

DIABETES CARE[®]

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

ORIGINAL ARTICLES

- Anti-Sympathetic Ganglia Antibodies and Postural Blood Pressure in IDDM Subjects of Varying Duration and Patients at High Risk of Developing IDDM
S.L. RABINOWE, F.M. BROWN, M. WATTS, M.M. KADROFSKE, A.I. VINIK 1
- Maleness as Risk Factor for Slowly Progressive IDDM
T. KOBAYASHI, K. NAKANISHI, T. SUGIMOTO, T. ITOH, T. MURASE, K. KOSAKA, K. TSUJI 7
- Psychomotor Performance and Counterregulatory Responses During Mild Hypoglycemia in Healthy Volunteers
A.B. STEVENS, W.R. MCKANE, P.M. BELL, P. BELL, D.J. KING, J.R. HAYES 12
- Stress in Parents of Children With Diabetes Mellitus
E.J. HAUENSTEIN, R.S. MARVIN, A.L. SNYDER, W.L. CLARKE 18

SPECIAL ARTICLE

- Lower-Extremity Amputation in People With Diabetes: Epidemiology and Prevention
D. BILD, J. SELBY, P. SINNOCK, W. BROWNER, P. BRAVEMAN, J. SHOWSTACK 24

SHORT REPORTS

- Hypoglycemic Convulsions Cause Serious Musculoskeletal Injuries in Patients With IDDM
D.A. HEPBURN, J.M. STEEL, B.M. FRIER 32
- Effect of Life-Style Activity of Varying Duration on Glycemic Control in Type II Diabetic Women
M. PATERNOSTRO-BAYLES, R.R. WING, R.J. ROBERTSON 34

LETTERS AND COMMENTS

- 38

BOOK REVIEW

- 45

SUPPLEMENT: Sweeteners in Diabetes

- 47

- Introduction 49

- Metabolism of Cyclamate and Its Conversion to Cyclohexylamine
A. COLLINGS 50

- Clinical Aspects of Sucrose and Fructose Metabolism
J. BANTLE 56

- Effects of Sucrose on Carbohydrate and Lipid Metabolism in NIDDM Patients
C. HOLLENBECK, A.M. COULSTON, G.M. REAVEN 62

- Aspartame Metabolism in Normal Adults, Phenylketonuric Heterozygotes, and Diabetic Subjects
L.J. FILER, JR., L.D. STEGINK 67

- Saccharin
S.A. MILLER, V.P. FRATTALI 75

- Summary and Comments
R. LEVINE 81

ORGANIZATION SECTION

INFORMATION FOR AUTHORS



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24-hour glycemic control can begin at the breakfast table.

When diet and exercise aren't enough, once-a-day MICRONASE provides 24-hour control of both postprandial and fasting blood glucose levels. The usual starting dosage, 2.5 mg to 5 mg once a day, should be taken with breakfast or the first main meal of the day. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

All sulfonylureas, including MICRONASE, can cause severe hypoglycemia. Proper patient selection, dosage, and instructions are important.

Micronase[®]
Tablets (glyburide) Usual starting dosage
2.5 mg-5 mg once a day

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Tablets (glyburide) Usual starting dosage
2.5 mg-5 mg once a day

CONTRAINDICATIONS: MICRONASE Tablets are contraindicated in patients with: 1. Known hypersensitivity or allergy to the drug. 2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin. 3. Type I diabetes mellitus, as sole therapy.

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 noninsulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (Diabetes, 19 [Suppl 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 2½ 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 MICRONASE 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 apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: General—Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may increase the risk of serious 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 and in people who are 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: In diabetic patients exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. It may then be necessary to discontinue MICRONASE and administer insulin. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure. **Information for Patients:** Patients should be informed of the potential risks and advantages of MICRONASE and of alternative modes of therapy. They also should be informed about the importance of adherence 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.

Laboratory Tests: Response to MICRONASE Tablets should be monitored by frequent urine glucose tests and periodic blood glucose tests. Measurement of glycosylated hemoglobin levels may be helpful in some patients.

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.

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, calcium channel blocking drugs, and isoniazid.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Pregnancy: Teratogenic effects: Pregnancy Category B. Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are no adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Insulin should be used during pregnancy to maintain blood glucose as close to normal as possible. **Nonteratogenic Effects:** 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. MICRONASE should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers: Some sulfonylurea drugs are known to be excreted in human milk. Insulin therapy should be considered.

