperglycemia, and additional metabolic abnormalities related to poorly regulated lipolysis (elevated levels of ketones and ketoacids in the blood), lead to this life threatening condition. Precipitating causes of diabetic ketoacidosis include intercurrent infections and other illnesses, serious accidents, and the failure to take adequate doses of insulin. IDDM is caused by autoimmune destruction of the insulin-producing β-cells in the pancreas. In early phases of the disease lymphocytes invade the islets of Langerhans in the pancreas and a variety of autoantibodies can be found in the circulation. The result of this self-directed attack by the immune system is destruction of the pancreatic β-cells and a resultant inability to produce insulin. Additional less common causes of insulin-requiring diabetes which do not result from autoimmune destruction of the islets include pancreatectomy, pancreatic cancers, and pancreatitis.

NIDDM is a much more common disease than IDDM, accounting for about 85–90% of all cases of diabetes mellitus. Whereas NIDDM may be present at any age, the incidence increases dramatically with advanced age; over 10% of the population reaching 70 years of age has NIDDM. Patients with NIDDM do not require insulin treatment to maintain life or prevent the spontaneous occurrence of diabetic ketoacidosis. Therefore, NIDDM is frequently asymptomatic and unrecognized, and diagnosis requires screening for elevations in blood or urinary sugar. Most forms of NIDDM are associated with a family history of the disease, and NIDDM is commonly associated with and exacerbated by obesity. The causes of NIDDM are not well understood and there may be many molecular defects which lead to NIDDM.

1. Therapy of Diabetes

The goals of diabetes therapy include elimination of the clinical symptoms of hyperglycemia, prevention of diabetic ketoacidosis, normalization of blood sugar values, prevention of long-term sequelae, and restoration of a sense of well-being. Therapeutic regimens are generally tailored to the individual. Patients having IDDM require treatment with insulin. For some patients having NIDDM careful attention to diet and exercise alone may have a profound impact on the disease. Some patients having NIDDM are best managed with insulin as well, whereas others are best treated using oral blood glucose lowering agents. In virtually all cases the requirement for insulin or an oral agent is reduced by proper attention to exercise and diet.

The efficacy of treatment regimens is gauged by the lack of symptoms and monitoring of blood chemistries, including blood glucose and glycosylated hemoglobin levels. The latter tests have revolutionized the approach to diabetic therapy. Blood glucose values can be monitored multiple times each day by the patient, with the goal of maintaining values as close to normal as possible. Various methods available for home blood glucose monitoring, including colorimetric dipsticks and electronic meters, require a small drop of blood; newer, less invasive methods for blood glucose monitoring are under development. Hemoglobin in circulating red blood cells undergoes a nonenzymatic glycosylation to produce what is referred to as glycosylated or glycated hemoglobin, also known as hemoglobin A_{1c}. This reaction takes place continuously over the life of a red blood cell, and its rate is governed by blood glucose concentrations. Therefore, the amount of glycosylated hemoglobin present at a given time reflects an averaged level of blood glucose control over the preceding 6–8 weeks. Taken together, home blood glucose monitoring and determination of glycosylated hemoglobin levels provide extremely useful parameters for assessing the efficacy of treatment.

Prior to the initiation of insulin therapy for IDDM in the 1920s, life expectancy was short owing to severe metabolic derangements and inanition (3). Subsequent to the common use of insulin therapy, life expectancies improved dramatically, but previously unrecognized long-term consequences of diabetes and/or its treatment became apparent with the increased longevity. Both IDDM and NIDDM lead to tissue damaging complications, which may be divided into microvascular and macrovascular. Microvascular refers to small blood vessels and the resulting complications include diseases of the eyes (retinopathy), kidneys (nephropathy), and nerves (neuropathy). Diabetic retinopathy is now the greatest cause of blindness in the United States among persons over 21 years of age. Proliferative retinopathy in particular leads to blindness, but if treated early by laser photocoagulation therapy, visual loss can be significantly reduced (see Lasers). Diabetic nephropathy may ultimately lead to renal failure requiring dialysis or kidney transplant. Neuropathies associated with diabetes can cause pain, burning or loss of sensation, loss of function (eg, impotence), diarrhea, and postural hypotension. Macrovascular complications arise from atherosclerosis, which results in reduced blood flow. Complications include angina and myocardial infarctions, stroke, and vascular insufficiency of the lower extremities leading to amputations.

A principal question in the therapy of diabetes has been whether normalization of blood glucose levels would reduce the incidence of these serious long-term complications of diabetes. Although tight glycemic control is desirable, it is often difficult to achieve and can be accompanied by the potentially life-threatening side effect of tight control, hypoglycemia. After years of debate a landmark study, the Diabetes Control and Complications Trial (DCCT), was designed. A total of 1441 patients with IDDM were recruited to the study from 29 centers between 1983–1989. The trial was terminated in 1993 when it became clear that tight glycemic control significantly reduced the risk of developing retinopathy, nephropathy, and neuropathy (4).

