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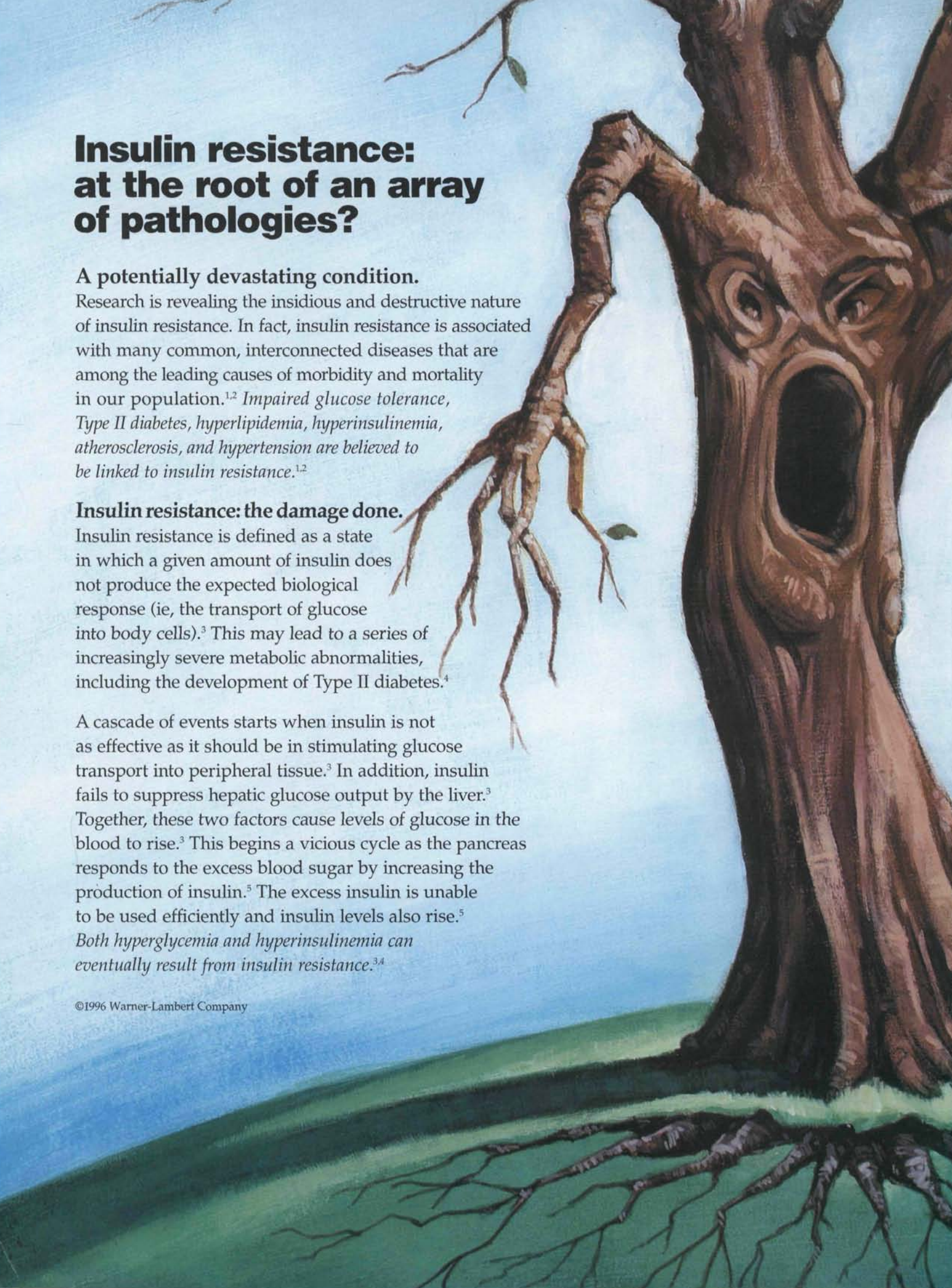

Insulin resistance: at the root of an array of pathologies?

A potentially devastating condition.

Research is revealing the insidious and destructive nature of insulin resistance. In fact, insulin resistance is associated with many common, interconnected diseases that are among the leading causes of morbidity and mortality in our population.[1,2] *Impaired glucose tolerance, Type II diabetes, hyperlipidemia, hyperinsulinemia, atherosclerosis, and hypertension are believed to be linked to insulin resistance.*[1,2]

Insulin resistance: the damage done.

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A cascade of events starts when insulin is not as effective as it should be in stimulating glucose transport into peripheral tissue.[3] In addition, insulin fails to suppress hepatic glucose output by the liver.[3] Together, these two factors cause levels of glucose in the blood to rise.[3] This begins a vicious cycle as the pancreas responds to the excess blood sugar by increasing the production of insulin.[5] The excess insulin is unable to be used efficiently and insulin levels also rise.[5] *Both hyperglycemia and hyperinsulinemia can eventually result from insulin resistance.*[3,4]

