Adverse Effects and Precautions

Guar gum can cause gastrointestinal disturbance with flatulence, diarrhoea, or nausea, particularly at the start of treatment.

Because guar gum swells on contact with liquid it should always be washed down carefully with water and should not be taken immediately before going to bed. It should not be used in patients with dysphagia, oesophageal disease, or intestinal obstruction.

Interactions

Guar gum may retard the absorption of other drugs; where this is likely to pose a problem the other drug should be taken at least an hour before guar gum.

Uses and Administration

Guar gum is used in diabetes mellitus (p.431) as an adjunct to treatment with diet, insulin, or oral antidiabetics since it results in some reduction in both postprandial and fasting blood-glucose concentrations. It is given with or immediately before meals in doses of 5 g usually 3 times daily. Adverse gastrointestinal effects may be reduced by using a lower initial dose of 5 g once daily before breakfast for 1 week, then increasing to 5 g twice daily, then 3 times daily, as required. Each dose of guar gum granules should be taken stirred in about 200 mL of a cold drink. Alternatively it can be sprinkled over or mixed with food which must be taken with about 200 mL of fluid.

Guar gum is also used to slow gastric emptying in some patients with the dumping syndrome (p.1695). It is also used as an adjunct in the treatment of hyperlipidaemias.

Guar gum is also used as a thickening and suspending agent, and as a tablet binder. It has been incorporated into processed foods.

◊ Guar gum is an example of a soluble fibre.[1] On contact with water it forms a highly viscous gel, the viscosity of which varies with such factors as its plant source or the form in which it is given.[2]

Fibres such as guar gum reduce postprandial and fasting blood-glucose concentrations as well as plasma-insulin concentrations in healthy subjects and diabetic patients.[1,3,4] Such reductions in blood-glucose concentrations and in glycosylated haemoglobin have been demonstrated in both type 1 and type 2 **diabetes,** but they have generally been small.[3] Possible mechanisms for these effects of guar gum include a delay in gastric emptying,[1,3-5] decreased small-bowel motility,[1,4] decreased glucose absorption resulting from increased viscosity of the contents of the gastrointestinal tract,[1,3] or inhibition of gastrointestinal hormones.[3]

Guar gum also lowers serum total cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations; high-density-lipoprotein (HDL) cholesterol and triglyceride concentrations appear to be unaffected.[4] The most likely mechanism is binding of bile acids, reducing their enterohepatic circulation in a similar way to bile-acid sequestrants.[3,4] When used alone in patients with **hypercholesterolaemia** guar gum has generally produced a modest reduction in plasma-cholesterol and LDL-cholesterol concentrations although some studies have been unable to demonstrate an effect. A few studies have suggested that the cholesterol-lowering effect is attenuated after 8 to 12 weeks of treatment but a long-term study observed a 17% decrease in total serum cholesterol that was maintained for 24 months.[6] Some studies have shown further reductions in cholesterol and LDL-cholesterol concentrations on addition of guar gum to therapy with other lipid regulating drugs.[4] The usual treatment of hyperlipidaemias is discussed on p.1169.

There have been suggestions that guar gum reduces appetite by promoting a feeling of fullness, but a meta-analysis has indicated that it is not effective for reducing body-weight.[7] Products containing guar gum have, however, been promoted as **slimming aids**. Their use cannot be advocated because of the risk of tablets swelling before reaching the stomach and causing oesophageal obstruction.

1. Hockaday TDR. Fibre in the management of diabetes 1: natural fibre useful as part of total dietary prescription. *BMJ* 1990; **300:** 1334–6.
2. Ellis PR, *et al.* Guar gum: the importance of reporting data on its physico-chemical properties. *Diabet Med* 1986; **3:** 490–1.
3. Anonymous. Guar gum: of help to diabetics? *Drug Ther Bull* 1987; **25:** 65–7.
4. Todd PA, *et al.* Guar gum: a review of its pharmacological properties, and use as a dietary adjunct in hypercholesterolaemia. *Drugs* 1990; **39:** 917–28.
5. Tattersall R, Mansell P. Fibre in the management of diabetes 2: benefits of fibre itself are uncertain. *BMJ* 1990; **300:** 1336–7.
6. Salenius J-P, *et al.* Long term effects of guar gum on lipid metabolism after carotid endarterectomy. *BMJ* 1995; **310:** 95–6.
7. Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. *Am J Med* 2001; **110:** 724–30.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Regudig†; ***Austral.:*** Benefiber†; ***Braz.:*** Benefiber†; Biofiber†; ***Fin.:*** Guarem; ***Ger.:*** Figur-Verlan; Guar Verlan; ***Hong Kong:*** Guarem†; ***Irl.:*** Guarem†; ***Ital.:*** Novafibra; ***NZ:*** Guarcol; ***Spain:*** Fibraguar; Plantaguar; ***Switz.:*** Leiguar; ***UK:*** Resource Benefiber; ***USA:*** Benefiber.

Multi-ingredient: ***Fr.:*** Carres Parapsyllium; Moxydar; Mucipulgite; Mulkine; Seroxydar; ***Ital.:*** Cruscasohn; Resource Gelificata; ***Switz.:*** Mucipulgite†.

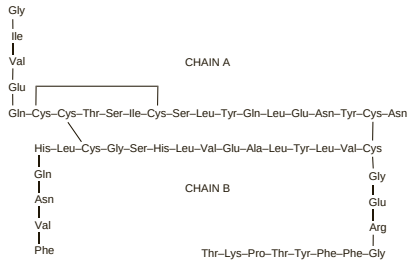
Insulin ⊗

Insuliini; Insülin; Insulina; Insuline; Insulinin; Insulinum.

CAS — 9004-10-8 (insulin; neutral insulin); 11070-73-8 (bovine insulin); 12584-58-6 (porcine insulin); 11061-68-0 (human insulin); 8063-29-4 (biphasic insulin); 9004-21-1 (globin zinc insulin); 68859-20-1 (insulin argine); 8049-62-5 (insulin zinc suspensions); 53027-39-7 (isophane insulin); 9004-17-5 (protamine zinc insulin); 116094-23-6 (insulin aspart); 9004-12-0 (dalanated insulin); 51798-72-2 (bovine insulin defalan); 11091-62-6 (porcine insulin defalan); 160337-95-1 (insulin glargine); 133107-64-9 (insulin lispro).

ATC — A10AB01 (human); A10AB02 (beef); A10AB03 (pork); A10AB04 (lispro); A10AB05 (aspart); A10AB06 (glulisine); A10AC01 (human); A10AC02 (beef); A10AC03 (pork); A10AC04 (lispro); A10AE01 (human); A10AE02 (beef); A10AE03 (pork); A10AE04 (glargine); A10AE05 (detemir).

ATC Vet — QA10AB01 (human); QA10AB02 (beef); QA10AB03 (pork); QA10AB04 (lispro); QA10AB05 (aspart); QA10AB06 (glulisine); QA10AC01 (human); QA10AC02 (beef); QA10AC03 (pork); QA10AC04 (lispro); QA10AD01 (human); QA10AD02 (beef); QA10AD03 (pork); QA10AD04 (lispro); QA10AD05 (aspart); QA10AE01 (human); QA10AE02 (beef); QA10AE03 (pork); QA10AE04 (glargine); QA10AE05 (detemir); QA10AF01 (human).



(human)

Pharmacopoeias. Most pharmacopoeias have monographs for insulin and a variety of insulin preparations.

Ph. Eur. 6.2 (Insulin, Bovine). The natural antidiabetic principle obtained from beef pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at –20° until released by the manufacturer. When thawed, insulin may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin, Porcine). The natural antidiabetic principle obtained from pork pancreas and purified. A white or almost white powder. Practically insoluble in water and in dehydrated alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at –20° until released by the manufacturer. When thawed, insulin may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin, Human). A protein having the structure of the antidiabetic hormone produced by the human pancreas. It is produced either by enzymatic modification and suitable purification of insulin obtained from the pancreas of the pig or by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and, with decomposition, in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below –18° or below until released by the manufacturer. When thawed, insulin is stored at 2° to 8° and used for manufacturing preparations within a short period of time. To avoid absorption of humidity from the air during weighing, the insulin must be at room temperature.

Ph. Eur. 6.2 (Insulin Aspart; Insulinum Aspartum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, except that it has aspartic acid instead of proline at position 28 of the B-chain. As in human insulin, insulin aspart contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in aqueous solutions with a pH around 5.1. In aqueous solutions below pH 3.5 or above pH 6.5, the solubility is greater than or equal to 25 mg/mL. Store in airtight containers. Protect from light. It should be stored at or below –18° until released by the manufacturer. When thawed, insulin aspart may be stored at 2° to 8° and used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

Ph. Eur. 6.2 (Insulin Lispro; Insulinum Lisprum). It is a 2-chain peptide containing 51 amino acids. The A-chain is composed of 21 amino acids and the B-chain is composed of 30 amino acids. It is identical in primary structure to human insulin, only differing in amino acid sequence at positions 28 and 29 of the B-chain. Human insulin is Pro(B28), Lys(B29), whereas insulin lispro is Lys(B28), Pro(B29). As in human insulin, insulin lispro contains 2 interchain disulfide bonds and 1 intrachain disulfide bond. It is produced by a method based on recombinant DNA (rDNA) technology. A white or almost white powder. Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and with decomposition in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light. It should be stored at or below –18°. When thawed, insulin lispro is used for manufacturing purposes within a short period of time. To avoid absorption of humidity from the air during weighing, insulin aspart must be at room temperature before opening the container.

USP 31 (Insulin). A protein that affects the metabolism of glucose obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at –10° to –25°.

USP 31 (Insulin Human). A protein corresponding to the active principle elaborated in the human pancreas that affects the metabolism of carbohydrate (particularly glucose), fat, and protein. It is derived by enzymatic modification of insulin from pork pancreas in order to change its amino acid sequence appropriately, or produced by microbial synthesis via a recombinant DNA process. Store in airtight containers. Protect from light. It should be stored at –10° to –25°.

USP 31 (Insulin Lispro). Insulin Lispro is identical in structure to Insulin Human, except that it has lysine and proline at positions 28 and 29, respectively, of chain B, whereas this sequence is reversed in Insulin Human. It is produced by microbial synthesis via a recombinant DNA process. White or practically white crystals. Soluble in solutions of dilute acids and alkalis. Store in airtight containers. Protect from light. It should be stored at –10° to –25°.

Definitions and Terminology

Insulin is a hormone produced by the beta cells of the islets of Langerhans of the pancreas and consists of 2 chains of amino acids, the A and B chains, connected by 2 disulfide bridges. Insulin produced by different species conforms to the same basic structure but has different sequences of amino acids in the chains. **Porcine insulin** ($C_{256}H_{381}N_{65}O_{76}S_6$ = 5777.5) differs from **human insulin** ($C_{257}H_{383}N_{65}O_{77}S_6$ = 5807.6) in only one amino acid in the B chain, whereas **bovine insulin** ($C_{254}H_{377}N_{65}O_{75}S_6$ = 5733.5) differs from human insulin not only in this same amino acid in the B chain but also in 2 amino acids in the A chain.

The precursor of insulin in the pancreas is proinsulin which is a single polypeptide chain incorporating both the A and B chains of insulin connected by a peptide termed the C-peptide (or connecting-peptide). Although the insulins of various species may be similar in composition the proinsulins are not, in that the sequence and number of amino acids in the C-peptide may vary considerably.

Early commercial insulins were obtained by extraction from bovine or porcine or mixed bovine and porcine pancreases and were purified by recrystallisation only.

Table 2. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Soluble insulins (also known as regular or unmodified insulin)	Soluble Insulin Injection (Ph. Eur. 6.2)	Neutral Insulin Neutral Insulin Injection Soluble Insulin Insulin Injection	Solution of bovine, porcine, or human insulin	6.9 to 7.8				
	Insulin Injection (USP 31)		Solution of bovine or porcine, or a mixture of bovine and porcine, insulin	7.0 to 7.8	Short-acting	30 minutes to 1 hour	2 to 5 hours	6 to 8 hours
	Insulin Human Injection (USP 31)		Solution of human insulin	7.0 to 7.8				
Insulin analogues, rapid	Insulin Aspart Injection (BP 2008)		Solution of insulin aspart	6.9 to 7.8				
	Insulin Lispro Injection (BP 2008)		Solution of insulin lispro	6.9 to 7.8	Short-acting	5 to 20 minutes	1 to 3 hours	2 to 5 hours
	Insulin Lispro Injection (USP 31)		Solution of insulin lispro	7.0 to 7.8				
Biphasic insulins	Biphasic Insulin Injection (Ph. Eur. 6.2)	Biphasic Insulin	Suspension of crystals containing bovine insulin in a solution of porcine insulin	6.6 to 7.2				
	Biphasic Isophane Insulin Injection (Ph. Eur. 6.2)	Biphasic Isophane Insulin	Buffered suspension of porcine insulin or human insulin complexed with protamine sulfate or other suitable protamine, in a solution of porcine insulin or human insulin respectively.	6.9 to 7.8				
	Human Insulin Isophane Suspension and Human Insulin Injection (USP 31)		Buffered suspension of human insulin complexed with protamine sulfate, in a solution of human insulin	7.0 to 7.8				
Insulin suspensions	Isophane Insulin Injection (Ph. Eur. 6.2)	Isophane Insulin Isophane Insulin (NPH) Isophane Protamine Insulin Injection	Suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine. Contains 300 to 600 micrograms of protamine sulfate per 100 units of insulin	6.9 to 7.8				
	Isophane Insulin Suspension (USP 31)		Buffered aqueous suspension of zinc-insulin (bovine or porcine) crystals and protamine sulfate, combined in a manner such that the solid phase of the suspension consists of crystals composed of insulin, protamine, and zinc	7.0 to 7.8	Intermediate-acting	Within 2 hours	4 to 12 hours	Up to 24 hours
	Isophane Insulin Human Suspension (USP 31)		Buffered aqueous suspension of zinc-insulin human crystals and protamine sulfate, combined in such a manner that the solid phase of the suspension consists of crystals composed of insulin human, protamine, and zinc	7.0 to 7.5				
	Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 6.2)	Amorph. I.Z.S. Insulin Semilente Insulin Zinc Suspension (Amorphous)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				

Table 2. Ph. Eur., BP, and USP insulin preparations.

