VOLUME 13 NUMBER 11 NOVEMBER 1990

DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

ORIGINAL ARTICLE

Prevalence of Diabetes and Impaired Glucose Tolerance in Elderly Subjects and Their Association With Obesity and Family History of Diabetes
L. MYKKÄNEN, M. LAAKSO, M. UUSITUPA, K. PYÖRÄLÄ 1099

SHORT REPORTS

Weight Gain Associated With Improved Glycemic Control in Population-Based Sample of Subjects With Type I Diabetes
R.R. WING, R. KLEIN, S.E. MOSS 1106

Effect of Captopril on Glucose Concentration: Possible Role of Augmented Postprandial Forearm Blood Flow
J. KODAMA, S. KATAYAMA, K. TANAKA, A. ITABASHI, S. KAWAZU, J. ISHII 1109

Self-Care Predictors of Metabolic Control in NIDDM Patients
K.M. ROST, K.S. FLAVIN, L.E. SCHMIDT, J.B. McGILL 1111

Effects of Thromboxane Synthesis Inhibitor Triflusal on Renal Hemodynamics in Microalbuminuric Diabetic Patients
E. ESMATJES, J.I. CONGET, J. GAYA, M.R. FERNANDEZ, J.P. FERRER, F. RIVERA, E. VILARDELL 1114

ADA RECOMMENDATIONS

Hospital Admission Guidelines for Diabetes Mellitus 1118

EDITORIALS 1120

LETTERS AND COMMENTS 1129

SUPPLEMENT 4: Diabetes in Black Populations: Current State of Knowledge 1139

Introduction
J.R. GAVIN III, N. GOODWIN 1140

Opening Remarks
L. SULLIVAN 1143

Obesity and Diabetes in Blacks
F.X. PI-SUNYER 1144

Genetics of NIDDM
M.A. PERMUTT 1150

Theoretical and Baseline Considerations for Diet and Weight Control of Diabetes Among Blacks
S.K. KUMANYIKA, C.K. EWART 1154

Exercise in Therapy and Prevention of Type II Diabetes: Implications for Blacks
N. RUDERMAN, A.Z. APELIAN, S.H. SCHNEIDER 1163

Diabetic Cardiomyopathy
F.S. FEIN 1169

Chronic Diabetic Complications and Tissue Glycosylation: Relevant Concern for Diabetes-Prone Black Population
H. VLASSARA 1180

Cross-Sectional Analysis of Renal Function in Black Americans With NIDDM
H.E. LEBOVITZ, J. PALMISANO 1186

Hypertension and Diabetes in Blacks
J.G. DOUGLAS 1191

Risk Factors for Gestational Diabetes in Black Population
D.S.H. BELL, B.O. BARGER, R.C.P. GO, R.L. GOLDENBERG, L.L. PERKINS, C.J. VANICHANAN, J. ROSEMAN, R.T. ACTON 1196

