VOLUME 12 NUMBER 4 APRIL 1989

DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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APRIL AUTHOR INDEX

(Volume 12, Number 4)

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APRIL 1989

DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

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IN THIS ISSUE

Children and Hypoglycemia: Assessing Risk

Conventional wisdom and common sense suggest that the greater the effort to normalize blood glucose levels in insulin-dependent diabetes mellitus (IDDM) patients, the higher the risk of severe hypoglycemia. Indeed, several studies support the contention that frequency of symptomatic hypoglycemia correlates indirectly with glycosylated hemoglobin (HbA_1) but directly with insulin dose. Bergada et al. (p. 239) studied 350 children with IDDM for 1 yr. During that time, 24 had at least one severe hypoglycemic reaction. As expected, insulin dose was greater in hypoglycemic children than in asymptomatic cohorts, although HbA_1 was not different. Recent diagnosis of IDDM and history of previous hypoglycemia were both associated with increased risk for subsequent occurrences. Although many episodes were after exercise or missed meals, the data suggest two other possible causes: some patients may be inherently prone to severely low blood glucose levels, whereas hypoglycemia itself may predispose patients to recurrent episodes.

Things That Go Low in the Night

Although we have been aware that many diabetic patients experience wide swings in blood glucose overnight and early in the morning, the connection between these fluctuations and their effect on daytime glycemia remains cloudy. Stephenson and Schernthaner (p. 245) examined dawn phenomenon and Somogyi effect in 231 blood glucose profiles from 97 patients with insulin-dependent diabetes mellitus. Although nighttime blood glucose levels below 60 mg/dl occurred in 25% of profiles, glucose levels the next day were lower when compared with profiles showing no nocturnal hypoglycemia. However, a rise in blood glucose between 0300 and 0600 did correlate to higher levels during the day; conversion from conventional twice-daily mixed insulin injections to basal-bolus insulin therapy achieved a modest reduction in the frequency and magnitude of these early-morning rises.

Another Pill for Diabetes?

Tissue resistance to insulin is the major identifiable defect in non-insulin-dependent diabetes mellitus (NIDDM). Numerous treatments, including diet-induced weight loss, exercise, and sulfonylurea drugs, can partially overcome this resistance and improve diabetic control. However, life-style modifications may have only limited long-term success, and therefore drug therapy is often required for suboptimally controlled NIDDM subjects. Pestell et al. (p. 252) report that fenfluramine, a sympathomimetic agent initially used to treat obesity, directly affects tissue sensitivity to insulin. Perhaps this or related compounds could be used to attack the obesity-induced insulin resistance–NIDDM puzzle at more than one locus, although further long-term studies elucidating interaction of the sympathetic nervous system with insulin action are clearly needed.

Magnesium and Insulin Sensitivity in the Elderly

Low plasma magnesium concentrations are common in people with diabetes. What is the effect of raising magnesium levels in these patients? Paolisso et al. (p. 265) studied insulin response and insulin action in eight elderly non-insulin-dependent diabetic subjects receiving 2 g magnesium supplement/day. The supplement effectively raised magnesium levels in erythrocytes. After 4 wk, this increase was associated with improved early insulin response to an intravenous challenge and with a 24% increase in insulin action as measured by glucose clamps. Clearly, magnesium intake affects early insulin response and insulin action. These results should provoke further exploration into how magnesium achieves these effects and what dietary recommendations may be indicated.

Neuropathy: Doctor Versus Doctor Versus Technology

The clinical management of diabetic peripheral neuropathy is seriously hampered by the absence of reliable tools to detect it and follow its course. Maser et al. (p. 270) investigate whether we can depend on the most important tool, clinical judgment. Independent assessments of neuropathy among 100 insulin-dependent diabetes mellitus patients were made by an internist, a neurologist, and by quantitative sensory-threshold testing for vibratory and pinprick sensations. Interobserver agreement concerning symptoms and various signs of damaged sensory nerves varied from fair to unimpressive. Threshold testing, on the other hand, doubled the clinically apparent prevalence of sensory neuropathy. However, it is premature to retire the tuning fork and hammer. The clinical relevance of quantitative sensory-threshold testing must be established by long-term follow-up.