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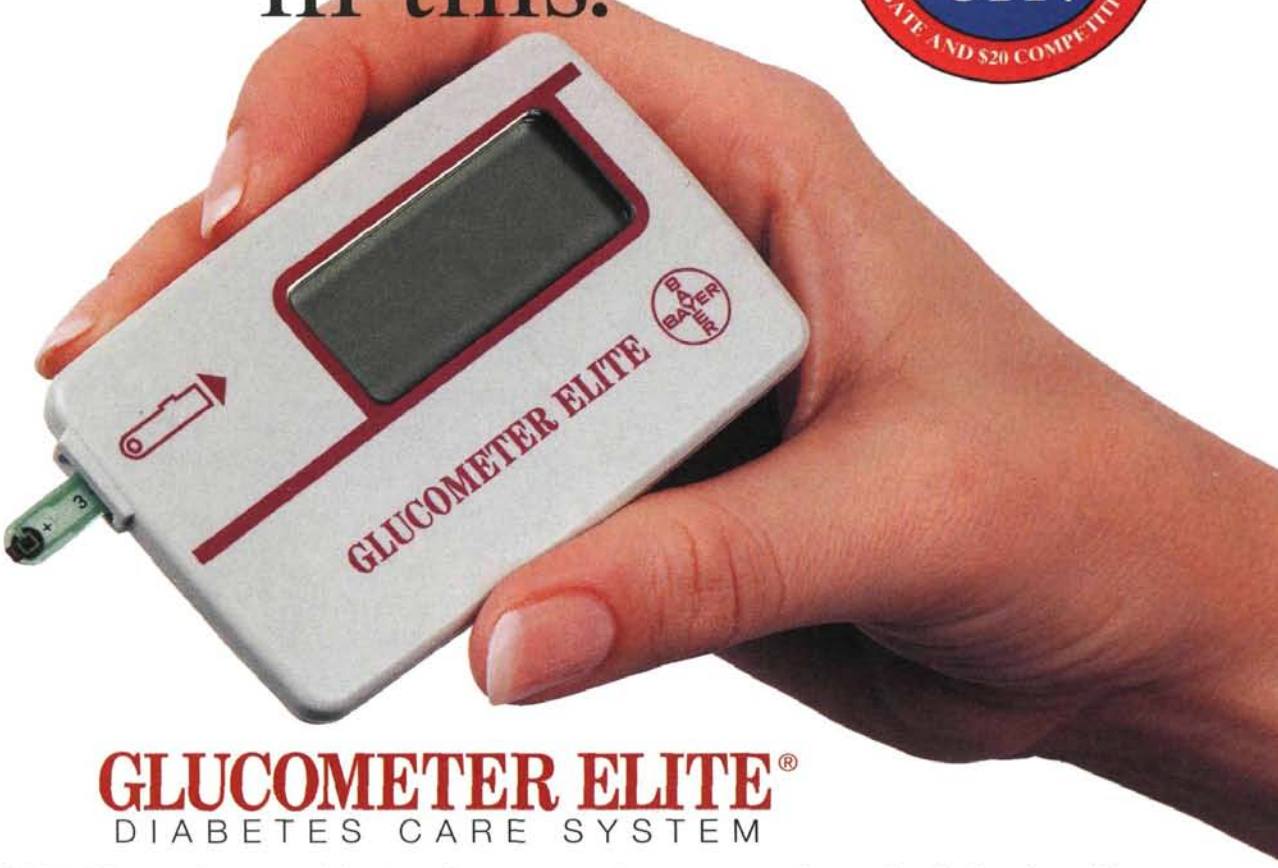

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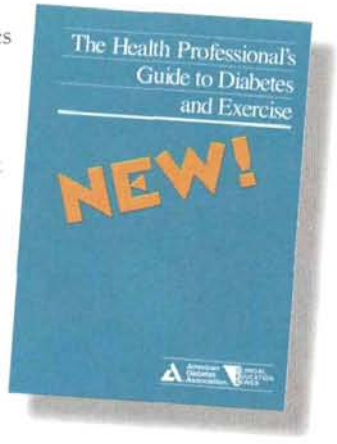

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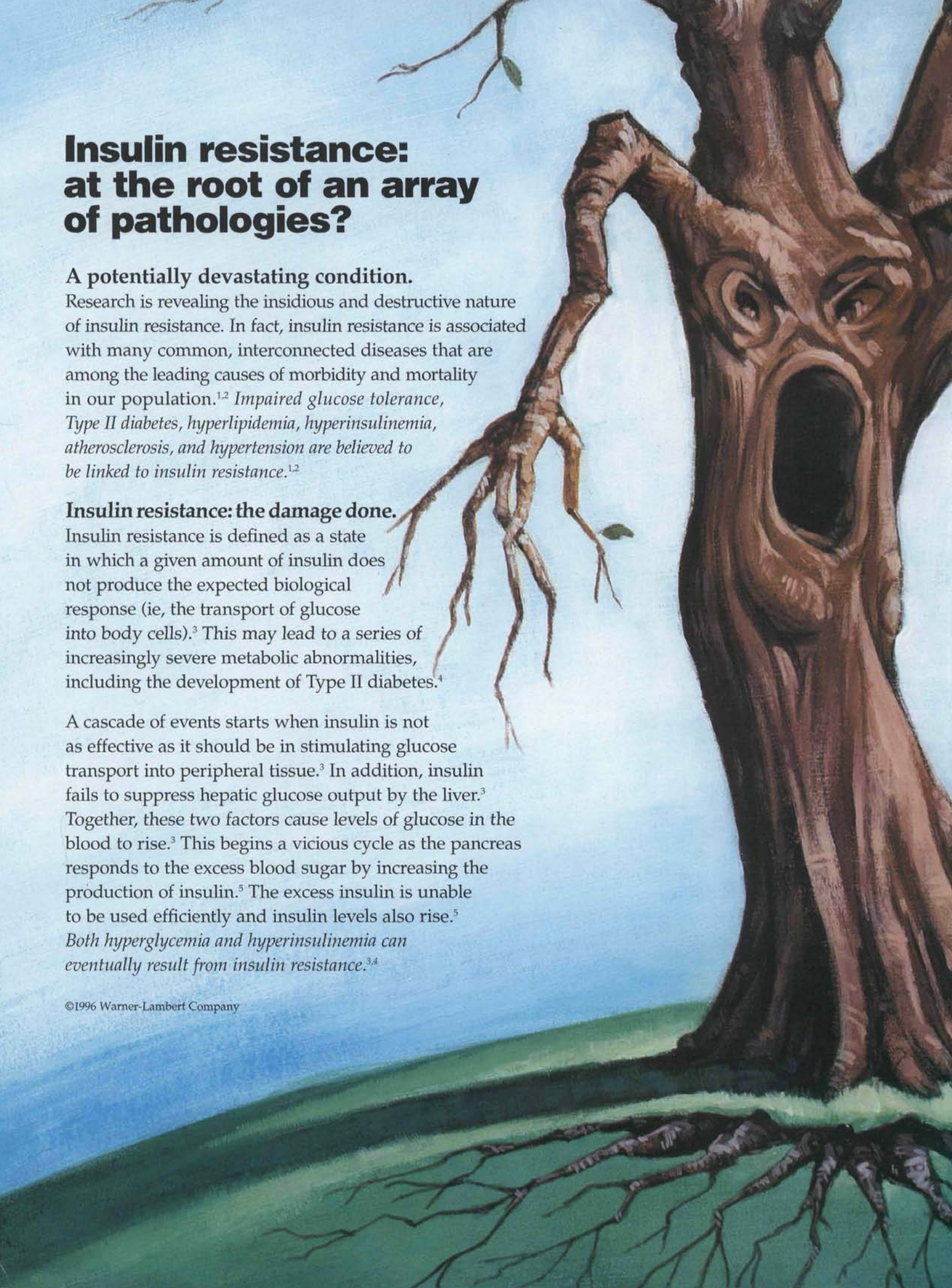