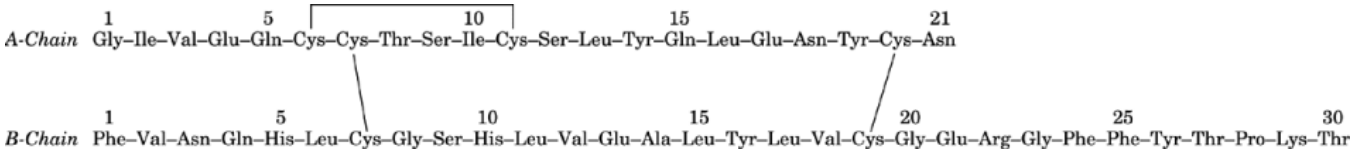


Fig. 1. Amino acid sequence for the A- and B-chains of human insulin [11061-68-0] where solid lines denote disulfide bonds. Porcine insulin [12584-58-6] differs by one amino acid in the B-chain where alanine replaces threonine at position 30. Bovine insulin [11070-73-8] differs by three amino acids. In the A-chain alanine replaces the threonine at position 8 and valine replaces the isoleucine at position 10. In the B-chain there is an alanine at position 30.

2. Insulin

Insulin [9004-10-8] is a peptide hormone produced in the islets of Langerhans within the pancreas, which acts as the principal regulator of glucose homeostasis. Under normal physiological conditions the β-cells within pancreatic islets secrete insulin into the bloodstream following nutrient ingestion. The insulin is then carried in the blood to targeted tissues, all of which have insulin receptors on their cellular surfaces. Tissues of insulin action include the liver, muscle, and fat. Insulin binding to the insulin receptors on these cells induces a series of intracellular events which culminate in the increased cellular uptake of circulating glucose and other nutrients as well as their storage as glycogen and fat, and increases in gene expression and protein synthesis.

The classic experiments of Von Mering and Minkowski in 1889 first implicated the pancreas in regulating blood glucose levels: removal of a dog's pancreas led directly to the development of hyperglycemia. Then in the early 1920s it was shown that an internal secretion of the pancreas could be isolated and used to lower the elevated blood glucose levels of pancreatectomized dogs. Subsequently pancreatic extracts were used to treat patients with diabetes as well (5). Frederick Banting and John Macleod were awarded the 1923 Nobel Prize in Medicine for these discoveries.

2.1. Chemistry

Although insulin was recognized to be a protein shortly after its discovery, its primary structure was not elucidated until the 1950s (6). Insulin was the first protein to have its entire primary sequence determined, and for this achievement Frederic Sanger received the 1959 Nobel Prize in Chemistry. All known insulins are composed of two polypeptide chains linked to one another by disulfide bonds; the structures of human, pig, and beef insulins are compared in Figure 1. The A-chain contains 21 amino acids (qv); the B-chain has 30 amino acids. These two peptide chains are covalently linked to one another by two cystine disulfides, one between CysA7 and CysB7, and the other between CysA20 and CysB19. An additional intrachain disulfide connects cysteines A6 and A11.

For many years patients with diabetes were treated with insulins that had been isolated from the pancreases of pigs and cows. The primary sequences of these insulins are closely related to the sequence of human insulin. There is only a single difference between the sequences of human and porcine insulins: human insulin has a threonine at position B30, and porcine insulin has an alanine. Bovine insulin differs from human insulin at three positions. There is an alanine at the B30 position, an alanine at A8, and a valine at A10. These conservative changes in primary sequence have no apparent effect on biologic activity, although there are slight differences in solubility (7).

In crystal structures the two chains of insulin form highly ordered globular structures (8). Two main structural types form depending on crystallization conditions. In both structures the A-chains form two α-helical segments, from residues A1–A8 and A13–A19, which are connected by a turn. In the structure referred to as the T-state, the B-chain contains two regions of extended chain, B1–B8 and B21–B30, connected by an

α-helix from B9–B19. In the R-state structure, the B-chain helix extends from B1–B19. The crystallographic T-state structure best matches the solution structure of insulin determined by nmr (9), although the R-state can be induced in solution under the appropriate conditions. The surface of insulin which interacts with the insulin receptor includes the N- and C-termini of the A-chain and the C-terminus of the B-chain.

