

diabetes

A JOURNAL OF
THE AMERICAN
DIABETES
ASSOCIATION®

PERSPECTIVES IN DIABETES

- MHC molecules and β -cell destruction: immune and nonimmune mechanisms
L.C. HARRISON, I.L. CAMPBELL, J. ALLISON, AND J.F.A.P. MILLER 815

ORIGINAL ARTICLES

- Microvascular blood flow, volume, and velocity measured by laser Doppler techniques in IDDM
M. RENDELL, T. BERGMAN, G. O'DONNELL, E. DROBNY, J. BORGOS, AND R.F. BONNER 819
- Membrane lipid alterations and Na^+ -pumping activity in erythrocytes from IDDM and NIDDM subjects P. BALDINI, S. INCERPI, S. LAMBERT-GARDINI, A. SPINEDI, AND P. LULY 825
- Effect of prostaglandin E₁ analogue TFC 612 on diabetic neuropathy in streptozocin-induced diabetic rats: comparison with aldose reductase inhibitor ONO 2235 H. YASUDA, M. SONOBE, M. YAMASHITA, M. TERADA, I. HATANAKA, Z. HUITIAN, AND Y. SHIGETA 832
- Effects of sorbinil on glomerular structure and function in long-term-diabetic rats
S.M. MAUER, M.W. STEFFES, S. AZAR, AND D.M. BROWN 839
- Effects of acute metabolic acidosis and alkalosis on leucine metabolism in conscious dogs
N.R. RODRIGUEZ, J.M. MILES, W.F. SCHWENK, AND M.W. HAYMOND 847
- Capillary basement membrane thickness and capillary density in sedentary and trained obese Zucker rats J.M. LASH, W.M. SHERMAN, AND R.L. HAMLIN 854
- Insulin and glucagon secretion after pancreatectomies: correlation of secretion and hormonal contents of remaining pancreas M. GOTOH, M. MONDEN, J. OKAMURA, T. MORI, AND K. SHIMA 861
- Differences in humoral insulin-antibody response among inbred Lou/M rats and epitope presentation differences in ELISA and radioimmune titration E.R. ARQUILLA, S. EDWARDS, B.R. McDOUGALL, L. MOSQUEDA, AND D.P. STENGER 868
- Effect of rise in cAMP levels on Ca^{2+} influx through voltage-dependent Ca^{2+} channels in HIT cells: second-messenger synarchy in β -cells A.S. RAJAN, R.S. HILL, AND A.E. BOYD III 874
- Erythrocyte O_2 transport and metabolism and effects of vitamin B₆ therapy in type II diabetes mellitus L.R. SOLOMON AND K. COHEN 881
- Genetic studies in inbred BB/Wor rats: analysis of progeny produced by crossing lymphopenic diabetes-prone rats with nonlymphopenic diabetic rats D.L. GUBERSKI, L. BUTLER, W. KASTERN, AND A.A. LIKE 887
- Reciprocal allogeneic bone marrow transplantation between NOD mice and diabetes-nonsusceptible mice associated with transfer and prevention of autoimmune diabetes D.M. LaFACE AND A.B. PECK 894
- Glucagonostatic and insulinotropic action of glucagonlike peptide 1-(7-36)-amide R. KOMATSU, T. MATSUYAMA, M. NAMBA, N. WATANABE, H. ITOH, N. KONDO, AND S. TARUI 902
- Indirect effect of catecholamines on development of insulin resistance in skeletal muscle from diabetic rats M. BOSTRÖM, Z. NIE, G. GOERTZ, J. HENRIKSSON, AND H. WALLBERG-HENRIKSSON 906
- Interferon- γ induces transcription and differential expression of MHC genes in rat insulinoma cell line RINm5F S.J. ONO, E. COLLE, R.D. GUTTMANN, AND A. FUKS 911
- Development of a method for isolation of islets from human fetal pancreas K. KOVER AND W.V. MOORE 917
- Decreased insulin- and glucagon-pulse amplitude accompanying β -cell deficiency induced by streptozocin in baboons C.J. GOODNER, D.J. KOERKER, D.S. WEIGLE, AND D.K. McCULLOCH 925
- Zinc-dependent low thymic hormone level in type I diabetes E. MOCHEGANI, M. BOEMI, P. FUMELLI, AND N. FABRIS 932

RAPID PUBLICATIONS

- Anti-sympathetic nervous system autoantibodies: diminished catecholamines with orthostasis
F.M. BROWN, S.J. BRINK, R. FREEMAN, AND S.L. RABINOWE 938
- Primary association of HLA-DQw8 with type I diabetes in DR4 patients
D. OWERBACH, S. GUNN, AND K.H. GABBAY 942

ORGANIZATION SECTION

INSTRUCTIONS FOR AUTHORS



DIAEAZ 38(7) 815-945 (1989)
ISSN 0012-1797

*As fast as
blood sugar spills,
Glucotrol
spells...*

Control



Choice
brand of
endocri-
nologists¹

Once-
daily
dosing

Near-
normal
insulin
response
to meals²

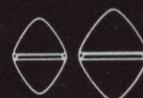
Tolerated
well by
elderly
patients^{*3}

Reliable
safety
profile^{*4}

Only 30
minutes
to onset
of action

Low
cost of
therapy⁵

Glucotrol[®]
(glipizide) 5-mg and 10-mg
Scored Tablets



When diet alone fails in non-insulin-dependent diabetes mellitus

*Please see brief summary
of GLUCOTROL[®] (glipizide)
prescribing information
on next page.*

