Traditionally, the American Diabetes Association has advised that more attention should be given to the control of blood glucose concentrations in patients with NIDDM. The association has suggested that action should be taken if a patient’s fasting plasma glucose concentration exceeds 140 mg per deciliter (7.8 mmol per liter) and the glycosylated hemoglobin value is more than 8 percent, and that the target values should be less than 120 mg per deciliter (6.7 mmol per liter) and under 7 percent, respectively. These target values may be feasible when NIDDM is detected at an early stage, but in later stages the severity of the disease often makes it difficult to achieve these values with any form of therapy.

Patients with NIDDM often have several risk factors for the development of atheroma, such as hypertension, dyslipidemia (particularly elevated plasma very-low-density lipoprotein triglyceride concentrations and low high-density lipoprotein cholesterol concentrations), insulin resistance with elevated plasma insulin concentrations, and tobacco use. Therapeutic attention should also be given to these abnormalities.

The Pathophysiology of Non-Insulin-Dependent Diabetes Mellitus

Patients with NIDDM nearly always have both insulin resistance and abnormal pancreatic beta-cell function. Insulin resistance has often been present for many years and is a major contributing factor to the development of NIDDM. It is due in part to obesity, especially abdominal obesity, and physical inactivity. In groups at high risk for NIDDM — for example, Native Americans, Mexican Americans, blacks, and Asian Indians — insulin resistance and obesity are particularly prevalent. The insulin resistance affects different insulin-sensitive tissues to different degrees. Insulin-stimulated uptake and use of glucose are impaired in muscle, and glycogen formation is reduced. In liver, insulin resistance leads to an inappropriately raised basal hepatic glucose output, which is due mainly to increased gluconeogenesis.

Impaired pancreatic beta-cell function becomes an increasingly important feature as NIDDM progresses, affecting the insulin responses to both glucose and amino acids. Progressive beta-cell deficiency is the chief reason for the characteristic deterioration seen in NIDDM.

Heathful Living and Its Limitations

Fundamental therapy for patients with NIDDM is a diet low in fats and high in carbohydrates and fiber, with energy restriction in obese patients, and increased...
physical activity. In practice only moderate weight loss is achieved — for example, about 4.5 kg (10 lb). Although the disease is initially well controlled by diet alone in less than 20 percent of patients, only about 5 percent maintain near-normal fasting plasma glucose concentrations of less than 108 mg per deciliter (6.0 mmol per liter). In addition, most patients are unable to maintain increased levels of physical activity. As the plasma glucose concentrations inorexably increase, it becomes necessary to add orally administered hypoglycemic drugs or insulin to the treatment regimen.

**SULfonylurea Therapy and Its Limitations**

Until recently the only orally administered glucose-lowering agents available in the United States were sulfonylureas. These drugs cause some improvement in beta-cell function and reduce fasting plasma glucose concentrations by approximately 20 to 30 percent (40 to 80 mg per deciliter [2.2 to 4.4 mmol per liter]). Many patients continue to have hyperglycemia, even though they are free of symptoms. Secondary failure, defined as the recurrence of symptomatic hyperglycemia (with fasting plasma glucose concentrations of approximately 250 mg per deciliter [13.9 mmol per liter]), occurs in approximately 10 percent of patients per year. There is therefore a need for additional drugs to improve glycemic control.

**History of biguanides**

The history of biguanides can be traced from the use of *Galega officinalis* (goat’s-rue or French lilac) as a treatment for diabetes in medieval Europe. Guanidine, the active component of galega, was used to synthesize several antidiabetic compounds in the 1920s, and metformin and phenformin (Fig. 1), the two main biguanides, were introduced in the late 1950s. Phenformin was withdrawn from clinical use in many countries in the late 1970s when an association with lactic acidosis was recognized. This tarnished the reputation of biguanides, but lactic acidosis is not a major problem with metformin, and metformin is now used in more than 90 countries. It has become the second most prescribed oral glucose-lowering drug in Europe (after glyburide), where it is used alone in approximately 40 percent of patients to whom it is prescribed and in combination with a sulfonylurea in approximately 60 percent.