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What's more, insulin's ability to inhibit lipolysis decreases, resulting in hyperlipidemia.[2] In addition to the known risk associated with elevated lipids, some studies have shown that hyperinsulinemia may also contribute to coronary artery disease and hypertension.[2] Accelerated insulin output also stresses the pancreas, and over time may contribute to beta cell failure in some patients.[6]

Vast numbers are at risk.

Unfortunately, insulin resistance is present in many individuals.[7,8] Patients with Type II diabetes are usually resistant to insulin (both endogenous and exogenous)—and probably have been for some time before their diabetes became clinically apparent.[9] Some degree of insulin resistance is also likely in overweight patients as well as in patients with impaired glucose tolerance or high lipid levels.[1,9]

Is it possible to specifically treat or even prevent the insulin resistance associated with Type II diabetes?

Changes in lifestyle such as weight loss and exercise can affect insulin resistance, but in many cases other interventions are necesssary. Despite the fact that we can treat hyperglycemia and delay some of its devastating sequelae, diabetes still remains a relentless, progressive disease. This reality may change as researchers find ways to gain additional information about the fundamental mechanisms involved.

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1. DeFronzo RA. Insulin resistance, hyperinsulinemia, and coronary artery disease: a complex metabolic web. *J Cardiovasc Pharmacol*. 1992;20(suppl 11):S1-S16. **2.** Horton ES. NIDDM—The devastating disease. *Diabetes Res Clin Pract*. 1995;28(suppl):S3-S11. **3.** Seeley BL, Olefsky JM. Potential cellular and genetic mechanisms for insulin resistance in the common disorders of diabetes and obesity. In: Moller DE, ed. *Insulin Resistance*. West Sussex, England: John Wiley & Sons Ltd; 1993: chap 7. **4.** Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med*. 1990;113(12):909-915. **5.** Vaaler S. Carbohydrate metabolism, insulin resistance, and metabolic cardiovascular syndrome. *J Cardiovasc Pharmacol*. 1992;20:S11-S14. **6.** Polonsky KS, Sturis J, Bell GI. Non-insulin-dependent diabetes mellitus—a genetically programmed failure of the beta cell to compensate for insulin resistance. *N Engl J Med*. 1996;334(12):777-783. **7.** American Diabetes Association, Inc. *Medical Management of Non-Insulin Dependent (Type II) Diabetes*. Alexandria, Va: American Diabetes Association; 1994:4-5,16. **8.** National Diabetes Data Group. Classification, diagnostic criteria, and screening for diabetes. In: Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, eds. *Diabetes in America, 2nd Edition*. Washington, DC: National Institute of Diabetes and Digestive and Kidney Diseases; 1995. NIH 95-1468. **9.** Reaven GM. Resistance to insulin-stimulated glucose uptake and hyperinsulinemia: role in non-insulin-dependent diabetes, high blood pressure, dyslipidemia and coronary heart disease. *Diabete Metab*. 1991;17:78-86.

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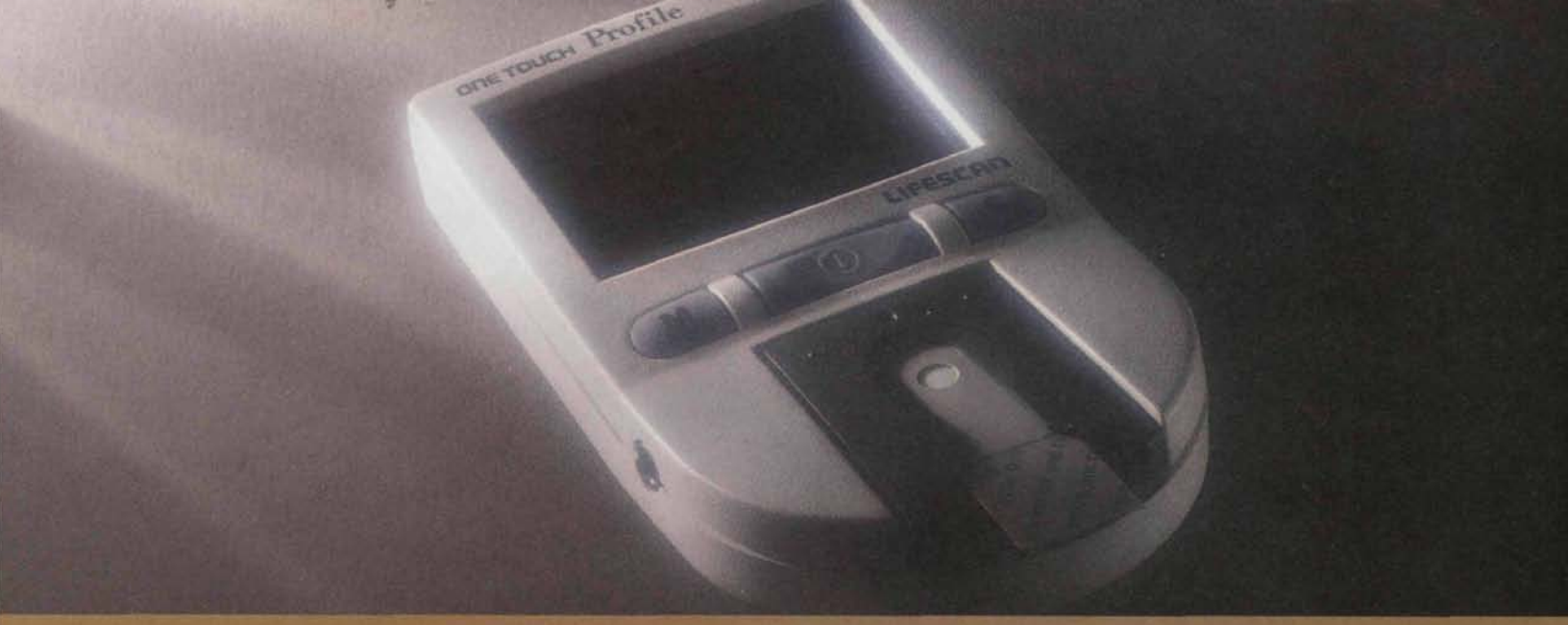

