The Pharmacological Treatment of Hyperglycemia in NIDDM

In the U.S. and throughout the world, the prevalence of diabetes is increasing, especially among non-white populations. The increase in non-insulin-dependent diabetes mellitus (NIDDM) may largely be due to an increased prevalence of obesity and decreased physical activity. About 90% of people with diabetes have NIDDM, which is a heterogeneous disorder involving impairment of both insulin secretion and insulin action.

People with diabetes suffer from increased morbidity and early mortality related to cardiovascular, microvascular, and neuropathic complications. The Diabetes Control and Complications Trial (DCCT) convincingly demonstrated the relationship of hyperglycemia to the development and progression of microvascular and neuropathic complications in people with insulin-dependent diabetes mellitus (IDDM) and showed that improved glycemic control achieved through an intensive insulin treatment regimen reduced these complications. Although no similar well-controlled prospective study has been completed in people with NIDDM, there is ample evidence supporting the same relationship between hyperglycemia and these complications. For example, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found a strong correlation between the degree of elevation of glycosylated hemoglobin and the development and progression of retinopathy in people with NIDDM regardless of the diabetes treatment.

The relationship between the cardiovascular complications of diabetes and hyperglycemia has been more difficult to determine and remains controversial. Additionally, it is not known to what extent, if any, reduction of hyperglycemia will reduce long-term macrovascular complications in both NIDDM and IDDM patients.

If one accepts the hypothesis that improved glycemic control may reduce the complications of NIDDM, then major efforts should be made to develop and implement more effective treatment regimens. Many studies have demonstrated that most people with NIDDM do not achieve the treatment goals recommended by the American Diabetes Association (Table 1). Diet and exercise therapy alone are not successful in controlling hyperglycemia in the majority of people with NIDDM. In contrast to IDDM, in which insulin deficiency is the problem and insulin replacement the treatment, in NIDDM the pharmacological approach to hyperglycemia is more varied and more rapidly evolving. With the goal of developing recommendations for the pharmacological treatment of hyperglycemia in NIDDM, the American Diabetes Association convened a Consensus Development Conference on 12–13 July 1995 in Philadelphia, PA. An eight-member panel, with audience participation, discussed the presentations of 18 experts in relevant subjects and subsequently addressed the following questions.

1. When should pharmacological agents be used in the treatment of NIDDM?
2. Should the characteristics of different patient populations influence treatment?
3. Do the differences in the mechanisms of action or side effects of pharmacological agents influence the choice of therapy?
4. Should the concern about possible adverse effects of hyperinsulinemia influence the choice of therapy?
5. Does combination therapy increase the effectiveness of treatment or influence drug side effects?
6. Considering the answers to the above questions, can recommendations for pharmacological therapy be proposed?
7. What are the desired properties of future drugs for the treatment of NIDDM?

QUESTION 1: WHEN SHOULD PHARMACOLOGICAL AGENTS BE USED IN TREATMENT OF NIDDM? —

Most data suggest that the pathogenesis of the microvascular complications seen in NIDDM and IDDM is similar. In the DCCT, a 50% reduction in microvascular complications was achieved with a mean HbA_{1c} of 7.2% in the intensive insulin treated cohort. Indeed, the data suggest that any improvement in the degree of blood glucose control will postpone development and slow the progression of microvascular complications.

As a result of the DCCT and other studies, the American Diabetes Association has recommended treatment goals for people with diabetes that emphasize glycemic control (Table 1). Many factors, however, influence the extent to which these goals can be achieved. The initial treatment of choice in patients with NIDDM is optimization of the meal plan and enhancement of physical activity. However, it is often difficult to sustain the desired level of glycemic control with nonpharmacological therapy alone, which results in an acceptable level of long-term glycemic control in less than 10% of patients.

If progress toward glycemic goals is not apparent within a 3-month period

Table 1—*Glycemic control for people with diabetes*

Biochemical index	Nondiabetic	Goal	Action suggested
Preprandial glucose	<115	80–120	<80 >140
Bedtime glucose (mg/dl)	<120	100–140	<100 >160
HbA_{1c} (%)	<6	<7	>8

These values are for nonpregnant individuals. Action suggested depends on individual patient circumstances, HbA_{1c} is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, SD 0.5%).

after initiation of diet and exercise therapy, then the use of a pharmacological agent is appropriate. Diet therapy and a physical activity program should always be reinforced. Some patients, however, require prompt pharmacological therapy (e.g., those with symptoms of hyperglycemia, those patients undergoing surgery, those with ketosis) at the time of diagnosis or first visit. The natural history of NIDDM results in a worsening of hyperglycemia and therefore requires frequent reevaluation of the treatment plan. A number of variables should be considered by the patient and physician when making the decision regarding when to initiate pharmacological therapy. Such factors may influence the decision about which agent or combination of agents is preferable. These variables include:

- Demographic characteristics (e.g., age, gender, race, socioeconomic status).
- Resources (e.g., access to health care, self-care skills, finances/health insurance, family support).
- Health/disease status (e.g., coexisting diseases, complications of diabetes).