The reasons to prescribe Glucotrol can pile up fast

Glucotrol[®]
(glipizide) 5-mg and 10-mg
Scored Tablets

References:

1. Medical Marketing Conference. *Antidiabetic Therapy Study V. Tabular Summary*. West Orange, NJ, Market Measures Inc, November 1987-January 1988. 2. 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. 3. Lipson LG. Diabetes in the elderly: Diagnosis, pathogenesis, and therapy. *Am J Med* 1986;80:10-21. 4. Sachs R, Frank M, Fishman SK. Overview of clinical experience with glipizide, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 163-172. 5. *Red Book UPDATE*. Oradell, NJ, Medical Economics Company, August 1988, pp 10, 14, 21.

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 the 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 fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity 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.

DOSE 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.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

ROERIG **Pfizer** A division of Pfizer Pharmaceuticals
New York, New York 10017

CLASSIFIED ADVERTISING

Diabetes Classified Ad rates are:

¼ Page \$370
(for non-ADA members, \$495)

⅓ Page \$180
(for non-ADA members, \$250)

All advertising must be prepaid
with order.

All advertisements will be
typeset uniformly.

The closing date for space in
Diabetes is: the first of the month
preceding month of publication;
(December 1st for the January
issue).

Circulation: 9,000 Paid

For information on classified
advertising in **Diabetes Care** and
Diabetes Spectrum; and Copy and
Contract Policies, contact:

Peggy B. Donovan
American Diabetes Association
1660 Duke Street
Alexandria, VA 22314

(800) 232-3472 ext. 312 or in Virginia
and the Washington, DC area dial
(703) 549-1500.

JULY AUTHOR INDEX (Volume 38, Number 7)

- | | |
|----------------------|---------------------------------|
| Allison, J., 815 | LaFace, D.M., 894 |
| Arquilla, E.R., 868 | Lambert-Gardini, S., 825 |
| Azar, S., 839 | Lash, J.M., 854 |
| | Like, A.A., 887 |
| | Luly, P., 825 |
| Baldini, P., 825 | |
| Bergman, T., 819 | Matsuyama, T., 902 |
| Boemi, M., 932 | Mauer, S.M., 839 |
| Bonner, R.F., 819 | McCulloch, D.K., 925 |
| Borgos, J., 819 | McDougall, B.R., 868 |
| Boström, M., 906 | Miles, J.M., 847 |
| Boyd, A.E., III, 874 | Miller, J.F.A.P., 815 |
| Brink, S.J., 938 | Mocchegiani, E., 932 |
| Brown, D.M., 839 | Monden, M., 861 |
| Brown, F.M., 938 | Moore, W.V., 917 |
| Butler, L., 887 | Mori, T., 861 |
| | Mosqueda, L., 868 |
| Campbell, I.L., 815 | |
| Cohen, K., 881 | Namba, M., 902 |
| Colle, E., 911 | Nie, Z., 906 |
| | |
| Drobny, E., 819 | O'Donnell, G., 819 |
| | Okamura, J., 861 |
| Edwards, S., 868 | Ono, S.J., 911 |
| | Owerbach, D., 942 |
| Fabris, N., 932 | |
| Freeman, R., 938 | Peck, A.B., 894 |
| Fuks, A., 911 | |
| Fumelli, P., 932 | Rabinowe, S.L., 938 |
| | Rajan, A.S., 874 |
| Gabbay, K.H., 942 | Rendell, M., 819 |
| Goertz, G., 906 | Rodriguez, N.R., 847 |
| Goodner, C.J., 925 | |
| Gotoh, M., 861 | Schwenk, W.F., 847 |
| Guberski, D.L., 887 | Sherman, W.M., 854 |
| Gunn, S., 942 | Shigeta, Y., 832 |
| Guttman, R.D., 911 | Shima, K., 861 |
| | Solomon, L.R., 881 |
| Hamlin, R.L., 854 | Sonobe, M., 832 |
| Harrison, L.C., 815 | Spinedi, A., 825 |
| Hatanaka, I., 832 | Steffes, M.W., 839 |
| Haymond, M.W., 847 | Stenger, D.P., 868 |
| Henriksson, J., 906 | |
| Hill, R.S., 874 | Tarui, S., 902 |
| Huitian, Z., 832 | Terada, M., 832 |
| | |
| Incerpi, S., 825 | Wallberg-Henriksson, H.,
906 |
| Itoh, H., 902 | Watanabe, N., 902 |
| | Weigle, D.S., 925 |
| Kastern, W., 887 | |
| Koerker, D.J., 925 | Yamashita, M., 832 |
| Komatsu, R., 902 | Yasuda, H., 832 |
| Kono, N., 902 | |
| Kover, K., 917 | |

diabetes

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION.