Diabetic Retinopathy in Blacks
M.F. RABB, D.A. GAGLIANO, H.E. SWEENEY 1202

Closing Remarks
L. SULLIVAN 1207

ORGANIZATION SECTION

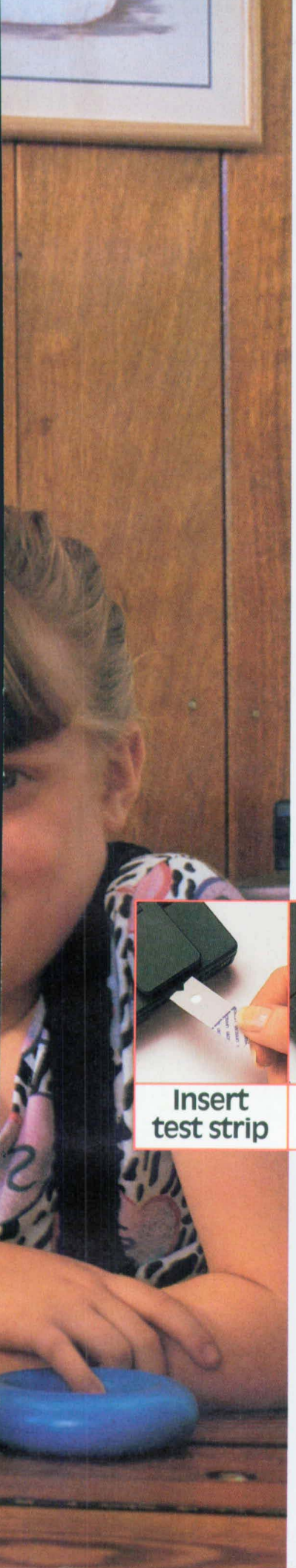
SYSTÈME INTERNATIONAL (SI) UNITS TABLE

American Diabetes Association®

ISSN 0149-5992

A JOURNAL OF THE AMERICAN DIABETES ASSOCIATION


Fisher-Price



IT PAYS TO BE ACCURATE
UP TO $100.00 CASH BACK
Offer good from 1/1/90 through 12/31/90 see Rebate Certificate for details.

"I USE THE ONE TOUCH® METER WITH CONFIDENCE"

—Pediatrician Peter Bove, M.D., San Bruno, California.

"One Touch makes accurate results easy to achieve."

"I can't afford to worry about the accuracy of my blood glucose test results. That's why I use the One Touch® Blood Glucose System from LifeScan."

"In testing my own blood glucose I have found it more difficult to make a mistake with One Touch, it's so simple."

"I use One Touch with confidence in testing my own blood glucose. And I recommend One Touch with confidence for my patients."

The One Touch System dramatically simplifies blood glucose testing. Results are obtained with only three easy steps.

Accurate results are easy to achieve with testing this simple. The One Touch System reduces the chance of user error because it eliminates three major demands on the user: Starting the Test, Timing the Test, and Removing the Blood. And that means greater accuracy where it matters most: in the hands of the people who use it[1].

To find out more about the One Touch Blood Glucose Monitoring System call:

Toll Free

United States	1 800 227-8862
Canada	1 800 663-5521

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

LIFESCAN INC.

a Johnson & Johnson company

Milpitas, California 95035

NOVEMBER AUTHOR INDEX
(Volume 13, Number 11)

Acton, R.T., 1196
Andersson, P.-O., 1135
Apelian, A.Z., 1163

Balestrieri, A., 1129
Barger, B.O., 1196
Bell, D.S.H., 1131, 1196

Cirillo, R., 1129
Conget, J.I., 1114
Conti, M., 1129

Davis, W.K., 1133
Dedrick, R.F., 1133
Douglas, J.G., 1191

Eggstein, M., 1136
Eicke, F.J., 1134
Esmatjes, E., 1114
Ewart, C.K., 1154

Fein, F.S., 1169
Fernandez, M.R., 1114
Ferrer, J., 1135
Ferrer, J.P., 1114
Flavin, K.S., 1111

Gagliano, D.A., 1202
Gatell, J.M., 1135
Gavin, J.R., III, 1140
Gaya, J., 1114
Go, R.C.P., 1196
Goday, A., 1135
Goldenberg, R.L., 1196
Gomis, R., 1135
Gonzalez-Clemente, J.M., 1135
Goodwin, N., 1140

Hino, M., 1130
Hörnquist, J.O., 1135

Inoue, T., 1130
Ishii, J., 1109
Itabashi, A., 1109

Joksch, G., 1136

Katayama, S., 1109
Kawazu, S., 1109
Keller, S.D.S., 1134
Klein, R., 1106
Kodama, J., 1109
Kumanyika, S.K., 1154

Laakso, M., 1099
Laron, Z., 1133
Lebovitz, H.E., 1186
Lowe, G.D., 1130

Mameli, G., 1129
Marongiu, F., 1129
McGill, J.B., 1111
Miki, T., 1130
Morii, H., 1130
Moss, S.E., 1106
Mykkänen, L., 1099

Nakatsuka, K., 1130
Nishizawa, Y., 1130

Palmisano, J., 1186
Perkins, L.L., 1196
Permutt, M.A., 1150
Phillips, D.M., 1134
Pi-Sunyer, F.X., 1144
Pyörälä, K., 1099