In initiating pharmacological therapy, it is prudent to have a well-ordered treatment plan developed by the health care professional and the patient. Progress toward glycemic goals should be evaluated regularly, permitting timely changes in therapy if goals have not been achieved.

The use of pharmacological agents in patients with NIDDM may vary not only from patient to patient but across time in the same patient. Compliance by the patient when using pharmacological therapy needs to be assessed regularly to ensure adherence to the treatment program. Compliance is heightened when the patient participates actively in determining the goals of treatment and the treatment plan. Patient education is a crucial element in achieving active patient involvement and commitment.

QUESTION 2: SHOULD THE CHARACTERISTICS OF VARIOUS PATIENT POPULATIONS INFLUENCE TREATMENT?

— Characteristics of the patient that should be taken into account when considering the choice of pharmacological treatment of NIDDM include:

1. Race or ethnic background.
2. Age and gender.
3. The possibility of unrecognized IDDM.

The regulation of blood glucose involves the pancreatic islet (insulin secretion), the muscle and fat (insulin action), and the liver (glucose production). The β-cell lesion of NIDDM is characterized by a defect in the ability to respond normally to changes in plasma glucose. Resistance to insulin action in muscle and fat is also present in nearly all patients and is closely associated with abdominal obesity. As long as β-cell function is preserved, insulin resistance per se does not lead to hyperglycemia. Inappropriately increased hepatic production of glucose contributes significantly to fasting hyperglycemia in NIDDM. In various populations, the relative contributions of abnormal islet β-cell function, insulin resistance, and hepatic glucose overproduction may vary, and pharmacological treatment might be influenced by these variations.

In many non-white (Japanese-American, Hispanic-American, and Native American) populations, the prevalence of NIDDM is much higher than in the white population. To a large extent this seems to be due to the unmasking of a genetic predisposition to NIDDM resulting from the adoption of lifestyle practices that include a reduction in physical activity and an increased consumption of calories, particularly from saturated fat. The resulting adiposity follows a central distribution pattern and, as found in studies where this has been specifically examined, is intra-abdominal (visceral). The visceral fat depot may increase substantially without much effect on body weight.

Central adiposity is associated with hyperinsulinemia and dyslipidemia (high triglycerides, low high-density lipoprotein (HDL) cholesterol, and small dense low-density lipoprotein particles) and an increased risk of developing hypertension and macrovascular disease. Populations in which this association has been demonstrated include whites, African-Americans, Asian Indians, and Japanese-Americans.

Even when central adiposity is associated with NIDDM in these four populations, there are several notable differences. Among African-Americans, coronary artery disease and hyperinsulinemia are not as frequently associated with NIDDM in comparison with other groups, whereas hypertension and microvascular disease are. Nonetheless, there is still a strong relationship between insulin resistance and intra-abdominal fat in African-Americans. Among Asian Indians, coronary artery disease and hyperinsulinemia are associated with NIDDM and central adiposity. There is also an increased occurrence of nephropathy associated with NIDDM. In Japanese-Americans, coronary artery disease, hypertension, and hyperinsulinemia are associated with NIDDM and intra-abdominal fat.

In Japan, however, coronary artery disease is not as prevalent in diabetic patients as it is in many other countries, although nephropathy and cerebrovascular disease are increased to a similar or even greater extent. In the U.K. Prospective Diabetes Study (UKPDS), Afro-Caribbean participants had lower insulin levels than Asian Indians, suggesting more β-cell dysfunction in Afro-Caribbeans and better β-cell function in Asian Indians. Insulin sensitivity was lower in Asian Indians than in Afro-Caribbeans. Pharmacological approaches that decrease adiposity and decrease insulin resistance may be preferred in these populations.

In addition to these differences in the pathogenesis of hyperglycemia, there is a suggestion of differences in racial susceptibility to severe diabetic retinopathy, the prevalence of which is higher in African-Americans and Mexican-Americans with NIDDM than in the white U.S. population. Whether this is due to intrinsic differences in the expression of diabetes or to differences in glycemic control is uncertain. The latter possibility is supported by several community-based population studies where the mean fasting and 2-h postchallenge plasma glucose levels tended to be higher in non-white than in white populations. The prevalence of NIDDM increases with age, such that the prevalence of diagnosed diabetes exceeds 10% of the U.S. population over 65 years of age. When considering pharmacological treatment in older individuals, the possibility of greater morbidity as a consequence of hypoglycemia must be considered. Thus, agents that have a lower likelihood of causing hypoglycemia may be preferred in older patients.