Type	Ph. Eur./BP/USP Title	Synonyms	Description	pH	Common classification	Approximate action profile after subcutaneous administration		
						Onset	Time to peak	Duration
Insulin suspensions *cont*	Prompt Insulin Zinc Suspension (USP 31)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is amorphous	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Ph. Eur. 6.2)	Insulin Lente I.Z.S. I.Z.S. (Mixed) Insulin Zinc Suspension (Mixed) Insulin Zinc Suspension	Suspension of bovine or porcine, or a mixture of bovine and porcine, or human insulin with a suitable zinc salt; the insulin is in a form practically insoluble in water. It may be produced by mixing Insulin Zinc Injectable Suspension (Amorphous) (Ph. Eur. 6.2) and Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 6.2) in a ratio of 3 to 7	6.9 to 7.8				
	Insulin Zinc Suspension (USP 31)	Insulin Zinc	Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8	Intermediate or long-acting	2 to 3 hours	6 to 15 hours	Up to 30 hours
	Insulin Human Zinc Suspension (USP 31)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension consists of a mixture of approximately 3 parts of amorphous insulin to 7 parts of crystalline insulin	7.0 to 7.8				
	Insulin Zinc Injectable Suspension (Crystalline) (Ph. Eur. 6.2)	Cryst. I.Z.S. Insulin Ultralente Insulin Zinc Suspension (Crystalline)	Suspension of bovine, porcine, or human insulin complexed with a suitable zinc salt; the insulin is in a form practically insoluble in water	6.9 to 7.8				
	Protamine Zinc Insulin Injection (BP 2008)	Protamine Zinc Insulin	Buffered suspension of bovine, porcine, or human insulin complexed with protamine sulfate or another suitable protamine and zinc chloride or another suitable zinc salt	6.9 to 7.8				
	Extended Insulin Zinc Suspension (USP 31)		Buffered aqueous suspension of bovine or porcine, or a mixture of bovine and porcine, insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase is predominantly crystalline	7.0 to 7.8	Long-acting	4 hours	10 to 20 hours	Up to 36 hours
	Extended Insulin Human Zinc Suspension (USP 31)		Buffered aqueous suspension of human insulin modified by the addition of a suitable zinc salt in a manner such that the solid phase of the suspension is predominantly crystalline	7.0 to 7.8				

Insulins obtained by such methods were often termed '**conventional insulins**' to distinguish them from insulins which have undergone further purification processes. An extract which has been recrystallised only once can be separated into 3 components or fractions termed the 'a', 'b', and 'c' components. The 'a' component consists of high molecular weight substances and is only usually found in very impure preparations since repeated recrystallisation will remove most of it. The 'b' component consists largely of proinsulin and insulin dimers, and the 'c' component consists of insulin, insulin esters, arginine insulin, and desamidoinsulin. Other pancreatic peptides such as glucagon, pancreatic polypeptide, somatostatin, and vasoactive intestinal peptide are also usually found in products which have not undergone further purification. Gel filtration will substantially reduce the content of proinsulin but will not significantly reduce the content of insulin derivatives or pancreatic peptides; products purified by gel filtration are often termed '**single-peak insulins**'. Addition of ion-exchange chromatography to the purification methods will further reduce the proinsulin content and also reduce the contamination by insulin derivatives and pancreatic peptides. In the UK '**highly purified insulins**' and '**monocomponent insulins**' are terms sometimes applied to insulins which have undergone both gel filtration and ion-exchange chromatography. In the USA the FDA has designated the term '**purified insulins**' for preparations similarly prepared and containing less than 10 ppm of proinsulin.

Much of the insulin now produced has an amino-acid sequence identical to that of human insulin. **Human insulin (emp)** is produced by the enzymatic modification of insulin obtained from the porcine pancreas; it is also sometimes called **semisynthetic human insulin**. The term **human insulin (crb)** is used for insulin produced by the chemical combination of A and B chains which have been obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (prb)** is produced from proinsulin obtained from bacteria genetically modified by recombinant DNA technology. **Human insulin (pyr)** is insulin produced from a precursor obtained from a yeast genetically modified by recombinant DNA technology. Human insulin obtained by recombinant DNA technology is sometimes termed **biosynthetic human insulin**.

Insulin or human insulin is supplied in a variety of forms in solution or suspension for injection (see Table 2, p.444). Crystalline insulin may be prepared for therapeutic use merely by making a solution, either of acidic or neutral pH. **Soluble insulin** or '**neutral insulin**' is a short-acting preparation that can be given intravenously if necessary to cover emergencies. Soluble formulations are sometimes referred to as '**regular insulin**' or '**unmodified insulin**'; these names reflect the fact that the preparation has not been formulated in order to prolong the duration of action of the insulin.

In order to prolong the duration of action of insulin, preparations may be formulated as suspensions in 2 general ways. The first involves complexing insulin with a protein from which it is slowly released; examples are **protamine zinc insulin**, which contains an excess of protamine, and **isophane insulin** (NPH insulin), which contains equimolecular amounts of insulin and protamine. The second method of prolonging the action of insulin is to modify the particle size and the various **insulin zinc suspensions** are in this category.

Biphasic insulins are mixtures providing for both immediate and prolonged action.

Chemical modification of the insulin molecule has resulted in insulins such as **dalanated insulin** (prepared by the removal of the C-terminal alanine from the B chain of insulin), **insulin defalan** (prepared by the removal of the terminal phenylalanine), and **sulfated insulin**, but these insulins have not been widely used.

More recently, recombinant DNA technology has enabled production of *insulin analogues* with altered pharmacokinetic profiles. **Insulin lispro** is one such analogue, in which the B28 and B29 amino acid residues of human insulin are replaced with lysine and proline. It is available as a rapidly acting alternative to soluble insulin and as an intermediate-acting complex with protamine. **Insulin aspart** and **insulin glulisine** are other rapidly acting analogues. **Insulin glargine** is a long-acting form for once-daily use, and **insulin detemir** is used once or twice daily. Further information on these can be found under the heading Insulin Analogues and Proinsulin, in Uses, below.

Stability and Storage

Both the Ph. Eur. 6.2 and the USP 31 recommend that insulin preparations be stored in a refrigerator at 2° to 8° and not be allowed to freeze. The Ph. Eur. 6.2 directs that insulin preparations should be protected from light, and the USP 31 that they should be protected from sunlight. It is recognised that patients may not follow such stringent storage guidelines and most manufacturers of commercial insulin preparations consider that storage by the patient at a temperature of up to 25° would be acceptable for up to one month. Patients should still be advised not to expose their vials or cartridges to excessive heat or sunlight.

It is advisable to shake suspensions gently before a dose is withdrawn.

Insulin in powder form should be stored in airtight containers and protected from light. Storage at a low temperature is also recommended. The Ph. Eur. 6.2 advises storage at a temperature of –20° for bovine and porcine insulin and at –18° or below for Human Insulin, and for Insulin Aspart and Insulin Lispro; the USP 31 requires storage at –10° to –25° for all types of insulin. It is stressed that this temperature is for the powder and not for the preparations; preparations should not be subjected to storage conditions that lead to freezing.

Adsorption. The adsorption of insulin onto glass and plastics used in giving sets has been decreased by the addition of albumin or polygeline to insulin solutions but it has been stated[1,2] that in practice this was unnecessary since insulin adsorption was not a major problem. However, in studies of insulin infusions used in neonatal hyperglycaemia, various methods have been investigated and found to reduce the amount of insulin lost by adsorption to the giving set. These included flushing[3] or priming[4] the system with the insulin infusion, or using a concentrated insulin solution to prime the tubing.[5] A study[6] that compared different methods found wide variation in insulin delivery depending on solution concentration, flow rate, addition of albumin, catheter type, and priming or flushing of the system.

1. Alberti KGMM. Diabetic emergencies. *Br Med Bull* 1989; **45:** 242–63.
2. Sanson TH, Levine SN. Management of diabetic ketoacidosis. *Drugs* 1989; **38:** 289–300.
3. Simeon PS, *et al.* Continuous insulin infusions in neonates: pharmacologic availability of insulin in intravenous solutions. *J Pediatr* 1994; **124:** 818–20.
4. Avent M, Whitfield J. Insulin infusions in extremely low birth weight infants. *Pediatrics* 2000; **105:** 915.
5. Fuloria M, *et al.* Effect of flow rate and insulin priming on the recovery of insulin from microbore infusion tubing. *Pediatrics* 1998; **102:** 1401–6.
6. Hewson MP, *et al.* Insulin infusions in the neonatal unit: delivery variation due to adsorption. *J Paediatr Child Health* 2000; **36:** 216–20.

Aggregation. For discussion of the problems of insulin aggregation, see Intensive Administration Regimens under Uses, below.

Units

One unit of *bovine insulin* is contained in 0.03891 mg of the first International Standard (1986). One unit of *porcine insulin* is contained in 0.03846 mg of the first International Standard (1986). One unit of *human insulin* is contained in 0.03846 mg of the first International Standard (1986).

Adverse Effects

The most frequent complication of insulin therapy is hypoglycaemia, the speed of onset and duration of which may vary according to the type of preparation and the route used. It is usually associated with an excessive dosage of insulin, the omission of a meal by the patient, or increased physical activity. Patients, especially the elderly or those with tightly controlled diabetes or diabetes of long standing, may not experience the typical early warning symptoms of a hypoglycaemic attack. There have been reports of hypoglycaemia, sometimes with decreased warning symptoms, in patients changing from animal (especially bovine) to human insulin (see under Hypoglycaemia, below). Symptoms of hypoglycaemia resulting from increased sympathetic activity include hunger, pallor, sweating, palpitations, anxiety, and tremulousness. Other symptoms include headache, visual disturbances such as blurred or double vision, slurred speech, paraesthesia of the mouth and fingers, alterations in behaviour, and impaired mental or intellectual ability. If untreated, hypoglycaemia may lead to convulsions and coma which should not be confused with hyperglycaemic coma.

Insulin, given subcutaneously, may cause either lipoatrophy or lipohypertrophy. Lipoatrophy appears to occur less frequently with purified insulins than with conventional insulins; if it has occurred, it may be reversed by the injection of a purer animal insulin or human insulin into and around the atrophied site. Lipohypertrophy is usually associated with repeated injections at the same site and may usually be overcome by rotating the site of injection, although absorption of insulin may vary from different anatomical areas. Prolonged insulin therapy may result in weight gain.

Insulin occasionally causes local or systemic hypersensitivity reactions. Local reactions, characterised by erythema and pruritus at the injection site, usually disappear with continued use. Generalised hypersensitivity may produce urticaria, angioedema, and very rarely anaphylactic reactions; if continued therapy with insulin is essential hyposensitisation may be needed. Again, hypersensitivity reactions occur less frequently with purified than with conventional insulins and porcine insulin is less immunogenic than bovine insulin. Although hypersensitivity reactions have been reported in patients transferred from animal to human insulins, there are only isolated reports of such reactions in patients treated exclusively with human insulin.

Many patients treated with insulin, either animal or human insulin, develop antibodies but the clinical significance of this is not entirely clear.

◊ Of patients who received intensive insulin therapy for type 1 diabetes as part of the Diabetes Control and Complications Trial, those who experienced the greatest weight gain also had increased blood concentrations of triglycerides and low-density-lipoprotein cholesterol, and lowered high-density-lipoprotein cholesterol.[1] These lipid changes, with higher blood pressure, increased waist-to-hip ratio, and greater insulin requirements, were held to be similar to the symptoms of insulin resistance and to indicate a possible increased risk of macrovascular disease. Results from the UK Prospective Diabetes Study indicated that type 2 diabetic patients treated with insulin had greater weight gain than those managed with other therapies,[2] but demonstrated no evidence of harmful cardiovascular effects.

For discussion of some of the specific problems associated with continuous infusion of insulin, see Intensive Administration Regimens under Uses, below.

1. Purnell JQ, *et al.* Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: results from the DCCT. *JAMA* 1998; **280:** 140–6. Correction. *ibid.*; 1484.
2. UK Prospective Diabetics Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.

Carcinogenicity. Primary lung malignancies have been found in a few patients receiving inhaled insulin; for further details, see Administration Routes, p.450.

Effects on the liver. For a report of hepatomegaly occurring after insulin overdosage, see under Abuse, in Precautions, below.

Effects on the skin. Delayed pressure urticaria, in the form of large wheals occurring 4 to 6 hours after prolonged pressure, and lasting for up to 24 hours, was seen in a patient with type 1 diabetes within 6 months of changing from animal to human insulin.[1] The condition improved after a switch back to insulin of animal origin, and grew worse again after a second attempt to switch to human insulin. Intermittent urticaria simultaneously affecting previous injection sites was reported in a child receiving human insulin, who had never received animal insulin.[2]

1. Payne CMER, *et al.* True delayed pressure urticaria induced by human Monotard insulin. *Br J Dermatol* 1996; **134:** 184.
2. Sackey AH. Recurrent generalised urticaria at insulin injection sites. *BMJ* 2000; **321:** 1449.

Hypersensitivity. Hypersensitivity reactions to insulin preparations may be caused not only by the insulin itself, but also by other components of the formulation such as zinc[1-3] or protamine.[4-9] Hypersensitivity reactions and lipoatrophy (which is also thought to have an immune basis) have become rare since the introduction of highly purified and human insulins.[10] Although insulin analogues have been used successfully in patients

with a history of hypersensitivity to human insulin,[11,12] there are also reports of both local and generalised reactions to insulin analogues.[13-15]

See also Adverse Effects, above and under Precautions, below.

1. Feinglos MN, Jegasothy BV. "Insulin" allergy due to zinc. *Lancet* 1979; **i:** 122–4.
2. Bruni B, *et al.* Case of generalized allergy due to zinc and protamine in insulin preparation. *Diabetes Care* 1986; **9:** 552.
3. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. *Diabetes Care* 1987; **10:** 789–90.
4. Sánchez MB, *et al.* Protamine as a cause of generalised allergic reactions to NPH insulin. *Lancet* 1982; **i:** 1243.
5. Hulshof MM, *et al.* Granulomatous hypersensitivity to protamine as a complication of insulin therapy. *Br J Dermatol* 1992; **127:** 286–8.
6. Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. *Del Med J* 1993; **65:** 17–23.
7. Dykewicz MS, *et al.* Immunologic analysis of anaphylaxis to protamine component in neutral protamine Hagedorn human insulin. *J Allergy Clin Immunol* 1994; **93:** 117–25.
8. Blanco C, *et al.* Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. *Allergy* 1996; **51:** 421–4.
9. Bollinger ME, *et al.* Protamine allergy as a complication of insulin hypersensitivity: a case report. *J Allergy Clin Immunol* 1999; **104:** 462–5.
10. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. *Diabetes Care* 1993; **16** (suppl 3): 155–65.
11. Airaghi L, *et al.* The insulin analog aspart: a safe alternative in insulin allergy. *Diabetes Care* 2001; **24:** 2000.
12. Yasuda H, *et al.* Human insulin analog insulin aspart does not cause insulin allergy. *Diabetes Care* 2001; **24:** 2008–9.
13. Takata H, *et al.* The human insulin analogue aspart is not the almighty solution for insulin allergy. *Diabetes Care* 2003; **26:** 253–4.
14. Durand-Gonzalez K-N, *et al.* Glargine insulin is not an alternative in insulin allergy. *Diabetes Care* 2003; **26:** 2216.
15. JiXiong X, *et al.* The human insulin analog aspart can induce insulin allergy. *Diabetes Care* 2004; **27:** 2084–5.

HYPOSENSITISATION. After failure of standard hyposensitisation measures in a patient with cutaneous hypersensitivity to insulin, hyposensitisation was attempted by giving insulin by mouth.[1] Aspirin 1.3 g three times daily by mouth was also given to antagonise vascular mediators of the reaction. After one week subsequent hyposensitisation using insulin by injection was successful. When the patient stopped taking aspirin after 6 months the original hypersensitivity reactions recurred; aspirin was then given permanently in a dose of 1.3 g twice daily.

1. Holdaway IM, Wilson JD. Cutaneous insulin allergy responsive to oral desensitisation and aspirin. *BMJ* 1984; **289:** 1565–6.