2.2. Preparation of Insulins

Until the early 1980s insulin for therapeutic purposes was produced almost exclusively by extraction from beef and pork pancreases. Between 100 and 400 mg of insulin can be obtained from each kg of pancreatic tissue, and it has been estimated that there would be sufficient supplies of animal insulin to meet the requirements of diabetic patients into the twenty-first century (2). Through modern purification procedures animal insulins can be prepared in essentially pure form, which eliminates the possibility of developing antibodies against impurities in the insulin preparations. However, patients treated with purified insulins still develop antibodies to insulin, suggesting that differences in the primary structures of these insulins might stimulate antibody production. Therefore, enzymatic and biosynthetic methods have been developed for the preparation of therapeutic insulin identical to human insulin.

2.2.1. Isolation of Animal Insulins

The underlying procedure for isolating insulin from pancreatic tissue has remained nearly unchanged since the 1930s (7). Frozen pancreases are extracted in acidified aqueous ethanol to solubilize the insulin and inactivate exocrine proteases. Following a neutralization step, the pH is readjusted to between 3 and 4 (near the isoelectric point of insulin), 2–3 *M* sodium chloride is added, and insulin precipitates. Salt cake insulin is then redissolved in acid and crystallized in the presence of zinc. After two crystallization steps insulin of 80–90% purity is obtained. This product contains substantial amounts of proinsulin and related conversion intermediates, arginyl- and ethyl-insulins, covalent insulin dimers, and monodesamido insulin. Because these impurities are potentially deleterious, most insulin preparations used to treat diabetic patients are further purified by gel-filtration, ion-exchange, and/or reversed-phase liquid chromatography. Highly purified insulin preparations for treating diabetic patients including single-component (SC) insulin (Eli Lilly and Co.) and monocomponent (MC) insulin (Novo/Nordisk) contain <1 ppm of impurities.

2.2.2. Preparation of Human Insulin

Porcine insulin can be converted to the human insulin sequence by an enzyme-catalyzed transpeptidation reaction (10, 11). Under appropriate conditions trypsin acts preferentially at LysB29 rather than ArgB22 to yield a covalent des[B30]insulin/trypsin complex (acyl–enzyme intermediate). In the presence of high concentrations of organic co-solvents and the *t*-butyl ester of threonine, transpeptidation predominates over hydrolysis to yield the *t*-butyl ester of human insulin. Following appropriate purification steps and acidolytic removal of the ester, human insulin suitable for treating patients is obtained.

Advances in recombinant deoxyribonucleic acid (DNA) technology make possible the commercial production of human insulin for therapeutic purposes from protein products produced either in bacteria or yeast. In fact, the biosynthetic production of human insulin can be viewed as the prototype for the biotechnology industry. Over 1000 kg of purified human insulin is made and consumed each year in the United States alone. Three basic strategies have been used (12–14). In the first, A- and B-chains were synthesized independently, the cysteine residues were converted to the respective S-sulfonates to ease handling and purification, and following mild reduction and air oxidation, intact human insulin was obtained. In the second approach, full-length proinsulin [9035-68-1] was produced in *E. coli* following a similar strategy, but the post-fermentation chemistry was simplified because proper chain combination is directed by the C-peptide. The proinsulin product was cleaved enzymatically to yield intact human insulin. In the third approach, a shortened miniproinsulin having a three residue C-peptide was produced in yeast (*S. cerevisiae*). The miniproinsulin was secreted by the yeast into the

Table 1. Characteristics of Insulin Preparations

Composition	Preparation[a]	Action profile, h[b] Onset	Peak	Duration	Insulin species[c]
	Short-acting				
insulin solution unbuffered, regular		0.5	2–5	6–8	H,P,B/P
phosphate buffer, buffered regular		0.5	2–5	6–8	H
	Intermediate-acting				
protamine zinc suspension, phosphate buffer, NPH		1–2	4–12	18–26	H,P,B,B/P
amorphous and crystalline suspension, acetate buffer, lente		1–3	6–15	18–26	H,P,B,B/P
NPH 70%, regular 30%, isophane/regular		0.5	2–12	24	H,P
NPH 50%, regular 50%		0.5	2–12	24	H
	Long-acting				
crystalline suspension, acetate buffer, ultralente		4–6	8–30	24–36	H,B

[a]See text.
[b]Times are averages and can vary markedly between patients, insulin species, injection site, etc.
[c]H = human insulin; P = porcine insulin; B = bovine insulin; B/P = bovine/porcine mixture.

media as a properly processed and folded product. After purification steps and trypsin-catalyzed transpeptidation and acidolysis, intact human insulin was obtained. Human insulin produced in *E. coli* is available from Eli Lilly and Co., whereas human insulin produced in yeast is marketed by the Novo/Nordisk Co. Nearly all patients initiating insulin therapy receive human insulin and many of those that have previously received bovine and/or porcine insulin have been switched to recombinant human insulin.