Rabb, M.F., 1202
Reinauer, K.-M., 1136
Renn, W., 1136
Replogle, W.H., 1134
Rivera, F., 1114
Robbins, D.C., 1132
Roseman, J., 1196
Rost, K.M., 1111
Ruderman, N., 1163

Schmidt, L.E., 1111
Schneider, S.H., 1163
Small, M., 1130
Sorano, G.G., 1129
Sullivan, L., 1143, 1207
Sweeney, H.E., 1202

Tabata, T., 1130
Tanaka, K., 1109

Uusitupa, M., 1099

Vanichanan, C.J., 1196
Vilardell, E., 1114
Vlassara, H., 1180

Werther, G., 1133
Wikby, A., 1135
Wing, R.R., 1106

VOLUME 13 NUMBER 11
NOVEMBER 1990

DIABETES CARE®

THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION

***Diabetes Care* publishes original articles and reviews of human and clinical research intended to increase knowledge, stimulate research, and promote better management of people with diabetes mellitus. Emphasis is on human studies reporting on the pathophysiology and treatment of diabetes and its complications; genetics; epidemiology; psychosocial adaptation; education; and the development, validation, and application of accepted and new therapies. Topics covered are of interest to clinically oriented physicians, researchers, epidemiologists, psychologists, diabetes educators, and other professionals.**

***Diabetes* publishes original research about the physiology and pathophysiology of diabetes mellitus. Submitted manuscripts can report any aspect of laboratory, animal, or human research. Emphasis is on investigative reports focusing on areas such as the pathogenesis of diabetes and its complications, normal and pathologic pancreatic islet function and intermediary metabolism, pharmacological mechanisms of drug and hormone action, and biochemical and molecular aspects of normal and abnormal biological processes. Studies in the areas of diabetes education or the application of accepted therapeutic and diagnostic approaches to patients with diabetes mellitus are not published.**

All manuscripts and other editorial correspondence should be sent by first class mail to David C. Robbins, MD, Editor, *Diabetes Care*, Medlantic Research Foundation, George Hyman Memorial Research Building, 108 Irving Street, NW, Washington, DC 20010. Manuscripts and correspondence regarding review articles should be sent to Ralph A. DeFronzo, MD, Review Editor, *Diabetes Care*, Department of Medicine, Division of Diabetes, UT-HSCSA, 7703 Floyd Curl Drive, San Antonio, TX 78284.

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

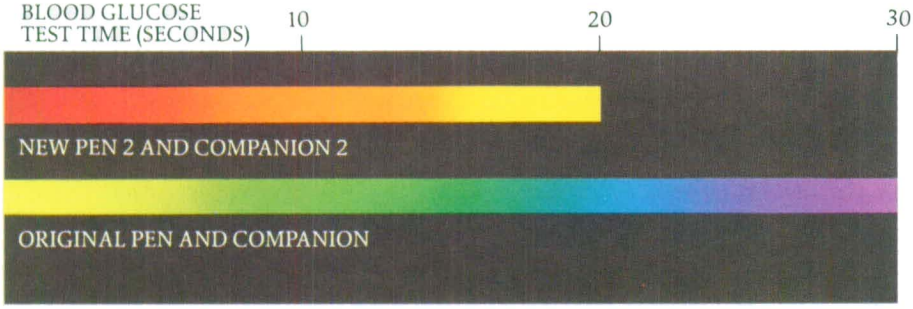
Manuscripts should be prepared in accord with the requirements specified in the document "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," *Annals of Internal Medicine* 96:766–71, 1982. An "Instructions for Authors" page containing specifications for manuscript preparation appears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

Diabetes Care (ISSN 0149-5992) is published monthly by the American Diabetes Association, Inc., 1660 Duke Street, Alexandria, VA 22314. The annual subscription rate is $65 for individuals in the U.S. and Canada. Professional Membership dues include $35 designated for *Diabetes Care*. The annual rate for all foreign subscriptions, excluding Canada, is $95. The fee for individual copies is $8 in the U.S. and Canada and $10 in all other countries. Second class postage paid at Alexandria, Virginia 22314, and at additional mailing offices. POSTMASTER: Send change of address to *Diabetes Care*, American Diabetes Association, Inc., P.O. Box 2055, Harlan, IA 51593-0238.