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

ADVERSE REACTIONS: Hypoglycemia: See Precautions and Overdosage sections. **Gastrointestinal Reactions:** Cholestatic jaundice and hepatitis may occur rarely; MICRONASE Tablets should be discontinued if this occurs. Gastrointestinal disturbances (nausea, epigastric fullness, and heartburn) occurred in 1.8% of patients during clinical trials. They were the most commonly reported adverse reactions. They tend to be dose related and may disappear when dosage is reduced. Liver function abnormalities have been reported. **Dermatologic Reactions:** Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of patients during trials. These may be transient and may disappear despite continued use of MICRONASE; 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 and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with MICRONASE and disulfiram-like reactions have been reported very rarely. Cases of hyponatremia have been reported with glyburide 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. (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.

OVERDOSAGE: Overdosage of sulfonylureas, including MICRONASE Tablets, 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 which 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.

Maximum Dose: Daily doses of more than 20 mg are not recommended.

Dosage Interval: Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 10 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations: MICRONASE is not recommended for use in pregnancy or for use in children. In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See Precautions Section).

For additional product information see your Upjohn representative.

Upjohn

THE UPJOHN COMPANY, Kalamazoo, MI 49001

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May 1988

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JANUARY AUTHOR INDEX

(Volume 12, Number 1)

Bantle, J., 56	McKane, W.R., 12
Bell, P., 12	Marvin, R.S., 18
Bell, P.M., 12	Miller, S.A., 75
Bild, D., 24	Murase, T., 7
Braveman, P., 24	
Brown, F.M., 1	Nakanishi, K., 7
Browner, W., 24	
	Paternostro-Bayles, M., 34
Clarke, W.L., 18	
Collings, A., 50	Rabinowe, S.L., 1
Coulston, A.M., 62	Reaven, G.M., 62
	Robertson, R.J., 34
Filer, L.J., 67	
Frattali, V.P., 75	Selby, J., 24
Frier, B.M., 32	Showstack, J., 24
	Sinnock, P., 24
Hayes, J.R., 12	Snyder, A.L., 18
Hepburn, D.A., 32	Steel, J.M., 32
Hollenbeck, C., 62	Stegink, L.D., 67
	Stevens, A.B., 12
Itoh, T., 7	Sugimoto, T., 7
Kadrofske, M.M., 1	
King, D.J., 12	Tsuji, K., 7
Kobayashi, T., 7	
Kosaka, K., 7	Watts, M., 1
	Wing, R.R., 34
Levine, R., 81	

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In Diabetes—

Poor control of blood glucose has been associated with complications and malaise that detract from the quality of life. While this is true for all diabetics, it seems to often be forgotten when managing NIDDM.

Random blood glucose testing often does not provide significant new information to detect possible physical damage caused by poor control.

A periodic glycated hemoglobin assay, however, provides you with a retrospective view of average blood glucose levels over the previous four to eight weeks. With that information, you can modify or change the treatment and reinforce adherence to diet and exercise.

Glycated hemoglobin values are something both you and your patients can understand.

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The True Value Affinity Assay

Because glycated hemoglobin results are so important, it is essential that the assay used provide true values time after time.

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Metabolic changes are detected sooner with Glyc-Affin GHb than with other assays, and they are more pronounced than HbA₁ or HbA_{1c} values. That's a clinical advantage for you and often a psychological boost for the patient, since they see progress sooner. It also provides an early warning system for lessening of control.