Editor

R. PAUL ROBERTSON, MD

Associate Editors

ROBERT P. ELDE, PhD

FRANK Q. NUTTALL, MD, PhD

STEPHEN RICH, PhD

ROBERT L. SORENSON, PhD

MICHAEL W. STEFFES, MD, PhD

Editorial Assistant

LUCILLE MARIE SHRADER

Editorial Board

LLOYD AXELROD, MD

RICHARD BERGMAN, PhD

AUBREY E. BOYD III, MD

WILLIAM CHICK, MD

WILLIAM DUCKWORTH, MD

DARYL GRANNER, MD

DOUGLAS GREENE, MD

GEROLD M. GRODSKY, PhD

EDWARD HORTON, MD

THOMAS HOSTETTER, MD

LEONARD JARETT, MD

VICTOR LAVIS, MD

ERROL MARLISS, MD

MICHAEL McDANIEL, PhD

STEWART A. METZ, MD

GERALD NEPOM, MD

STEPHEN POHL, MD

KEN POLONSKY, MD

ALEXANDER RABINOVITCH, MD

ROBERT RIZZA, MD

ALDO ROSSINI, MD

DAVID SUTHERLAND, MD

Publisher

CAROLINE STEVENS

Director of Professional

Publications

BEVERLY BRITTAN COOK

Managing Editor

ORIT LOWY CHICHERIO

Assistant Managing Editor

CHRISTINE B. WELCH

Assistant Editors

MAUREEN GALLAGHER

JEFFREY SCOTT JONES

Publications Assistant

DANIELLE BEST

Advertising Coordinator

PEGGY B. DONOVAN

Diabetes and *Diabetes Care* are scientific research journals published by the American Diabetes Association. Both publish original high-quality reports on biomedical research related to the broad field of diabetes mellitus.

All manuscripts and other editorial correspondence should be sent by first-class mail to R. Paul Robertson, MD, University of Minnesota, P.O. Box 731, Minneapolis, MN 55440-0731. Express mail or correspondence requiring street address should be addressed to R. Paul Robertson, MD, Phillips-Wangensteen Building, Room 6-124, 516 Delaware Street, SE, Minneapolis, MN 55455.

Diabetes publishes only original material. When submitting a manuscript, authors must state in their transmittal letter that the material has not been published or submitted simultaneously to another journal.

Manuscripts should be prepared in accordance with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *Annals of Internal Medicine* 96:766-71, 1982. An "Instructions for Authors" page containing specifications for manuscript preparation appears in the January and July issues of each volume.

All material published in *Diabetes* is copyrighted by the American Diabetes Association, Inc. All manuscripts submitted to *Diabetes* must include a transmittal letter stating the following before they will be considered for publication: "In consideration of ADA reviewing my (our) submission, the undersigned author(s) transfers, assigns, or otherwise conveys all copyright ownership to ADA in the event the work is published." Permission to reproduce copyrighted material from *Diabetes* will be granted for limited, noncommercial purposes. Permission requests should be addressed to the Permissions Editor, ADA, 1660 Duke Street, Alexandria, VA 22314, and should be accompanied by a letter of permission from the senior author of the article.

Diabetes (ISSN 0012-1797) is published monthly by the American Diabetes Association, Inc., 1660 Duke Street, Alexandria, Virginia 22314. Professional membership dues include \$50 designated for *Diabetes*. Subscription rates for nonmembers: \$70 for 1 year/\$125 for 2 years in the United States and Canada; \$105 for 1 year/\$195 for 2 years in all other countries. Individual copies: \$8 in the United States and Canada; \$12 in all other countries. Second-class postage paid at Alexandria, Virginia 22314, and at additional mailing offices. POSTMASTER: Send change of address to *Diabetes*, American Diabetes Association, P.O. Box 2055, Harlan, IA 51593-0238.

Diabetes is listed in *Science Citation Index*, *MEDLARS*, *Index Medicus*, and *Current Contents (Basic Science and Clinical Medicine)* data bases, and *Automatic Subject Citation Alert*. *Diabetes* and *Diabetes Care* are available online on *BRS Colleague*; for more information call 800-468-0908.

© 1989 by the American Diabetes Association, Inc.

American Diabetes Association Officers 1989-1990

Chairman of the Board

STERLING TUCKER

President

SHERMAN M. HOLVEY, MD

Chairman of

the Board-Elect

ARNOLD BERESON

President-Elect

EDWARD S. HORTON, MD

Senior Vice-President

MARY LOU MARAS, RD

Vice-Chairman of the Board

TODD E. LEIGH

Vice-Presidents

CHARLENE FREEMAN, RN

JAY S. SKYLER, MD

Secretary

ROSS V. HICKEY, JR.