**Mechanisms of Action of Metformin**

The pharmacokinetics of metformin are outlined in Table 1. Metformin therapy improves insulin sensitivity, as shown by a reduction in fasting plasma glucose and insulin concentrations; it is not effective in the absence of insulin. In patients with NIDDM the glucose-lowering effect is attributed mainly to decreased hepatic glucose output and enhanced peripheral glucose uptake (Table 2). Several other actions may contribute, such as increased intestinal use of glucose and decreased fatty-acid oxidation.

Metformin decreases basal hepatic glucose output in patients with NIDDM, providing an important mechanism through which the drug lowers fasting plasma glucose concentrations. In isolated hepatocytes, therapeutic concentrations of metformin enhance the suppression of gluconeogenesis by insulin and reduce gluconic-stimulated gluconeogenesis.

Metformin has increased glucose disposal in most studies using hyperinsulinemic-, euglycemic-, and hyperglycemic-clamp procedures in patients with NIDDM, with muscle implicated as its main site of action. In animals, metformin increases insulin-stimulated uptake of glucose by muscle, resulting in increased glycogen formation and glucose oxidation, but not extra lactate production. Metformin also increases the uptake and oxidation of glucose by adipose tissue as well as lipogenesis. However, the actions of metformin on peripheral tissues in vitro require high concentrations and are slow in onset. Metformin increases the binding of insulin to its receptors, phosphorylation, and tyrosine kinase activity of insulin receptors in vivo, but these actions may be due to reduced plasma glucose concentrations, since they cannot be reproduced in vitro. Metformin also increases translocation of the GLUT-1 and GLUT-4 isoforms of glucose transporters in different types of cells, and it prevents the development of insulin resistance in cultured hepatocytes and adipocytes exposed for long periods to high insulin concentrations.

Metformin improves oral glucose tolerance, whereas the plasma insulin response to glucose is unchanged or may be decreased in patients with hyperinsulinemia. Often, the reduction in the incremental increase in plasma glucose concentrations after oral glucose administration is similar to the reduction in fasting plasma glucose concentrations. However, during daytime glucose profiles, postprandial plasma glucose concentrations are lowered by metformin therapy, especially after the midday meal. These changes may be due to delayed glucose absorption, although overall absorption of a glucose load is not reduced by metformin, or they may reflect the time required for the absorption of
metformin and accumulation of the drug in tissue.

Metformin decreases fatty-acid oxidation by 10 to 20 percent, which in turn reduces plasma glucose concentrations by means of the glucose–fatty-acid cycle. Indirect calorimetry indicates that metformin has little overall effect on oxidative metabolism (it causes a small decrease in fatty-acid oxidation and a small increase in glucose oxidation), implicating glycogen formation as an important part of the increased glucose disposal. Metformin appears to be ineffective in tissues that are acutely insensitive to insulin (e.g., brain, renal medulla, and skin). Metformin therapy causes a small increase in basal and postprandial blood lactate concentrations, within the normal range. The interpretation of these increases, however, needs to take into account the fact that obesity and diabetes slightly raise blood lactate concentrations. The increased blood lactate concentrations are probably caused by metformin-induced conversion of glucose to lactate by the intestinal mucosa. The lactate then enters the portal circulation and is largely cleared by the liver, in which it serves as a gluconeogenic substrate. When the liver is inundated with fuels after a meal, more lactate gains entry into the systemic circulation. Enhanced splanchnic glucose–lactate–glucose cycling contributes to the overall increase in glucose turnover noted after metformin administration in animals.

Long-term therapy with metformin, particularly in patients with marked hyperglycemia, results in a moderate (10 to 20 percent) reduction in plasma triglyceride concentrations due to decreased hepatic synthesis of very-low-density lipoprotein. Small decreases (5 to 10 percent) in plasma total cholesterol and small increases in plasma high-density lipoprotein cholesterol have been noted in some studies.