34 New Grants Awarded in November 1988 by the Diabetes Research and Education Foundation

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John L. Beggs, PhD,
Peter C. Johnson, MD, Phoenix, AZ
"Pancreas Transplantation: Regression of Diabetic Induced Nerve Changes"

Thomas A. Buchanan, MD, Los Angeles, CA
"Development of a New Method for Measuring Hepatic Glucose Production *In Vivo*"

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Roger Mazze, PhD, Minneapolis, MN
Arlan Rosenbloom, MD, Tallahassee, FL
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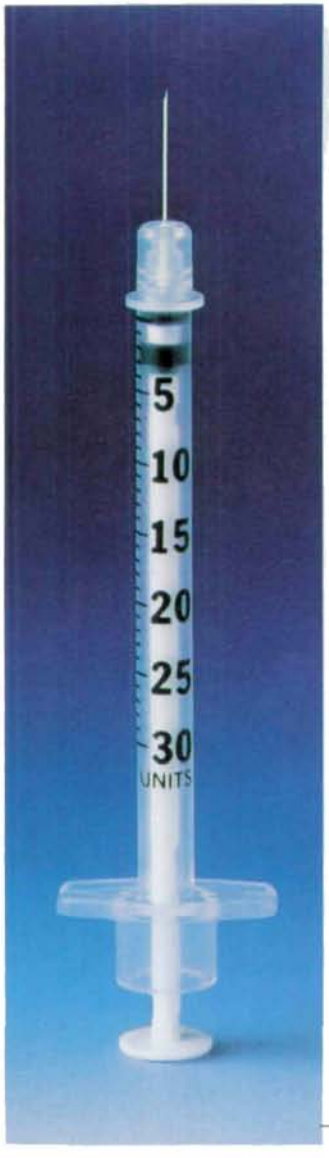