Diabetes Care is listed in *Science Citation Index, Current Contents/Life Sciences, Current Contents/Clinical Medicine, SCISEARCH, ISI/BIOMED* databases, and *Automatic Subject Citation Alert. Diabetes Care* is available online on *BRS Colleague*. For more information call 800-468-0908. It is also available in machine-readable format from University Microfilms International. *Diabetes Care* is printed on acid-free paper starting with Vol. 11(1), 1988.

Our sensor users already test 50% more often.

Now they'll test 33% faster.



When we first introduced our exclusive BioSensor technology, the Pen™ and Companion™ sensors quickly became the fastest testing—and fastest growing—blood glucose monitors available. So easy to use, patients with diabetes report testing with our sensors 50% more often.

Now MediSense introduces the second generation Pen™ 2 and Companion™ 2 sensors, with new Sensor Electrodes (strips). Faster, more convenient, and more user-friendly than ever.

AS ALWAYS, COMPLIANCE IS THE KEY TO BETTER HEALTH.

Frequent blood glucose testing helps patients manage their diabetes better. And no one makes testing easier than MediSense.

Patients simply insert our patented Sensor Electrode into the sensor, apply a small drop of blood to the target area, and see accurate results in record time—now just 20 seconds.

There's no need to wipe or blot, saving time and reducing technique errors. No blood ever enters the sensor, eliminating the need for cleaning and the possibility of cross-contamination between samples. And calibration is a simple one-step process.

NOW THE BEST IS EVEN BETTER.

Today, after years of research, testing, and refinement, MediSense can offer patients with diabetes even more:

For *increased ease of use,* the sensor starts automatically as soon as a small blood drop is applied to the Sensor Electrode. This eliminates the need for timing or "button-pushing" and further helps to reduce technique errors.

For *even faster test results,* we reduced the testing time from 30 seconds to *20 seconds,* making the quickest test on the market even quicker.

For *increased flexibility,* our assay reading range has been expanded to 20–600 mg/dL. And an added control feature compensates for temperature variances and eliminates interferences from uric acid and other substances in the blood.

NO OTHER SYSTEM MAKES MORE SENSE THAN MEDISENSE.

Only our sensors are so easy to learn (and teach), so fast to use, so simple to maintain, and so convenient to carry. And no other system offers a better combination of accuracy, speed, and convenience, with:

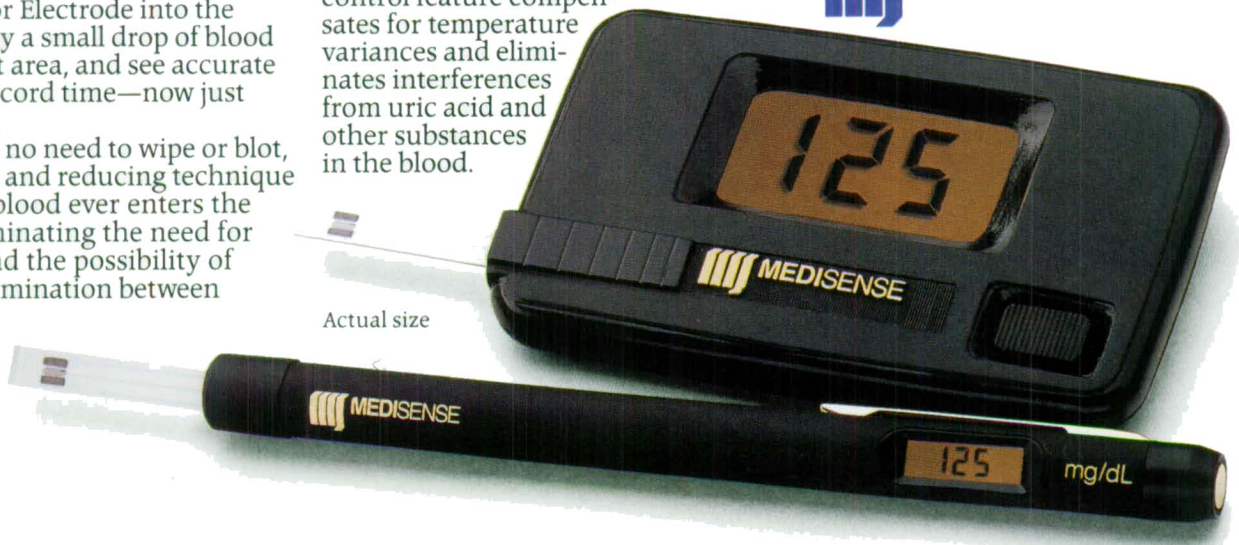
- The two smallest monitors available: the ingeniously designed Pen 2 and the credit-card sized Companion 2.
- Individually foil-wrapped, easily opened Sensor Electrodes, in packages of 25, 50 and, 100.*