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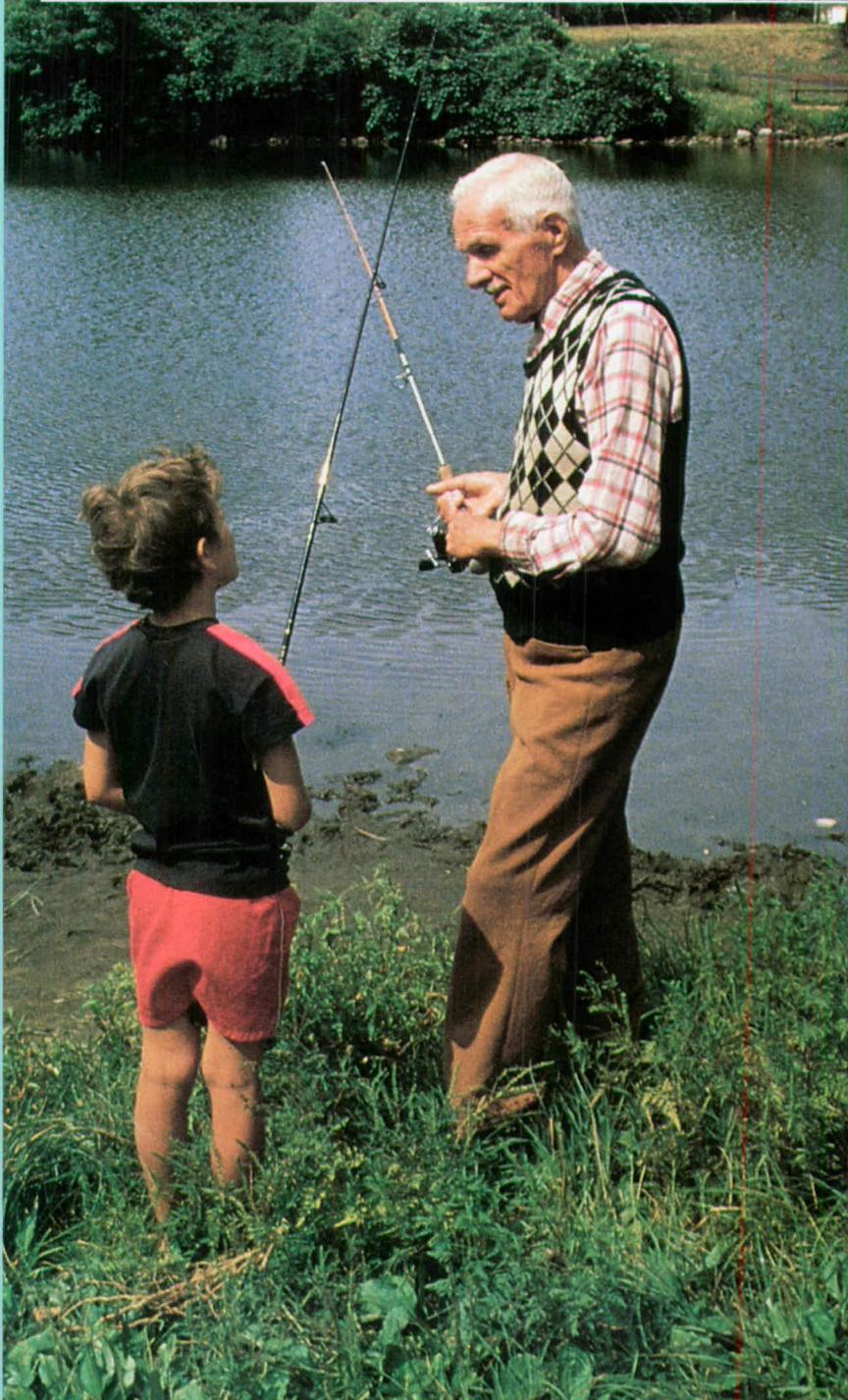
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Control Means Quality of Life



IN THIS ISSUE

Autoimmunity in IDDM: The Plot Thickens

The immune system plays an important role in the pathogenesis of insulin-dependent diabetes mellitus (IDDM). Immunologic markers, reflecting the autoimmune destruction of pancreatic β -cells, are detectable in people at high risk for developing IDDM in the near future. Rabinowe et al. (p. 1) report finding antibodies to sympathetic ganglia in a high proportion of IDDM subjects, which suggests that at least one of the complications of diabetes, autonomic neuropathy, may have an autoimmune basis. Whether such antibodies can be used to identify diabetic subjects at high risk for developing autonomic neuropathy is an important area for future research.

Men: Add This to the List

As if pattern baldness, the draft, and a statistically shorter life span were not enough, maleness itself may be a risk factor for worsening diabetes mellitus. Kobayashi et al. (p. 7) report that progressive loss of insulin secretion is more likely to occur in men than women. In a longitudinal study of 2858 non-insulin-dependent diabetic (NIDDM) individuals spanning 48 mo, islet cell antibody-positive men were more likely to become insulin dependent than women. The difference could not be explained by the titer of islet cell antibody or HLA tissue type, giving weight to the speculation that sex may play a role in the progression of this disease.

The Chicken or the Egg: Low Blood Glucose or Symptoms?

Which comes first? Is psychomotor performance impaired by hypoglycemia or some factor associated with the onset of hypoglycemic symptoms? Stevens et al. (p. 12) administered psychometric tests and a questionnaire assessing hypoglycemic symptoms to 12 healthy subjects at either normal or slightly lowered glucose levels. Although fine motor performance, memory, and information processing were diminished during mild hypoglycemia, these impairments were not observed before the onset of warning symptoms and hormonal counterregulation.

Parental Stress: When Your Child Has Diabetes

The family of a diabetic child may bear an unusually heavy stress load. How much stress exists and how it affects the child are unknown. Hauenstein et al. (p. 18) measured the perceived level of stress in mothers of diabetic children and assessed its relationship to glycemic control. The authors quantitated difficulties in parent-child relationships and compared the results with an age-matched control group. Mothers of diabetic children had more negative feelings about their offspring and more frequently perceived themselves as less competent and more isolated from receiving spousal support than did mothers of healthy children. Although stress levels were generally higher in mothers of diabetic children, there was no clear relationship to glycemic control.