The use of oral pharmacological agents in women of child-bearing potential or who are breast-feeding deserves special mention. Because of the possibility of teratogenicity, these drugs should be stopped as soon as pregnancy is known or preferably when pregnancy is planned, and if appropriate, insulin therapy should be initiated to achieve glycemic goals. Nursing mothers should not take these drugs because of the possibility of secretion into breast milk.

There is also the possibility that some of the so-called NIDDM cases may really be late-onset IDDM, a subcategory of diabetes in adults that may not present in the classic manner of IDDM in younger individuals. This condition is more common than formerly believed and tends to occur more often in patients of European than of Asian or African descent. In white populations, perhaps as many as 10–20% of people diagnosed with diabetes in adulthood have evidence of markers related to autoimmune diabetes. The typical patient is 35 years or older, is not obese, presents with what appears to be NIDDM, can often be controlled with diet, but within a short period of months to a few years requires oral agents and subsequently progresses to insulin dependency.

QUESTION 3: DO DIFFERENCES IN THE MECHANISMS OF ACTION OR SIDE EFFECTS OF PHARMACOLOGICAL AGENTS INFLUENCE THE CHOICE OF THERAPY?

— The four classes of widely used antidiabetic therapeutic agents have mechanisms of action that have different effects on one or more of the pathogenetic abnormalities of NIDDM. Theoretically, an argument can be made to individualize pharmacological therapy based on the predominant pathogenesis of hyperglycemia in the patient. In practice, however, this approach is not easily accomplished because several factors, including cost, side-effect profile, urgency of glucose normalization, and ease of administration, must be considered in addition to mechanism of action.

Mechanisms of action

The sulfonylurea agents have been in clinical use in the U.S. for about four decades. Both short- and long-acting agents have been approved by the Food and Drug Administration (FDA) for use in NIDDM. Although the side-effect profiles and pharmacokinetics differ for each member of the group, all appear to act primarily by potentiating insulin secretion. Their ability to increase insulin sensitivity is probably secondary to the lowering of plasma glucose concentration.

In contrast, the biguanides have no direct effect on insulin secretion. Their mechanism or mechanisms of action are not completely understood but include a reduction in hepatic glucose production and perhaps an increase in peripheral insulin sensitivity and reduction in intestinal glucose absorption.

A third class of drugs is the α-glucosidase inhibitors, one of which (acarbose) has recently been approved by the FDA. These agents inhibit specific enzymes that break down starches in the small intestine, thereby delaying carbohydrate absorption and attenuating postprandial hyperglycemia.

A fourth class of therapeutic drugs is the insulin preparations that supplement endogenous insulin. In addition to suppressing hepatic glucose production, exogenous insulin may improve insulin sensitivity indirectly by correcting hyperglycemia.

Choice of therapy

Sulfonylureas are a rational choice to begin pharmacological intervention because almost all patients with NIDDM are relatively insulin deficient. It is beyond the scope of this report to describe the various pharmacokinetic properties, side effects, drug-drug interactions, and costs of sulfonylurea preparations that may influence drug selection. An increase in endogenous insulin secretion and reduction in plasma glucose is usually observed with these agents. Unfortunately, this beneficial response is not necessarily maintained for the duration of therapy. After a variable time period (usually several years), the patient's endogenous insulin secretion declines so that it is no longer sufficient to maintain near-normal glycemia.

Biguanides have been used to treat NIDDM as monotherapy or in combination with sulfonylureas. The initial clinical response to biguanides alone depends on the initial fasting glucose con-

centration and is similar to that observed when sulfonylureas are used alone, i.e., a decline of fasting plasma glucose of ~60 mg/dl. One advantage of biguanide treatment compared with sulfonylurea or insulin treatment is that the patient does not usually gain weight after initiation of therapy. Another advantage when compared with sulfonylureas is a greater improvement in the dyslipidemic profile characteristic of NIDDM. However, similar to that of sulfonylureas, the effectiveness of biguanides slowly declines over time so that other therapeutic approaches become necessary.

An α-glucosidase inhibitor (acarbose) has been widely used in Europe for several years with varying success. The glycated hemoglobin level usually declines by 0.5–1.0% in patients who take this medication, in contrast to about a 1.5–2.0% reduction in patients taking sulfonylureas and biguanides. This agent is particularly useful in patients who have significant postprandial hyperglycemia. Because it acts by delaying the hydrolysis of complex carbohydrates thereby slowing their absorption, there is essentially no risk of hypoglycemia.