Hypoglycaemia. Hypoglycaemia is the major adverse effect of insulin treatment, with severe hypoglycaemic episodes occurring in up to a third of all insulin-treated patients at some point in their lives. Moves towards more intensive insulin therapy, in order to reduce the development of diabetic complications, increase the risk of hypoglycaemic episodes.[1,2] Patients maintaining strict glycaemic control are prone to 'hypoglycaemia unawareness' in which the normal adrenergic counter-response to hypoglycaemia (characterised by symptoms such as pallor, sweating, and tremor) is reduced or lost,[3] so that hypoglycaemia can develop without warning. Such a loss of awareness of impending hypoglycaemia also seems to develop as duration of diabetes increases.[4] One of the main reasons for reduced awareness of hypoglycaemia is that repeated hypoglycaemic episodes seem to trigger an adaptive conservation of glucose concentrations in the brain, resulting in higher central than peripheral blood glucose values;[5] avoidance of hypoglycaemia helps restore awareness.

When recombinant human insulin became generally available in the late 1980s a number of patients complained of a loss of awareness of impending hypoglycaemia after transfer to human insulin,[6,7] and there were reports of severe or even fatal hypoglycaemia occurring in patients who had been well stabilised on animal insulins.[6-8]

This was, and remains, a somewhat controversial area. Despite some small studies suggesting a problem, others failed to find evidence of a difference between animal and human insulins, and a systematic review[9] concluded that the available evidence did not support the suggestion that human insulin increased the frequency or severity of hypoglycaemia, or affected the symptoms of hypoglycaemia, compared with animal insulins. However, most commentators appear to consider that patients should continue to have access to animal insulins if desired, and that those well maintained on animal insulin should not be transferred to human insulin without appropriate clinical grounds,[4,8,10-12] and then only with careful monitoring.

There has also been concern about possible long-term sequelae of hypoglycaemic episodes on the CNS. However, a report on patients participating in the Diabetes Control and Complications Trial (DCCT) suggested that the increased risk of hypoglycaemia seen with intensive therapy was not associated with neuropsychological impairment.[13]

For the treatment of insulin-induced hypoglycaemia, see below.

1. The Diabetes Control and Complications Trial Research Group. 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* 1993; **329:** 977–86.
2. Egger M, *et al.* Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; **14:** 919–28.
3. Widom B, Simonson DC. Glycemic control and neuropsychologic function during hypoglycemia in patients with insulin-dependent diabetes mellitus. *Ann Intern Med* 1990; **112:** 904–12.
4. Everett J, Kerr D. Changing from porcine to human insulin. *Drugs* 1994; **47:** 286–96.
5. Cranston I, *et al.* Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 1994; **344:** 283–7.
6. Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 1987; **ii:** 382–5.
7. Pickup J. Human insulin: problems with hypoglycaemia in a few patients. *BMJ* 1989; **299:** 991–3.
8. Gale EAM. Hypoglycaemia and human insulin. *Lancet* 1989; **ii:** 1264–6.
9. Airey CM, *et al.* Hypoglycaemia induced by exogenous insulin - 'human' and animal insulin compared. *Diabet Med* 2000; **17:** 416–32.
10. Gerich JE. Unawareness of hypoglycaemia and human insulin. *BMJ* 1992; **305:** 324–5.
11. Williams G, Patrick AW. Human insulin and hypoglycaemia: burning issue or hot air? *BMJ* 1992; **305:** 355–7.
12. Teuscher A, Kiln MR. Patient-empowerment and free insulin market. *Lancet* 1994; **344:** 1299–1300.
13. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 1996; **124:** 379–88.

Oedema. Severe, acute oedema is a rare adverse effect of insulin treatment, occurring most often when starting therapy.[1-4] It should be distinguished from chronic and subacute forms of oedema which may be complications of the diabetic disease process.[2,3] Possible mechanisms of acute oedema are sodium retention resulting from a direct action of insulin on the renal tubule or an effect of insulin on vascular permeability.[1,3] The oedema is usually self-limiting,[2,4] but does respond to a decrease in insulin dosage, or diuretic therapy.[1,3]

1. Bleach NR, *et al.* Insulin oedema. *BMJ* 1979; **2:** 177–8.
2. Lawrence JR, Dunnigan MG. Diabetic (insulin) oedema. *BMJ* 1979; **2:** 445.
3. Evans DJ, *et al.* Insulin oedema. *Postgrad Med J* 1986; **62:** 665–8.
4. Hirshberg B, *et al.* Natural course of insulin edema. *J Endocrinol Invest* 2000; **23:** 187–8.

Treatment of Insulin-induced Hypoglycaemia

In the conscious and cooperative patient hypoglycaemia is treated by eating a readily absorbable form of carbohydrate, such as sugar lumps or a glucose-based drink; all diabetics should always carry a suitable sugar source by way of precaution.

If the patient is drowsy or unconscious, then glucose must be given parenterally. Doses of 50 mL of a 20% solution of glucose or 25 to 50 mL of glucose 50% can be given intravenously; the higher concentration is more viscous and irritant to the veins. Lower concentrations are equally effective, and carry less risk of irritant effects, but larger volumes are required, e.g. up to 500 mL of glucose 5%, or 250 mL of 10%, titrated to patient response. Smaller quantities (e.g. 5 to 10 mL/kg of a 10% solution) are required in children. Bolus doses may need to be repeated, or a maintenance infusion started, to prevent persistent hypoglycaemia. If the patient has not regained consciousness within a few minutes after a bolus dose of glucose, the possibility of cerebral oedema should be considered.

In situations where giving intravenous glucose is impractical or not feasible, glucagon 1 mg for adults and children above 25 kg or 0.5 mg for children below 25 kg by subcutaneous, intramuscular, or intravenous injection may arouse the patient sufficiently to allow oral glucose to be given. If the patient fails to respond to glucagon within about 10 to 15 minutes, then glucose has to be given intravenously despite any impracticalities.

After a return to consciousness, oral carbohydrates may need to be given until the action of insulin has ceased, which for preparations with a relatively long duration of action such as isophane insulin, some insulin zinc suspensions, and protamine zinc insulin, may be several hours.

Carbohydrate. A comparative study[1] of 7 different preparations of oral carbohydrate for the treatment of hypoglycaemia in the conscious patient found no significant difference in effectiveness between glucose or sucrose in solution or tablet form; a hydrolysed polysaccharide solution containing glucose, maltose, and various more complex saccharides (*Glucidex 19*) was also roughly comparable. However, a glucose gel and orange juice were each less effective than the other formulations in treating hypoglycaemia.

1. Slama G, *et al.* The search for an optimized treatment of hypoglycemia: carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med* 1990: **150:** 589–93.

Glucagon. A discussion of the relative merits of parenteral glucose and glucagon in unconscious hypoglycaemic patients[1] suggested that glucagon should be encouraged as first-line treatment, although in practice (see above) parenteral glucose is usually preferred. The effect of glucagon relies upon the patient having adequate liver glycogen stores, which may not always be the case.

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; **306:** 600–601.

Overdose. The requirements for glucose are greater and more prolonged when hypoglycaemia is caused by insulin overdosage rather than therapeutic doses.[1] Correction of insulin-induced hypokalaemia may also be required. Surgical excision of tissue at the site of injection has been used for massive overdose of a long-acting insulin.[2,3]

1. Roberge RJ, *et al.* Intentional massive insulin overdosage: recognition and management. *Ann Emerg Med* 1993; **22:** 228–34.
2. Campbell IW, Ratcliffe JG. Suicidal insulin overdose managed by excision of insulin injection site. *BMJ* 1982; **285:** 408–9.
3. Levine DF, Bulstrode C. Managing suicidal insulin overdose. *BMJ* 1982; **285:** 974–5.

Precautions

Dosage requirements of insulin may be altered by many factors. Increased doses are usually necessary during infection, emotional stress, accidental or surgical trauma, puberty, and the latter two trimesters of pregnancy. Decreased doses are usually necessary in patients with impaired renal or hepatic function or during the first trimester of pregnancy. On first stabilising therapy in newly diagnosed diabetic patients, a temporary decrease in requirements may also occur (the so-called honeymoon period).

Because of the possibility of differing responses to insulins from different species, inadvertent change from insulin of one species to another should be avoided. Reduction in insulin dosage may be required on transfer from animal (especially bovine) to human insulin. Hypoglycaemic problems associated with a change to human insulin are discussed under Adverse Effects, above. Care is also necessary during excessive exercise; hypoglycaemia caused by metabolic effects and increased insulin absorption is the usual response, but hyperglycaemia may sometimes occur.

The use of insulin requires monitoring of therapy, such as testing blood or urine for glucose concentrations and the urine for ketones, by the patient.

Drugs which have an effect on blood-glucose concentrations may alter glycaemic control with consequent need for a change in insulin dose (see Interactions, below).

CAUTION. *Biphasic insulin, insulin zinc suspensions, isophane insulin, protamine zinc insulin, insulin detemir, and insulin glargine should never be given intravenously and they are not suitable for the emergency treatment of diabetic ketoacidosis.*

Abuse. Transient recurrent hepatomegaly associated with hypoglycaemia was associated with the surreptitious injection of additional insulin doses in an insulin-dependent diabetic. Increased storage of glycogen in the liver resulting from insulin excess was considered responsible for the hepatomegaly.[1]

Decreased plasma C-peptide concentrations or the presence of anti-insulin antibodies may be used to confirm insulin abuse as a cause of hypoglycaemia in patients who have never been treated with insulin medically.[2] Insulin has been abused by bodybuilders and other sportspersons;[3,4] severe brain damage after prolonged neuroglycopenia has resulted.[3] There are rare reports of the misuse of insulin to induce mind-altering effects of hypoglycaemia.[5]

1. Asherov J, *et al.* Hepatomegaly due to self-induced hyperinsulinism. *Arch Dis Child* 1979; **54:** 148–9.
2. Grunberger G, *et al.* Factitious hypoglycemia due to surreptitious administration of insulin: diagnosis, treatment, and long-term follow-up. *Ann Intern Med* 1988; **108:** 252–7.
3. Elkin SL, *et al.* Bodybuilders find it easy to obtain insulin to help them in training. *BMJ* 1997; **314:** 1280.
4. Honour JW. Misuse of natural hormones in sport. *Lancet* 1997; **349:** 1786.
5. Cassidy EM, *et al.* Insulin as a substance of misuse in a patient with insulin dependent diabetes mellitus. *BMJ* 1999; **319:** 1417–18.

Accelerated absorption. Factors such as a hot bath, sauna, or use of a sunbed have been reported to accelerate the absorption of subcutaneous injection, presumably by an increase in skin blood flow.[1-4] There may, therefore, be a risk of hypoglycaemia.[4]

1. Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *BMJ* 1980; **280:** 1411–13.
2. Cüppers HJ, *et al.* Sauna-induced acceleration in insulin absorption? *BMJ* 1980; **281:** 307.
3. Koivisto VA. Sauna-induced acceleration in insulin absorption. *BMJ* 1980; **281:** 621–2.
4. Husband DJ, Gill GV. "Sunbed seizures": a hypoglycaemic hazard for insulin-dependent diabetics. *Lancet* 1984; **ii:** 1477.

Adrenocortical insufficiency. Recurrent severe hypoglycaemia, which occurred in 2 patients with type 1 diabetes, persisted despite a reduction in insulin doses and proved to be due to Addison's disease.[1] Insulin requirements rose again in both patients after replacement therapy with fludrocortisone and hydrocortisone.

1. Armstrong L, Bell PM. Addison's disease presenting as reduced insulin requirement in insulin dependent diabetes. *BMJ* 1996; **312:** 1601–2.

Driving. In the UK, patients with diabetes mellitus treated with insulin or oral hypoglycaemics are required to notify their condition to the Driver and Vehicle Licensing Agency, who then assess their fitness to drive. Patients treated with oral hypoglycaemics are generally allowed to retain standard driving licences; those treated with insulin receive restricted licences which must be renewed (with appropriate checks) every 1 to 3 years. Patients should be warned of the dangers of hypoglycaemic attacks while driving, and should be counselled in appropriate management of the situation (stopping driving as soon as it is safe to do so, taking carbohydrate immediately, and quitting the driving seat and removing the ignition key from the car) should such an event occur. Patients who have lost hypoglycaemic awareness, or have frequent hypoglycaemic episodes, should not drive. In addition, eyesight must be adequate (field of vision of at least 120°) for a licence to be valid. Patients treated with diet or oral hypoglycaemics are normally allowed to hold vocational driving licences for heavy goods vehicles or passenger carrying vehicles; those treated with insulin may not drive such vehicles, and are restricted in driving some other vehicles such as small lorries and minibuses.[1,2]

Regulations in other countries differ widely.[3]

1. British Diabetic Association (Diabetes UK). Information sheet: driving and diabetes: May 2008. Available at: http://www.diabetes.org.uk/Documents/catalogue/driving_and_diabetes-may_08.pdf (accessed 20/08/08)
2. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)
3. DiaMond Project Group on Social Issues. Global regulations on diabetics treated with insulin and their operation of commercial motor vehicles. *BMJ* 1993; **307:** 250–3.

Exercise. Discussions[1,2] of the metabolic effects of exercise and the precautions to be taken by the exercising type 1 diabetic.

1. Greenhalgh PM. Competitive sport and the insulin-dependent diabetic patient. *Postgrad Med J* 1990; **66:** 803–6.
2. American Diabetes Association. Physical activity/exercise and diabetes. *Diabetes Care* 2004; **27** (suppl 1): S58–S62. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s58.pdf (accessed 08/07/04)

Fasting. Reduction in food intake or alteration in the pattern of meal times may affect insulin requirements and predispose to the development of hypoglycaemia (above). Muslim patients who are receiving antidiabetic therapy and who fast during Ramadan have been shown to be at increased risk of severe hypoglycaemic episodes during this month.[1] A study in 17 fasting patients with type 1 diabetes recommended reduction of the total insulin dose to 85% of that before the fasting period, and supplying 70% as long-acting ultralente insulin and 30% as a rapidly acting soluble insulin; the daily dose was divided into 2 equal portions given before sunrise and after sunset.[2] Others have made similar recommendations: 2 daily injections of an intermediate- or long-acting insulin, given before the predawn and sunset meals, together with a short-acting insulin at the meal itself; or possibly a single daily injection of insulin glargine, or twice-daily insulin detemir, plus a rapidly acting analogue just before the meal.[3]

Patients with type 2 diabetes maintained on insulin may be managed similarly, by judicious use of intermediate or long-acting insulin plus a short-acting insulin given before meals. A single injection of a long-acting analogue such as insulin glargine, or two injections of isophane or lente insulin or insulin detemir before the sunset and predawn meals, may provide adequate coverage provided the dosage is appropriately individualised. However, most patients will still require a short-acting insulin to be added at the sunset meal to cover the large caloric load. Many will also require an additional dose of short-acting insulin at predawn.[3] Studies have suggested that insulin lispro may produce good blood sugar control in fasting patients with type 2 diabetes during Ramadan.[4,5]

Care is also required in patients with type 2 diabetes being treated with oral antidiabetic drugs. Patients being treated with metformin or insulin sensitisers such as the glitazones have a low risk of hypoglycaemia, although it has been suggested that the timing of metformin doses be altered so that two-thirds of the daily dose is taken just before the sunset meal and the other third before the predawn meal. Short-acting secretagogues such as repaglinide or nateglinide can also be taken twice daily before the sunset and predawn meals. However, sulfonylureas should be used with caution, and the use of chlorpropamide may be contra-indicated because of the high risk of prolonged and unpredictable hypoglycaemia.[3]

1. Salti I, *et al.* A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; **27:** 2306–11.
2. Kassem HS, *et al.* Insulin therapy during Ramadan fast for type 1 diabetes patients. *J Endocrinol Invest* 2005; **28:** 802–5.
3. Al-Arouj M, *et al.* Recommendations for management of diabetes during Ramadan. *Diabetes Care* 2005; **28:** 2305–11.
4. Akram J, De Verga V. Ramadan Study Group. Insulin lispro (Lys(B28), Pro(B29)) in the treatment of diabetes during the fasting month of Ramadan. *Diabet Med* 1999; **16:** 867–74.
5. Mattoo V, *et al.* A comparison of insulin lispro Mix25 and human insulin 30/70 in the treatment of type 2 diabetes during Ramadan. *Diabetes Res Clin Pract* 2003; **59:** 137–43.