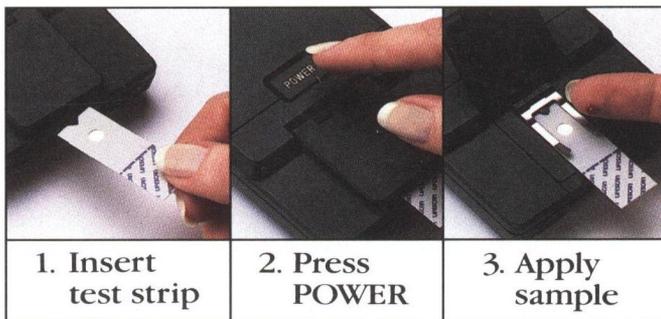
In Search of the Perfect Sweetener: A Symposium

The role of sugar in the diet of individuals with diabetes is unclear and controversial. This issue of *Diabetes Care* (p. 47) includes a symposium dealing with caloric sweeteners and various old and new noncaloric substitutes. The article addresses many important questions. What, for example, is the role of fructose as a sweetener in the diabetic diet? How much and what type of sweeteners can be ingested safely? Should the ban on cyclamates be continued? What other options are available? Is there any truth in the rumors about health hazards regarding aspartame? The answers are timely and important.



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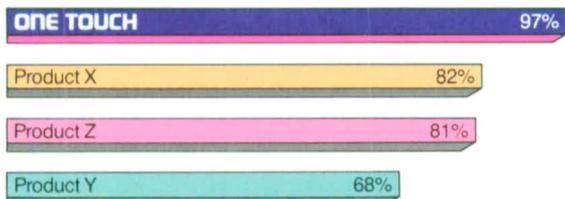
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Blood glucose readings obtained by patients using blood glucose meters were compared to readings obtained by a technician using a laboratory reference standard. Figures indicate the percentage of patient readings within 15% of reference standard.

1. Jovanovic-Peterson L, Peterson CM, Dudley JD, Kilo C, Ellis B: Identifying sources of error in self-monitoring of blood glucose. *Diabetes Care* 1988;11(10)791-794.

The One Touch System helps patients achieve greater accuracy because test results are virtually technique-independent. When you recommend the One Touch System, you put simpler, more accurate monitoring within your patients' grasp.