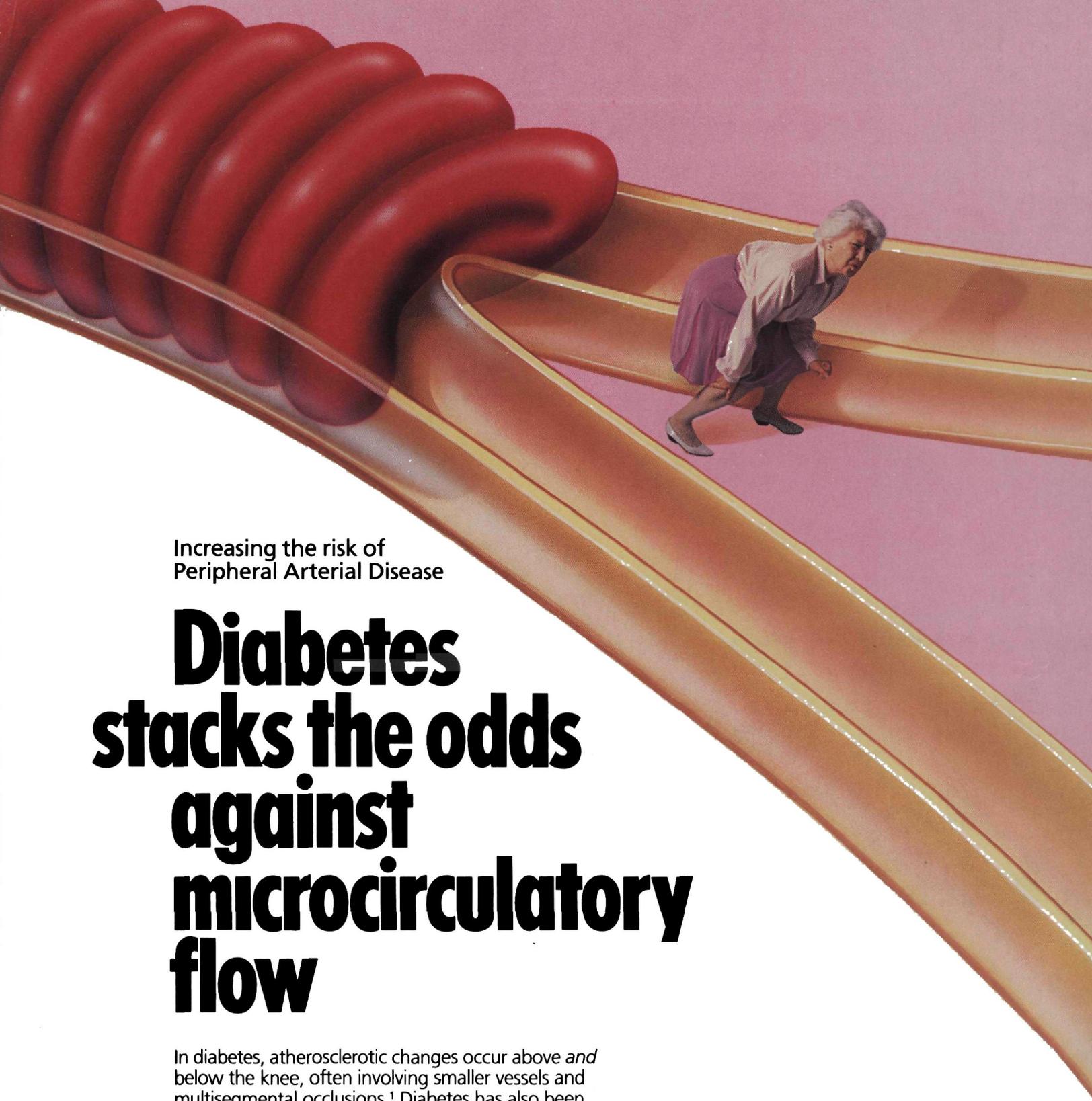
Treasurer

DOUGLAS LUND

Executive Vice-President

ROBERT S. BOLAN

 American
Diabetes
Association, Inc.