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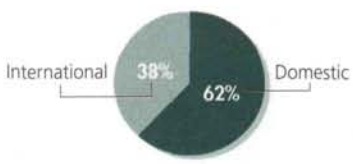

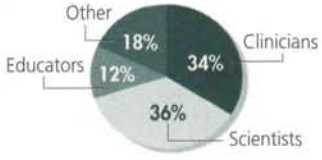

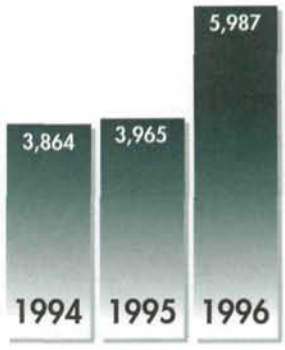

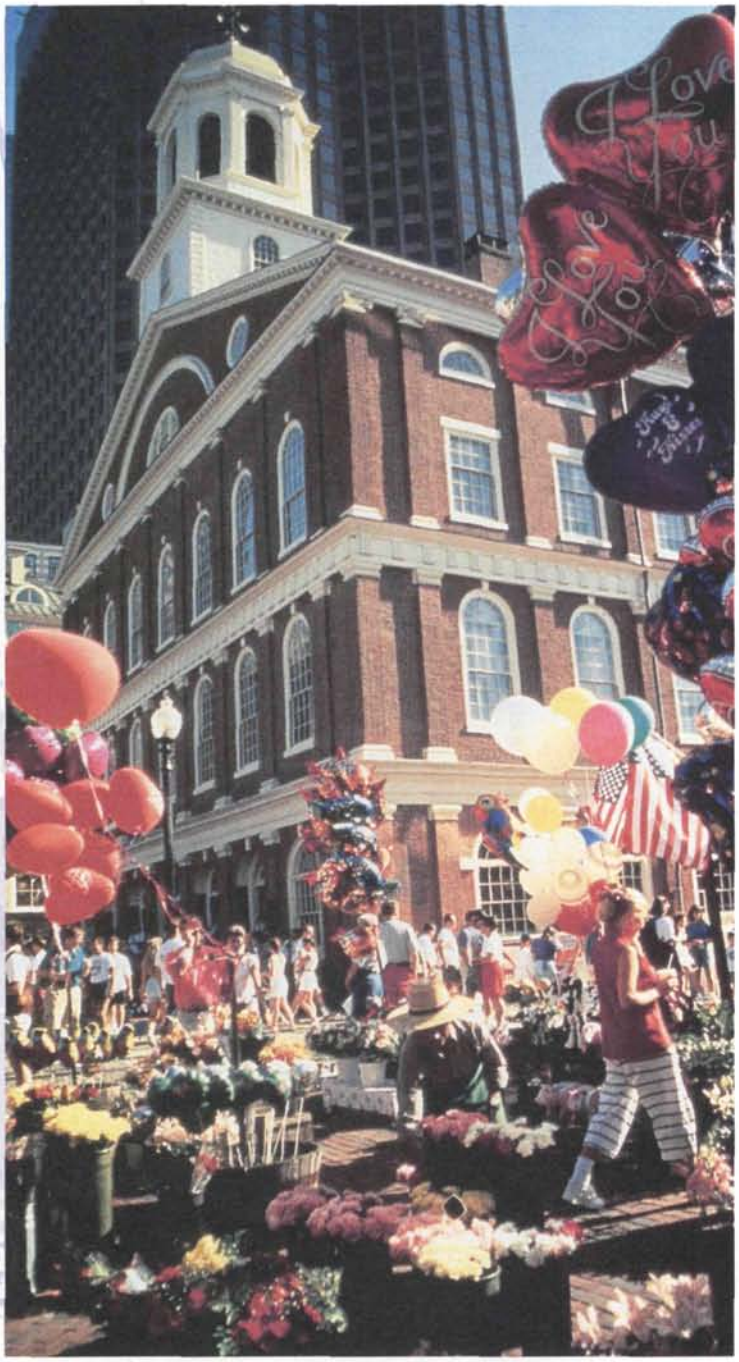

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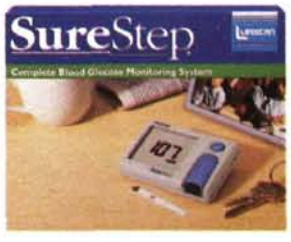