As the effectiveness of oral agents declines, the initiation of insulin therapy is frequently required. Some physicians use insulin as the initial pharmacological agent in patients with NIDDM. The choice of insulin regimen should be tailored to the needs of the patient.

Factors affecting compliance

The choice of a pharmacological agent to treat NIDDM is influenced by the likely compliance with the regimen. Sulfonylureas are relatively inexpensive, particularly since some are widely available in generic preparations. They can be taken once a day and have few side effects when taken as directed. Hypoglycemia is the main concern, and a tendency to gain weight on sulfonylureas may be disconcerting to the patient.

Metformin, the only biguanide approved for use in the U.S., is more expensive than sulfonylureas, does not cause hypoglycemia, and is not associated with weight gain. The incidence of lactic acidosis with metformin is 0.03 per 1,000 patient years of use and is usually seen in patients who have renal disease or other known risk factors. Of most concern is the occurrence of gastrointestinal side effects, most commonly diarrhea, which may be present early in the course of therapy in up to 30% of individuals. Appropriate dosing schedules and the passage of time may significantly reduce this side effect.

Acarbose dosing schedules require it to be taken before each meal, potentially reducing compliance. Its side effects are almost exclusively gastrointestinal secondary to the presence of undigested carbohydrate in the large intestine, which induces flatulence and abdominal discomfort. Avoidance of large amounts of starch in the diet may lessen these side effects.

Finally, insulin is relatively inexpensive, but therapy requires a subcutaneous injection, which most patients initially prefer to avoid. Associated costs of therapy may include the need for more glucose monitoring and physician visits. Also, insulin therapy is often associated with weight gain.

QUESTION 4: SHOULD THE CONCERN ABOUT POSSIBLE ADVERSE EFFECTS OF HYPERINSULINEMIA INFLUENCE THE CHOICE OF THERAPY?

— The relationship between hyperglycemia and macrovascular disease in NIDDM has been difficult to demonstrate. This relationship is particularly important, since coronary, peripheral, and cerebral vascular disease are the major causes of morbidity and mortality in these patients. It has been proposed that factors in addition to hyperglycemia may contribute to the increased incidence of macrovascular disease in NIDDM. Many of these factors have been identified (e.g., hypertension, low HDL cholesterol, high triglycerides, abdominal obesity, and hypercoagulability). Recent attention has focused on the potential role of insulin resistance and/or hyperinsulinemia.

If cardiovascular disease is a direct complication of diabetes, then its incidence should increase in proportion to the severity and duration of exposure to hyperglycemia. Some cross-sectional studies in elderly populations support this association. In contrast, several population-based studies have shown that the incidence of vascular events begins to rise very early in the course of NIDDM or is seen even in patients with impaired glucose tolerance before overt diabetes develops. This finding suggests that both NIDDM and atherosclerotic cardiovascular disease may arise from (or be closely associated with) a common set of predisposing environmental and genetic risk factors. Evidence suggests that these factors include insulin resistance and/or hyperinsulinemia, dyslipidemia, hypertension, and abdominal obesity. The association of these factors has commonly been called the insulin resistance syndrome or syndrome X.

Several epidemiological studies have examined these relationships. Over a decade ago, the Helsinki Policeman Study, the Busselton (Australia) Study, and the Paris Prospective Study all demonstrated significant associations between either fasting or postprandial hyperinsulinemia and increased risk of coronary heart disease. In contrast, more recent reports in Pima Indians, San Luis Valley Hispanics, the Rancho Bernardo Study, and patients with NIDDM in the Multiple Risk Factor Intervention Trial (MRFIT) have not shown this association. Important differences between the early studies and these latter reports are that *1*) the effect of insulin was analyzed in a multivariate analysis to remove the confounding effects of obesity, aging, and other factors on insulin levels and 2) the populations included more African-Americans, Hispanics, Native Americans, and women. In addition, many small retrospective studies have suggested that patients with NIDDM receiving insulin therapy have higher mortality, worse coronary artery disease as determined by angiography, and more frequent ECG ab-

normalities. Unfortunately, many of these studies did not control for confounding variables such as duration and severity of diabetes, obesity, or other risk factors. Thus, hyperinsulinemia appears to be more of a marker for other risk factors rather than a risk factor itself, and it is a better marker in white populations than in some other racial and ethnic groups.