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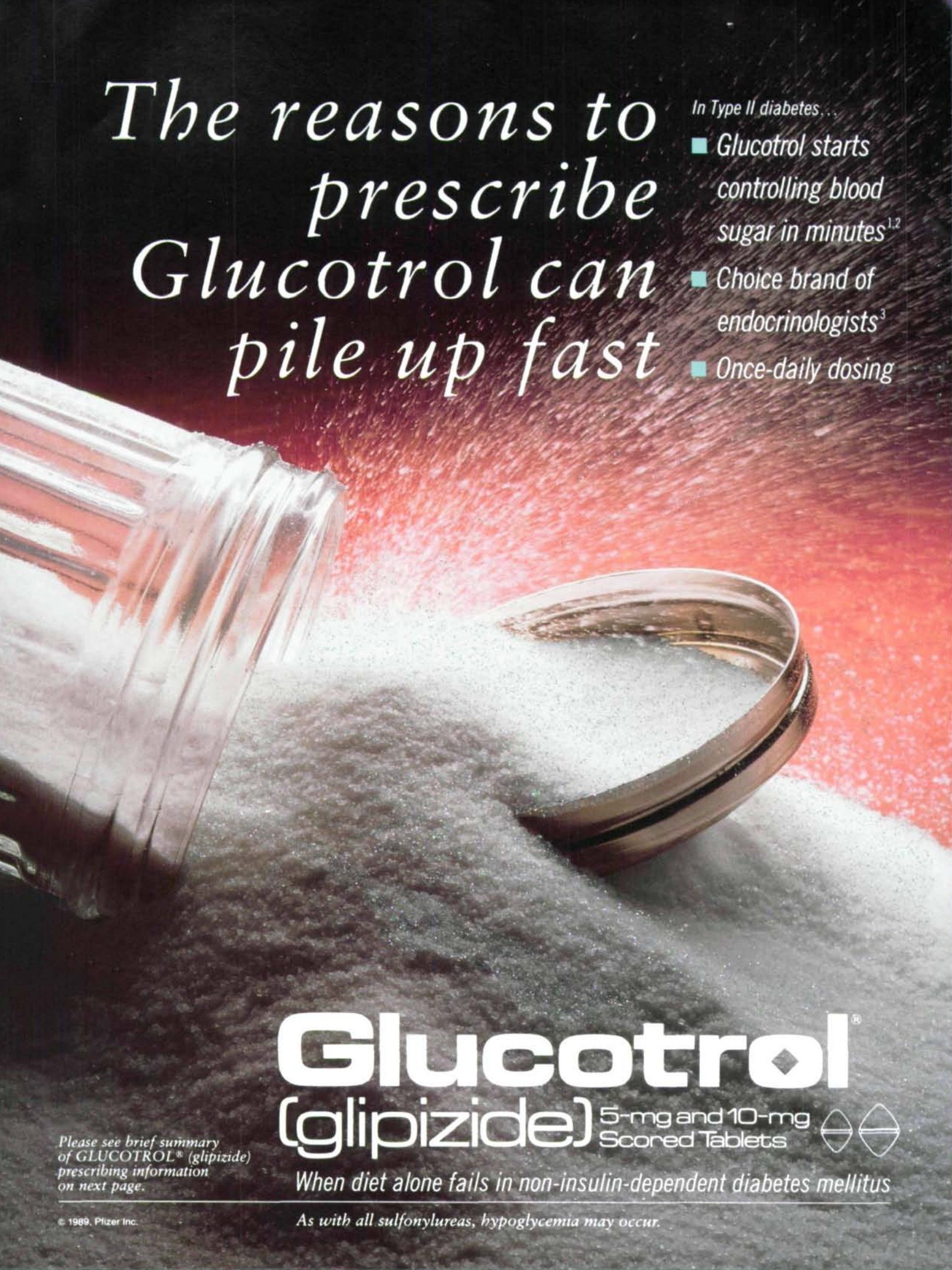
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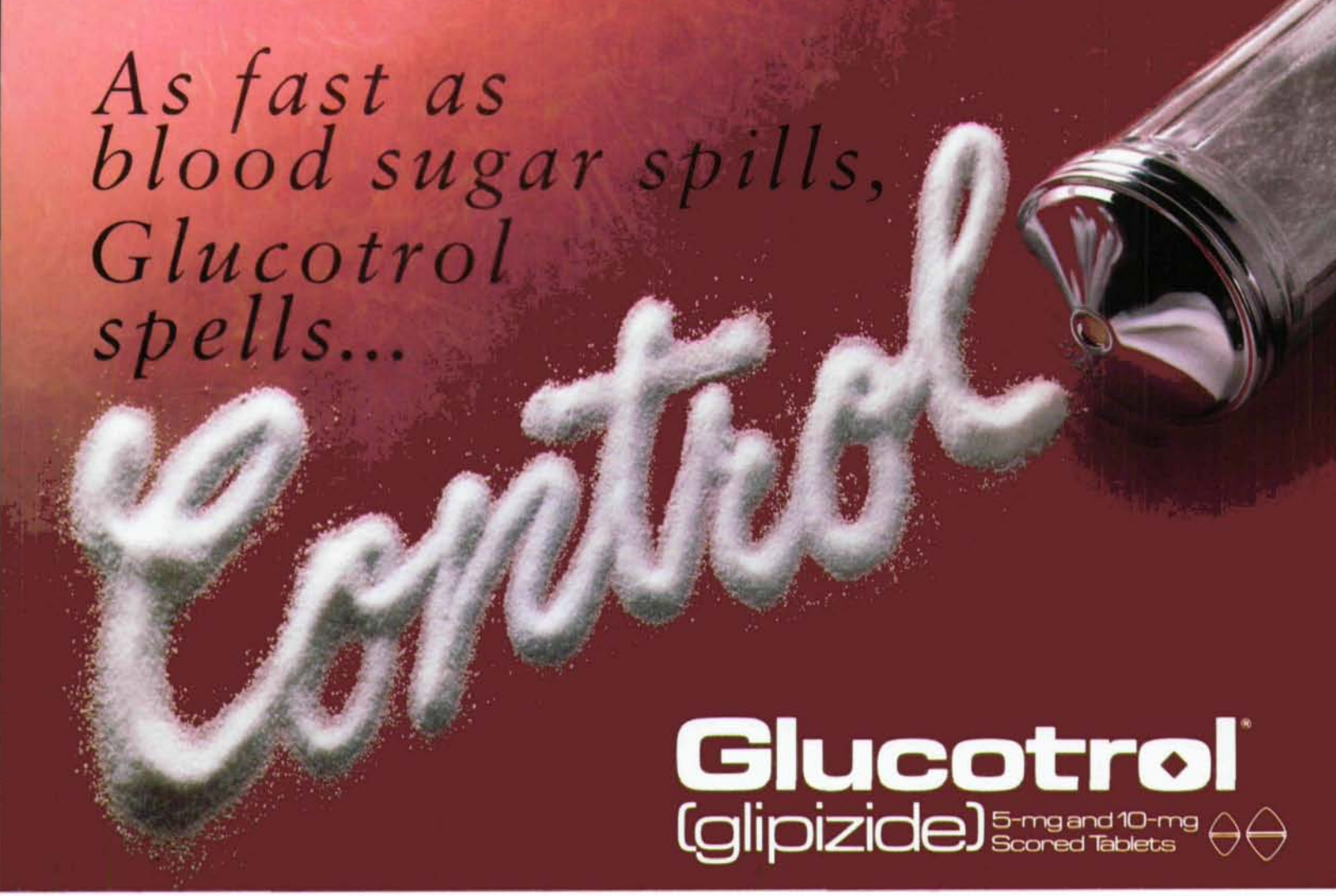