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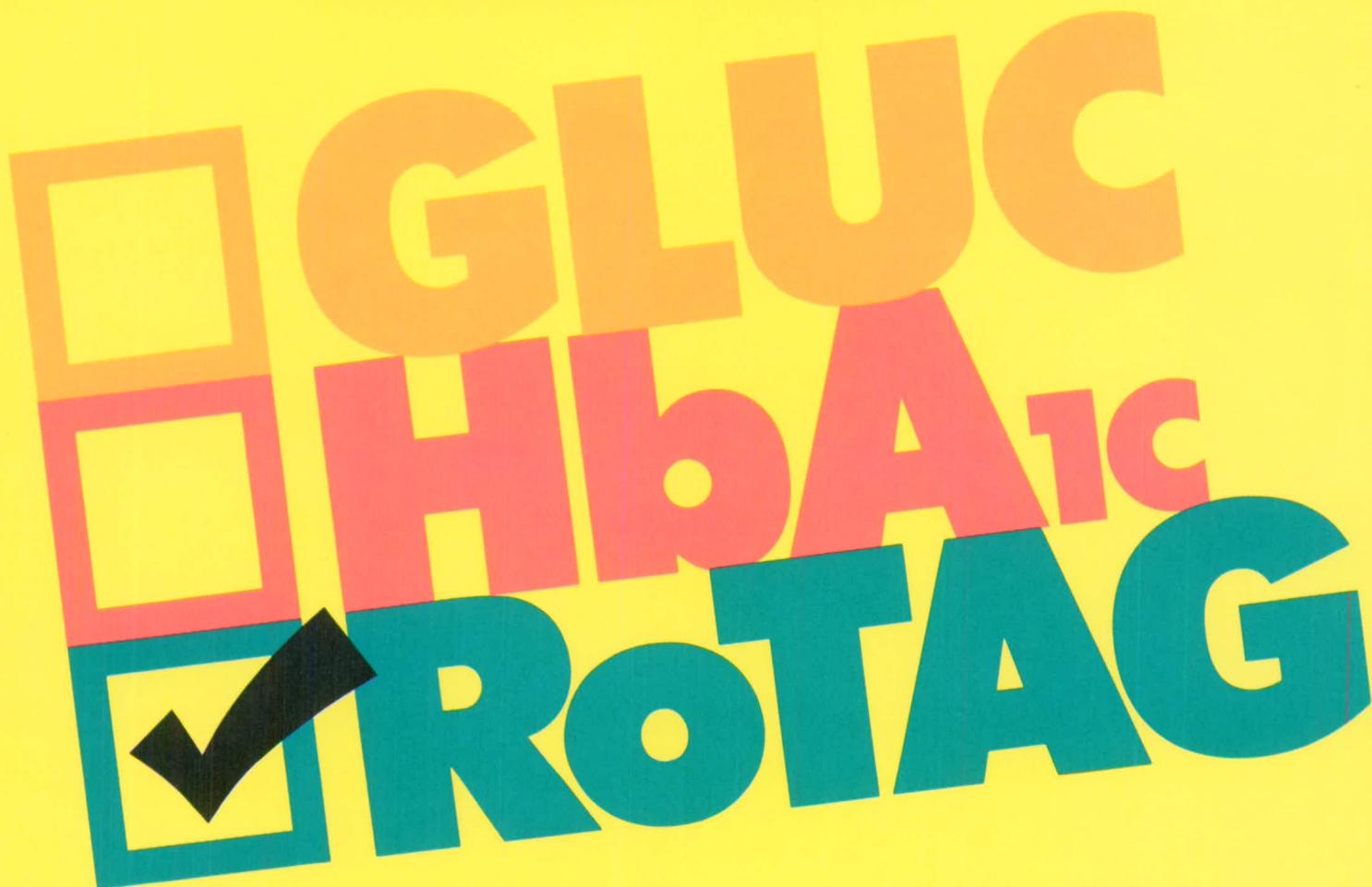
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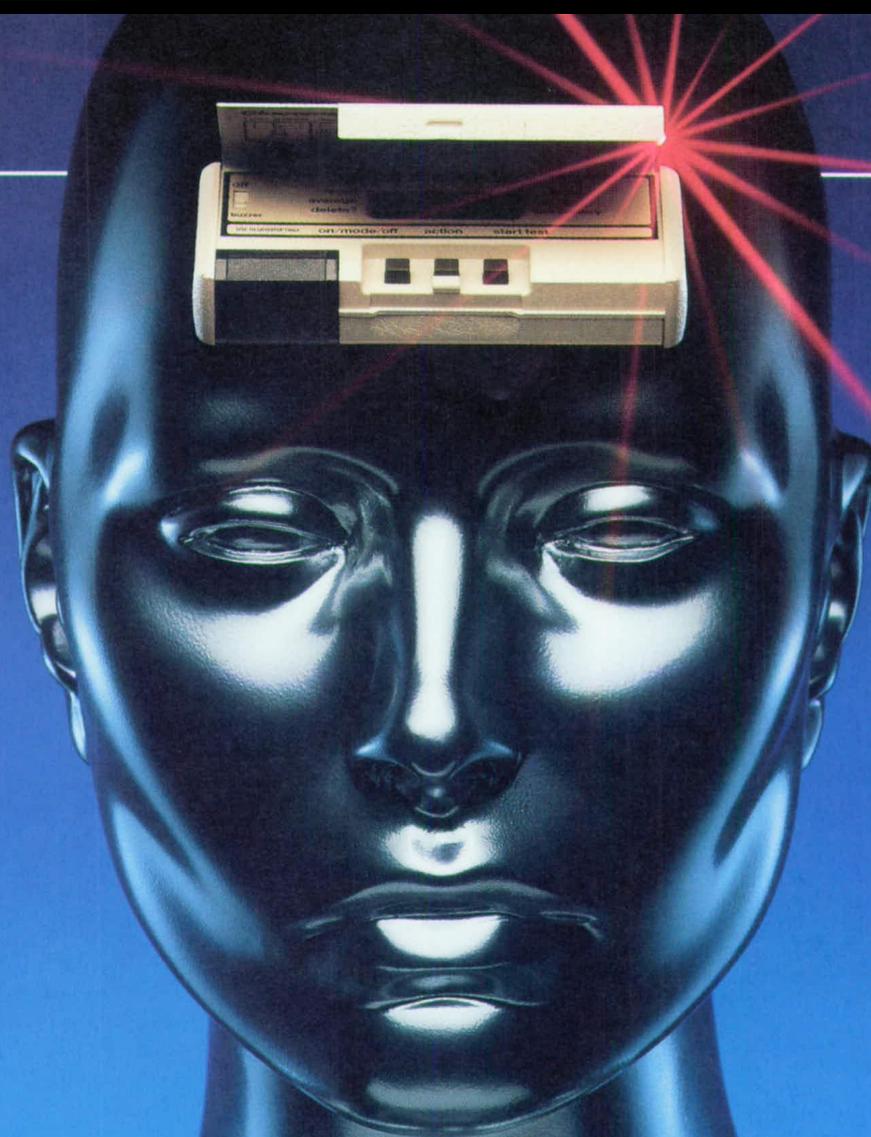
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Help ease the concerns that make self blood glucose monitoring a challenge. A piece of mind from the GLUCOMETER II with Memory can mean peace of mind for your patients. And for you.