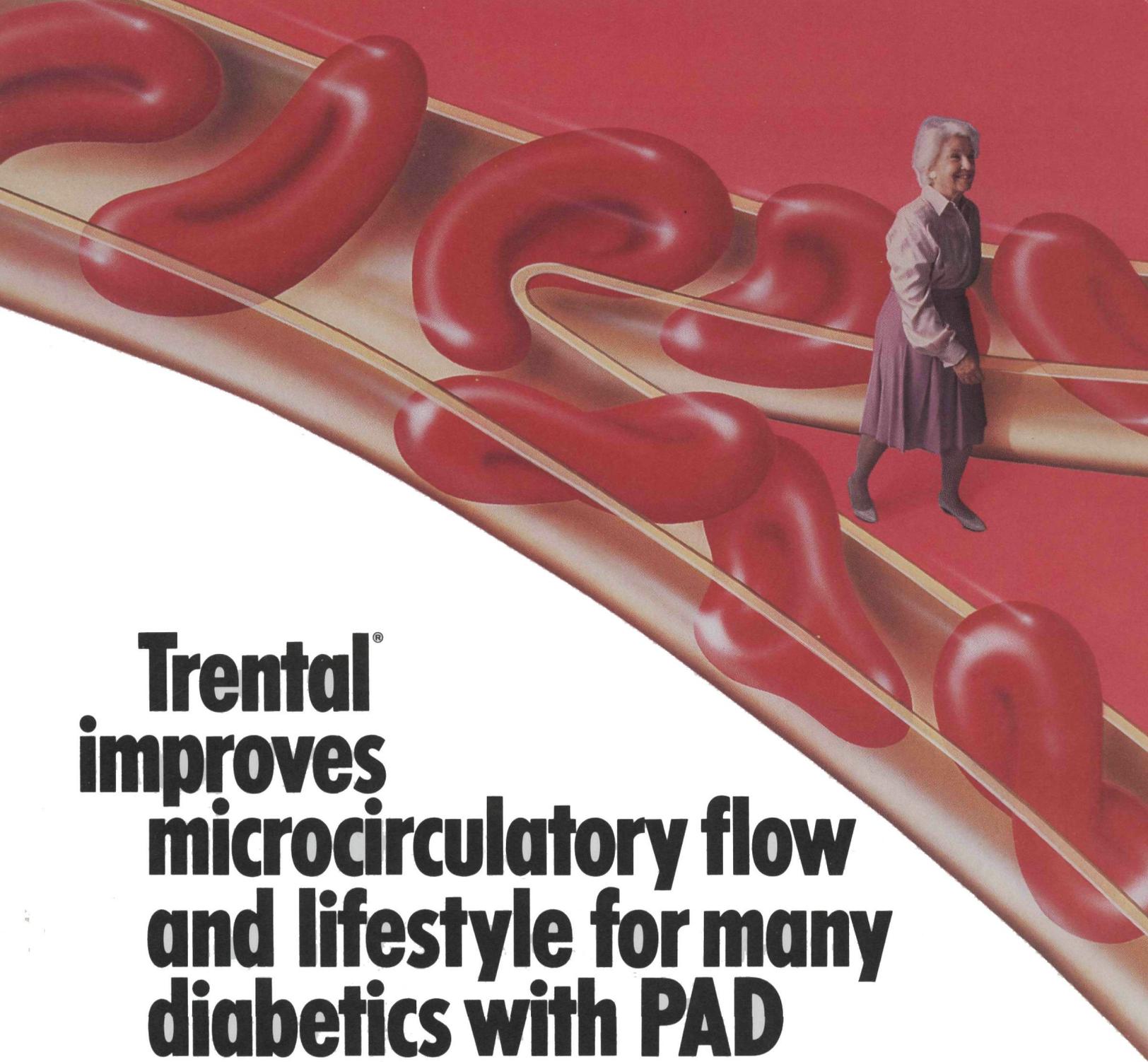


Increasing the risk of
Peripheral Arterial Disease

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%



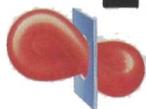
Trental[®] improves microcirculatory flow and lifestyle for many diabetics with PAD

Trental[®] (pentoxifylline) increases red cell flexibility² while decreasing elevated plasma fibrinogen levels,³ aggregation of platelets⁴ and red cells.⁵ The resulting increase in microcirculatory flow enhances tissue perfusion and oxygenation.⁶

With Trental, patients experience significant improvement in pain-free walking distance, paresthesia, skin temperature and subjective overall response.⁷

Not a vasodilator • Not an anticoagulant • Not related to aspirin or dipyridamole

Trental[®] 400 mg Tablets
(pentoxifylline)



**The only proven-effective agent for intermittent claudication,
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:

- Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/June 1987; 2.
- Stormer B, Kleinschmidt K, Loose D, et al: Rheological changes in the blood of patients with chronic arterial occlusive disease after the administration of vasoactive drugs. *Curr Med Res Opin* 1977; 4: 588-595.
- Perego MA, Sergio G, Artale F: Haemorrhological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983; 3(1): 91.
- Seiffge D: *IRCS Med Sci* 1980; 8: 727.
- Lowe GDO, Drummond MM, Forbes CD, et al: Blood and plasma viscosity in prediction of venous thrombosis. Abstracts: 77, International Symposium on Filterability and Red Blood Cell Deformability, Göteborg, Sweden, Sep 11-13, 1980.
- Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982; 10: 401.
- Schubotz R: Double-blind trial of pentoxifylline in diabetes with peripheral vascular disorders. *Pharmatherapeutica* 1976; 1(3): 172-179.

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 Hemic 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

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876



The name and logo HOECHST are registered trademarks of Hoechst AG

Help your patients take a step toward early detection and treatment of P.A.D....

Send away today or ask your Hoechst-Roussel representative for your free supply of our patient education booklet, "Step Lively".

Name _____
Address _____
City _____ State _____ Zip _____

Cut out and mail to: Step Lively, HOECHST-ROUSSEL PHARMACEUTICALS INC., P.O. Box 831, Andover, New Jersey 07821



Trental® 400 mg Tablets
(pentoxifylline)

The only proven-effective agent for intermittent claudication, a symptom of peripheral arterial disease

ERRATUM

In the article titled "Epidemiology of IDDM in Black and White Children in Jefferson County, Alabama, 1979–1985," by Wagenknecht et al. (*Diabetes* 38:629–33), Table 2 (p. 632) was printed incorrectly. The corrected table in its entirety is printed below. The staff apologizes for the oversight.

TABLE 2

Average annual incidence rates (IRs) of IDDM per 100,000 in Jefferson County, Alabama, 1979–1985, in <20-yr-old people by mean annual income for families in 1979

1979 Average annual income (\$)	Whites*				Blacks				χ^2
	IR	Observed (n)	Expected (n)	Annual population at risk†	IR	Observed (n)	Expected (n)	Annual population at risk†	
5,000–15,999	20.1	5	3.7	3 549	6.4	24	26.3	53 850	6.12
16,000–19,999	11.7	18	23.2	21 999	8.7	14	11.2	22 864	0.67
20,000–29,999	15.2	79	78.1	74 082	6.7	3	3.1	6 395	2.07
30,000–70,000	16.8	29	26.0	24 676	0	0	0.4	867	1.02
χ^2	1.98				1.30				

$\chi^2_{05,3} = 7.8$, $\chi^2_{05,1} = 3.8$.