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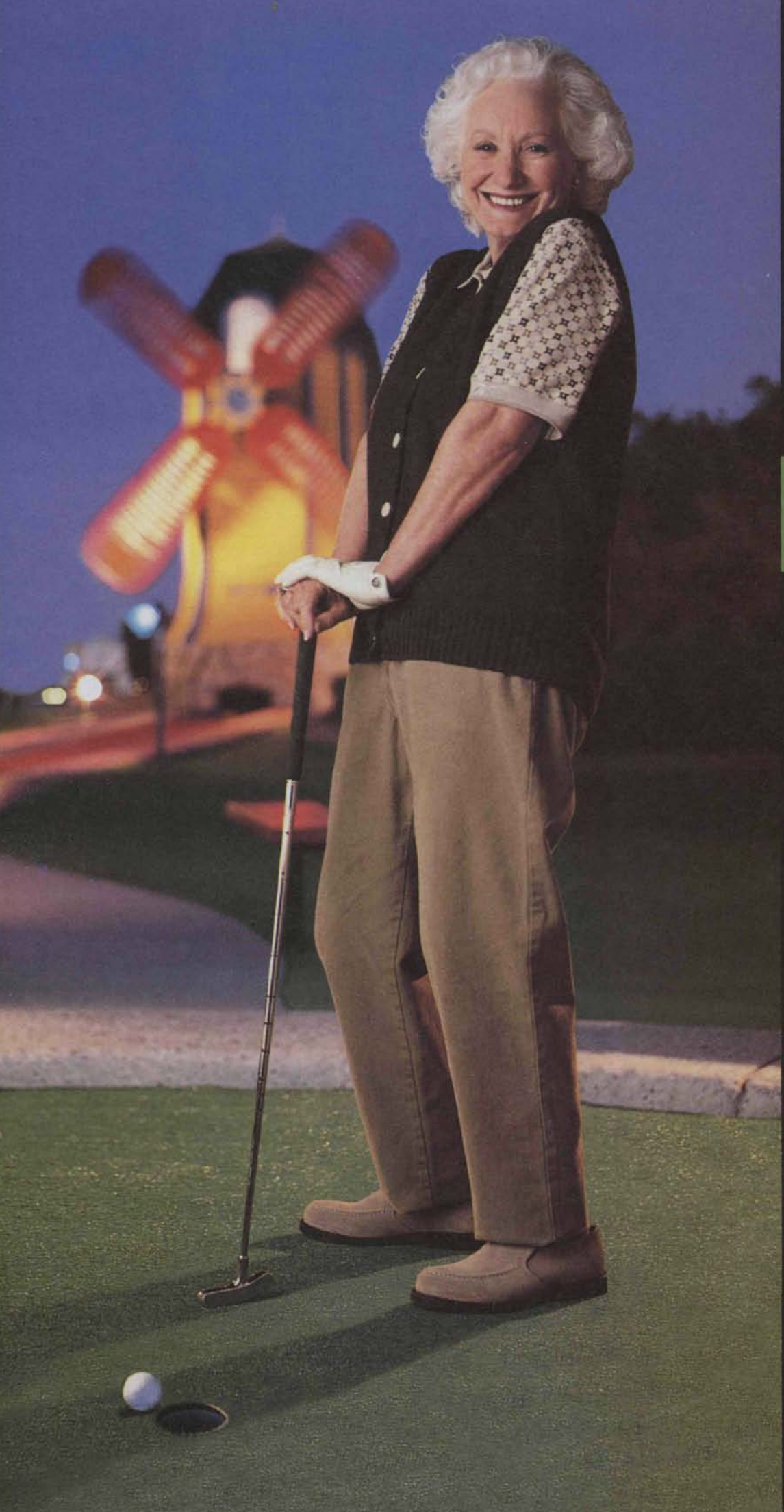