2.3. Therapeutic Insulin Preparations

Insulin preparations for therapeutic use differ in time of onset, duration of action, purity, and species of origin (15). The concentration of all nonprescription insulins available in the United States is U100 (100 units/mL). A unit is the amount of insulin required to reduce the blood glucose of a fasting rabbit to 2.5 mmol/L (45 mg/dL). There are generally 24 – 30 units/mg of purified insulin. A U500 insulin preparation, Regular (Concentrated) Iletin II, is available by prescription for the treatment of severe insulin resistance. Insulin must be given by hypodermic injection or infusion pump because the hormone is destroyed in the gastrointestinal tract. Individuals having diabetes are trained to inject themselves. For this purpose a special syringe measuring the dosage of insulin directly in units is employed. Insulins may be divided into rapid-, intermediate-, and long-acting preparations depending on the rapidity of onset and duration of action (Table 1).

2.3.1. Rapid-Acting Insulin Preparations

2.3.1.1. Insulin Injection. Regular insulin, crystalline zinc insulin, has both a relatively rapid onset and a short duration of action. It may be given intravenously and intramuscularly, as well as subcutaneously. It is substantially free from turbidity and insoluble matter, and contains 0.1 – 0.25% wt/vol of either phenol or cresol and 1.4 – 1.8% wt/vol of glycerol. Its pH is 2.5–3.5 for acidified injection and 7.0–7.8 for neutral injection. The unpurified is known as Regular Insulin or Regular Iletin I; the purified as Purified Pork Insulin, Regular Iletin II, or Velosulin. Regular insulin [9004-10-8] is widely used to supplement intermediate- and long-action preparations, and, when buffered, it is the insulin used with infusion pumps. Insulin mixtures provide more flexibility in delivering appropriate amounts of insulin at the time of food intake. Regular insulin is the preparation of choice in unstable diabetes when complications such as infection, shock, or surgical trauma occur. It may be administered intravenously to treat ketoacidosis or during surgery.

2.3.1.2. Regular Human Insulin Injection. Known as Humulin R, Novolin R, or Velosulin Human, this rapid-acting form of human insulin [11061-68-0] is produced by recombinant DNA techniques (biosynthetic) or enzymatic conversion (semisynthetic) of porcine insulin. It may be administered subcutaneously, intravenously, intramuscularly, or through an infusion pump. Therapeutically, this preparation is probably equivalent to purified porcine insulin injection. Human regular insulins are absorbed faster than the corresponding purified porcine product in some patients. Although the peak serum concentration of human insulin injection after subcutaneous administration is slightly higher than that of purified porcine insulin injection, the times to peak concentration and overall bioavailability are similar and control of blood glucose appears to be equivalent. No differences are apparent in binding, actions, metabolism, or potency.

2.3.2. Intermediate-Acting Preparations

2.3.2.1. Isophane Insulin Suspension. Isophane insulin [8052-74-2] is an intermediate-acting preparation. The unpurified is known as NPH Iletin I or NPH Insulin; the purified as Insulatard NPH, NPH Iletin II, or NPH Purified Pork Insulin. Absorption is delayed because the insulin is conjugated with protamine in a complex of reduced isoelectric solubility, such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc. The protamine sulfate [9009-65-8] is prepared from the sperm or from the mature testes of fish. This preparation is useful in all forms of diabetes except the initial treatment of diabetic ketoacidosis or in emergencies. Isophane insulin is never given intravenously. Hypoglycemic reactions in mid-to-late afternoon may be less obvious in onset, more prolonged, and more frequent than for rapid-acting preparations because of the prolonged effect of the dose.

Isophane insulin is a white suspension of rod-shaped crystals approximately 30-μm long, and free from large aggregates of crystals after being subjected to moderate agitation. It contains either 1.4–1.8% glycerol, 0.15–0.17% *meta*-cresol, and 0.06–0.07% phenol on a wt/vol basis, or 1.4–1.8% glycerol and 0.20–0.25% phenol (wt/vol), at a pH of 7.1–7.4. It also contains 0.15–0.25% (wt/vol) of sodium phosphate, 0.01–0.04 mg of zinc, and 0.3–0.6 mg of protamine for each USP insulin unit. The insoluble matter in the suspension is crystalline and contains not more than traces of amorphous material.

2.3.2.2. NPH Isophane Human Insulin Suspension. NPH isophane insulin, also called Humulin N, Insulatard NPH Human, or Novolin N is an intermediate-acting form of human insulin produced by recombinant DNA techniques. Mixtures Humulin 70/30 and Novolin 70/30 contain 70% NPH isophane and 30% regular, whereas Humulin 50/50 contains 50% NPH isophane and 50% regular. It is administered subcutaneously and should not be given intravenously. Absorption is delayed because the insulin is conjugated with protamine in a complex of reduced isoelectric solubility. Therapeutically, this preparation is probably comparable to purified porcine NPH insulin. However, human NPH insulin may have a slightly shorter duration of action than comparable purified porcine products.