Since many patients with hypertension and vascular disease are insulin resistant and hyperinsulinemic, it has frequently been assumed that hyperinsulinemia is directly involved in the pathogenesis of elevated blood pressure or subsequent vascular events. In favor of this concept, several in vitro studies, animal models, or short-term physiological studies in humans suggest that hyperinsulinemia *1*) stimulates the accumulation of lipid in vascular intimal plaques, 2) enhances the proliferation of vascular smooth muscle, 3) stimulates the release of plasminogen activator inhibitor 1 and endothelin, 4) reverses the protective effects of estrogen or low-cholesterol diet on regression of atherosclerosis, 5) increases sympathetic nervous system activity, and *6*) promotes sodium retention. Conversely, other studies have now clearly demonstrated that *1*) insulin has predominantly acute vasodilatory effects in vivo, 2) insulin is capable of antagonizing the vasoconstrictor effects of norepinephrine, angiotensin II, and other pressor agents, and *3*) these vasodilatory effects are closely related to the ability of insulin to enhance glucose uptake (i.e., insulin sensitivity). Finally, states of chronic hyperinsulinemia that are not primarily associated with insulin resistance (for example, insulinoma) are not associated with increased blood pressure or cardiovascular risk. Thus, it appears clear that insulin has significant vasoregulatory functions, but it is not well established how (or even whether) it contributes to the actual development of elevated blood pressure.

There are very few prospective interventional studies that have carefully examined the effect of insulin dose (or circulating insulin levels) on cardiovascular morbidity or mortality. In the University Group Diabetes Program (UGDP), insulin treatment of NIDDM patients did not affect cardiovascular outcomes when compared with diet treatment alone. Similarly, the UKPDS has compared the outcomes in NIDDM patients initially randomized to either diet, glyburide, chlorpropamide, or insulin and has not detected any difference in cardiovascular risk factors (specifically blood pressure, triglycerides, and HDL cholesterol) or cardiovascular events among the four groups in 6-year follow-up data. Conversely, the preliminary results of the Veterans Affairs Cooperative Study of Diabetes Mellitus (VA-CSDM) suggest that intensive glucose control achieved by combination therapy with sulfonylureas and insulin or with two or more daily injections of insulin may have a higher rate of cardiovascular events than standard treatment, although the single greatest predictor of such events was a previous history of cardiovascular disease and the insulin dose itself was not predictive. In addition to these prospective interventional studies, short-term physiological studies of intensive glycemic management by exogenous insulin administration have shown improvement in lipid profiles, which may reduce cardiovascular disease.

Perhaps the two best-documented adverse effects of administration of exogenous insulin are hypoglycemia and weight gain. Hypoglycemia most commonly occurs when decreases in dietary intake or increases in physical activity are not accompanied by appropriate adjustment in therapy or when vigorous efforts are made to achieve near-normal glycemia. Fortunately, most patients with NIDDM possess intact glucose counterregulatory mechanisms, and severe hypoglycemia is rare except in patients receiving long-term insulin therapy.

Weight gain is very commonly seen in patients after initiation of insulin therapy and has been attributed to decreased caloric loss in the urine, increased appetite, and reduced basal metabolic rate. Although modest weight gain probably has minimal effects, excessive weight gain may adversely affect other cardiovascular risk factors including dyslipidemia, hypercholesterolemia, and hypertension.

In summary,

1. The hyperinsulinemia associated with NIDDM, hypertension, dyslipidemia, obesity, and atherosclerotic cardiovascular disease (syndrome X) is likely to be a marker of the insulin-resistant state rather than a causative agent in the specific components of the syndrome.
2. Efforts to reduce insulin resistance by nonpharmacological means (diet and exercise) are a crucial component of the management of NIDDM.
3. As mentioned previously, any pharmacological agent that improves glycemic control (including sulfonylureas, biguanides, α-glucosidase inhibitors, and insulin) will enhance insulin sensitivity because of the overall improvement in the metabolic milieu and the amelioration of the hyperglycemia-induced defects in insulin action and secretion.
4. Therapies that stimulate endogenous insulin secretion or that involve exogenous insulin administration tend to enhance weight gain.
5. Exogenous insulin administration does not appear to have *direct* adverse effects on cardiovascular events and may even favorably affect the cardiovascular risk profile if the improved glycemic control and lipid profile are sustained.
6. Exogenous insulin or sulfonylureas should be used with the goal of achieving optimal glucose control, since simultaneous exposure to chronic hyperglycemia and hyperinsulinemia may be particularly deleterious.

QUESTION 5: DOES COMBINATION THERAPY INCREASE THE EFFECTIVENESS OF TREATMENT OR INFLUENCE DRUG SIDE EFFECTS?