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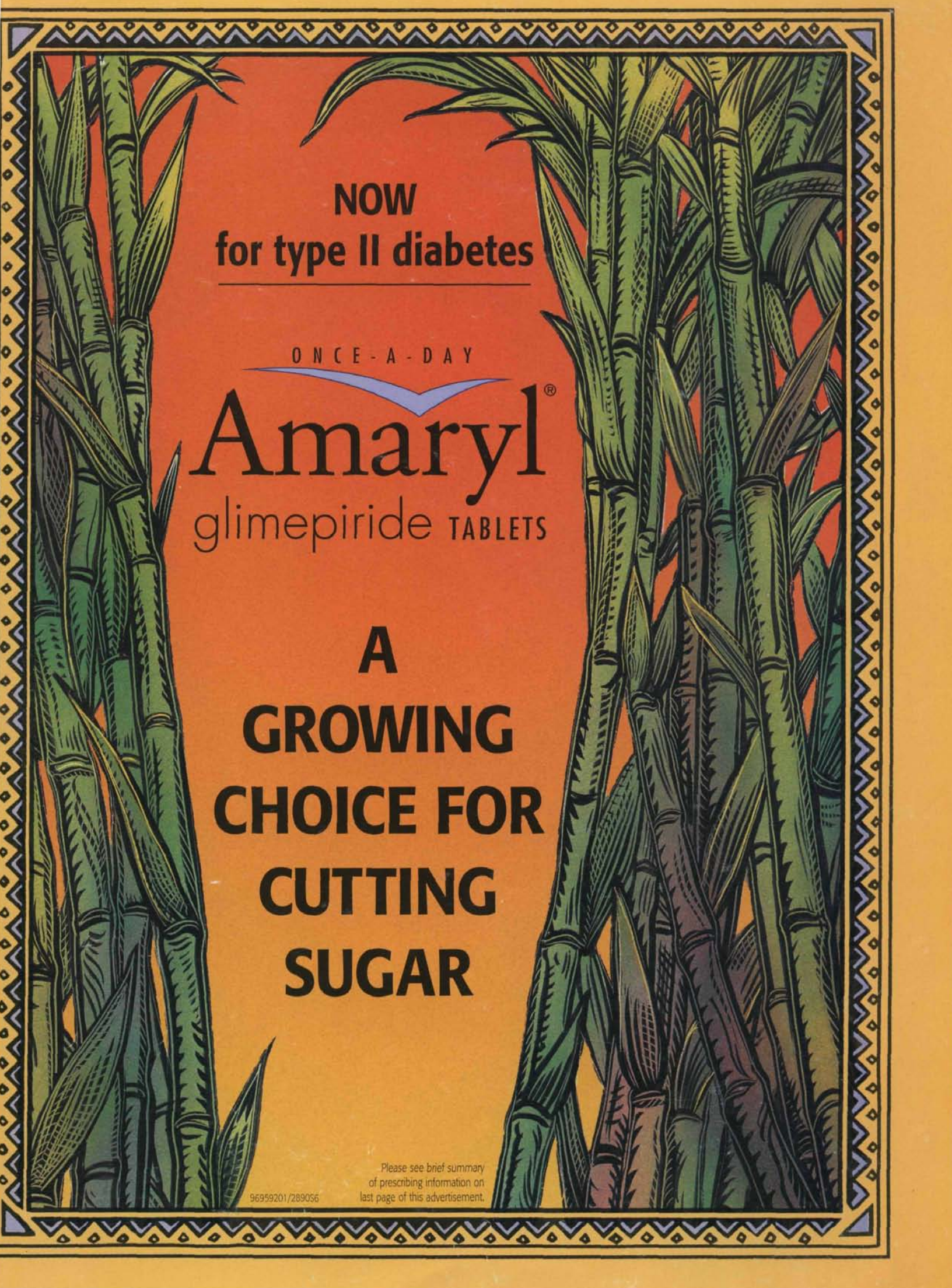
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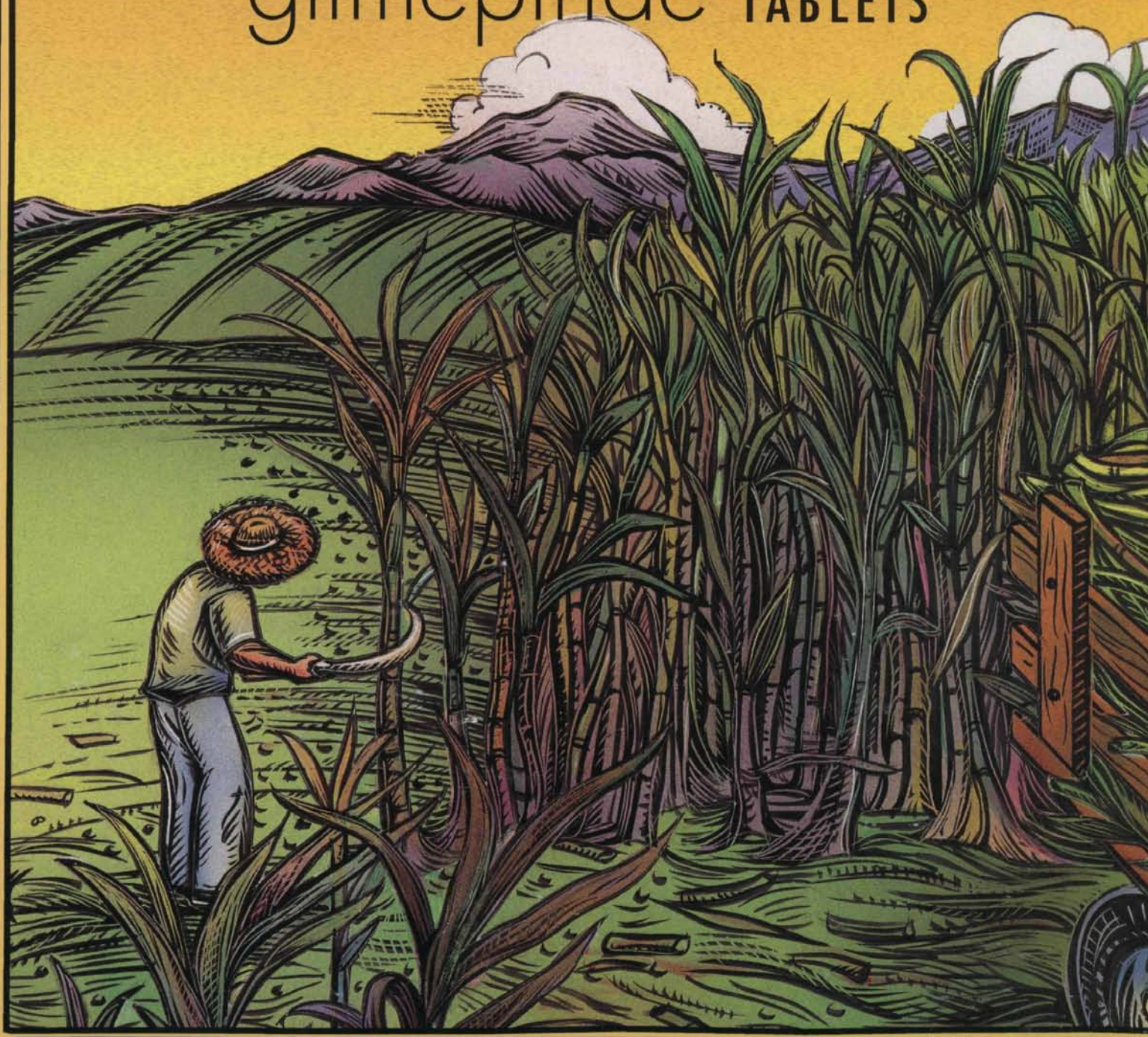

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- **Proven 24-hour control** with once-daily dosing

*Data derived from preclinical animal model. The mechanism by which sulfonylureas lower blood glucose during long-term use has not been clearly established.

†Combined use of Amaryl and insulin may increase the potential for hypoglycemia.

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1, 2, and 4 mg

Brief Summary

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs, including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound, such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, and isoniazid.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known. Potential interactions of glimepiride with other drugs metabolized by cytochrome P450 II C9 also include phenytoin, diclofenac, ibuprofen, naproxen, and mefenamic acid.