2.3.2.3. Insulin Zinc Suspension. Lente insulin [8049-62-5], where the unpurified is called Lente Iletin I or Lente Insulin, and the purified, Lente Iletin II or Lente Purified Pork Insulin, is an intermediate-acting preparation composed of 30% prompt insulin zinc suspension (semilente insulin) and 70% extended insulin zinc suspension (ultralente insulin) (see Table 1). Insulin zinc suspension or isophane insulin (usually in combination with regular insulin) is often used for previously untreated diabetic patients who require insulin. Insulin zinc suspension is not a suitable substitute for regular insulin in emergencies because of its delayed onset of action. Insulins of the lente series can be mixed in any proportion to obtain the desired dose and modified activity. The advantage of zinc insulin suspension is its freedom from foreign proteins, eg, globin or protamine, to which some patients are sensitive.

Lente insulin is an almost colorless suspension of a mixture of characteristic crystals predominantly 10–40 μm in maximum dimension, and many particles that have no uniform shape and do not exceed 2 μm in maximum dimension. On a wt/vol basis, it contains 0.15–0.17% sodium acetate, 0.65–0.75% sodium chloride,

0.09–0.11% methylparaben, and 0.20–0.25 mg of zinc of which 40–65% is in the supernatant liquid. Its pH is 7.1–7.5.

2.3.2.4. Human Insulin Zinc Suspension. This insulin, Humulin L or Novolin L, is an intermediate-acting form of human insulin produced by recombinant DNA techniques. It is administered subcutaneously and should not be given intravenously. Therapeutically, this preparation is probably comparable to purified porcine insulin zinc suspension. However, human insulin may have a slightly shorter duration of action than comparable purified pork products.

2.3.3. Long-Acting Insulin Preparations

2.3.3.1. Extended Insulin Zinc Suspension. Ultralente insulin is an unpurified, sterile suspension of insulin in buffered water for injection, modified by the addition of zinc chloride in a manner such that the solid phase of the suspension is crystalline. The actions, indications, and potential for hypoglycemic reactions of this long-acting preparation resemble those of protamine zinc insulin. Like prompt insulin zinc suspension (semilente insulin), this form contains no modifying protein to which patients may be sensitive. Because of its long duration of action, this insulin preparation has limited usefulness when given alone. It is usually administered in combination with a shorter acting form. In slightly reduced doses, it may be combined with insulin zinc suspension (lente insulin) when blood glucose levels are not adequately controlled during the day. Insulins of the lente series can be mixed in any proportion to obtain the desired dose and modified activity. Extended zinc insulin suspension is not suitable for use in emergencies because of its delayed onset of action.

Ultralente Insulin is an almost colorless suspension of a mixture of characteristic crystals, the maximum dimension of which is predominantly 10–40 μm. It contains, for each 100 USP units of insulin, 0.20–0.25 mg of zinc (of which 40–65% is in the supernatant liquid), and not more than 0.70 mg of nitrogen. It also contains on a wt/vol basis 0.15–0.17% sodium acetate, 0.65–0.75% sodium chloride, and 0.09–0.11% methylparaben. The purified form is available as Ultralente Purified Beef Insulin.

2.3.3.2. Human Extended Insulin Zinc Suspension. Ultralente Humulin U is a long-acting form of human insulin produced by recombinant DNA techniques. It is administered subcutaneously and should not be given intravenously. The time course of this preparation is similar for onset of activity but shorter for maximum activity and duration of action compared with ultralente preparations of animal origin. Insulins of the lente series can be mixed in any proportion to obtain the desired dose and modified activity.

3. Oral Hypoglycemic Agents

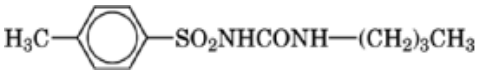
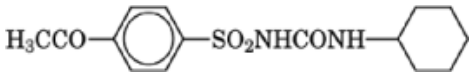
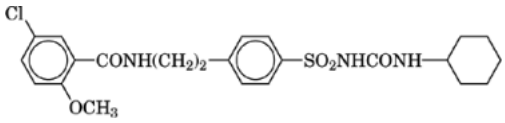
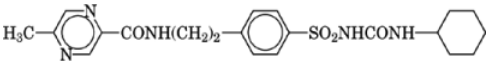
Three classes of oral therapeutic agent are available for treating patients with diabetes mellitus (NIDDM): the arylsulfonylureas (known simply as sulfonylureas), biguanides, and α-glycosidase inhibitors. Since 1977, only the sulfonylureas have been approved for use in the United States, although the other classes are used elsewhere.