References: 1. Goebel R, Leb G. Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar, in *Glipizide: A Worldwide Review*. Princeton, NJ: Excerpta Medica; 1984; pp 9-15. 2. Melander A, Wåhlin-Boll E. Clinical pharmacology of glipizide. *Am J Med* 1983;75 8-14. 3. Medical Marketing Conference. *Acid-abetic Thomas Study V, Tabular Summary*. West Orange, NJ: Market Measures, Inc; November 1987-January 1988.

GLUCOTROL® (glipizide) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to this drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

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. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes*, 19, supp. 2:747-830, 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking 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: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or 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. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C. GLUCOTROL (glipizide) was found to be mildly tetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This teratotoxicity has been similarly noted with other sulfonylureas such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic hypoglycemic action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia 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. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas. GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL. If skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

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

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. 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 since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL, dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL, in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored, diamond-shaped tablets imprinted as follows: 5 mg tablet — Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet — Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

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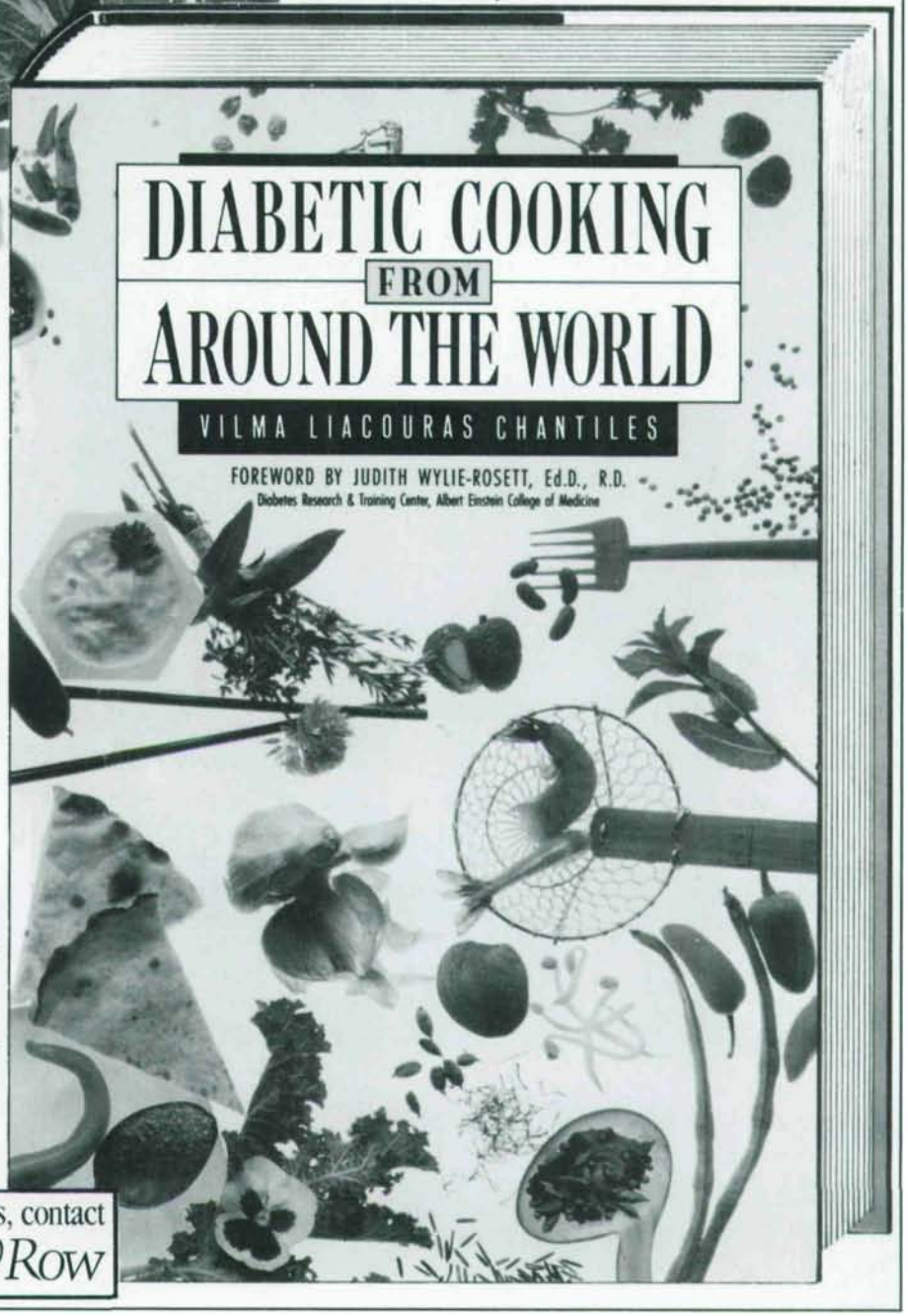