Although no specific interaction studies were performed, pooled data from clinical trials showed no evidence of clinically significant adverse interactions with uncontrolled concurrent administration of calcium-channel blockers, estrogens, fibrates, NSAIDs, HMG CoA reductase inhibitors, sulfonamides, or thyroid hormone.

INDICATIONS AND USAGE

AMARYL is indicated as an adjunct to diet and exercise to lower the blood glucose in patients with noninsulin-dependent (Type II) diabetes mellitus (NIDDM) whose hyperglycemia cannot be controlled by diet and exercise alone.

AMARYL is also indicated for use in combination with insulin to lower blood glucose in patients whose hyperglycemia cannot be controlled by diet and exercise in conjunction with an oral hypoglycemic agent. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

CONTRAINDICATIONS

AMARYL is contraindicated in patients with

1. Known hypersensitivity to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

PRECAUTIONS

General

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Patients with impaired renal function may be more sensitive to the glucose-lowering effect of AMARYL. A starting dose of 1 mg once daily followed by appropriate dose titration is recommended in those patients. Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times, it may be necessary to add insulin in combination with AMARYL or even use insulin monotherapy. Should secondary failure occur with AMARYL monotherapy, AMARYL-insulin combination therapy may be instituted. Combined use of glimepiride and insulin may increase the potential for hypoglycemia.

Information for Patients

Patients should be informed of the potential risks and advantages of AMARYL and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. The potential for primary and secondary failure should also be explained.

Laboratory Tests

Fasting blood glucose should be monitored periodically to determine therapeutic response. Glycosylated hemoglobin should also be monitored, usually every 3 to 6 months, to more precisely assess long-term glycemic control.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies in rats at doses of up to 5000 ppm in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation which was dose related and is thought to be the result of chronic pancreatic stimulation. The no-effect dose for adenoma formation in mice in this study was 320 ppm in complete feed, or 46-54 mg/kg body weight/day. This is about 35 times the maximum human recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,700 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

Pregnancy

Teratogenic Effects

Pregnancy Category C. Glimepiride did not produce teratogenic effects in rats exposed orally up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area) or in rabbits exposed up to 32 mg/kg body weight (approximately 60 times the maximum recommended human dose based on surface area). Glimepiride has been shown to be associated with intrauterine fetal death in rats when given in doses as low as 50 times the human dose based on surface area and in rabbits when given in doses as low as 0.1 times the human dose based on surface area. This fetotoxicity, observed only at doses inducing maternal hypoglycemia, has been similarly noted with other sulfonylureas, and is believed to be directly related to the pharmacologic (hypoglycemic) action of glimepiride.

There are no adequate and well-controlled studies in pregnant women. On the basis of results from animal studies, AMARYL should not be used during pregnancy. Many experts recommend that insulin be used during pregnancy to maintain glucose levels as close to normal as possible.

Nonteratogenic Effects

In some studies in rats, offspring of dams exposed to high levels of glimepiride during pregnancy and lactation developed skeletal deformities consisting of shortening, thickening, and bending of the humerus during the postnatal period. Significant concentrations of glimepiride were observed in the serum and breast milk of the dams as well as in the serum of the pups. These skeletal deformations were determined to be the result of nursing from mothers exposed to glimepiride.

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. Patients who are planning a pregnancy should consult their physician, and it is recommended that they change over to insulin for the entire course of pregnancy and lactation.

Nursing Mothers

In rat reproduction studies, significant concentrations of glimepiride were observed in the serum and breast milk of the dams, as well as in the serum of the pups. Although it is not known whether AMARYL is excreted in human milk, other sulfonylureas are excreted in human milk. AMARYL should be discontinued in nursing mothers. If AMARYL is discontinued, and if diet and exercise alone are inadequate for controlling blood glucose, insulin therapy should be considered. (See above ***Pregnancy, Nonteratogenic Effects***)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of hypoglycemia with AMARYL, as documented by blood glucose values <60 mg/dL, ranged from 0.9-1.7% in two large, well-controlled, 1-year studies. (See **WARNINGS** and **PRECAUTIONS**)

AMARYL has been evaluated for safety in 2,013 patients in US controlled trials, and in 1,551 patients in foreign controlled trials. More than 1,650 of these patients were treated for at least 1 year.

Adverse events, other than hypoglycemia, considered to be possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with AMARYL are shown below.

Adverse Events Occurring in ≥1% AMARYL Patients

	AMARYL		Placebo	
	No.	%	No.	%
Total Treated	746	100	294	100
Dizziness	13	1.7	1	0.3
Asthenia	12	1.6	3	1.0
Headache	11	1.5	4	1.4
Nausea	8	1.1	0	0.0

Gastrointestinal Reactions

Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. Isolated transaminase elevations have been reported. Cholestatic jaundice has been reported to occur rarely with sulfonylureas.

Dermatologic Reactions

Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of AMARYL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of AMARYL. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of AMARYL, the incidence of blurred vision was placebo, 0.7%, and AMARYL, 0.4%.

OVERDOSAGE

Overdosage can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent.

Usual Starting Dose

The usual starting dose of AMARYL as initial therapy is 1-2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See **PRECAUTIONS** Section for patients at increased risk).

No exact dosage relationship exists between AMARYL and the other oral hypoglycemic agents. The maximum starting dose of AMARYL should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Usual Maintenance Dose

The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1-2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example, every 3 to 6 months.

AMARYL®-Insulin Combination Therapy

Combination therapy with AMARYL and insulin may be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of >150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.

Specific Patient Populations

AMARYL is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See **PRECAUTIONS**, ***General***).