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

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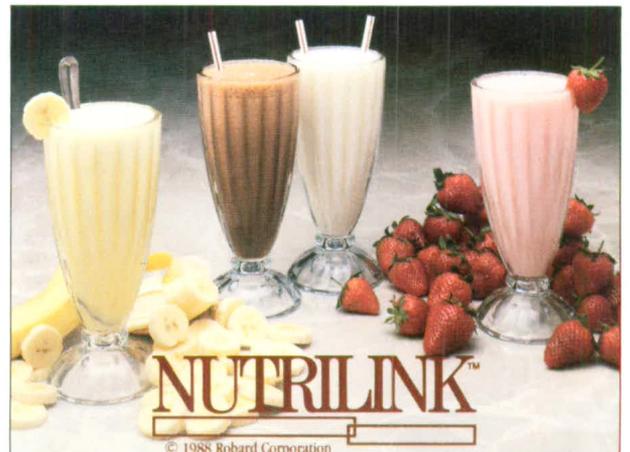
Your overweight patients can become quite a problem. As a physician, you know all too well that their obesity can lead to kidney problems, heart disease, diabetes, and more. Problems that can probably be avoided if they would only lose weight. But no matter how hard they try, they can't seem to. They become frustrated. And so do you. If you could only help them lose, you could also help them avoid these graver conditions.