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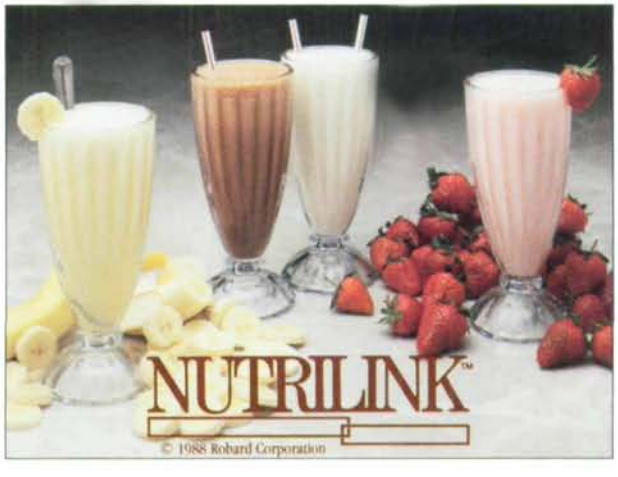

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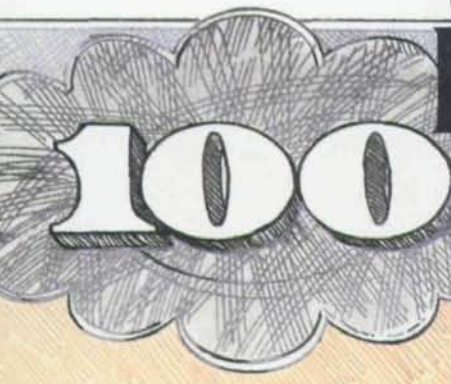


FREE $100 U.S. Savings Bond When They Buy Accu-Chek® II/IIm

Blood Glucose Monitor or Diabetes Care Kit

Now, when you recommend that your patient make a small investment in an Accu-Chek II/IIm Blood Glucose Monitor or Diabetes Care Kit, they'll get a healthy return—A Free $100 U.S. Savings Bond.

The Accu-Chek® II Diabetes Care Kit comes complete with everything your patients need to better control their diabetes. Plus, each kit comes with a free step-by-step instructional/educational video to help them stay in balance and in control. No wonder it's the blood glucose monitor used by more people with diabetes than any other brand.[1]

So the next time you prescribe a Blood Glucose Monitor for one of your patients with diabetes, make sure it's an Accu-Chek® II/IIm monitor. And they'll get a healthy return with a small investment.

OFFER EXPIRES 05/31/89

1. Data on file at Boehringer Mannheim Diagnostics.

THE LINE OF CONFIDENCE™ IN DIABETES CONTROL

BOEHRINGER MANNHEIM DIAGNOSTICS

In NIDDM START HIM ON

Lower dosage

In a recent study,[1] two groups of patients were started on similar daily doses of Glucotrol®* (glipizide) and DiaBeta® (glyburide). After 3½ months, the mean daily dose of Glucotrol needed to maintain glucose control had nearly doubled, while that of DiaBeta had changed only slightly.