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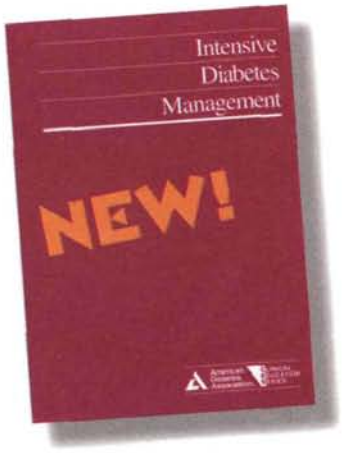

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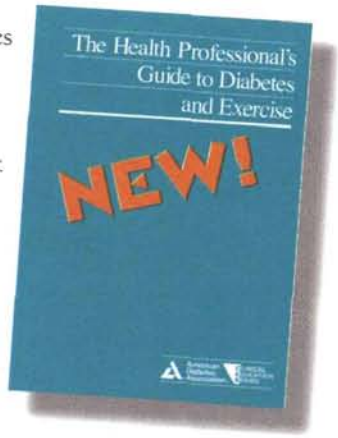

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Dues:

- ❑ Domestic Members: $125
- ❑ Overseas Members: $180
- ❑ Domestic in Training Dues: $65
- ❑ Overseas in Training Dues: $95

Journal Selection (choose one):

- ❑ Diabetes **(monthly)**: Basic research on the pathophysiology of diabetes
- ❑ Diabetes Care **(monthly)**: Clinical care and research

Category II:

Dues:

- ❑ Domestic Members: $75
- ❑ Overseas Members: $115
- ❑ Domestic in Training Dues: $38
- ❑ Overseas in Training Dues: $45

Journals (includes journals listed below):

Diabetes Spectrum **(quarterly)**: Education and counseling strategies

Diabetes Forecast **(monthly)**: Lifestyle magazine for patients and their families

If you received your first professional degree, diploma, or certificate in the last five years, you qualify for 50% savings offered with In-Training Membership. Just fill out information below.

University or college attended: _____ Degree(s) _____ Date Earned: _____

4. Order Additional Publications at "Members-only" Rates: Domestic/International Rates ***(only single subscriptions available for each of the following journals)***

	Dom/Intern'l		Dom/Intern'l		Dom/Intern'l		Dom/Intern'l
❑ Diabetes Care (monthly)	$75/$130	❑ Diabetes Reviews (quarterly)	$45/$65	❑ Diabetes Spectrum (quarterly)	$30/45	❑ 1996 Abstract Book (annual)	$10/$18
❑ Diabetes (monthly)	$75/$130	❑ Clinical Diabetes (bi-monthly)	$15/$21	❑ Diabetes Forecast (monthly)	$12/$37		

5. Select One FREE Council Membership:

Extra Council Memberships are $25 each.

- ❑ Behavioral Medicine and Psychology **(PP)**
- ❑ Diabetes in Pregnancy **(BB)**
- ❑ Complications **(TT)**
- ❑ Education **(SS)**
- ❑ Exercise **(XX)**
- ❑ Foot Care **(RR)**
- ❑ Molecular, Cellular and Biochemical Aspects of Diabetes **(MM)**
- ❑ Clinical Endocrinology, Health Care Delivery and Public Health **(FF)**
- ❑ Diabetes in Youth **(EE)**
- ❑ Epidemiology and Statistics **(CC)**
- ❑ Immunology, Immunogenetics and Transplantation **(JJ)**
- ❑ Nutritional Sciences and Metabolism **(NN)**

6. Mark Your Primary Work Setting:

- ❑ University/Academic (1)
- ❑ Private/Group Practice (2)
- ❑ Hospital (3)
- ❑ HMO (4)
- ❑ Public Health (5)
- ❑ Government (7)
- ❑ Pharmacy (8)
- ❑ Pharmaceutical/Manufacturing (9)
- ❑ Nursing Home (10)
- ❑ Home Health (11)

7. Circle one Primary (P) and one Secondary (S)Specialty

P	S	AD Administration	P	S	IU Immunology	P	S	PH Public Health
P	S	BC Biochemistry	P	S	ME Metabolism	P	S	PM Pharmacy
P	S	CA Cardiology	P	S	NE Nephrology	P	S	PN Pediatric Endocri
P	S	DE Dermatology	P	S	NR Neurology	P	S	PO Podiatry
P	S	DO Dentistry	P	S	NS Nursing	P	S	PR Pedorthic Manage.
P	S	ED Education	P	S	NU Nutrition	P	S	PS Psychiatry
P	S	EN Adult Endocrinology	P	S	OG Obstetrics/Gyn.	P	S	PT Pathology
P	S	EP Epidemiology	P	S	OP Ophthalmology	P	S	PX Physical Therapy
P	S	EX Exercise Physiology	P	S	OR Orthopedics	P	S	PY Physiology
P	S	FP Family Practice	P	S	OS Osteopathy	P	S	SU Surgery
P	S	GE Geriatrics	P	S	OT Optometry	P	S	SW Social Work
P	S	GP General Practice	P	S	PA Pharmacology	P	S	UR Urology
P	S	GT Genetics	P	S	PC Psychology			
P	S	IM Internal Medicine	P	S	PE Pediatrics			

8. Enclose Payment and Mail Today!

❑ New Membership or ❑ Renewing Membership

Member Dues:

Category I $ _____ or **Category II** $ _____

Additional Subscriptions: $ _____ $ _____

Additional Councils _____ x $25 = _____

Taxes: Canadians must add 7% GST tax $ _____

TOTAL ENCLOSED: $ _____

❑ Check: *payable to the American Diabetes Association*

❑ Charge my ❑ VISA ❑ MasterCard ❑ American Express

Account No.# _____

Expiration Date _____

Date: _____ Signature _____

JMAD995

Dues amount set aside for publications are:

- Category I (Diabetes or Diabetes Care): $75
- Category II (Diabetes Spectrum): $30 (Diabetes Forecast): $12

Payment Options: Mail payment and application to:

American Diabetes Association
Professional Section Membership
1660 Duke Street
Alexandria, VA 22314

For fast service, call or send a fax to our membership department:

Phone: **(703) 549-1500**
Fax: **(703) 549-6995.**

Allow 4-6 weeks to process your order. Prices are subject to change. Payment must accompany order in US funds drawn on US bank.

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