There have been reports of decreased platelet sensitivity to aggregating agents during metformin therapy, possibly due to reduced blood glucose concentrations. Increased fibrinolytic activity and small reductions in plasma concentrations of the fibrinolytic inhibitor plasminogen-activator inhibitor type 1 have also been described.

### Comparison of Sulfonylurea and Metformin Therapy

Metformin and sulfonylureas cause similar reductions in fasting plasma glucose concentrations in patients with NIDDM. Sulfonylureas can induce hypoglycemia, whereas this is rare with metformin therapy alone. Therefore, metformin has an antihyperglycemic action, whereas sulfonylureas and insulin have hypoglycemic actions.

Sulfonylureas increase fasting plasma insulin concentrations, whereas metformin may decrease them. In theory the reduced plasma concentrations of insulin or plasminogen-activator inhibitor type 1 could decrease the risk of macrovascular disease, but there is no clinical data to support this possibility.

### Initiating and Monitoring Therapy with Metformin

When patients with NIDDM continue to have hyperglycemia despite dietary and exercise therapy, treatment with metformin or a sulfonylurea is indicated. Since the two drugs are equally effective in reducing fasting plasma glucose concentrations, either can be used initially. A sulfonylurea may be preferred because its effects are well known and it targets the decreased insulin secretion that is a particular problem in nonobese patients with NIDDM. Metformin has the potential advantage of targeting insulin resistance, which is an early feature of the disease, and reducing rather than increasing plasma insulin concentrations. Metformin does not cause weight gain and may reduce adipose-tissue mass. Thus, metformin may be preferred in obese patients with insulin resistance, although its antihyperglycemic efficacy is similar in obese and nonobese pa-

### Table 1. Pharmacokinetic Aspects of Metformin

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>50–60 percent; absorbed mainly from the small intestine; estimated absorption half-life, 0.9 to 2.6 hours</td>
</tr>
<tr>
<td>Plasma concentration</td>
<td>Maximal, 1 to 2 μg per milliliter (approximately 10⁻⁴ M) 1 to 2 hours after an oral dose of 500 to 1000 mg; negligible binding to plasma proteins</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>Estimated at 1.5 to 4.9 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Not measurably metabolized</td>
</tr>
<tr>
<td>Elimination</td>
<td>About 90 percent is eliminated in urine in 12 hours; multieponential pattern involving glomerular filtration and tubular secretion</td>
</tr>
<tr>
<td>Tissue distribution</td>
<td>Distributed in most tissues at concentrations similar to those in peripheral plasma; higher concentrations in liver and kidney; highest concentrations in salivary glands and intestinal wall</td>
</tr>
</tbody>
</table>

### Table 2. Mechanisms of the Antihyperglycemic Effect of Metformin

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppression of hepatic glucose output</td>
<td>Contributes to postsorptive and postprandial plasma glucose–lowering effect</td>
</tr>
<tr>
<td>Increased insulin-mediated glucose disposal</td>
<td>Demonstrated by glucose-clamp procedures; due at least in part to a reduction in blood glucose concentrations</td>
</tr>
<tr>
<td>Increased intestinal glucose use</td>
<td>Shown only in studies in animals</td>
</tr>
<tr>
<td>Decreased fatty-acid oxidation</td>
<td>—</td>
</tr>
</tbody>
</table>

*The quantitative contribution of each mechanism has yet to be established.*

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In two recent studies, glycemic control or a sulfonylurea is started first, the other drug will need to be added. In patients whose blood glucose concentrations were inadequately controlled by treatment with one drug, in one study 44 percent of patients taking metformin had a fasting blood glucose concentration below 121 mg per deciliter (6.7 mmol per liter), as compared with 66 percent after a sulfonylurea was added. Metformin was similarly effective as an additional treatment in patients in whom the response to treatment with a sulfonylurea alone was suboptimal. In another study, combination therapy with metformin and a sulfonylurea decreased the mean fasting plasma glucose concentration by more than 60 mg per deciliter (3.3 mmol per liter) in patients in whom glucose concentrations were poorly controlled with a sulfonylurea alone (initial mean fasting plasma glucose, 250 mg per deciliter [13.9 mmol per liter]).