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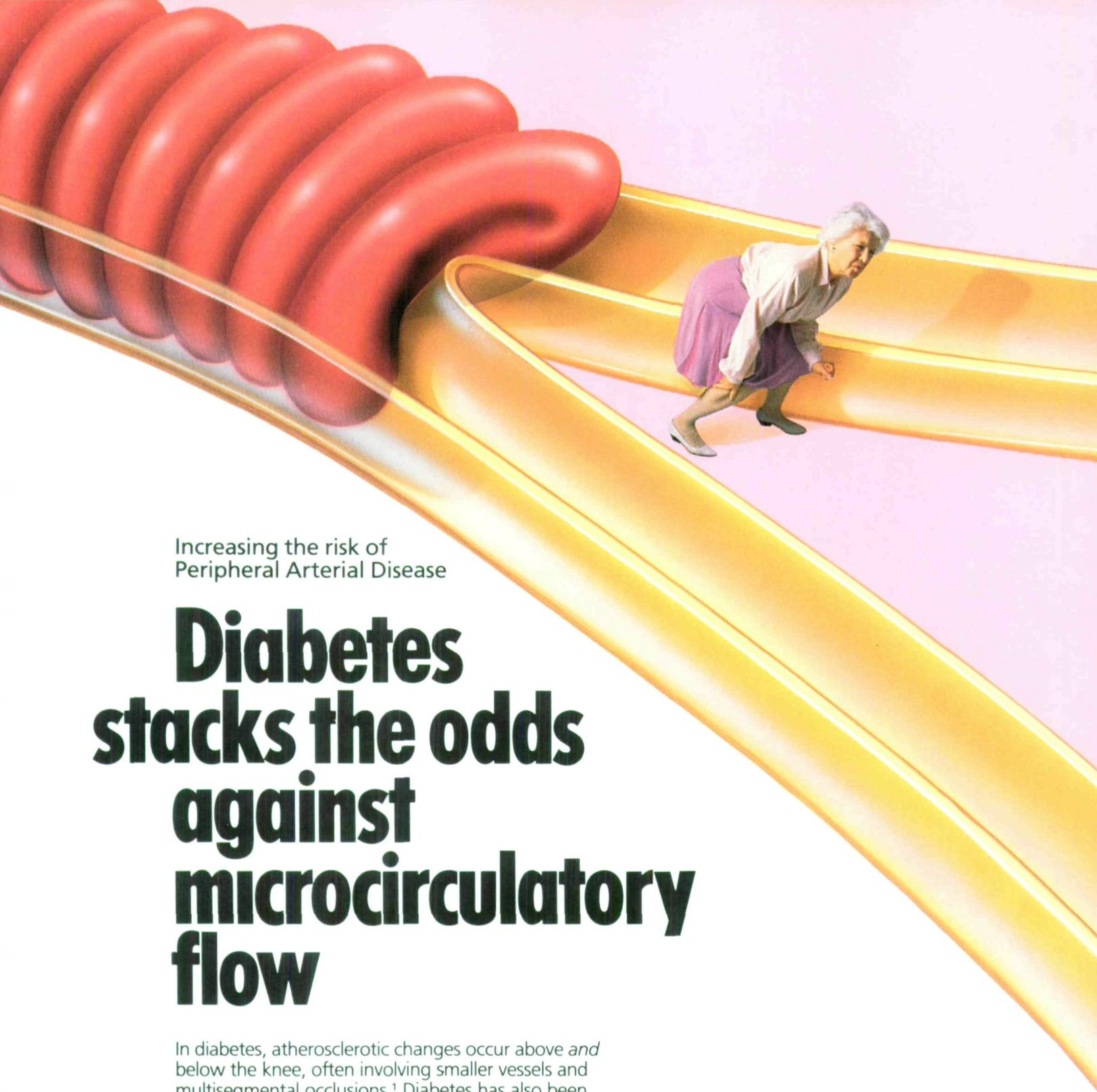
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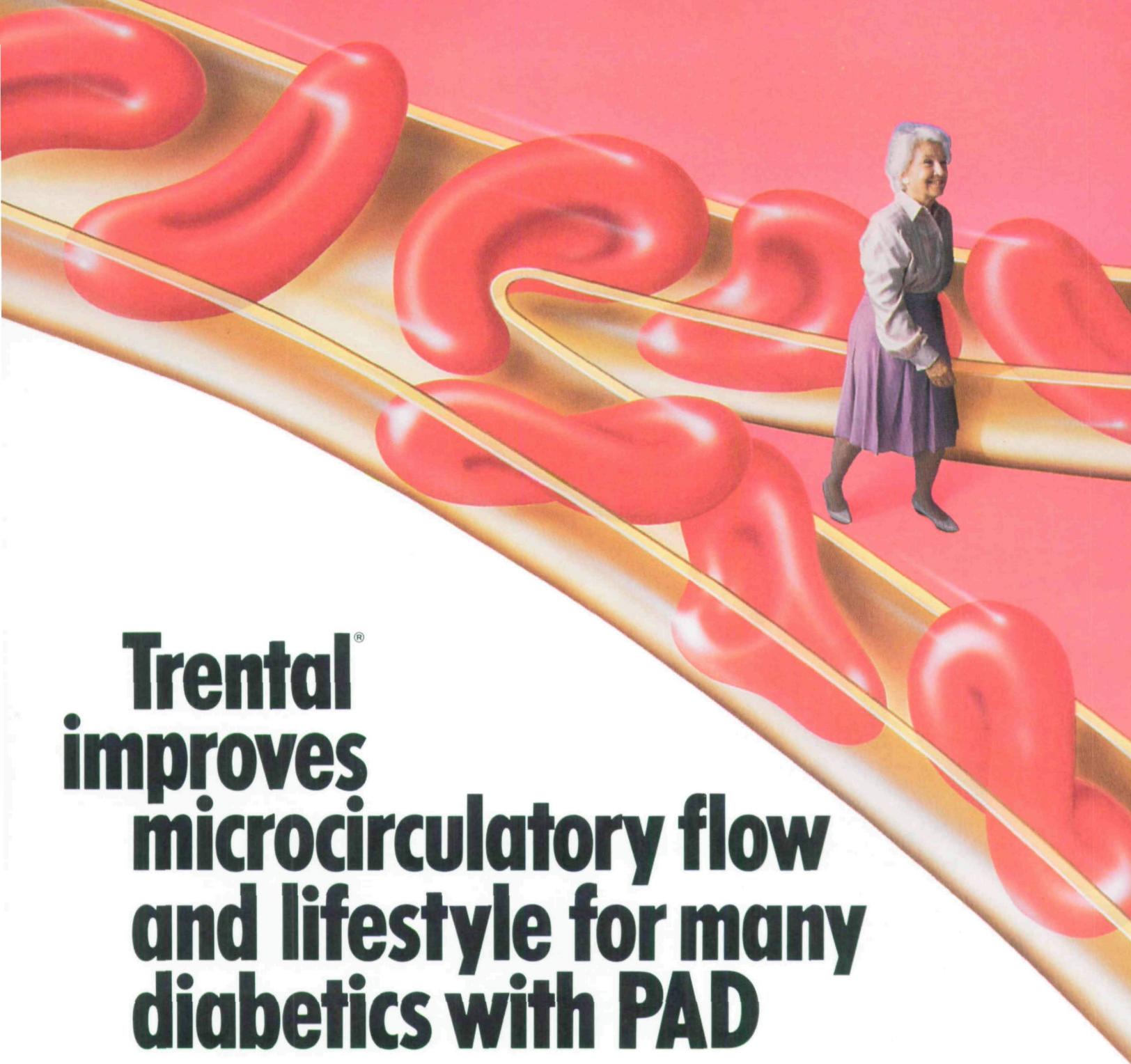