Hypersensitivity to protamine. Retrospective surveys have indicated that patients receiving isophane insulin, which contains protamine, have an increased risk of severe anaphylactoid reactions when protamine is used to reverse systemic heparinisation after cardiac catheterisation or cardiac surgery. The degree of increase in risk is unclear, however, as it has been reported as both large[1] and small.[2,3] A review of the literature suggested that surgical patients may be at greater risk because of a higher rate of prior sensitisation to protamine and the larger doses used.[3] A mechanism involving IgE and IgG antibodies to protamine has been proposed.[4]

See also Hypersensitivity under Adverse Effects, above.

1. Stewart WJ, *et al.* Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. *Circulation* 1984; **70:** 788–92.
2. Levy JH, *et al.* Evaluation of patients at risk for protamine reactions. *J Thorac Cardiovasc Surg* 1989; **98:** 200–204.
3. Vincent GM, *et al.* Protamine allergy reactions during cardiac catheterization and cardiac surgery: risk in patients taking protamine-insulin preparations. *Cathet Cardiovasc Diagn* 1991; **23:** 164–8.
4. Weiss ME, *et al.* Association of protamine IgE and IgG antibodies with life-threatening reactions to intravenous protamine. *N Engl J Med* 1989; **320:** 886–92.

Infections. Decreased requirements of insulin, added to the dialysate, occurred in 6 diabetic patients undergoing continuous ambulatory peritoneal dialysis for chronic renal failure during episodes of severe bacterial peritonitis.[1] This was contrary to the increased insulin requirements of most diabetic patients during severe infections and probably resulted from increased absorption of insulin due to mesothelial damage.

1. Henderson IS, *et al.* Decreased intraperitoneal insulin requirements during peritonitis on continuous ambulatory peritoneal dialysis. *BMJ* 1985; **290:** 1474.

Menstruation. Changes in glycaemic control associated with the menstrual cycle have been recorded in women with type 1 diabetes mellitus. In a retrospective review of 124 women,[1] 61% reported perimenstrual changes in glucose concentrations and 36% made adjustments to their insulin dose, usually a small increase in the premenstrual insulin dose followed by a small decrease at the onset of menstruation. Based on mean glycosylated haemoglobin measurements, there was no evidence of improved glycaemic control in women adjusting their insulin dose compared with those leaving it unchanged despite changes in capillary glucose measurements. Changes in appetite and food consumption associated with the menstrual cycle may affect variations in glucose concentrations and insulin requirements.

1. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Morning hyperglycaemia. Morning hyperglycaemia may be the result of mere waning of subcutaneously injected insulin. It may also be rebound hyperglycaemia (posthypoglycaemic hyperglycaemia or the Somogyi phenomenon) occurring after an episode of nocturnal hypoglycaemia. Morning hyperglycaemia has also been observed without antecedent hypoglycaemia even during constant intravenous infusion of insulin, when the waning of previously injected insulin would not be a factor and this is commonly referred to as the dawn phenomenon. Clinically, it is important to distinguish between the dawn phenomenon, simple waning of previously injected insulin, and rebound hyperglycaemia as a cause of early-morning hyperglycaemia because their treatment differs. Management of the dawn phenomenon and insulin waning generally consists of adjusting the evening dose of insulin to provide additional coverage between 4 a.m. and 7 a.m. Management of rebound hyperglycaemia consists of reducing insulin doses or providing additional late-evening carbohydrate, or both, to avoid nocturnal hypoglycaemia. Mistaking rebound hyperglycaemia for the dawn phenomenon or mere waning of injected insulin could result in more serious nocturnal hypoglycaemia, if evening doses of insulin were increased.[1]

1. Cryer PE, Gerich JE. Glucose counterregulation, hypoglycemia, and intensive insulin therapy in diabetes mellitus. *N Engl J Med* 1985; **313:** 232–41.

Pregnancy. For discussion of the precautions necessary in the management of diabetes mellitus during pregnancy, see p.431.

There has been a report of 2 cases of fetal malformation in the offspring of well-controlled diabetic women who received *insulin lispro*.[1] However, the incidence of fetal malformation is increased in infants of women with diabetes. At that time the manufacturers were aware of 19 live births among women treated with insulin lispro, 1 of which exhibited a congenital abnormality.[2] Since then, a number of retrospective studies[3-7] have looked at the rates of fetal malformations in the offspring of women treated with insulin lispro, for either pre-existing diabetes mellitus or gestational diabetes. These have included groups ranging in size from 62 to 496 women, and none have found any evidence of an increase in the incidence of abnormalities with insulin lispro compared with rates published for women treated with other insulins.

There is less information available about the use of other insulin analogues, but a few cases and studies of *insulin glargine* use during pregnancy have been described. It was started in one woman[8] during the fourteenth week of gestation, and continued until delivery with no apparent adverse effect on the baby. In another report,[9] insulin glargine was inadvertently continued by 5 women during the first 6 to 12 weeks of unplanned pregnancies. In these cases, therapy was changed from insulin glargine to isophane insulin, and no fetal malformations were detected. The use of insulin glargine during the entire pregnancy, without adverse effect, has also been described,[10] and successful pregnancies were reported in 4 women given insulin glargine for gestational diabetes.[11] Furthermore, a small case-control study[12] found no significant difference in neonatal outcomes for insulin glargine and human insulin in women with type 1 or gestational diabetes, and another study[13] found no unexpected adverse effects in the babies of 115 women given insulin glargine. A single-dose study has reported[14] that *insulin aspart* was effective in reducing postprandial glucose concentration in gestational diabetes. Randomised studies in women with type 1 diabetes[15] or gestational diabetes[16] have also found no indication of an increase in congenital malformations with insulin aspart compared with human insulin.

1. Diamond T, Kormas N. Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1009.
2. Anderson JH, *et al.* Possible adverse fetal effect of insulin lispro. *N Engl J Med* 1997; **337:** 1010.
3. Bhattacharyya A, *et al.* Insulin lispro and regular insulin in pregnancy. *Q J Med* 2001; **94:** 255–60.
4. Garg SK, *et al.* Insulin lispro therapy in pregnancies complicated by type 1 diabetes: glycemic control and maternal and fetal outcomes. *Endocr Pract* 2003; **9:** 187–93.
5. Masson EA, *et al.* Pregnancy outcome in type 1 diabetes mellitus treated with insulin lispro (Humalog). *Diabet Med* 2003; **20:** 46–50.
6. Wyatt JW, *et al.* Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med* 2005; **22:** 803–7.
7. Lapolla A, *et al.* Outcome of pregnancy in type 1 diabetic patients treated with insulin lispro or regular insulin: an Italian experience. *Acta Diabetol* 2008; **45:** 61–6.
8. Devlin JT, *et al.* Use of insulin glargine during pregnancy in a type 1 diabetic woman. *Diabetes Care* 2002; **25:** 1095–6.
9. Di Cianni G, *et al.* Use of insulin glargine during the first weeks of pregnancy in five type 1 diabetic women. *Diabetes Care* 2005; **28:** 982–3.
10. Caronna S, *et al.* Pregnancy and the long-acting insulin analogue: a case study. *Acta Biomed* 2006; **77:** 24–6.
11. Graves DE, *et al.* The use of insulin glargine with gestational diabetes mellitus. *Diabetes Care* 2006; **29:** 471–2.
12. Price N, *et al.* Use of insulin glargine during pregnancy: a case-control pilot study. *BJOG* 2007; **114:** 453–7.
13. Gallen IW, *et al.* Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med* 2008; **25:** 165–9.
14. Pettitt DJ, *et al.* Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 2003; **26:** 183–6.
15. Hod M, *et al.* Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. *Am J Obstet Gynecol* 2008; **198:** 186.e1–186.e7.
16. Pettitt DJ, *et al.* Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med* 2007; **24:** 1129–35.

Prion disease transmission. Studies of cattle with proven bovine spongiform encephalopathy (BSE) have not detected infectivity in the pancreas, from which bovine insulin is derived.[1]

1. Wickham EA. Potential transmission of BSE via medicinal products. *BMJ* 1996; **312:** 988–9.

Renal impairment. See under Infections, above.

Smoking. Smoking has been reported to decrease the absorption of insulin and dosage adjustment may be necessary, although glycaemic control does not seem to be significantly affected.[1]

1. Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999; **36:** 425–38.

Surgery. For a discussion of the management of diabetes mellitus during surgery, see p.431.

Travelling. Advice for the diabetic patient when travelling, including adjustment of insulin dosage when crossing time zones.[1-3] Since insulin solution or suspension must not be frozen, it should not be carried in the luggage hold of an aircraft.

1. Barry M, Bia F. Advice for the traveling diabetic. *JAMA* 1989; **261:** 1799.
2. Sane T, *et al.* Adjustment of insulin doses of diabetic patients during long distance flights. *BMJ* 1990; **301:** 421–2.
3. Dewey CM, Riley WJ. Have diabetes, will travel. *Postgrad Med* 1999; **105:** 111–13, 117–18, 124–6.

Interactions

Many drugs have an effect on blood-glucose concentrations and may alter insulin requirements. Drugs with hypoglycaemic activity or which may decrease insulin requirements include ACE inhibitors, alcohol, anabolic steroids, aspirin, beta blockers (which may also mask the warning signs of hypoglycaemia), disopyramide, fenfluramine, guanethidine, some MAOIs, mebendazole, octreotide, some tetracyclines, and the tricyclic antidepressant amitriptyline.

On the other hand, increased requirements of insulin may possibly be seen with chlordiazepoxide, chlorpromazine, some calcium-channel blockers such as diltiazem or nifedipine, corticosteroids, diazoxide, lithium, thiazide diuretics, and thyroid hormones.

Both increased and decreased requirements may occur with cyclophosphamide, isoniazid, and oral contraceptives.

ACE inhibitors. Although ACE inhibitors are favoured for use in diabetic patients with hypertension or evidence of incipient nephropathy or both, they may increase insulin sensitivity and thus decrease insulin requirements.[1,2] A study[3] of hospital admissions found that ACE inhibitors increased the risk of severe hypoglycaemia in patients receiving insulin. However, an analysis of pharmacovigilance data[4] and a case-control study[5] have both found no such increase in risk.

1. Ferriere M, *et al.* Captopril and insulin sensitivity. *Ann Intern Med* 1985; **102:** 134–5.
2. McMurray J, Fraser DM. Captopril, enalapril, and blood glucose. *Lancet* 1986; **i:** 1035.
3. Morris AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. *Diabetes Care* 1997; **20:** 1363–7.
4. Moore N, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; **44:** 513–8.
5. Thamer M, *et al.* Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21:** 1387–1400.

Alcohol. Severe hypoglycaemic episodes have been reported in type 1 diabetics after heavy drinking episodes.[1,2] Alcohol inhibits gluconeogenesis, and its effects are therefore likely to be greatest if taken without food; however, it seems to be generally agreed that diabetics need not abstain from a moderate alcohol intake with meals.

1. Arky RA, *et al.* Irreversible hypoglycemia. *JAMA* 1968; **206:** 575–8.
2. Potter J, *et al.* Insulin induced hypoglycaemia in an accident and emergency department: the tip of an iceberg. *BMJ* 1982; **285:** 1180–2.

Aspirin. Aspirin produces a modest decrease in blood-glucose concentrations but a significant interaction at conventional analgesic doses appears to be unlikely. One study in children with type 1 diabetes found an average 15% decrease in blood glucose values following treatment with aspirin 1.2 to 2.4 g daily for 3 days, but there were no significant changes in insulin requirements.[1] However, high doses of aspirin can reduce or even replace the insulin dose required.[2] Other salicylates might be expected to have similar properties.

1. Kaye R, *et al.* Antipyretics in patients with juvenile diabetes mellitus. *Am J Dis Child* 1966; **112:** 52–5.
2. Reid J, Lightbody TD. The insulin equivalence of salicylate. *BMJ* 1959; **1:** 897.

Beta blockers. There are a few reports of severe hypoglycaemia in patients, including insulin-treated diabetics, who were given *propranolol* or *pindolol*;[1-3] there is also a report of an interaction with *timolol* given as eye drops.[4] Some evidence exists of an interaction with *metoprolol*,[5] but little evidence for some of the more selective beta blockers. Because of the effects of beta blockers on the sympathetic nervous system the usual premonitory signs of hypoglycaemia may not occur, allowing a severe episode to develop before the patient is aware and able to counter it.

1. Kotler MN, *et al.* Hypoglycaemia precipitated by propranolol. *Lancet* 1966; **ii:** 1389–90.
2. McMurtry RJ. Propranolol, hypoglycemia, and hypertensive crisis. *Ann Intern Med* 1974; **80:** 669–70.
3. Samii K, *et al.* Severe hypoglycaemia due to beta-blocking drugs in haemodialysis patients. *Lancet* 1976; **i:** 545–6.
4. Angelo-Nielsen K. Timolol topically and diabetes mellitus. *JAMA* 1980; **244:** 2263.
5. Newman RJ. Comparison of propranolol, metoprolol, and acebutolol on insulin-induced hypoglycaemia. *BMJ* 1976; **2:** 447–9.

Calcium-channel blockers. Diabetes worsened in an insulin-treated diabetic when given *diltiazem*.[1] The resultant intractable hyperglycaemia improved when the drug was withdrawn, and recurred, although at a more manageable level, when diltiazem was restarted at a lower dose. There are also reports of a diabetogenic effect of *nifedipine*.[2,3] However, reports of significant disturbances of metabolic control appear to be uncommon.

1. Pershadsingh HA, *et al.* Association of diltiazem therapy with increased insulin resistance in a patient with type I diabetes mellitus. *JAMA* 1987; **257:** 930–1.
2. Bhatnagar SK, *et al.* Diabetogenic effects of nifedipine. *BMJ* 1984; **289:** 19.
3. Heyman SN, *et al.* Diabetogenic effect of nifedipine. *DICP Ann Pharmacother* 1989; **23:** 236–7.

Interferons. Markedly increased insulin requirements developed in a previously well controlled diabetic after treatment with *interferon alfa 2a*.[1] Insulin requirements rapidly fell once interferon therapy was stopped.

1. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.