*Income data unavailable for 3 subjects.

†Totals do not equal other denominators because of the method used to calculate the number of children per census tract.

AMERICAN DIABETES ASSOCIATION MISSING ISSUE POLICY

Replacements for missing issues will be sent free of charge provided we are notified within two months of the issue date for U.S. and Canadian subscribers/members or within four months of the issue date for all other foreign subscribers/members.

To order back issues, please prepay in U.S. funds drawn on a U.S. bank.

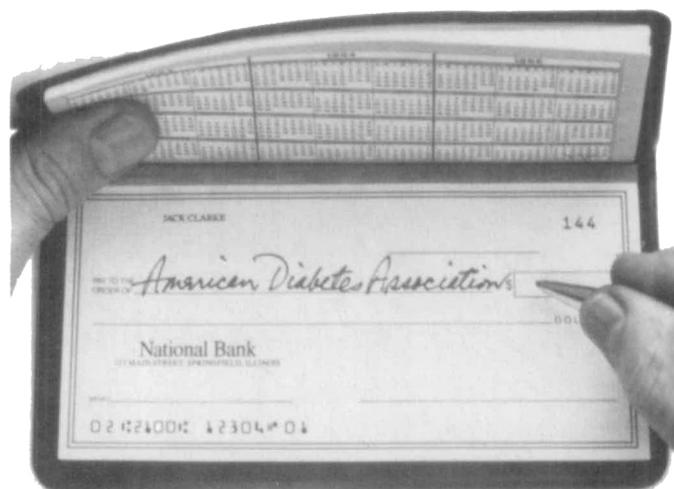
Diabetes and Diabetes Care
(Single copy price)

U.S.	Foreign Surface Mail	Foreign Air Mail
\$8.00	\$10.50	\$14.00

Make check payable to:

American Diabetes Association
Back Issue Department
1660 Duke Street
Alexandria, VA 22314

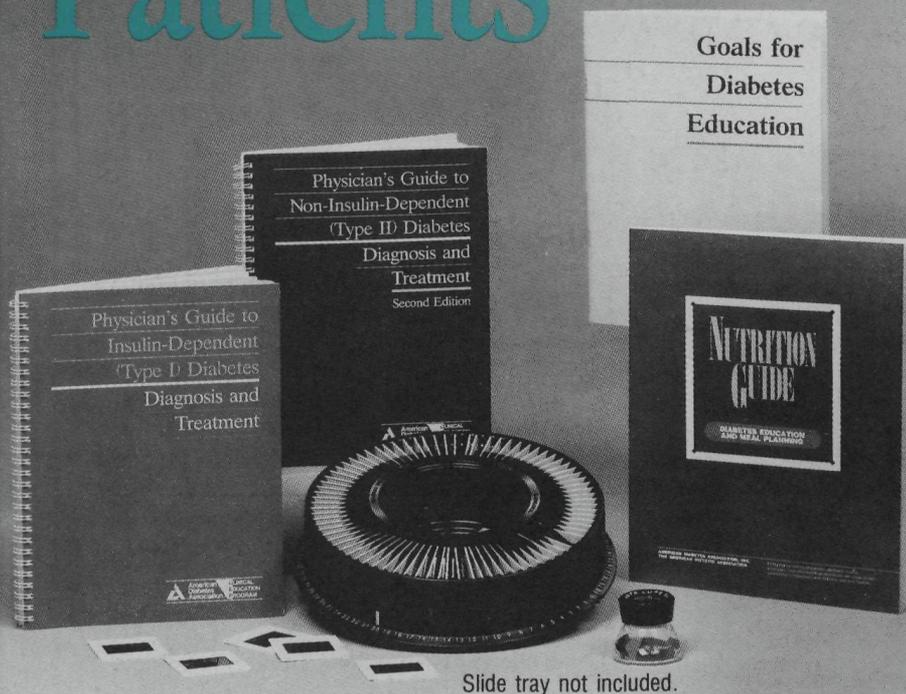
FIGHT HEART DISEASE KIDNEY DISEASE AND BLINDNESS IN ONE STROKE.



Diabetes is a major contributor to heart disease, kidney disease, and blindness. So when you support the American Diabetes Association, you fight some of the worst diseases of our time. See the White Pages for the American Diabetes Association office nearest you or call 1-800-ADA-DISC.

FIGHT SOME OF THE WORST DISEASES OF OUR TIME.
Support the American Diabetes Association. 

Educate and Motivate Your Patients



Slide tray not included.

Get the resources you need from the American Diabetes Association.

YES! I want to order the ADA publications I have chosen below.
 _____ I am an ADA Member and want to take advantage of my member discount.
 My Membership Number is _____
 (See mailing label on *Diabetes Forecast*.)