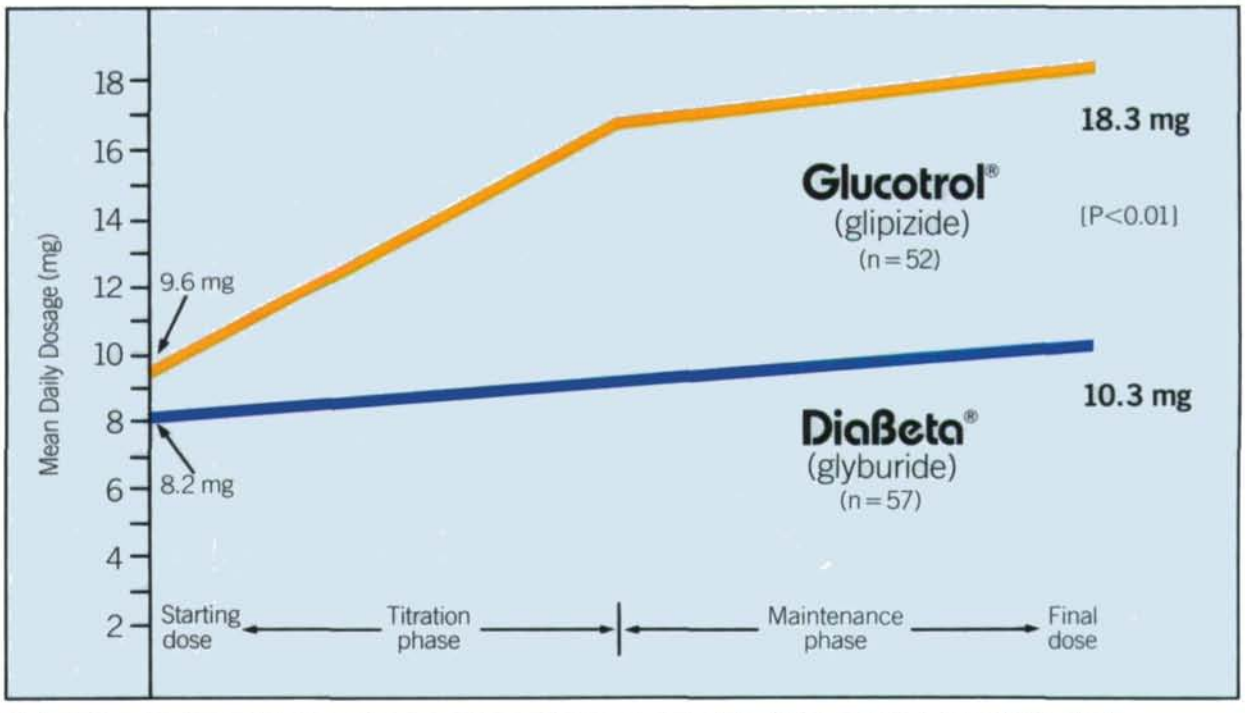
Lower cost

If the dosage of your patient's oral hypoglycemic doesn't increase, neither does the cost. Based on this study,[1] the dosage of DiaBeta required to maintain glucose control was lower than that of glipizide, resulting in a lower cost — savings your patients will appreciate over a lifetime of therapy.

1. Kilo C: Multicenter comparison of glyburide and glipizide in the treatment of non-insulin-dependent diabetes mellitus. *Clin Ther* 1988;10(3):294-302.

*Brand of glipizide/Roerig.

THE SMOOTH ROAD



Study design: Interim report of an ongoing multicenter, randomized study involving 109 non-insulin-dependent diabetics.[1]

Diet &

DiaBeta® TABLETS 1.25, 2.5 & 5 mg

GLYBURIDE HOECHST-ROUSSEL

The first choice of the second generation.

Hoechst COMMITTED TO DIABETES RESEARCH AND EDUCATION

Please see following page for brief summary of prescribing information.

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Washington DC Area dial (703) 549-1500.

SIXTH ANNUAL NATIONAL CLINICAL CARE CONFERENCE
"The Nuts and Bolts of Diabetes Care"

Sponsored by
Department of Internal Medicine/Diabetes Center of Eastern Virginia
Eastern Virginia Medical School

May 17 & 18, 1989 **Virginia Beach, Virginia**

PURPOSE: Provide physicians, nurses, and other members of the diabetes health care team the most recent information about diabetes and its complications.

OBJECTIVES:

1. Review current approaches to insulin therapy
2. Examine modern management of type II diabetes
3. Discuss treatment of diabetic complications
4. Analyze impact of external factors on patient care

The faculty will present down to earth approaches to major problems encountered in treating patients with diabetes. Topics in the areas of current insulin therapy, approaches to managing type II diabetes, and assessing complications will be presented in a way that incorporates important recent research advances into clinical practice. Although the primary format of the conference will be lecture, there will be ample opportunity to interact with conference faculty about specific issues and questions.