— The recent interest in combination therapy, defined as the use of two or more pharma-

cological agents, reflects two general goals. First, the availability of agents that act by differing mechanisms or may have differing side effects permits the design of individualized regimens that address the heterogeneity of the pathophysiology of NIDDM. This approach may facilitate the optimization of pharmacotherapy, whether for reasons of effectiveness of metabolic control, cost-effectiveness, or ease of patient adherence and clinical use. Thus, it may be theoretically desirable to use combination therapy in some patients when pharmacological therapy is initiated. Second, and perhaps more important, the goal of metabolic control may not be attainable with a single agent. The combination approach reflects the likelihood that monotherapy with any currently available oral agent is likely to fail over time in the majority of patients.

It should be emphasized that most trials of combination therapy have been conducted in NIDDM patients later in the course of their disease and no convincing data exist to support the immediate application of such regimens from the time of diagnosis. Furthermore, these complex regimens require better patient and physician knowledge and a readiness to adapt to the changing needs of an evolving disease process and therapeutic environment.

Data from recent U.S. national surveys indicate that ~54% of patients with NIDDM are treated with sulfonylurea agents and/or diet and exercise, while 36% are treated with insulin. Only 10–15% of patients are treated with diet alone. Furthermore, over the course of 15 years' duration of diabetes, the proportion of patients using oral agents alone declines from ~65 to ~25%, with a corresponding increase in the proportion of patients using insulin rising from ~20 to ~60%. This pattern in the pharmacological treatment of NIDDM presumably reflects the inadequacy of metabolic control or the progression of the underlying disease. Moreover, in the UKPDS, 95% of newly diagnosed patients failed to normalize their fasting plasma glucose and HbA_{1c} after a 3-month dietary intervention and required treatment with a pharmacological agent.

This primary therapy failure is manifested by rising fasting and/or postprandial plasma glucose concentrations with or without concomitant development of symptoms of uncontrolled diabetes. Although the classical symptoms and signs of hyperglycemia frequently lead to the clinical decision to alter therapy, it is not appropriate to delay change in treatment until symptoms develop. The determinants of progressively worsening hyperglycemia in NIDDM are not established. Clearly, the pathophysiology of NIDDM involves both progressive failure of β-cell insulin secretion and worsening insulin resistance, and one or both factors must certainly play a role in primary treatment failure. Concomitant changes in body weight and fat distribution, either independently or as a consequence of therapy, may be important. In addition, factors such as dyslipidemia and other metabolic derangements, aging, decreased physical activity, and treatment of comorbidities such as hypertension may render previously effective therapy no longer adequate. Finally, it remains uncertain whether initial treatment strategies have been adequately exploited and whether patients have complied with such treatment.

Clinical trials of combination therapy have thus been undertaken generally in individuals with established NIDDM of relatively long duration and usually poor glycemic control. Combination therapy could have the potential advantages of increasing therapeutic effectiveness of both agents (lowering glycemia may improve insulin secretion and action per se), decreasing side effects (assuming that lower doses of the agents could be used), and delaying the initiation of insulin therapy in some individuals. Two approaches to combination therapy will be discussed: first, regimens of two or more oral agents (sulfonylureas, biguanides, and α-glucosidase inhibitors) and second, regimens of oral agent(s) combined with insulin.

Evidence regarding combined treatment with sulfonylureas and metformin comes from several studies, both controlled and uncontrolled and in obese and nonobese individuals, with follow-up durations ranging from several weeks to 6 months. Many studies examined the effect of metformin in doses from 1.5 to 2.5 g daily in patients with NIDDM who had failed monotherapy with sulfonylureas. In these studies, both first- and second-generation sulfonylureas were used at relatively high doses. The reductions in fasting plasma glucose (25–30%) and glycated hemoglobin (20–30%) were achieved in a reasonably consistent fashion. There did not appear to be an increase in side effects of either drug type; indeed, metformin seemed not to potentiate the frequency of hypoglycemia and may have had a beneficial effect on dyslipidemia associated with poor metabolic control. In a single controlled trial in subjects with mild hyperglycemia with diet failure in which lower-dose combinations of metformin and glyburide were compared with either drug alone, there was no additive benefit in glucose control beyond that achieved with either drug alone. In contrast, when fasting plasma glucose exceeds 200 mg/dl and HbA_{1c} is above 8%, combined therapy with maximally or near-maximally effective doses of the two agents may be indicated. Short-term studies have not demonstrated that the sequence of such therapeutic additions will significantly alter the effectiveness of combined therapy. Furthermore, there is no evidence of significant drug interactions in such regimens, though they place greater demands in terms of complexity of dosing and potential for errors. Finally, it seems prudent to consider titration of both agents in individual patients.