Oral contraceptives. Both increases and decreases (mainly the former) in insulin requirements have been reported in insulin-dependent diabetics given various oral contraceptives.[1] However, it appears that in most cases the effects of a hormonal contraceptive on diabetic control are modest or insignificant: limited data suggest that progestogen-only and combined oral contraceptives in general have little effect.[2,3]

1. Zeller WJ, *et al.* Verträglichkeit von hormonalen Ovulationskemmern bei Diabetikerinnen. *Arzneimittelforschung* 1974; **24:** 351–7.
2. Rådberg T, *et al.* Oral contraception in diabetic women: diabetes control, serum and high density lipoprotein lipids during low-dose progestogen, combined oestrogen/progestogen and non-hormonal contraception. *Acta Endocrinol (Copenh)* 1981; **98:** 246–51.
3. Lunt H, Brown LJ. Self-reported changes in capillary glucose and insulin requirements during the menstrual cycle. *Diabet Med* 1996; **13:** 525–30.

Pharmacokinetics

Insulin has no hypoglycaemic effect when given by mouth since it is inactivated in the gastrointestinal tract.

It is fairly rapidly absorbed from subcutaneous tissue on injection and although the half-life of unmodified insulin in blood is very short (being only a matter of minutes), the duration of action of most preparations is considerably longer because of their formulation (for further details see Uses and Administration, below). The rate of absorption from different anatomical sites depends on local blood flow, with absorption from the abdomen being faster than that from the arm, and that from the arm faster than from buttock or thigh. Absorption may also be increased by exercise. The absorption of insulin after intramuscular injection is more rapid than that after subcutaneous doses. Human insulin may be absorbed slightly faster from subcutaneous tissue than porcine or bovine insulin.

Insulin is rapidly metabolised, mainly in the liver but also in the kidneys and muscle tissue. In the kidneys it is reabsorbed in the proximal tubule and either returned to venous blood or metabolised, with only a small amount excreted unchanged in the urine.

◊ For discussion of factors which may affect the absorption of insulin, see under Precautions, Accelerated Absorption, above, and Uses, Administration Routes, below.

Resistance to Insulin

The term insulin resistance has traditionally been used to describe a state in which diabetic patients exhibit considerably increased insulin requirements. It is now used in a much wider sense, and is for instance also applied to patients in whom a subnormal biological response to insulin can be demonstrated, although many of these patients do not apparently present difficulties in their clinical management. Insulin resistance is found particularly in obese patients; resistance to endogenous insulin is thought to be linked to the development of type 2 diabetes in such patients. Insulin resistance is frequently associated with lipid disorders, hypertension, and ischaemic heart disease, a complex sometimes described as the metabolic syndrome. In women, it may also be linked to polycystic ovary syndrome.

Insulin resistance of the type manifested by greatly increased insulin requirements may be due to factors including antibody formation and inadequate absorption of insulin from subcutaneous sites. A few patients with severe insulin resistance have responded to insulin lispro (see Insulin Analogues and Proinsulin under Uses, below).

Mecasermin (insulin-like growth factor I) has been observed to improve insulin sensitivity in insulin resistance (see p.1808).

◊ References.

1. Moller DE, Flier JS. Insulin resistance—mechanisms, syndromes, and implications. *N Engl J Med* 1991; **325:** 938–48.
2. Eckel RH. Insulin resistance: an adaptation for weight maintenance. *Lancet* 1992; **340:** 1452–3.
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4. Davidson MB. Clinical implications of insulin resistance syndromes. *Am J Med* 1995; **99:** 420–6.
5. Krentz AJ. Insulin resistance. *BMJ* 1996; **313:** 1385–9. Correction. *ibid.* 1997; **314:** 134.
6. Cochran E, *et al.* The use of U-500 in patients with extreme insulin resistance. *Diabetes Care* 2005; **28:** 1240–4. Correction. *ibid.* 2007; **30:** 1035.
7. Kurtz TW. New treatment strategies for patients with hypertension and insulin resistance. *Am J Med* 2006; **119** (suppl 1): S24–S30.
8. Ballani P, *et al.* Clinical experience with U-500 regular insulin in obese, markedly insulin-resistant type 2 diabetic patients. *Diabetes Care* 2006; **29:** 2504–5. Correction. *ibid.* 2007; **30:** 455.

Uses and Administration

Insulin is a hormone that plays a key role in regulating carbohydrate, protein, and fat metabolism. The main stimulus for its secretion is glucose, although many other factors including amino acids, catecholamines, glucagon, and somatostatin, are involved in its regulation. The secretion of insulin is not constant and peaks occur in response to the intake of food.

The major effects of insulin on carbohydrate homoeostasis follow its binding to specific cell-surface receptors on insulin-sensitive tissues, notably the liver, muscles, and adipose tissue. It inhibits hepatic glucose production and enhances peripheral glucose disposal thereby reducing blood-glucose concentration. It also inhibits lipolysis thereby preventing the formation of ketone bodies.

Therapy with insulin is essential for the long-term survival of all patients with type 1 diabetes mellitus. It may also be necessary in some patients with type 2 disease. The management of diabetes mellitus and the role of insulin in type 1 and type 2 disease is discussed on p.431. Insulin is generally the treatment chosen for all types of diabetes mellitus during pregnancy.

Choice of insulin. The different types of insulin and their formulations are described under Definitions, above. In some countries including the UK the commercially available preparations have been standardised to a single **strength** containing 100 units/mL; a strength of 40 units/mL is still available in some other countries, and in others concentrated injections (500 units/mL) are available to enable high doses to be given subcutaneously in a small volume. All formulations can be given by subcutaneous injection, most by intramuscular injection, but only soluble insulins can be given by the intravenous **route**. The long-term management of diabetic patients usually involves the subcutaneous route. Syringes and needles for subcutaneous injection are preferably disposable. Pen-injector devices which hold the insulin in cartridge form and meter the required dose are becoming increasingly popular. Soluble insulin is often given by the intraperitoneal route to patients on continuous ambulatory peritoneal dialysis. More recently, products supplying short-acting insulin by inhalation have been developed.

The various formulations of insulin are classified, according to their **duration of action** after subcutaneous injection, as short-, intermediate-, or long-acting. The exact duration of action for any particular preparation, however, is variable and may depend upon factors such as interindividual variation, the patient's antibody status, whether the insulin is of human or animal origin, the dose, and the site of injection. *Short-acting* insulins are the soluble insulins, which have an onset after about 30 minutes to 1 hour, a peak activity at about 2 to 5 hours, and a duration of about 6 to 8 hours. Some analogues, such as insulins lispro and aspart, are also short-acting, with a faster onset and shorter duration of action than soluble insulin and are sometimes known

as rapid-acting insulins. *Intermediate-acting* insulins include biphasic insulins, isophane insulins, and amorphous insulin zinc suspensions. In general these have an onset within about 2 hours, peak activity after about 4 to 12 hours, and a duration of up to 24 hours. Commercially available mixtures of soluble insulins and isophane insulins have activities which would normally place them within the intermediate-acting category. Mixed insulin zinc suspensions may be classified as either *intermediate- or long-acting* as the duration of action may be up to 30 hours; the onset of action is generally 2 to 3 hours and the time to peak activity 6 to 15 hours. *Long-acting* insulins include crystalline insulin zinc suspensions and protamine zinc insulins. These generally have an onset after about 4 hours, a peak activity at about 10 to 20 hours, and a duration of up to 36 hours. The insulin analogues insulin glargine and insulin detemir are also long-acting. After intramuscular injection, the onset of action of all insulins is generally more rapid and the duration of action shorter.

The type of formulation, its dose, and the frequency of administration are chosen to suit the needs of the individual patient. Whatever the formulation, human insulin is generally used for all newly diagnosed diabetics.

Control. The **dosage** of insulin must be determined for each patient and although a precise dose range cannot be given a total dose in excess of about 80 units daily would be unusual and may indicate the presence of a form of insulin resistance. The dose should be adjusted as necessary according to the results of regular monitoring of blood concentrations (or occasionally urine concentrations) of glucose by the patient.

The WHO has recommended that the glucose concentration of venous whole blood under fasting conditions should be kept within the range of 3.3 to 5.6 mmol/litre (60 to 100 mg per 100 mL) and after meals should not be allowed to exceed 10 mmol/litre (180 mg per 100 mL); blood-glucose concentrations should not be allowed to fall below 3 mmol/litre (55 mg per 100 mL). In practice it seems to be generally acceptable for patients to aim for blood-glucose concentrations between 4 and 10 mmol/litre, with the understanding that occasional variations outside this range may occur. It should be remembered that the glucose concentrations in venous plasma, venous whole blood, and capillary whole blood may be slightly different. Control may also be determined by monitoring of glycosylated haemoglobin concentrations; ideally the aim is an HbA_{1c} level of less than 7% or an HbA_1 of less than 8.8%, compared with normal ranges of 4 to 6% and 5 to 7.5% respectively. Insulin requirements may be altered by various factors (see Precautions, above). The aim of any regimen should be to achieve the best possible control of blood glucose by attempting to mimic as closely as possible the pattern of optimum endogenous insulin secretion. Many **regimens** involve the use of a short-acting soluble insulin with an intermediate-acting insulin, such as isophane insulin or mixed insulin zinc suspension, often given twice daily. It may sometimes be necessary, though, to give 3 or 4 injections daily to achieve good control and this typically involves giving a soluble insulin before meals and an intermediate- or long-acting insulin in the evening. A once-daily injection of an intermediate- or long-acting insulin is now generally considered to be acceptable only for those patients with type 2 diabetes mellitus who still retain some endogenous insulin secretion but nevertheless require insulin therapy, or for those patients with type 1 disease unable to cope satisfactorily with more intensive regimens. If a more intensive regimen is desired, **continuous subcutaneous infusion** may be employed using soluble insulin in an infusion pump. This delivers a constant basal infusion of insulin supplying about half of the total daily requirements, the remainder being provided by patient-activated bolus doses before each meal. The technique has a limited place in the management of diabetes; patients using it need to be well-motivated, reliable, and able to monitor their own blood glucose, and must have access to expert advice at all times. Formulations in which the insulin is in suspension are not suitable for continuous subcutaneous infusion and some brands of soluble insulin are unsuitable for this purpose because of the risk of precipitation in the pump catheter.

Ketoacidosis. Insulin is also an essential part of the emergency management of diabetic ketoacidosis. Only short-acting soluble insulins should be used. Treatment includes adequate fluid replacement, usually by infusing sodium chloride 0.9% initially, and the use of potassium salts to prevent or correct hypokalaemia. Insulin should be given by continuous intravenous infusion if possible, although other routes have also been used—for details of regimens see Diabetic Emergencies, under Diabetes Mellitus, below. Since insulin normally corrects hyperglycaemia before ketosis it is usually necessary to continue giving insulin once normoglycaemia has been achieved but to change the rehydration fluid to glucose-saline so that the additional glucose prevents the development of hypoglycaemia.

◊ General reviews of insulin and its use.[1-5] It has been suggested that the plethora of insulin preparations available might sensibly be reduced,[2] although others dispute this.[6]

1. MacPherson JN, Feely J. Insulin. *BMJ* 1990; **300:** 731–6.
2. Anonymous. Insulin preparations—time to rationalise. *Drug Ther Bull* 1996; **34:** 11–14.
3. American Diabetes Association. Insulin administration. *Diabetes Care* 2004; **27** (suppl 1): S106–S109. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106.pdf (accessed 08/07/04)
4. Mooradian AD, *et al.* Narrative review: a rational approach to starting insulin therapy. *Ann Intern Med* 2006; **145:** 125–34.
5. Bell DSH. Insulin therapy in diabetes mellitus: how can the currently available injectable insulins be most prudently and efficaciously utilised? *Drugs* 2007; **67:** 1813–27.
6. von Kriegstein E, *et al.* Need for many types of insulin. *Lancet* 1996; **347:** 1045.

Administration. ***ADMINISTRATION ROUTES.*** The long-term management of diabetic patients usually involves injection by the **subcutaneous** route. The advice to diabetics has been to inject their insulin using a full-depth perpendicular injection.[1] In many non-obese patients, however, such a technique can result in inadvertent intramuscular injection.[1,2] Since insulin is absorbed more rapidly after intramuscular than subcutaneous injection, this may lead to greater day-to-day variability in blood-glucose control. In particular, overnight control may be inadequate if intermediate-acting preparations such as isophane insulin are used.[1] Some therefore consider that extended-action insulins should be injected at an angle into a raised skin fold. Although injection of soluble insulin into muscle may produce a more physiological action profile, until more data are available a technique that ensures subcutaneous injection may be prudent with soluble insulins as well.[1]

The anatomic *site* of subcutaneous insulin injection is usually rotated in an attempt to decrease local adverse effects (see Adverse Effects, above). However, the rate of absorption varies between sites and such a practice may also contribute to day-to-day variability in blood-glucose concentrations.[3] For example, large variations in blood-glucose concentrations have been reported on subcutaneous injection into the thigh.[4] Some have suggested rotation of injection sites within an anatomic region, or possibly use of the same anatomic region for injections given at a specific time of day.[3]

Jet injectors deliver insulin at high pressure across the skin into the subcutaneous tissue without use of a needle.[5,6] The greater dispersion obtained gives more rapid absorption of short- and intermediate-acting insulins and consequently reduces the total duration of action.[5] Mild pain, bruising, and bleeding may be a problem.[5-7] Despite having been available for some years, there is little information about their benefits and risks and they are not widely used.[6] However, results in a small study in women with gestational diabetes have suggested that jet injection may be associated with less variation in postprandial blood-glucose concentration and a lower incidence of insulin antibodies.[8]

Insulin preparations may also be given by **intramuscular** injection. Absorption is more rapid than from a subcutaneous injection. However, exercise may produce considerable variations in insulin absorption after intramuscular injection.[1] Soluble insulins may be given **intravenously**; this route is used in diabetic ketoacidosis, and also in surgery and labour.[9] Intermittent pulsed intravenous insulin therapy added to a conventional subcutaneous regimen has been reported to improve symptoms of orthostatic hypotension[10] and hypertension.[11]

The subcutaneous and intravenous routes, and, rarely, the intramuscular route have all been used for the continuous administration of insulin (see Intensive Administration Regimens, below).

Formulations of insulin for **intranasal** use are under investigation.[7,12,13] They have been tried in both type 1 and type 2 diabetes, but bioavailability is low and variable. Absorption enhancers have been used to facilitate uptake of insulin from the nasal mucosa and local adverse effects are dependent, in part, on their irritancy. Similarly, **buccal** formulations are under investigation,[7] and have become available in some countries.

Devices for delivering insulin to the lungs via oral **inhalation** have been developed.[7,14,15] Inhaled insulin is effective in maintaining glycaemic control in both type 1 and type 2 diabetes,[16-19] although there is some evidence from longer-term studies that it is slightly less effective than subcutaneous injection; however, patient acceptability is higher.[16] It is given before meals as a short-acting insulin in patients also receiving intermediate or long-acting subcutaneous insulins or oral antidiabetics; in type 2 diabetes it has also been used alone. UK recommendations from NICE are that it should be reserved for patients who are unable to start or intensify subcutaneous insulin therapy because of a marked, persistent fear of injections or severe difficulties with injection sites (for example, due to lipoatrophy).[17] Data regarding the long-term safety of inhaled insulin also need to be collected, given reports of pulmonary effects and higher levels of insulin antibodies in people with type 1 diabetes. A few cases of primary lung malignancies have occurred in clinical trials of inhaled insulin, at a higher incidence than in comparator-treated patients. However, the number of cases was too small to determine whether these events were related to inhaled insulin, and all affected patients had a history of cigarette smoking.