Increasing the risk of
Peripheral Arterial Disease

Diabetes stacks the odds against microcirculatory flow

In diabetes, atherosclerotic changes occur above *and* below the knee, often involving smaller vessels and multisegmental occlusions.¹ Diabetes has also been associated with decreased red cell flexibility, and increasing fibrinogen levels, platelet aggregation and platelet adherence, factors which predispose patients to peripheral arterial disease.¹

Duration of Diabetes	Incidence of PAD
10 years	15%
20 years	45%



Trental[®] improves microcirculatory flow and lifestyle for many diabetics with PAD

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a symptom of peripheral arterial disease

Please see references and brief summary of prescribing information on following page.
Trental[®] can improve function and symptoms, but is not intended to replace more definitive therapy, such as surgery.

References:

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Trental® (pentoxifylline) Tablets, 400 mg

A brief summary of the Prescribing Information follows.

INDICATIONS AND USAGE:

Trental® (pentoxifylline) is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. Trental® (pentoxifylline) can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS:

Trental® (pentoxifylline) should not be used in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS:

General: Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. Trental® (pentoxifylline) has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that Trental® (pentoxifylline) causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses.

Drug Interactions: Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with Trental® (pentoxifylline) with and without anticoagulants or platelet aggregation inhibitors. Patients on warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Trental® (pentoxifylline) has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with Trental® (pentoxifylline); periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to approximately 24 times (570 mg/kg) the maximum recommended human daily dose (MRHD) of 24 mg/kg for 18 months in mice and 18 months in rats with an additional 6 months without drug exposure in the latter. No carcinogenic potential for pentoxifylline was noted in the mouse study. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females in the high dose group (24 x MRHD). The relevance of this finding to human use is uncertain since this was only a marginal statistically significant increase for a tumor that is common in aged rats. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) when tested in the presence and absence of metabolic activation.

Pregnancy: Category C. Teratogenic studies have been performed in rats and rabbits at oral doses up to about 25 and 10 times the maximum recommended human daily dose (MRHD) of 24 mg/kg, respectively. No evidence of fetal malformation was observed. Increased resorption was seen in rats at 25 times MRHD. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Trental® (pentoxifylline) should be used during pregnancy only if clearly needed.

Nursing Mothers: Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS:

Clinical trials were conducted using either controlled-release Trental® (pentoxifylline) tablets for up to 60 weeks or immediate-release Trental® (pentoxifylline) capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid. The table summarizes the incidence (in percent) of adverse reactions considered

drug related, as well as the numbers of patients who received controlled-release Trental® (pentoxifylline) tablets, immediate-release Trental® (pentoxifylline) capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available Trental® (321)	Placebo (128)	Used only for Controlled Clinical Trials Trental® (177)	Placebo (138)
(Numbers of Patients at Risk)				
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	—	1.1	2.2
Arrhythmia/Palpitation	—	—	1.7	0.7
Flushing	—	—	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	—	—	4.0	1.4
Belching/Flatus/Bloating	0.6	—	9.0	3.6
Diarrhea	—	—	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	—	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	—	—	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	—	—	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	—	—	2.3	2.2
Tremor	0.3	0.8	—	—
Blurred Vision	—	—	2.3	1.4

Trental® (pentoxifylline) has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

- Cardiovascular—dyspnea, edema, hypotension.
- Digestive—anorexia, cholecystitis, constipation, dry mouth/thirst.
- Nervous—anxiety, confusion.
- Respiratory—epistaxis, flu-like symptoms, laryngitis, nasal congestion.
- Skin and Appendages—brittle fingernails, pruritus, rash, urticaria, angioedema.
- Special Senses—blurred vision, conjunctivitis, earache, scotoma.
- Miscellaneous—bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians: Cardiovascular—angina, arrhythmia, tachycardia; Digestive—hepatitis, jaundice, increased liver enzymes; and Hemetic and Lymphatic—decreased serum fibrinogen, pancytopenia, aplastic anemia, purpura, thrombocytopenia.

OVERDOSAGE:

Overdosage with Trental® (pentoxifylline) has been reported in children and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered.

In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to adsorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION:

The usual dosage of Trental® (pentoxifylline) in controlled-release tablet form is one tablet (400 mg) three times a day with meals. While the effect of Trental® (pentoxifylline) may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration. Digestive and central nervous system side effects are dose related. If patients develop these side effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of Trental® (pentoxifylline) should be discontinued. Edition 2/88 Trental® REG TM HOECHST AG

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