The addition of an α-glucosidase inhibitor (acarbose) to a sulfonylurea has been studied as part of a series of trials conducted recently in the U.S. and Canada. In these studies, the addition of acarbose in progressively titrated doses resulted

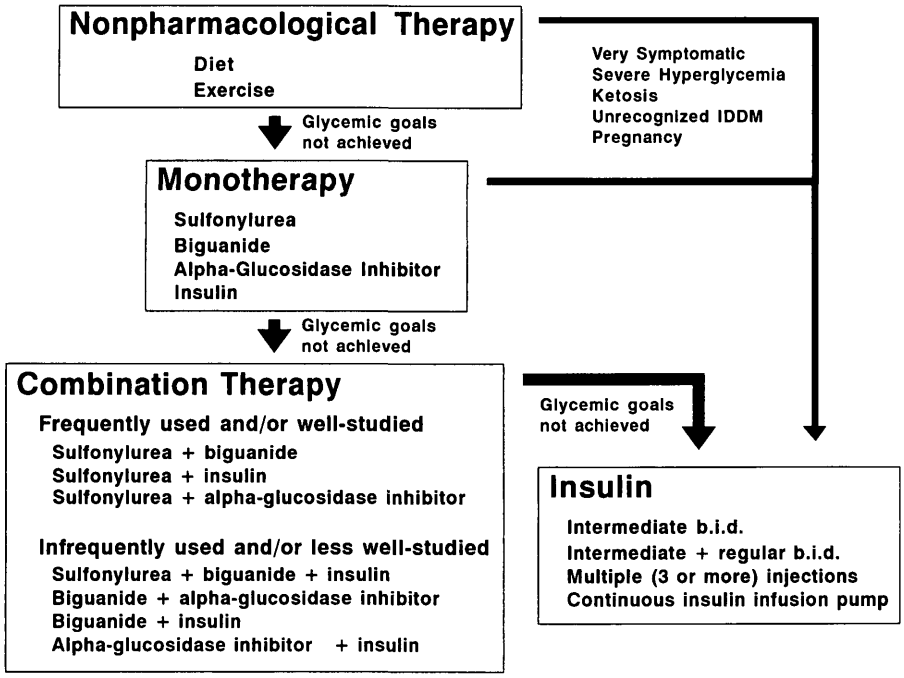

Figure 1—*Pharmacological therapy of NIDDM.*

in significant reduction in postprandial glycemia, modest declines in fasting plasma glucose concentrations, and an overall decrease in HbA_{1c} by 0.5–1.0%. There was no greater prevalence of hypoglycemia due to the sulfonylurea or gastrointestinal side effects due to acarbose than in monotherapy with either agent.

At present, there is a paucity of experience with acarbose combined with metformin. At least from a theoretical perspective, the potential for a greater frequency of gastrointestinal side effects exists for such combination therapy. Furthermore, there may be a reduction in the bioavailability of metformin with concomitant use of acarbose, though it remains unclear whether these pharmacokinetic changes influence clinical outcome.

The use of combined insulin–oral agent therapy has received a great deal of attention in the past decade. Adding insulin to sulfonylurea therapy is based on the premise that correction of fasting hyperglycemia by insulin injected at bedtime may allow for improved action of the sulfonylurea during the daytime. In general, therefore, these combinations have focused on the use of intermediate- or long-acting insulin preparations taken in the evening or at bedtime. Two meta-analyses and several recent controlled trials suggest that reductions of ~1.0–1.5% in glycated hemoglobin values may be expected. The potential advantage of this approach is improved glycemia with relatively lower doses of insulin and a reduced tendency to gain weight. Finally, in those studies that have been extended beyond 6 months, the tendency for HbA_{1c} levels to rise both in nonobese and, especially, in obese patients may necessitate increasing insulin doses. Not all studies have shown a benefit of combination therapy over optimized insulin therapy.

The clinical utility of combined insulin–oral agent regimens initiated early in the course of NIDDM needs to be established. There is as yet insufficient evidence from controlled clinical trials to permit the recommendation for the use of insulin with metformin or a sulfonylurea in patients with less severe hyperglycemia.

QUESTION 6: CONSIDERING THE ANSWERS TO THE ABOVE QUESTIONS, CAN RECOMMENDATIONS FOR PHARMACOLOGICAL THERAPY BE PROPOSED?

— If the patient has not achieved the desired glycemic goals after reasonable attempts at nonpharmacological therapy (typically 3 months), then pharmacological intervention is indicated (Fig. 1). If the patient is very symptomatic, has severe hyperglycemia, or is suspected as having IDDM, then insulin therapy may be initiated, typically requiring two or more injections per day. In most patients, however, pharmacological therapy begins with low doses of an agent from one of the four available classes of antidiabetic agents.