Endogenous insulin is delivered into the portal venous system, and then passes immediately to the liver where a large fraction of the insulin is extracted. The above routes of administration all deliver insulin into the peripheral circulation, with the risk of peripheral hyperinsulinaemia which has been considered a risk factor for atherosclerotic complications.[20] Giving insulin via the **intraperitoneal** or **oral** routes may overcome this problem to some extent. Peritoneal insulin is used routinely in diabetics undergoing chronic ambulatory peritoneal dialysis, but has also been used for continuous administration (see Intensive Administration Regimens, below). Various formulations of insulin for oral delivery are also under investigation.[7,13,21] **Rectal**[13] or **transdermal**[7] insulin has also been tried.

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INSULIN ANALOGUES AND PROINSULIN. Recombinant-DNA technology has enabled the production of insulin analogues with altered pharmacokinetic profiles.[1,2] Most of the insulin in pharmaceutical preparations is in the form of hexamers, which require time to dissociate before absorption from a subcutaneous site. Substitution of amino-acid residues at the monomer-monomer interface has produced monomeric insulin analogues that retain the biological activity of insulin.

Good results have been reported with an analogue, **insulin lispro**, in which the B28 and B29 residues are replaced with lysine

and proline. This analogue is commercially available and has been widely reviewed.[3-7] In comparative studies of insulin lispro versus soluble insulin given before meals to patients also receiving a long-acting insulin, insulin lispro was reported to result in good glycaemic control, and could be given immediately before meals (5 to 15 minutes) rather than 20 to 40 minutes before as with soluble insulin. There is a suggestion that it may result in fewer severe hypoglycaemic episodes in such regimens.[8] However, an analysis of 10 clinical trials did not find any difference between insulin lispro and neutral insulin (Humulin R) with respect to overall adverse effects or development of long-term diabetic complications.[9] (See also insulin aspart, below.) A few cases of response to insulin lispro in patients with severe insulin resistance have been reported.[10,11] Insulin lispro has been complexed with protamine to produce an intermediate-acting form, which is available as a biphasic preparation.

Insulin aspart is another short-acting insulin analogue, with aspartic acid substituted for proline at position B28.[12-15] It is also used immediately before meals and controls postprandial blood glucose concentrations at least as well as regular human insulin, and may cause fewer hypoglycaemic episodes. A meta-analysis involving 42 studies of insulin lispro or insulin aspart versus regular insulin found that there was evidence of a minor benefit of the analogues in improving HbA_{1c} values in adult patients with type 1 diabetes; no superiority could be shown in patients with type 2 diabetes.[16]

Insulin glulisine is another insulin analogue, with asparagine at position B3 replaced by lysine, and lysine at B29 replaced by glutamic acid. It also has a rapid onset and short duration of action.[17,18]

Recombinant-DNA technology has also been used to produce a long-acting basal insulin analogue, **insulin glargine**, suitable for once-daily use.[19-23] It is available as a solution at pH 4; on subcutaneous injection and neutralisation by tissue buffering processes, microprecipitates are formed that slowly release insulin glargine over 24 hours with no pronounced peak in concentration or in metabolic activity. Controlled studies have reported insulin glargine to be more effective than human isophane insulin in producing glycaemic control as part of a basal-bolus regimen, and to be associated with fewer hypoglycaemic episodes.

Insulin detemir is another long-acting insulin analogue that may have some benefit over isophane insulin. It is a neutral soluble human insulin analogue in which the terminal amino acid at B30 has been replaced by a 14-carbon fatty acid chain. This allows insulin detemir to bind reversibly to albumin, producing slow absorption and a prolonged and consistent metabolic effect for up to 24 hours. It appears to be at least as effective as isophane insulin in maintaining overall glycaemic control but with less intrapatient variability, a similar or lower risk of hypoglycaemia, and less body-weight gain.[24]

Proinsulin (the natural precursor of insulin) appears to be more active than insulin in suppressing the hepatic production rather than the peripheral uptake of glucose.[25,26] It has therefore been studied particularly in patients with type 2 diabetes mellitus. However, development by some manufacturers has been suspended because of a higher rate of adverse cardiac effects in patients treated with proinsulin than in controls.[25]

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25. Zinman B. The physiologic replacement of insulin: an elusive goal. *N Engl J Med* 1989; **321:** 363–70.
26. Goran EA. Human proinsulin—a new therapeutic agent? *Pharm J* 1986; **236:** 667.

INTENSIVE ADMINISTRATION REGIMENS. Intensive insulin regimens aim to mimic more closely the physiological insulin pattern in which a basal insulin concentration is supplemented by a preprandial boost of insulin. Such intensive regimens are used to provide tight control in an attempt to avoid long-term complications (see p.433).

Intensified insulin regimens have the advantage of improving the patient's lifestyle and allowing flexibility in timing of meals. However, careful dietary control must still be maintained and regular monitoring of blood-glucose concentrations is an important component of such regimens. Therefore patients must be well-motivated, reliable, and able to monitor their own blood glucose, and must have access to expert 24-hour help. Although there are reports of success with intensive regimens in brittle (labile) diabetics,[1] these patients are generally unlikely to benefit from such regimens.

In **multiple-injection regimens**, the basal insulin is provided by an injection of intermediate- or long-acting insulin given usually at night, and soluble insulin is given before each main meal. Systems for **continuous administration** may be designed on an open-loop or closed-loop delivery system. *Open-loop systems* comprise an infusion pump with the infusion rate programmed or controlled manually according to manual blood-glucose monitoring. *Closed-loop systems* (the 'artificial pancreas') consist of an insulin pump, a glucose sensor, and a computer for analysis of blood-glucose data. Systems for continuous administration have most commonly used the subcutaneous route, but intraperitoneal, intravenous, or intramuscular infusion have also been used.

The most extensively used **open-loop** system is *continuous subcutaneous insulin infusion* (CSII) using an external pump. A battery-powered pump infuses soluble insulin via a subcutaneous catheter which is resited every 2 to 3 days. A background infusion is given at a predetermined rate, and preprandial bolus doses given using an override switch or manual drive.[2] CSII provides better glycaemic control than conventional injection therapy, but may be only slightly more effective than optimised multiple daily injection therapy.[3] Complications include erythema, abscess, or cellulitis at the injection site and, rarely, contact dermatitis to components of the giving set, pump malfunction, or precipitation of insulin and catheter obstruction.[2] Pump therapy increases the risk of ketoacidosis and intensive regimens are associated with decreased hypoglycaemic awareness and more severe hypoglycaemic episodes compared with conventional therapy,[4] although there is some suggestion that CSII might reduce the risk of severe hypoglycaemia compared with multiple daily injection therapy.[2] If the pump fails or there is an acute increase in insulin requirements, the onset of ketoacidosis may be more rapid and more likely to be associated with dangerous hyperkalaemia than with conventional regimens because there is no depot of insulin.[2,5]

Further development of open-loop delivery systems has been in the design of *implantable insulin pumps*. The first pumps delivered insulin at a constant basal rate, but variable rate models are now available. Studies[6,7] have shown that intravenous or intraperitoneal delivery of insulin from an implantable pump can produce excellent glycaemic control, and fewer episodes of severe hypoglycaemia than are associated with intensive subcutaneous multiple-injection regimens. The main problems associated with such therapy are pump slow-down or catheter obstruction due to aggregation of insulin within the device; these can normally be corrected by procedures to flush the pump and catheter,[7,8] although alternative insulin formulations (e.g. with poloxamer) have been investigated. Other problems may include fibrinous obstruction of the catheter or local intolerance of the pump.[8]

Closed-loop continuous infusion systems are generally confined to research and experimental work because glucose sensors suitable for implantation are still being developed.[8] However, results in *animals* have suggested that an alternative to such systems may be a vascularised artificial pancreas containing islet cells.[9]

1. Wood DF, *et al.* Management of "brittle" diabetes with a preprogrammable implanted pump delivering intraperitoneal insulin. *BMJ* 1990; **301:** 1143–4.
2. Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Arch Intern Med* 2001; **161:** 2293–2300.
3. Pickup J, *et al.* Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2002; **324:** 705–8.
4. Egger M, *et al.* Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; **14:** 919–28.
5. Knight G. Risks with continuous subcutaneous insulin infusion can be serious. *BMJ* 2001; **323:** 693–4.
6. Broussolle C, *et al.* French multicentre experience of implantable insulin pumps. *Lancet* 1994; **343:** 514–15.
7. Dunn FL, *et al.* Long-term therapy of IDDM with an implantable insulin pump. *Diabetes Care* 1997; **20:** 59–63.
8. Selam JL. Implantable insulin pumps. *Lancet* 1999; **354:** 178–9.
9. Maki T, *et al.* Novel delivery of pancreatic islet cells to treat insulin-dependent diabetes mellitus. *Clin Pharmacokinet* 1995; **28:** 471–82.

MIXING OF INSULINS. Mixtures of insulin with differing durations of action may be used in order to produce a more normal pattern of blood glucose variation than can be achieved with a single insulin. However, physicochemical changes in the mixture may occur, either immediately on mixing or over time, and the physiological response to the mixture may therefore be different than if the components were given separately. An early review[1] suggested that insulins from different manufacturers should not be mixed, since formulation differences might render them incompatible. It is important that a consistent routine is followed in preparing and using such mixtures, and manufacturers advise that the shorter-acting insulin should be drawn into the syringe first, to avoid contamination of the vial with the longer-acting component. Pre-prepared mixtures are available from many manufacturers and may be preferable provided that the proportions are suited to the patient's needs.

The American Diabetes Association has issued guidelines[2] for mixing of insulins, including:

- patients well controlled on a particular mixed regimen should maintain their standard procedure for preparing doses
- no other medication or diluent should be mixed with insulin unless approved by the prescriber
- insulin glargine should not be mixed with other forms of insulin because of the low pH of its diluent
- currently available isophane and short-acting insulin formulations when mixed may be used immediately or stored for future use
- rapid-acting insulins (insulin aspart, insulin lispro) can be mixed with isophane, lente, and ultralente insulins. Ultralente insulins do not affect the onset of action of the rapid-acting component; a slight decrease in absorption rate but not bioavailability is seen if rapid-acting insulins are mixed with isophane insulin but postprandial blood-glucose response is similar to that seen with mixtures of rapid-acting and ultralente insulin
- mixtures of rapid-acting insulin with an intermediate- or long-acting insulin should be injected within 15 minutes before a meal
- mixing of short-acting (soluble) and lente or ultralente insulin is not recommended, as zinc ions present in the lente insulin may bind with the short-acting insulin and delay its effects. The degree and rate of binding vary with the insulins used, and may not reach equilibrium for 24 hours; if such mixtures are used the patient should standardise the interval between mixing and injection
- phosphate-buffered insulins (e.g. isophane insulin) should not be mixed with zinc-containing (lente or ultralente) insulins, as zinc phosphate may be precipitated, and the longer acting insulin may be partially and unpredictably converted to a short-acting form

Insulin formulations may change and the manufacturers should be consulted if their recommendations differ from those in the guidelines.

1. Fisher BM. Choosing an insulin. *Prescribers' J* 1988; **28:** 138–43. Correction. *ibid.*; 169.
2. American Diabetes Association. Insulin administration. *Diabetes Care* 2004; **27** (suppl 1): S106–S109. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s106.pdf (accessed 08/07/04)

Diabetes mellitus. Insulin is the mainstay of the treatment of **type 1 diabetes mellitus**. For a discussion of the treatment of diabetes mellitus, including the contexts in which insulin is used, see p.431. The possible role of tight glycaemic control with insulin to prevent the development of microvascular and macrovascular complications in patients with type 1 diabetes is discussed on p.433, while further discussion of specific regimens and approaches to insulin therapy is given under Administration, above.

DIABETIC EMERGENCIES. As discussed on p.435, **diabetic ketoacidosis** and hyperosmolar hyperglycaemic state are medical emergencies and should be treated immediately with fluid replacement and insulin. Potassium, and possibly phosphate, replacement may also be required, but bicarbonate should not be given unless acidaemia is very severe. In the *UK* the *BNF* recommends that insulin be given by intravenous infusion for diabetic ketoacidosis, as a solution of soluble insulin 1 unit/mL via an infusion pump. An infusion rate of 6 units/hour in adults and 0.1 units/kg per hour in children is recommended initially, with the rate doubled or quadrupled if the blood glucose concentration fails to decrease by about 5 mmol/litre per hour. When blood glucose concentrations have fallen to 10 mmol/litre the infusion rate can be reduced to 3 units/hour in adults or about 0.05 units/kg per hour in children, and continued, with glucose 5% to prevent hypogly-

caemia, until the patient is ready to take food by mouth. The insulin infusion should not be stopped before subcutaneous insulin has been started. Potassium chloride is included in the infusion as appropriate to prevent insulin-induced hypokalaemia. If facilities for intravenous infusion are not available the insulin is given by intramuscular injection: in adults an initial loading dose of 20 units intramuscularly is followed by 6 units intramuscularly every hour until the blood glucose concentration falls to 10 mmol/litre, when the dose is given every 2 hours. Late hypoglycaemia due to insulin accumulation should be watched for and managed appropriately.

In the *USA* the intramuscular or the subcutaneous route have been used as alternatives to intravenous insulin, with other appropriate management. One successful set of protocols for insulin dosage in diabetic ketoacidosis is as follows:[1] an initial intravenous bolus of 0.15 units/kg is followed by infusion of 0.1 units/kg per hour; if blood glucose does not fall by about 2.5 to 3.5 mmol/litre in the first hour the infusion rate is doubled every hour until this rate of decline is achieved. (A similar insulin regimen has proved effective in patients with hyperosmolar hyperglycaemic state.[1]) When given by the intramuscular or subcutaneous routes an initial bolus of 0.4 units/kg is divided and given half by the intravenous route and half either intramuscularly or subcutaneously as appropriate. This is followed by 0.1 units/kg every hour intramuscularly or subcutaneously; if response is inadequate it is replaced by an intravenous bolus of 10 units until blood glucose falls by 2.5 to 3.5 mmol/litre. In children intravenous infusion of 0.1 units/kg per hour is recommended, or if intravenous infusion is impractical an initial intramuscular bolus of 0.1 units/kg followed by 0.1 units/kg per hour either intramuscularly or subcutaneously. Treatment is continued at this rate until a serum-glucose concentration of about 12.5 mmol/litre is reached (or about 15 mmol/litre for hyperosmolar hyperglycaemic state), when the rate is decreased to 0.05 to 0.1 units/kg per hour until acidosis is controlled and subcutaneous insulin replacement treatment can be started.

1. American Diabetes Association. Hyperglycemic crises in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S94–S102. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s94.pdf (accessed 26/05/04)

TYPE 2 DIABETES MELLITUS. Traditionally the use of insulin in patients with type 2 diabetes has tended to be reserved for those who cannot be controlled by diet and oral antidiabetics alone.[1,2] Given the possible association between circulating insulin and atherosclerotic cardiovascular symptoms[3] there has been some concern about the use of exogenous insulin in insulin-resistant patients who are already hyperinsulinaemic. Furthermore, patients switched to insulin tend to gain weight[2] which is undesirable in a frequently obese patient group.