_____ copies, <i>Goals for Diabetes Education</i> #201	\$ _____
_____ copies, <i>Physician's Guide to IDDM</i> #038	\$ _____
_____ copies, <i>IDDM Slide Presentation</i> #040	\$ _____
_____ copies, <i>Physician's Guide to NIDDM</i> #037	\$ _____
_____ copies, <i>NIDDM Slide Presentation</i> #034	\$ _____
_____ copies, <i>Nutrition Guide for Professionals</i> #111	\$ _____
	Subtotal \$ _____
	VA Residents add 4.5% State Sales Tax \$ _____
	TOTAL \$ _____

Name _____
 Address _____
 City _____
 State _____ Zip _____

JX01

Make checks or money orders payable to: American Diabetes Association. Mail to: *American Diabetes Association, 1970 Chain Bridge Road, McLean, VA 22109-0592.*
 Payment must be in U.S. funds and be drawn on a U.S. bank. Shipping and handling are included for orders to the North American continent. Contact the ADA for foreign price list for shipping charges to other destinations. Please allow 6-8 weeks for delivery. Prices subject to change without notice.

Goals for Diabetes Education

Presented in an easy-to-use checklist format, this manual provides you with a logical, thorough approach to patient education. Some topics covered include diabetes and pregnancy, nutrition, exercise, and psychosocial adjustment. A *must* for all professionals involved in patient education! 1986

Nonmember: \$6.00
 ADA Member: \$4.80

Physician's Guide to Insulin-Dependent (Type I) Diabetes: Diagnosis and Treatment

This authoritative new *Guide* covers treatment advice about all areas of IDDM including diagnosis, routine management, special programs, and complications. 1988

Nonmember: \$22.45
 ADA Member: \$18.95

Principles of Good Care in the Management of Insulin-Dependent (Type I) Diabetes Mellitus: A Lecture Program

This color slide program, ideal for group presentations, follows the outline of the IDDM *Guide*. Presenter's script included. 1988

Nonmember: \$91.75
 ADA Member: \$76.75

Physician's Guide to Non-Insulin-Dependent (Type II) Diabetes: Diagnosis and Treatment, 2nd Edition

Newly revised, this *Guide* is essential for you if you treat patients with NIDDM. Learn about the latest advances in the areas of classification and pathogenesis, treatment, and complications. 1988

Nonmember: \$22.45
 ADA Member: \$18.95

Principles of Good Care in the Management of Non-Insulin-Dependent (Type II) Diabetes Mellitus: A Lecture Program

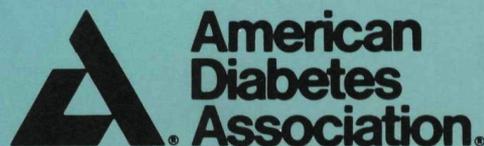
This color slide program, ideal for group presentations, follows the outline of the NIDDM *Guide*. Presenter's script included. 1988

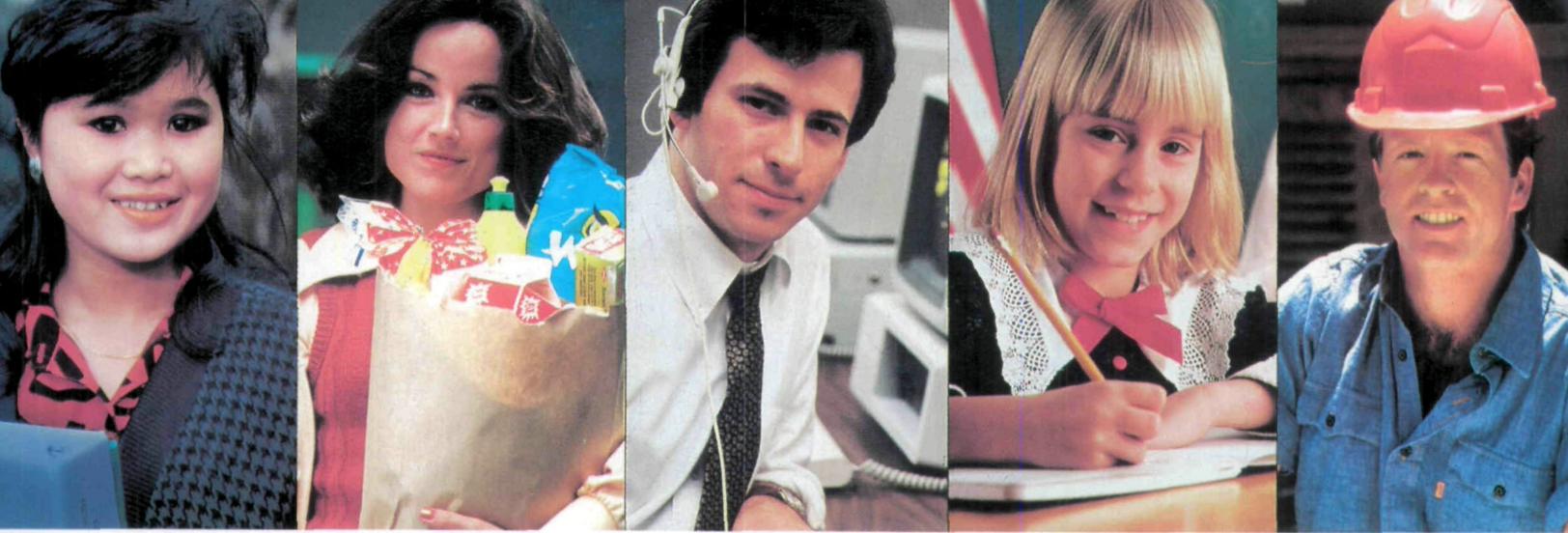
Nonmember: \$91.75
 ADA Member: \$76.75

Nutrition Guide for Professionals: Diabetes Education and Meal Planning

This new book helps you use the *Exchange Lists for Meal Planning* effectively. Some topics covered include calculating an exchange meal plan, self-monitoring of blood glucose and diet, and the complete data bases of nutrients that form the basis for the *Exchange Lists*. 1988