To have optimal benefit, combination therapy should probably be instituted before the onset of symptomatic hyperglycemia. When treatment with a sulfonylurea fails, the addition of metformin to the regimen reduces symptoms but has only a limited effect on glycemia and, in practice, only temporarily defers the need for insulin therapy. Patients in whom metformin therapy is effective are also prone to subsequent deterioration of glycemic control, usually because of progressive beta-cell failure rather than loss of effectiveness of the drug.

When marked hyperglycemia cannot be controlled by maximal doses of combination therapy, insulin therapy is indicated. The decision will depend in part on the age of the patient: the younger the patient, the more likely that physicians will believe that the results of the Diabetes Control and Complications Trial apply and therefore that insulin therapy is indicated. In elderly patients, the main goal may be to reduce the blood glucose concentrations sufficiently to prevent symptoms of hyperglycemia. These symptoms usually occur improved when the second drug was added in patients whose blood glucose concentrations were inadequately controlled by treatment with one drug.

Table 3. Clinical Use of Metformin.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of therapy</td>
<td>Monotherapy; combination therapy with a sulfonylurea</td>
</tr>
<tr>
<td>Indications</td>
<td>After failure of dietary therapy in NIDDM, especially in overweight patients; after failure to achieve acceptable glycemic control with sulfonylurea therapy</td>
</tr>
<tr>
<td>Tablet sizes</td>
<td>500 mg: 850 mg</td>
</tr>
<tr>
<td>Treatment schedule</td>
<td>Should be taken with meals; dose should be increased slowly; maximal dose, 2550 mg daily</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Renal and hepatic disease; cardiac or respiratory insufficiency; any hypertrophic condition; severe infection; alcohol abuse; history of lactic acidosis; use of intravenous radiographic contrast agents; pregnancy</td>
</tr>
<tr>
<td>Side effects</td>
<td>Gastrointestinal symptoms (diarrhea, nausea, abdominal discomfort, anorexia) and metallic taste, which improve with dose reduction; may impair absorption of vitamin B12 and folic acid</td>
</tr>
<tr>
<td>Adverse reactions</td>
<td>A risk of lactic acidosis in patients with any of the listed contraindications; hypoglycemia if taken with a sulfonylurea or in the presence of alcohol abuse</td>
</tr>
<tr>
<td>Precautions</td>
<td>Medical history should be checked for contraindications; hemoglobin and plasma creatinine concentrations should be checked periodically; should be administered with caution in patients receiving concomitant cimetidine therapy (may reduce renal tubular secretion of metformin)</td>
</tr>
</tbody>
</table>

Table 4. Exclusion Criteria for the Use of Metformin.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Plasma creatinine values ≥1.5 mg per deciliter (132 μmol per liter) for men and ≥1.4 mg per deciliter (124 μmol per liter) for women</td>
</tr>
<tr>
<td>Cardiac or respiratory insufficiency</td>
<td>That is likely to cause central hypoxia or reduced peripheral perfusion</td>
</tr>
<tr>
<td>History of lactic acidosis</td>
<td>Severe infection that could lead to decreased tissue perfusion</td>
</tr>
<tr>
<td>Liver disease, including alcoholic liver disease, as demonstrated by abnormal liver-function tests</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse with binge drinking sufficient to cause acute hepatic toxicity</td>
<td></td>
</tr>
</tbody>
</table>

*Use of intravenous radiographic contrast agents?

†It is uncertain whether the reported occurrence of lactic acidosis after the intravenous administration of radiographic contrast agent was due in part to preexisting renal disease and reduced fluid intake before the imaging was performed.
when fasting plasma glucose concentrations exceed 200 to 250 mg per deciliter (11.1 to 13.9 mmol per liter), and in the elderly such concentrations may be regarded as reasonable provided that the patient is not thirsty or tired.