Insulin is nonetheless being used more frequently in type 2 patients. This is largely because of a trend toward more intensive regimens designed to produce tighter glycaemic control, on the hypothesis that, as in patients with type 1 disease, this will reduce the development and progression of diabetic complications. Results from the UK Prospective Diabetes Study,[4-6] show that insulin is an effective option in type 2 diabetes, and confirm both the value of intensive therapy in retarding microvascular complications,[6] and that oral therapy should be used before insulin in patients with primary diet failure.[7]

In order to minimise the dose of insulin required, and any risks it may entail, it has been suggested that insulin therapy in type 2 diabetes should be combined with other measures including oral hypoglycaemic drugs.[8] There has long been debate about the value of combined therapy, but a meta-analysis indicated that glycaemic control was better, and insulin requirements lower, in type 2 diabetics who received insulin with a sulfonylurea.[9] For evidence that the insulin analogues insulin lispro and insulin aspart have no advantage over regular insulin in type 2 patients see Insulin Analogues, above.

For further discussion of the management of type 2 diabetes mellitus see p.431.

1. Tattersall RB, Scott AR. When to use insulin in the maturity onset diabetic. *Postgrad Med J* 1987; **63:** 859–64.
2. Taylor R. Insulin for the non-insulin dependent? *BMJ* 1988; **296:** 1015–16.
3. Stern MP. Do non-insulin-dependent diabetes mellitus and cardiovascular disease share common antecedents? *Ann Intern Med* 1996; **124** (suppl): 110–16.
4. United Kingdom Prospective Diabetes Study Group. United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin-dependent diabetes followed for three years. *BMJ* 1995; **310:** 83–8.
5. Turner R, *et al.* United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; **124** (suppl): 136–45.
6. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352:** 837–53. Correction. *ibid.* 1999; **354:** 602.
7. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med* 1998; **128:** 165–75.
8. Henry RR. Glucose control and insulin resistance in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; **124** (suppl): 97–103.
9. Johnson JL, *et al.* Efficacy of insulin and sulfonylurea combination therapy in type II diabetes: a meta-analysis of the randomized placebo-controlled trials. *Arch Intern Med* 1996; **156:** 259–64.

Diagnosis and testing. ***PITUITARY FUNCTION.*** Insulin-induced hypoglycaemia has been used to provide a stressful stimulus in order to assess hypothalamic-pituitary function. The insulin stress or insulin-tolerance test has been used as a standard test for assessment of growth hormone or corticotropin deficiency. However, it is unpleasant, expensive, and not without risk, and is contra-indicated in patients with angina, heart failure, cerebrovascular disease, or epilepsy; some recommend its use only when results of alternative tests are equivocal,[1-3] and it should only be performed in specialist units under strict surveillance.[4]

1. Clayton RN. Diagnosis of adrenal insufficiency. *BMJ* 1989; **298:** 271–2.
2. Stewart PM, *et al.* A rational approach for assessing the hypothalamic-pituitary-adrenal axis. *Lancet* 1988; **1:** 1208–10.
3. Lindholm J. The insulin hypoglycaemia test for the assessment of the hypothalamic–pituitary–adrenal function. *Clin Endocrinol (Oxf)* 2001; **54:** 283–6.
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; **72:** 362–8.

Hyperkalaemia. Insulin promotes the intracellular uptake of potassium. It is therefore used in the management of moderate to severe hyperkalaemia, when it is given with glucose (see p.1669).

Liver disorders. There have been reports[1,2] of benefit from the use of insulin and glucagon in the treatment of liver disorders, based on their reported hepatotrophic effect. However, randomised studies have found no benefit from insulin and glucagon infusions in fulminant hepatic failure[3] and acute alcoholic hepatitis.[4]

1. Baker AL, *et al.* A randomized clinical trial of insulin and glucagon infusion for treatment of alcoholic hepatitis: progress report in 50 patients. *Gastroenterology* 1981; **80:** 1410–14.
2. Jaspan JB, *et al.* Insulin and glucagon infusion in the treatment of liver failure. *Arch Intern Med* 1984; **144:** 2075–8.
3. Harrison PM, *et al.* Failure of insulin and glucagon infusion to stimulate liver regeneration in fulminant hepatic failure. *J Hepatol* 1990; **10:** 332–6.
4. Bird G, *et al.* Insulin and glucagon infusion in acute alcoholic hepatitis: a prospective randomized controlled trial. *Hepatology* 1991; **14:** 1097–1101.

Myocardial infarction. Discussions on the effects of insulin with glucose and potassium in the ischaemic heart, including its effect in reducing blood free fatty acids, have emphasised its potential benefits in left ventricular failure and cardiogenic shock.[1,2] A meta-analysis[3] of randomised controlled studies performed before the widespread use of thrombolytics found a reduction in mortality in recipients of glucose-insulin-potassium solutions. However, although a pilot study[4] that included patients undergoing reperfusion (thrombolysis or percutaneous coronary intervention) reported benefit, this was not confirmed in larger randomised studies using standard glucose-insulin-potassium infusions.[5,6] A further study[7] found that routine use of such infusions in patients undergoing reperfusion had no effect on myocardial salvage, although some improvement was reported in diabetics.

Intensive glucose control, with insulin-glucose infusion followed by multiple daily subcutaneous insulin injections has been reported to reduce mortality in diabetics who suffered a myocardial infarction.[8,9] A similar study[10] of treatment after myocardial infarction included only patients with type 2 diabetes mellitus who were treated with routine care, or insulin-glucose infusion followed by either long-term subcutaneous insulin or standard glucose control. The study was stopped early due to slow patient recruitment, but results did suggest that although glucose concentration was a strong independent predictor of long-term mortality, the use of long-term insulin treatment did not improve survival compared with conventional treatment at similar levels of glucose control. An observational study[11] in non-diabetics with hyperglycaemia suggested that intensive glucose control also improved outcomes in this population, but another study[12] found no benefit. However, the glucose control achieved in this study was similar in both the intensive and the conventional treatment groups and an analysis based on blood glucose concentrations suggested that strict glucose control was beneficial.[12]

For the conventional management of myocardial infarction, see p.1175.

1. Opie LH. Glucose and the metabolism of ischaemic myocardium. *Lancet* 1995; **345:** 1520–1.
2. Taegtmeyer H, *et al.* Metabolic support for the postischaemic heart. *Lancet* 1995; **345:** 1552–5.
3. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. *Circulation* 1997; **96:** 1152–6.
4. Díaz R, *et al.* Metabolic modulation of acute myocardial infarction: the ECLA Glucose-Insulin-Potassium Pilot Trial. *Circulation* 1998; **98:** 2227–34.
5. Mehta SR, *et al.* Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. *JAMA* 2005; **293:** 437–46.
6. Díaz R, *et al.* Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. *JAMA* 2007; **298:** 2399–2405.
7. Pache J, *et al.* A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. *Am Heart J* 2004; **148:** e3.
8. Malmberg K, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; **26:** 57–65.
9. Malmberg K, *et al.* Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997; **314:** 1512–15.
10. Malmberg K, *et al.* Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J* 2005; **26:** 650–61.
11. Weston C, *et al.* Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome. *Heart* 2007; **93:** 1542–6.
12. Cheung NW, *et al.* The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care* 2006; **29:** 765–70.

Neonatal hyperglycaemia. Hyperglycaemia is common in very immature neonates because of delayed or reduced insulin production. It can be treated by glucose restriction until glucose tolerance improves. However, this may not provide enough glucose to meet basal metabolic needs, and the use of an insulin infusion can allow sufficient glucose to be given. It has been suggested that insulin is best given intravenously in a separate, easily titratable solution because of the frequent fluctuations of requirement in these infants.[1]

1. Ditzenberger GR, *et al.* Continuous insulin intravenous infusion therapy for VLBW infants. *J Perinat Neonatal Nurs* 1999; **13:** 70–82.

Overdosage with calcium-channel blockers. High-dose insulin, with glucose and potassium as required to maintain normal plasma concentrations of these, has been reported to be of value in the treatment of overdosage with calcium-channel blockers that has not been adequately managed with conventional therapy (which is described under Treatment of Adverse Effects under Nifedipine, p.1352). A review[1] of 13 reported cases found that various dosage regimens had been tried. These included bolus doses of insulin 10 to 20 units, and continuous infusions of 0.1 to 1 unit/kg per hour. The authors of one report[2] have proposed a regimen that includes an initial intravenous bolus dose of insulin 1 unit/kg, followed by a continuous infusion of 0.5 units/kg per hour; this may be increased to 1 unit/kg per hour if necessary.

1. Shepherd G, Klein-Schwartz W. High-dose insulin therapy for calcium-channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923–30.
2. Boyer EW, *et al.* Hyperinsulinemia/euglycemia therapy for calcium channel blocker poisoning. *Pediatr Emerg Care* 2002; **18:** 36–7.

Preparations

BP 2008: Insulin Aspart Injection; Insulin Lispro Injection; Protamine Zinc Insulin Injection;
Ph. Eur.: Biphasic Insulin Injection; Biphasic Isophane Insulin Injection; Insulin Zinc Injectable Suspension; Insulin Zinc Injectable Suspension (Amorphous); Insulin Zinc Injectable Suspension (Crystalline); Isophane Insulin Injection; Soluble Insulin Injection;
USP 31: Extended Insulin Human Zinc Suspension; Extended Insulin Zinc Suspension; Human Insulin Isophane Suspension and Human Insulin Injection; Insulin Human Injection; Insulin Human Zinc Suspension; Insulin Injection; Insulin Lispro Injection; Insulin Zinc Suspension; Isophane Insulin Human Suspension; Isophane Insulin Suspension; Prompt Insulin Zinc Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Actrapid HM; Actrapid MC†; Apidra; Biohulin C; Biohulin N; Densulin; Humalog; Humalog Mix 25; Humulin 70/30; Humulin L†; Humulin NPH; Humulin R; Humulin U†; Insulatard HM; Insulatard MC†; Insuman N; Insuman R; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; Monotard MC†; NovoMix 30; NovoRapid; ***Austral.:*** Actrapid; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin NPH; Humulin R; Humulin UL†; Hypurin Isophane; Hypurin Neutral; Lantus; Levemir; Mixtard 20/80, 30/70, 50/50; Monotard†; NovoMix 30; NovoRapid; Protaphane; Ultratard†; ***Austria:*** Actrapid HM; Humalog; Humalog Mix 25 and 50; Huminsulin Basal; Huminsulin Long; Huminsulin Normal; Huminsulin Profil II and III; Huminsulin Ultralong; Insulatard HM; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Mixtard HM 10/90, 20/80, 30/70, 40/60, and 50/50; Monotard HM; Ultratard HM; ***Belg.:*** Actrapid HM; Humaject 30/70†; Humaject NPH†; Humaject Regular†; Humalog; Humalog Mix 25 and 50; Humuline 30/70, 50/50; Humuline Long†; Humuline NPH; Humuline Regular; Humuline Ultralong†; Insulatard; Lantus; Levemir; Mixtard 10, 20, 30, 40, 50; Monotard HM†; NovoMix 30; NovoRapid; Ultratard†; Velosulin; ***Braz.:*** Actrapid MC†; Biohulin 70/30, 80/20, and 90/10†; Biohulin Lenta†; Biohulin NPH; Biohulin Regular; Biohulin Ultralenta†; Exubera; Humalog; Humalog Mix 25; Humulin 70/30; Humulin Lenta; Humulin NPH; Humulin Regular; Insuman Comb 85N/15R and 75N/25R; Insuman N; Insuman R; Lantus; Levemir; Monotard MC†; Novolin 70/30; Novolin L†; Novolin N; Novolin R; Novolin U†; NovoRapid; Protaphane MC†; ***Canad.:*** Humalog; Humalog Mix 25; Humulin 20/80, 30/70; Humulin L; Humulin N; Humulin R; Humulin U; Hypurin NPH; Hypurin Regular; Iletin II Pork Lente; Iletin II Pork NPH; Iletin II Pork Regular; Lantus; Novolin 10/90, 20/80, 30/70, 40/60, 50/50; Novolin Lente†; Novolin NPH; Novolin Toronto; Novolin Ultralente†; NovoRapid; ***Chile:*** Actrapid HM; Actrapid†; Humalog; Humalog Mix 25; Humulin 70/30†; Humulin L†; Humulin N†; Humulin R†; Insulatard HM; Insulatard†; Insuman N; Insuman R; Lantus; Lenta†; Mixtard 30 HM; Monotard HM†; NovoMix 30; NovoRapid; Wosulin 30/70; Wosulin-N; Wosulin-R; ***Cz.:*** Actraphane; Actrapid; Exubera; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humulin L†; Humulin M3; Humulin N; Humulin R; Humulin U†; Hypurin Bovine Isophane†; Hypurin Bovine Protamin Zink Sulfat†; Hypurin Porcin Neutral†; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman

Rapid; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10, 20, 30, 40, and 50; Monotard HM†; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Ultratard HM†; Velosulin; ***Denm.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin Mix 30/70; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Velosulin; ***Fin.:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humulin NPH; Humulin Regular; Humutard†; Insulin Lyhyt†; Insulin Pitkä†; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, and 50; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard†; Velosulin†; ***Fr.:*** Actrapid; Apidra; Exubera; Humalog; Humalog Mix 25 and 50; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Insuplant; Lantus; Levemir; Lillypen Rapide†; Mixtard 10, 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; Umuline NPH; Umuline Profil 30; Umuline Rapide; Umuline Zinc Compose†; Umuline Zinc†; Velosulin†; ***Ger.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; B-Insulin†; Berlinsulin H 30/70; Berlinsulin H Basal; Berlinsulin H Normal; Depot-Insulin S†; Depot-Insulin†; H-Tronin†; Humalog; Humalog Mix 25 and 50; Huminsulin Basal; Huminsulin Normal; Huminsulin Profil III; Insulatard Human†; Insulin Basal; Insulin Comb 30/70; Insulin Monotard HM†; Insulin Novo Semilente MC; Insulin Rapid; Insulin S†; Insulin SNC†; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Komb-Insulin S†; Komb-Insulin†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 30/70†; Monotard; NovoMix 30; NovoRapid; Protaphane; Semilente†; Ultratard; Velosulin; ***Gr.:*** Actraphane HM†; Actrapid; Apidra; Exubera; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humulin Lente; Humulin M2, M3; Humulin NPH; Humulin Regular; Humulin Ultralente; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; PenMix 10, 20, 30, 40, or 50†; Protaphane; Ultratard; ***Hong Kong:*** Actrapid HM; Actrapid MC†; Humalog; Humulin 70/30; Humulin L; Humulin N; Humulin R; Insulatard MC†; Lantus; Mixtard 30 HM; Monotard HM; Monotard MC†; NovoMix 30; NovoRapid; Protaphane HM; Ultratard HM; ***Hung.:*** Actrapid; Apidra; Humalog; Humalog Mix25 and Mix50; Humulin L†; Humulin M3; Humulin N; Humulin R; Humulin U†; Insulatard; Insulin Monotard†; Insulin Semilente†; Insulin Ultratard†; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard MC†; NovoMix 30; NovoRapid; ***India:*** Actrapid; Human Actrapid; Human Insulatard; Human Mixtard 30 and 50; Human Monotard; Insuman Rapid; Insuman 25/75 and 50/50; Lantus; Lentard; Mixulin; Rapidica; Rapimix; Wosulin Biphasic 30/70 and 50/50; Wosulin-N; Wosulin-R; Zinulin; ***Indon.:*** Actrapid HM; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin N; Humulin R; Insulatard HM; Lantus; Mixtard 30 HM; Monotard HM; ***Irl.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin I; Humulin Lente†; Humulin M3; Humulin S; Humulin Zn†; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 10 , 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; ***Israel:*** Humalog; Humalog Mix 25; Humulin 70/30; Humulin N; Humulin R; Humulin U†; Lantus; Levemir; NovoMix 30; NovoRapid; ***Ital.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Bio-Insulin 30/70 and 50/50†; Bio-Insulin I†; Bio-Insulin L†; Bio-Insulin R†; Bio-Insulin U†; Humalog; Humalog Mix 25 and 50; Humulin 30/70 and 50/50; Humulin I; Humulin L†; Humulin R; Humulin U†; Lantus; Levemir; Monotard; NovoMix 30; NovoRapid; Protaphane; Ultratard; ***Jpn:*** Humacart 3/7; InnoLet 10R, 20R, 30R, 40R, and 50R; InnoLet N; InnoLet R; Monotard†; NovoLet 10R,20R, 30R, 40R, 50R†; NovoLet N†; NovoLet R†; Novolin 10R, 20R, 30R, 40R, and 50R; Novolin N; Novolin R; Novolin U†; NovoRapid; NovoRapid 30 Mix chu; Penfill N; Penfill R; Penfill 10R, 20R, 30R, 40R, 50R; Velosulin; ***Malaysia:*** Actrapid HM; Humalog; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Insulatard; Lantus; Levemir; Mixtard 30 HM; Monotard HM†; NovoMix; NovoRapid; Ultratard HM†; ***Mex.:*** Glinux 70/30; Glinux-N; Humalog; Humalog Mix 25; Humanilusin; Humulin 70/30, 80/20; Humulin L; Humulin N; Humulin R; Insulex; Insuman 100N; Insuman 15R/85N, 25R/75N, and 50R/50N; Insuman R; Lantus; Levemir; Novolin 30/70; Novolin L†; Novolin N; Novolin R; NovoMix 30; NovoRapid; Prodiabin-N; ***Neth.:*** Actraphane 10, 20, 30, 40, 50; Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humuline; Humuline 30/70; Humuline NPH; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Infusat; Insuman Rapid; Isuhuman Infusat†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Protaphane; Ultratard; Velosulin; ***Norw.:*** Actrapid; Humalog; Humalog Mix 25; Humulin NPH; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard†; NovoMix 30; NovoRapid; Ultratard†; Velosulin†; ***NZ:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humulin 70/30; Humulin L†; Humulin NPH; Humulin R; Humulin U†; Insulatard MC; Lantus; Levemir; Mixtard 30 or 50; Monotard; NovoRapid; PenMix 10, 20, 30, 40, or 50; Protaphane; Ultratard; Velosulin HM; Velosulin MC; ***Philipp.:*** Actrapid HM; Biosulid L; Humalog; Humulin 70/30; Humulin N (NPH); Humulin R (Regular); Insulatard HM; Lantus; Mixtard 30 HM; NovoMix 30; SciLin M30; SciLin N; SciLin R; ***Pol.:*** Actrapid; Apidra; Gensulin N; Gensulin R; Gensulin M10, M20, M30, M40, or M50; Humaject M3 (30/70)†; Humaject R†; Humalog; Humalog Mix 25 and 50; Humulin M3 (30/70); Humulin N; Humulin R; Insulatard; Insulinum Lente; Insulinum Maxirapid; Insulinum Semilente; Insulinum Ultralente; Insuman Basal; Insuman Comb 25; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; Polhumin Mix-3; Polhumin N; Polhumin R; Ultratard HM; ***Port.:*** Actrapid; Apidra; Exubera; Humalog; Humulin Lenta†; Humulin M3; Humulin NPH; Humulin Regular; Humulin Ultralenta†; Insulatard; Isuhuman Basal†; Isuhuman Comb 25†; Isuhuman Rapid†; Lantus; Levemir; Liprolog; Liprolog Mix 25 and 50; Mixtard 10 , 20, 30, 40, and 50 HM; Monotard†; NovoMix 30, 50, and 70; NovoRapid; Optisulin; Protaphane; Ultratard†; Velosulin; ***Rus.:*** Actrapid HM (Актрапид НМ); Actrapid MC (Актрапид МС); Biosulin N (Биосулин Н); Biosulin R (Биосулин Р); Humalog (Хумалог); Humalog Mix 25 (Хумалог Микс 25); Humulin M3 (Хумулин М3); Humulin NPH (Хумулин НПХ); Humulin Regular (Хумулин Регуляр); Insulidd L (Инсулидд Л); Insulidd N (Инсулидд Н)†; Insulidd R (Инсулидд Р)†; Insulin Lt (Инсулин Лт); Insulin Maxirapid (Инсулин Максирапид); Insuman Basal (Инсуман Базал); Insuman Comb 25 (Инсуман Комб 25); Insuman Rapid (Инсуман Рапид); Lantus (Лантус); Levemir (Левемир); Levulin L (Левулин Л); Levulin N (Левулин Н)†; Levulin R (Левулин Р)†; Mixtard 30 HM (Микстард 30 НМ); Monotard MC (Монотард Мс); NovoMix 30 (НовоМикс 30); NovoRapid (Новорапид); Protaphane HM (Протафан НМ); ***S.Afr.:*** Actraphane HM; Actrapid HM; Apidra; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Lantus; Levemir; Mixtard 20/80†; Monotard HM†; NovoMix 30; NovoRapid; Protaphane HM; Ultratard HM†; ***Singapore:*** Actrapid HM; Humalog; Humalog Mix 25; Humulin 30/70; Humulin L†; Humulin N; Humulin R; Insulatard HM; Lantus; Levemir; Mixtard 30 or 50; Monotard HM†; NovoMix 30; NovoRapid; Ultratard HM†; ***Spain:*** Actrapid; Humalog; Humalog Mix 25 and 50; Humalog NPL; Humaplus 30/70†; Humaplus NPH†; Humaplus Regular†; Humulina 30:70; Humulina Lenta†; Humulina NPH; Humulina Regular; Humulina Ultralenta†; Insulatard; Insulatard NPH†; Lantus; Levemir; Mixtard 30; Mixtard 30/70†; Monotard†; NovoMix 30; NovoRapid; Ultratard†; ***Swed.:*** Actrapid; Apidra; Humalog; Humalog Mix 25 and 50; Humulin Mix 30/70; Humulin NPH; Humulin Regular; Insulatard; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Levemir; Mixtard 10, 20, 30, 40, and 50; Monotard; NovoMix 30; NovoRapid; Ultratard; Velosulin†; ***Switz.:*** Actrapid HM; Actrapid MC; Apidra; Humalog; Huminsulin Basal (NPH); Huminsulin Long; Huminsulin Normal; Huminsulin Profil III; Huminsulin Ultralong; Hypurin 30/70 Mix; Hypurin Isophane; Hypurin Neutral; Insulatard HM; Insulatard MC; Insuman Basal; Insuman Comb 25; Insuman Infusat; Insuman Rapid; Lantus; Lente MC†; Levemir; Mixtard 30 MC; Mixtard HM 10, 20, 30, 40, 50; Monotard HM; NovoMix 30; NovoRapid; Semilente MC; Ultratard HM; Velosulin HM†; ***Thai.:*** Actrapid HM; Humalog; Humalog Mix 25; Humulin 70/30; Humulin N; Humulin R; Insulatard; Lantus; Mixtard HM; Monotard HM†; NovoMix 30; NovoRapid; ***Turk.:*** Humalog; Humalog Mix 25 and 50; Humulin M 70/30 and 80/20; Humulin N; Humulin R; Insulatard; Lantus; Mixtard 10, 20, 30, 40, and 50; NovoMix 30; NovoRapid; Orgasulin Mix 30/70; ***UAE:*** Jusline 70/30; Jusline N; Jusline R; ***UK:*** Actrapid; Apidra; Exubera†; Humaject S†; Humalog; Humalog Mix 25 and 50; Humulin I; Humulin Lente†; Humulin M3; Humulin S; Humulin Zn†; Hypurin 30/70; Hypurin Isophane; Hypurin Lente; Hypurin Neutral; Hypurin Protamine Zinc; Insulatard; Insuman Basal; Insuman Comb 15, 25, and 50; Insuman Rapid; Lantus; Levemir; Mixtard 30; Monotard†; NovoMix 30; NovoRapid; Pork Actrapid†; Pork Insulatard†; Pork Mixtard 30†; Ultratard†; Velosulin†; ***USA:*** Apidra; Exubera; Humalog; Humalog Mix 75/25 and 50/50; Humulin 70/30, 50/50; Humulin L†; Humulin N; Humulin R; Humulin U Ultralente†; Lantus; Lente; Lente Iletin II; Levemir; Novolin 70/30; Novolin N; Novolin R; NovoLog; NovoLog Mix 70/30; NPH Iletin II†; Regular Iletin II; Ultralente; Velosulin Human BR†; ***Venez.:*** Humalog; Humalog Mix 25; Humulin 70/30; Humulin L†; Humulin N; Humulin R; Insuman N; Insuman R; Lantus; Novolin 70/30†; Novolin L†; Novolin N†; Novolin R†.

Metformin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de metformina; LA-6023 (metformin or metformin hydrochloride); Metformiinihydrokloridi; Metformin Hidroklorür; Metformin hydrochlorid; Metformine, chlorhydrate de; Metformin-hidroklorid; Metforminhydroklorid; Metformini hydrochloridum; Metformino hidrochloridas. 1,1-Dimethylbiguanide hydrochloride.

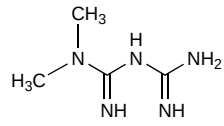
Метформина Гидрохлорид

$C_4H_{11}N_5,HCl$ = 165.6.

CAS — 657-24-9 (metformin); 1115-70-4 (metformin hydrochloride).

ATC — A10BA02.

ATC Vet — QA10BA02.



(metformin)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn,* and *US.*

Ph. Eur. 6.2 (Metformin Hydrochloride). White or almost white crystals. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

USP 31 (Metformin Hydrochloride). A white crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in dichloromethane.

Adverse Effects, Treatment, and Precautions

As for biguanides in general, p.437.

Breast feeding. Based on *animal* studies the UK and US licensed product information warns that metformin may be distributed into breast milk, and that the possible effects on the infant should be considered if women wish to breast feed while receiving the drug. However, a study in 7 breast-feeding women receiving metformin at a median dose of 1.5 g daily found the concentrations in milk to be about a third of those in maternal plasma, resulting in a mean calculated dose to the infants of 40 micrograms/kg daily. Blood samples were taken from 4 of the infants: metformin concentrations were undetectable in 2, and were very low (10 to 15% of maternal values) in the others. Given these results the authors considered that women receiving metformin need not be discouraged from breast feeding.[1] Similar results from 3 other studies[2,3] that included 13 women have provided further evidence that metformin is distributed into breast milk, that concentrations in milk are less than those in maternal plasma, and that breast-fed infants would be exposed to a very small percentage of the maternal dose. Six infants were breast-fed with no adverse effects that could be attributed to metformin. A prospective study[4] of weight, height, and motor-social development over 6 months, in infants of women taking metformin (1.5 to 2.55 g daily) for polycystic ovary syndrome, found no difference between 61 infants who were breast-fed and 50 who were formula-fed.

1. Hale TW, *et al.* Transfer of metformin into human milk. *Diabetologia* 2002; **45:** 1509–14.
2. Gardiner SJ, *et al.* Transfer of metformin into human milk. *Clin Pharmacol Ther* 2003; **73:** 71–7.
3. Briggs GG, *et al.* Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol* 2005; **105:** 1437–41.
4. Glueck CJ, *et al.* Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr* 2006; **148:** 628–32.

Fasting. For the view that metformin could be used with little risk of hypoglycaemia in fasting Muslim patients during Ramadan, and suggestions for modifying the timing of doses, see under Precautions of Insulin, p.448.

Pregnancy. Insulin is generally preferred for treatment of diabetes during pregnancy. However, there are limited data to suggest that metformin does not increase the risk of congenital abnormalities[1,2] and does not adversely affect pregnancy outcome in diabetic women.[2] A controlled study comparing insulin with metformin in gestational diabetes is underway.[3]

The use of metformin to improve ovulation in polycystic ovary syndrome (PCOS) is increasing. There is growing evidence to suggest that metformin used before and during pregnancy in these women does not increase the risk of congenital abnormalities,[1,4-6] and may reduce first trimester spontaneous abortion,[4,6] which is common in women with PCOS.

1. Gilbert C, *et al.* Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertil Steril* 2006; **86:** 658–63.
2. Hughes RCE, Rowan JA. Pregnancy in women with type 2 diabetes: who takes metformin and what is the outcome? *Diabet Med* 2006; **23:** 318–22.
3. Brown FM, *et al.* Metformin in pregnancy: its time has not yet come. *Diabetes Care* 2006; **29:** 485–6.
4. Glueck CJ, *et al.* Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002; **17:** 2858–64.
5. Glueck CJ, *et al.* Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Hum Reprod* 2004; **19:** 1323–30.
6. Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertil Steril* 2006; **85:** 1002–9.

Interactions

As for biguanides in general, p.438.

Pharmacokinetics

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract; the absolute bioavailability of a single 500-mg dose is reported to be about 50 to 60%, although this is reduced somewhat if taken with food. Once absorbed, protein binding in plasma is negligible; the drug is excreted unchanged in the urine. The plasma elimination half-life is reported to range from about 2 to 6 hours after oral doses. Metformin crosses the placenta and is distributed into breast milk in small amounts.

◊ References.

1. Scheen AJ. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 1996; **30:** 359–71.
2. Sambol NC, *et al.* Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *J Clin Pharmacol* 1996; **36:** 1012–21.
3. Charles B, *et al.* Population pharmacokinetics of metformin in late pregnancy. *Ther Drug Monit* 2006; **28:** 67–72.

Uses and Administration

Metformin hydrochloride is a biguanide antidiabetic (p.437). It is given orally in the treatment of type 2 diabetes mellitus (p.431), and is the drug of first choice in overweight patients. Initial dosage is 500 mg two or three times daily or 850 mg once or twice daily with or after meals, gradually increased if necessary, at intervals of at least 1 week, to 2 to 3 g daily; doses of 3 g daily are associated with an increased incidence of gastrointestinal adverse effects. Gastrointestinal effects are also common on beginning therapy, and the *BNF* recommends starting therapy more gradually with 500 mg at breakfast for at least 1 week, then increasing to 500 mg twice daily for at least 1 week, with further increases as required, up to a usual maximum of 2 g daily in 3 divided doses with meals. A modified-release preparation is also available, which is given in an initial dose of 500 mg once daily and may be increased in increments of 500 mg, at intervals of at least 1 week, to a maximum of 2 g once daily with the evening meal. If glycaemic control is not adequate the dose may be divided to give 1 g twice daily with meals. If doses above 2 g daily are required, they should be given as