Nonmember: \$14.70
 ADA Member: \$12.75





Good news for your patients who inject 30 units or less

B-D Introduces the first 3/10cc syringe

- Easier-to-read scale
- More precise measurement
- More accurate dosage

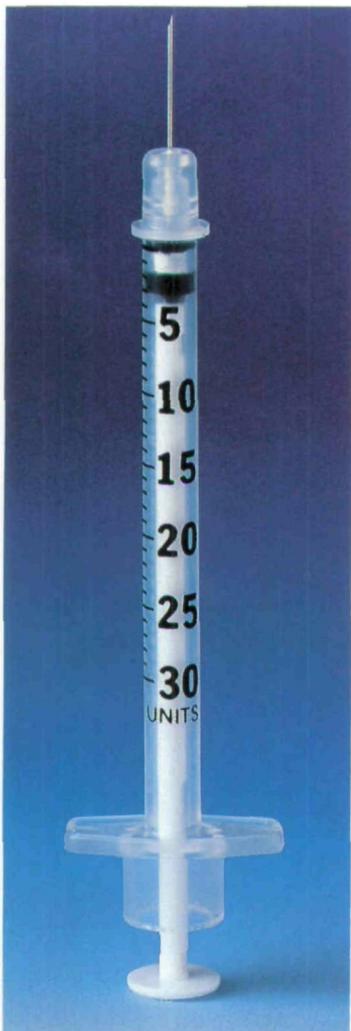
Almost half of all patients with diabetes who are being treated with insulin are prescribed smaller, more frequent injections—30 units or less.

Which makes the new B-D 3/10cc syringe the ideal insulin syringe for many of your patients.

That's because this new 3/10cc syringe helps assure more precise dosage measurements. Extra-wide spacing between single-unit markings makes it a lot easier to read the scale. And makes it a lot more accurate when measuring the dosage...an important improvement.

The unique new 3/10cc syringe comes with the famous B-D MICRO-FINE® III Needle—for unequalled injection comfort.

Another reason why physicians, nurses and hospitals use B-D syringes more than all other brands combined.



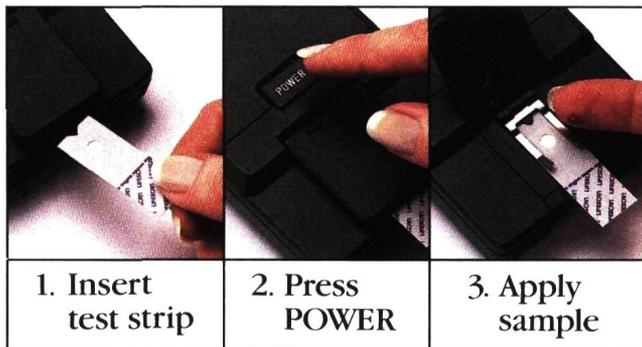
B-D and MICRO-FINE III are trademarks of Becton Dickinson and Company.

BETTER B-D
DIABETES CARE



With One Touch, simplicity and

With its breakthrough technology, the One Touch System dramatically simplifies blood glucose self-monitoring for your patients with diabetes. The One Touch procedure eliminates three major demands on the user: starting the test, timing the test and removing the blood.



Patients rated One Touch simplest to use¹



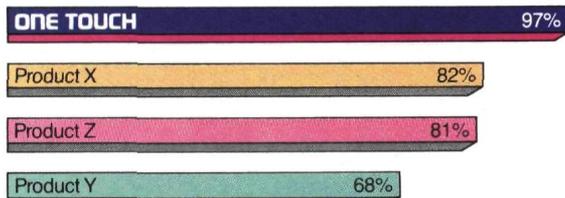
Mean scores of blood glucose monitoring systems rated by 45 patients with diabetes, using a 7-point scale. A score of 1 indicates strong agreement with the statement "Easy to do." A score of 7 indicates strong disagreement.

**No timing. No wiping. No blotting.
Results in 45 seconds.**



accuracy go hand in hand.

Unsurpassed accuracy in the hands of patients¹



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.

For a One Touch System demonstration and a complete review of clinical data, contact your LifeScan Professional Representative. For the name of your representative, call toll-free: **1 800 227-8862.**

ONE TOUCH[®]

BLOOD GLUCOSE MONITORING SYSTEM

LIFESCAN INC.

a *Johnson & Johnson* company
Mountain View, California 94043

For treatment of diabetes:

REPLACE Human Insulin



With Human Insulin



Humulin® 
human insulin
(recombinant DNA origin)

*Any change of insulin should be made
cautiously and only under medical supervision.*



Leadership
In Diabetes Care