Patients with IDDM are not candidates for metformin therapy. For patients with NIDDM who require insulin, it is customary to stop metformin before starting insulin therapy. Although metformin can be given with insulin to reduce the dose of insulin, this is not a common practice.\textsuperscript{1,30}

\section*{Lactic Acidosis}

Lactic acidosis is a rare but serious adverse effect in metformin-treated patients, with an estimated incidence of less than 0.01 to 0.08 case (average, 0.03) per 1000 patient-years.\textsuperscript{1,30,34} In most patients it occurs because one or more contraindications were overlooked, predominately renal insufficiency, leading to high plasma metformin concentrations. Additional factors that increase blood lactate concentrations are often present — for example, a major illness causing hypotension with low tissue perfusion, other causes of hypoxia, liver disease, or alcohol abuse. In these situations the plasma metformin concentration is not necessarily abnormally high. It is important to realize that blood lactate concentrations become elevated in any patient in whom cardiogenic shock or other illnesses decrease tissue perfusion, and in some reported cases, the metformin was probably an incidental factor and not responsible for the lactic acidosis. The mortality in reported cases is about 50 percent.\textsuperscript{1,30,51,62} The risk of death from lactic acidosis in metformin-treated patients is similar to that of hypoglycemia in sulfonylurea-treated patients.\textsuperscript{52,63} Should a patient have lactic acidosis attributable to metformin, the drug can be removed by hemodialysis.\textsuperscript{64,65}

In practice, in countries where metformin is used widely, lactic acidosis is not regarded as a major problem, probably because of adherence to the exclusion criteria (Table 4). This situation is quite different from the earlier experience with phenformin, which is estimated to have a risk of lactic acidosis that is 10 to 20 times greater than that for metformin.\textsuperscript{30,51,63} After phenformin was withdrawn from clinical use, it was found that some people (e.g., about 10 percent of whites) have an inherited defect in the hydroxylation of this drug.\textsuperscript{66} Because they are unable to metabolize phenformin adequately, these patients have an increased risk of drug accumulation, which probably accounts for the higher incidence of lactic acidosis with phenformin. This condition does not occur with metformin, which is not metabolized. In addition, metformin does not inhibit peripheral glucose oxidation and does not enhance peripheral lactate production, as occurs with phenformin.

\section*{USE OF METFORMIN THERAPY DURING INTERVENING ILLNESSES}

If a metformin-treated patient has a serious illness that is one of the exclusion criteria listed in Table 4, metformin should be stopped and treatment with insulin initiated. Metformin therapy should also be stopped if the blood lactate concentration is substantially increased by any illness. In practice it is advisable to apply the exclusion criteria in a blanket fashion, rather than waiting for the results of blood lactate measurements.

Long-term therapy with metformin is associated with decreased intestinal absorption of vitamin B\textsubscript{12} and folate,\textsuperscript{1,30} however, anemia has developed in very few patients. Low plasma vitamin B\textsubscript{12} or folate concentrations are rarely clinically important and are reversed by the discontinuation of metformin or by appropriate supplementation.

Metformin therapy is practical in elderly patients, provided that the exclusion criteria are applied, but lower doses and more frequent assessments are recommended. The plasma creatinine concentration should be measured periodically in all patients, but especially the elderly.

\section*{Conclusions}

The efficacy of metformin in lowering blood glucose concentrations in obese and nonobese patients with NIDDM is similar to that achieved with a sulfonylurea. However, metformin does not cause weight gain, reduces rather than increases plasma insulin concentrations, and rarely causes overt hypoglycemia. It can be used either as first-line therapy or in combination with a sulfonylurea. The rare but serious condition of lactic acidosis must be recognized as a potential adverse effect. However, if metformin is avoided in patients with contraindications to its use, the drug is safe. Metformin is complementary to sulfonylurea and dietary therapy and represents a useful additional drug for the management of NIDDM.

\section*{References}