FMI: 804/446-6140 EVMS-CME

ames

PIECE OF MIND.

How the meter with memory helps ease the concerns of patients with diabetes—and your concern for compliance.

The GLUCOMETER® II Blood Glucose Meter with Memory gives patients the convenience and security they need to comply with your blood glucose monitoring recommendations.

It's convenient, because it stores 26 readings (and calculates averages too) so that patients can record their results when they have time. Patients can feel secure, because they need not worry about forgetting the readings the meter remembers.

It even takes the worry out of your patients leaving their meters at home. Because the GLUCOMETER II with Memory uses GLUCOSTIX® Reagent Strips, which patients can use to make visual readings when the meter's out of sight.

Help ease the concerns that make self blood glucose monitoring a challenge. A piece of mind from the GLUCOMETER II with Memory can mean peace of mind for your patients. And for you.

The GLUCOMETER® II Blood Glucose Meter with Memory.
The meter with a mind of its own.

MILES

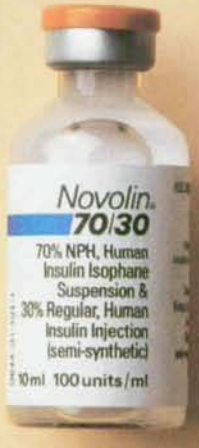
Miles Inc.
Diagnostics Division
Elkhart, IN 46515

For patients who need to mix insulins

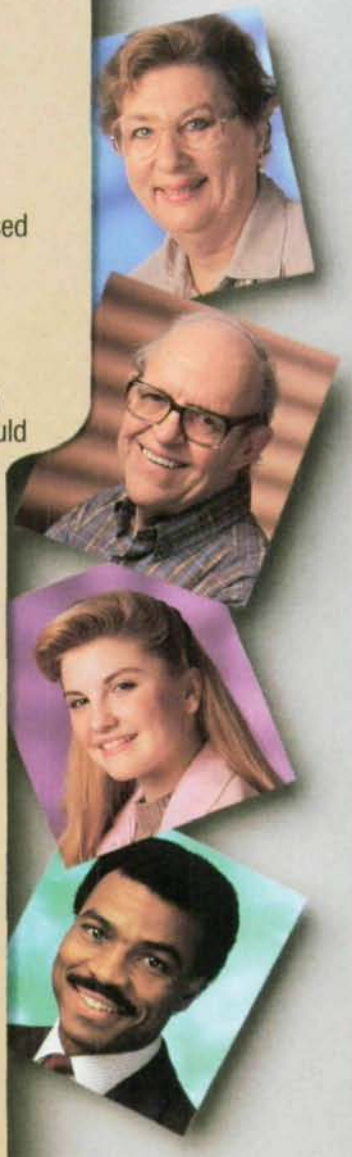
Novolin® 70/30

70% NPH Human Insulin Isophane Suspension &
30% Regular Human Insulin Injection (semi-synthetic)

- **Physiologic**—Closely approximates nondiabetic insulin secretion profile
- **Convenient**—Eliminates complicated mixing procedures
- **Accurate**—Eliminates risk of patients' mixing errors
- **Stable**—Premixed 70/30 ratio remains constant
- **Efficacious**—Effective in lowering blood glucose levels[1]
- **Nonimmunogenic**—Minimal IgG antibody development[2]



For additional information concerning Squibb-Novo products, call 1-800-727-6500.



Newly diagnosed patients

Current insulin users who would benefit from a 70/30 mixture

Patients now mixing in approximately a 70/30 ratio*

Patients who could benefit from human insulin

70% NPH Human
+30% Regular Human
100% Human Insulin

SQUIBB® NOVO®
The diabetes care specialists

References: 1. Sonnenberg GE, Kemmer FW, Cüppers HJ, et al: Subcutaneous use of regular human insulin (Novo): Pharmacokinetics and continuous insulin infusion therapy. *Diabetes Care* 1983;6(suppl 1):35-39. **2.** Schernthaner G, Borkenstein M, Fink M, et al: Immunogenicity of human insulin (Novo) or pork monocomponent insulin in HLA-DR-typed insulin-dependent diabetic individuals. *Diabetes Care* 1983;6(suppl 1):43-48.

*Dosage adjustments may be necessary for patients now using other human or beef insulin.