3.1. Sulfonylureas

The hypoglycemic effect of sulfonylureas was first noted in the early 1940s when several patients died in hypoglycemic coma after testing glyprothiazole, a synthetic sulfonamide used to treat typhoid. Chemical modifications which enhanced activity and lowered toxicity led to the development of the first-generation sulfonylureas. Carbutamide [339-43-5], $C_{11}H_{17}N_3O_3S$, the first commercial sulfonylurea, came onto the European market in 1955 as a blood-sugar lowering agent, but was later withdrawn owing to toxicity. Tolbutamide [64-77-7], $C_{12}H_{18}N_2O_3S$, was the first sulfonylurea to be used widely in the treatment of NIDDM.

Structures of sulfonylureas commonly used as oral hypoglycemic agents are shown in Table 2. The central moiety of these compounds confers the hypoglycemic activity. Substituents on the phenyl ring (R) and the urea

Table 2. Sulfonylureas Used as Oral Hypoglycemic Agents

Compound	CAS Registry Number	Molecular formula	R R′
		First generation	
tolbutamide	[64-77-7]	$C_{12}H_{18}N_2O_3S$	
chlorpropamide	[94-20-2]	$C_{10}H_{13}ClN_2O_3S$	
tolazamide	[1156-19-0]	$C_{14}H_{21}N_3O_3S$	
acetohexamide	[968-81-0]	$C_{15}H_{20}N_2O_4S$	
		Second generation	
glyburide (glibenclamide)	[10238-21-8]	$C_{23}H_{28}ClN_3O_5S$	
glipizide	[29094-61-9]	$C_{21}H_{27}N_5O_4S$	
gliclazide	[21187-98-4]	$C_{15}H_{21}N_3O_3S$	

groups (R′) affect differences in potency, duration of action, and toxicity. Additional chemical modifications of substituents lead to the development of the second-generation sulfonylureas. The mechanism of action of all sulfonylureas are similar, although second-generation agents have much higher intrinsic activity.

The absorption of sulfonylureas from the upper gastrointestinal tract is fairly rapid and complete. The agents are transported in the blood as protein-bound complexes. As they are released from protein-binding sites, the free (unbound) form becomes available for diffusion into tissues and to sites of action. Specific receptors are present on pancreatic islet β-cell surfaces which bind sulfonylureas with high affinity. Binding of sulfonylureas to these receptors appears to be coupled to an ATP-sensitive K^+ channel to stimulate insulin secretion. These agents may also potentiate insulin-stimulated glucose transport in adipose tissue and skeletal muscle.

Metabolism of sulfonylureas occurs mainly in the liver, either to inactive (tolbutamide, tolazamide, glipizide, glyburide) or active (acetohexamide, chlorpropamide) compounds that are excreted mainly in the urine. Metabolism of chlorpropamide is incomplete, and about 20% is excreted unchanged; the metabolites of acetohexamide are more potent than the parent compound. Therefore, these drugs can be a problem in patients having impaired renal function. All sulfonylureas are metabolized in the liver and should be avoided in patients having significant hepatic dysfunction. Metabolites of glyburide on the other hand are secreted in the bile, as well as the urine, making glyburide the agent of choice in patients experiencing compromised renal function.

3.1.1. Drug Selection

Studies comparing the effectiveness of sulfonylurea agents have shown that chlorpropamide, tolazamide, glyburide, and glipizide are equally effective; tolbutamide and acetohexamide are less effective. If blood glucose is not controlled in a patient receiving the maximal dose of one of the four most effective sulfonylureas, substituting the maximal dose of another of these agents restores diabetic control in only a small ($<10\%$) percentage of patients.

The second-generation drugs are nearly equivalent therapeutically, but some differences exist. Although both glipizide and glyburide often can be administered once daily, the former has a shorter serum half-life and usually requires twice-daily administration. Its concentration in the serum rises higher and more rapidly and is accompanied by greater insulin secretion initially. Glyburide is more likely to increase sensitivity to insulin. Glipizide may reduce post-prandial blood glucose more effectively, whereas glyburide may be effective in decreasing fasting blood glucose levels and enhancing basal insulin secretion.

Relative potency alone does not determine drug selection because maximal effectiveness is similar for all agents. A single daily dose of any sulfonylurea, except tolbutamide, is sometimes adequate to control blood glucose in NIDDM patients.

3.1.1.1. Acetohexamide. Acetohexamide or 1-[(*p*-acetylphenyl)sulfonyl]-3-cyclohex-ylurea, mol wt 324.42, is a white, practically odorless crystalline powder that has the trade name Dymelor. It is practically insoluble in water and in ether, soluble in pyridine and in dilute solutions of alkali hydroxides, and slightly soluble in alcohol and in chloroform.