Although all four classes of agents are clearly effective as initial monotherapy, certain characteristics of the agents may help guide the initial choice. Sulfonylureas (acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide) generally have few side effects, have been used for many years, and are less expensive since most are available as generic preparations. The various agents have differences in pharmacokinetic and pharmacodynamic properties. These agents are generally comparable in their effectiveness in reducing hyperglycemia, although differences in pharmacokinetics and pharmacodynamics may influence the choice in an individual patient. The major adverse effects of treatment are risk of hypoglycemia and weight gain. Prescribing instructions, as detailed in the package insert, in patients with renal disease, liver disease, cardiovascular disease, and other conditions should be followed.

Biguanides (metformin) are also effective as initial monotherapy and have been used extensively worldwide for almost 40 years. Potential benefits of metformin include lack of weight gain (or even moderate weight loss), beneficial effects on lipid profiles independent of the improvement in glycemia, and low risk of hypoglycemia. However, self-limited gas-

trointestinal side effects are common, and the drug should not be used in patients with renal, liver, or advanced cardiovascular disease. Direct comparisons between metformin and sulfonylureas have generally shown equal efficacy in the initial treatment of NIDDM.

α-Glucosidase inhibitors (acarbose) may also be used as initial therapy, although they tend to be somewhat less efficacious than sulfonylureas or biguanides. They have a low risk of hypoglycemia and are associated with little or no weight gain. Gastrointestinal distress (flatulence, bloating, diarrhea) occurs frequently but tends to abate with continued treatment.

When used properly and in adequate doses, insulin is effective in lowering glucose levels. Potential disadvantages of insulin therapy include hypoglycemia, weight gain, an inconvenient method of administration, and the need for more frequent self-monitoring of blood glucose.

If glycemic goals are not maintained with the initial medication, there are little data to support that changing to a different oral agent as monotherapy provides clinically meaningful benefit. Thus, the physician is faced with two major options. If the patient is very symptomatic, hyperglycemic, and shows other signs of severe insulin deficiency (ketonuria, uncontrolled weight loss), then the oral agent should be discontinued and insulin therapy initiated. However, in most patients, it is reasonable to consider combination therapy.

The most widely used and most extensively studied combinations are a sulfonylurea plus metformin or a sulfonylurea plus insulin. If the latter approach is used, the insulin generally should be given as an intermediate- or long-acting preparation (NPH, lente, or ultralente) at bedtime to reduce the fasting plasma glucose level. Several other potential combinations of agents have been examined in smaller studies and are less widely used in clinical practice. Although there is no logical reason to exclude these combinations from therapeutic consideration, there is not sufficient experience at this time to recommend how, when, or in which patients they should be used.

If glycemic goals are not achieved with combination therapy, then treatment with insulin alone is indicated. The glucose profile as determined by self-monitoring of blood glucose can be helpful in choosing the specific insulin regimen. Insulin should usually be administered at least twice daily to provide adequate circulating insulin levels throughout the day. These doses may use an intermediate insulin preparation (NPH or lente), mixtures of intermediate and regular insulins, or premixed preparations of NPH and regular insulin. In some patients, multiple (three or more) daily injections or the use of an insulin pump may be needed to control blood glucose adequately.

QUESTION 7: WHAT ARE THE DESIRED PROPERTIES OF FUTURE DRUGS FOR THE TREATMENT OF NIDDM?

— The choice of pharmacological agents in the U.S. is limited to insulin, sulfonylureas, the biguanide metformin, and the α-glucosidase inhibitor acarbose. Although these agents have been effective in many patients, the difficulty of achieving near-normal glycemia in the majority of NIDDM patients emphasizes the need for additional therapeutic options. In the future, it is anticipated that more effective agents with fewer side effects will become available and that they will target specific pathogenic abnormalities.

What areas need to be addressed in the future?

First, since both insulin deficiency and insulin resistance are components of the metabolic derangement of NIDDM, a greater understanding of these abnormalities will permit targeted pharmacological therapy at specific receptor or postreceptor sites. Second, the tendency of NIDDM to progress in spite of successful initial therapy will require new pharmacological approaches to prevent β-cell deterioration and its consequent metabolic abnormalities. Third, prevention of NIDDM by initiating therapy in high-risk patients with either normal or impaired glucose tolerance will require improved markers to identify susceptibility to NIDDM and safer pharmacological agents that can be used in all patients, including women of child-bearing potential. Fourth, pharmacological agents that reverse the microvascular and/or macrovascular complications of NIDDM would greatly reduce patient morbidity and the excessive costs associated with this disease. Fifth, and even more challenging because of the heterogeneous nature of NIDDM, will be therapy to correct the genetic abnormality or abnormalities in the susceptible individual.

The challenges facing pharmacological intervention in NIDDM are clear. The substantial morbidity and mortality that results from NIDDM requires that adequate resources be allocated toward the improved understanding, prevention, and treatment this disease.

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