The incidence of untoward effects is low and the reactions are reversible when acetohexamide is discontinued. Relatively severe hypoglycemic reactions have been observed occasionally in patients given large doses for a prolonged period without close observation. It is contraindicated in patients having hyperglycemia and glycosuria owing to primary renal disease, and in those who are hypersensitive to sulfonylurea compounds.

3.1.1.2. Chlorpropamide. Chlorpropamide (1-[(*p*-chlorophenyl)sulfonyl]-3-propylurea), mol wt 276.75, is a white, crystalline powder, having a slight odor, mp 127–129°C. It is sold as Diabinese, is soluble in water at pH 6 (2.2 mg/mL), and practically insoluble at pH 7.3, soluble in alcohol, and sparingly soluble in chloroform, ether, and benzene.

Untoward reactions have been reported more frequently with chlorpropamide than with other sulfonylureas, and the drug should be used with caution. In a few older patients, hypoglycemic reactions have been severe. Water retention with hyponatremia can be life-threatening in patients having a tendency to retain water, eg, those with congestive heart failure or hepatic cirrhosis. Elderly patients and those taking thiazide diuretics may be more likely to develop this complication. This drug should not be used in patients with renal insufficiency, because the duration of action is greatly prolonged. This drug generally is not given to elderly patients.

Facial flushing after ingestion of alcohol occurs in up to one-third of patients taking chlorpropamide. The mechanism, like that of the disulfiram reaction, probably involves inhibition of the oxidation of acetaldehyde, a metabolite of ethanol. The plasma concentration of chlorpropamide may be correlated with chlorpropamide–alcohol flushing.

3.1.1.3. Glipizide. Glipizide (1-cyclohexyl-3[[*p*-[2-(5-methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea), mol wt 445.55, forms crystals from ethanol, mp 208–209°C. It is known commercially as Glucotrol.

Glipizide is relatively free of serious adverse effects and only approximately 1.5% of patients discontinue this drug because of adverse reactions. Gastrointestinal disturbances are most common (incidence 1.7–3.7%); skin rashes occur in up to 1.4% of patients.

3.1.1.4. Glyburide. Glyburide or 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea, mol wt 494.00, forms crystals from methanol, mp 169–170°C. Its pK_a is 5.3 and it is sparingly soluble in water and soluble in the usual organic solvents.

The incidence of serious side effects with glyburide, sold as DiaBeta and Micronase, is low. Gastrointestinal disturbances develop in 1.8% of patients. Skin rashes occur in 1.5% of patients and may disappear with continued use.

3.1.1.5. Tolazamide. Tolazimide (1-(hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolysulfonyl)urea), mol wt 311.40, is a white to off-white crystalline powder, odorless or having a slight odor, mp 170–173°C, with a pK_a of −3.6 at 25°C and 5.68 at 37.5°C. It is very slightly soluble in water, freely soluble in chloroform, soluble in acetone, and slightly soluble in alcohol. The trade name is Tolinase.

Generally, the untoward effects associated with tolazamide are the same as those noted with the other sulfonylureas; the incidence is low and reactions are reversible when tolazamide is discontinued. Hypoglycemia has been reported occasionally.

3.1.1.6. Tolbutamide. Tolbutamide (1-butyl-3-(*p*-tolylsulfonyl)urea), with mol wt 270.35, is known as Orinase. It is a white to off-white practically odorless crystalline powder having a slightly bitter taste, mp 126–132°C. It is practically insoluble in water, and soluble in alcohol and chloroform. The toxicity of tolbutamide appears to be low, and reactions are similar to those observed with other sulfonylureas.

3.1.1.7. Tolbutamide Sodium USP. Orinase Diagnostic [473-41-6] (*N*-[(butylamine)carbonyl]-4-methylbenzenesulfonamide, monosodium salt), mol wt 292.33, is a white to off-white practically odorless crystalline powder having a slightly bitter taste. It is freely soluble in water, soluble in alcohol and chloroform, and very slightly soluble in ether and can be prepared by dissolving tolbutamide in aqueous NaOH.

Because of its water solubility, tolbutamide sodium may be given intravenously (1 g of tolbutamide equivalent over a period of 2–3 min). By this route, its rapid onset of action lends itself to the diagnosis of diabetes mellitus in persons in whom the usual studies are equivocal. The normal person responds with a more rapid and intense drop in blood glucose than does the diabetic, especially during the first hour after injection. Persons having pancreatic insulinoma respond with a prolonged hypoglycemia, so that the drug may also be used diagnostically when that condition is suspected. Tolbutamide sodium is an irritant, and thrombophlebitis and thrombosis of the vein occur in ca 1–2% recipients.

3.2. Biguanides

Biguanides, which are guanidine derivatives, were introduced into clinical use for the treatment of hyperglycemia in patients with Type II diabetes mellitus in the 1950s. Three biguanides were available initially: phenformin, metformin, and butformin. Phenformin, an investigational drug widely prescribed in the United States, and butformin have both been banned for clinical use because of a significant incidence of associated lactic acidosis. Metformin, introduced in France in 1959, continues to be used worldwide and is undergoing clinical investigation in the United States. Because of a different mechanism of action, biguanides might be used instead of or in combination with sulfonylureas.

3.2.1. Phenformin

Phenformin hydrochloride [834-28-6] (1-phenethylbiguanide, *N*-(2-phenylethyl)imidodicarbonimidic diamide), is a white to off-white odorless crystalline power having a bitter taste. The melting point is 175–178°C. It

is freely soluble in water and alcohol, and practically insoluble in chloroform, ether, and hexane. Its pH in solution is 6.0–7.0.

3.2.2. Metformin

Metformin [657-24-9] (1,1-dimethylbiguanide), mol wt 129.17, forms crystals from propanol, mp 218–220°C, and is soluble in water and 95% ethanol, but practically insoluble in ether and chloroform. Metformin, an investigational drug in the United States, does not increase basal or meal-stimulated insulin secretion. It lowers blood glucose levels in hyperglycemic patients with Type II diabetes but has no effect on blood glucose levels in normal subjects. It does not cause hypoglycemia. Successful metformin therapy usually is associated with no or some weight loss.

Clinical studies have shown that metformin is as effective as chlorpropamide, tolbutamide, or gliclazide in lowering fasting and post-prandial hyperglycemia in patients with newly diagnosed Type II diabetes. However, metformin treatment produces a modest mean weight loss of 1–2 kg as compared with a mean weight gain of 1.5–5.0 kg produced by sulfonylurea therapy. Therapy using metformin results in better glycemic control in about 80% of both obese and nonobese patients having newly diagnosed Type II diabetes. Reported rates of primary failure with metformin are about 12%, and those of secondary failure are about 5%.

3.3. Inhibitors of α-Glucosidase

Acarbose [56180-94-0] (*O*-4,6-dideoxy-4-[[[1*S*-(1α,5β,6α)]-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1 → 4)-*O*-α-D-glucopyranosyl-(1 → 4)-D-glucose), with mol wt 645.63, is an investigational drug. It is a pseudotetrasaccharide isolated from strains of *Actinoplanes* and contains an unsaturated cyclitol moiety.

Acarbose is a nonabsorbable α-glucosidase inhibitor which blocks the digestion of starch, sucrose, and maltose. The digestion of complex carbohydrates is delayed and occurs throughout the small intestine rather than in the upper part of the jejunum. Absorption of glucose and other monosaccharides is not affected. Acarbose is administered orally three times a day and chewed with the first mouthful of food.

4. Miscellaneous Agents

Diazoxide [364-98-7] (3-methyl-7-chloro-1,2,4-benzothiadiazine 1,1-dioxide) is a nondiuretic thiazide used for its hyperglycemic actions when given orally (Proglycem) and for its antihypertensive effects when given intravenously (Hyperstat I.V.) (see Cardiovascular agents). Diazoxide produces a prompt dose-related increase in blood glucose by directly inhibiting insulin secretion and, possibly, by stimulating epinephrine secretion by the adrenal medulla (see Epinephrine and norepinephrine). Diazoxide is used to counteract hyperinsulinism in conditions such as insulinoma. It is not indicated in the treatment of functional hypoglycemia.

Glucagon [16941-32-5] is a polypeptide produced by the alpha cells of the pancreas. Like insulin, its normal function appears to be to control the homeostasis of glucose, amino acids, and possibly free fatty acids. However, its potent glycogenolytic and gluconeogenic effects are opposite to those of insulin and form the basis for glucagon's clinical usefulness which is the treatment of severe hypoglycemia in patients with diabetes. Glucagon must be administered parenterally. It often is given to a patient by a family member or other caretaker when a severe hypoglycemic episode occurs and the patient is unable to ingest sugar or simple carbohydrates or is unconscious. Glucagon increases the blood glucose concentration by mobilizing hepatic glycogen and thus is effective only when hepatic glycogen is available. Patients having reduced glycogen stores, eg, starvation, adrenal insufficiency, or alcoholic hypoglycemia, cannot respond to glucagon.

Glucagon also has been used to diagnose insulinoma and pheochromocytoma. For the former, the rise in plasma insulin concentration following intravenous glucagon may be diagnostic.

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