MEDISENSE SENSORS. MORE PATIENTS CHOOSE THEM, MORE PATIENTS USE THEM.

For more information on the Pen 2 and Companion 2 Blood Glucose System, or a free videotape demonstration suitable for both you and your patients, please call 1-800-537-3575.

Because the faster they test, the more they test. And no monitors test faster than Pen 2 and Companion 2 Sensors from MediSense.

MEDISENSE



Actual size

Sensors for a better life.

*100-count size available in early 1991. Cambridge, MA 02139

IN THIS ISSUE

Getting Diabetes: A Matter of Time?

If you get old enough, you will get diabetes. Such statements are based on the observation that the prevalence of diabetes, or at least abnormal glucose tolerance tests, increases as the test population becomes older. Mykkänen et al. (p. 1099) report on the results of 75-g oral glucose tolerance tests administered to a randomly selected population of elderly people in small town in east Finland. The average age was ~69 yr. The results of the survey demonstrate a remarkably high prevalence of abnormal tests ranging from frank diabetes to impaired glucose tolerance. All told, >33% of the study population was abnormal based on World Health Organization criteria. Central obesity and a family history of diabetes increased an individual's risk. This study raises the suspicion that diabetes is, at least for some, an inevitable consequence of aging. On the other hand, therapeutic attention to the companions of aging such as treatment of additional disease, loss of lean tissue, change in diet composition, and inactivity may allow us to alter the inevitable. Further studies are needed to confirm this final speculation.

Weight Gain: A Bitter Fruit?

From a diabetologist's point of view, the 1980s was the decade of tight glycemic control. The 1990s, in contrast, is a time of circumspection as we begin to see the dark side of overly zealous "insulinization." One of the downsides is weight gain. Wing et al. (p. 1106) examine data gleaned from the Wisconsin Epidemiologic Study of Retinopathy to determine whether weight gain correlates with changes in glycosylated hemoglobin among type I (insulin-dependent) diabetic subjects. The analysis demonstrated a strong relationship between the two factors. In fact, those experiencing the greatest drop in HbA, levels gained slightly less than 1 kg/yr. Other circumstances predictive of greater weight gain included switching to multiple daily injections or combinations of long- and short-acting insulin. Now we need to know what are the long-term risks of insulinogenic weight gain. Will such individuals experience accelerated atherosclerosis and hypertension? Meanwhile, we continue to walk the therapeutic tightrope between too much and too little control.

The Good, the Bad, and the Glycosylated Hemoglobin

What makes a good patient good? Do lower percentages of glycosylated hemoglobin levels reflect the patient's hard work, genetics, or just plain luck? Rost et al. (p. 1111) attempt to answer this question by studying a group of non-insulin-dependent diabetic patients who were divided by the use or nonuse of insulin. The investigators measured frequencies of such behaviors as exercise and meal skipping by self-report. Patients who skipped meals and infrequently performed self-monitoring of blood glucose testing were generally those with the worst diabetic control. This finding applied equally to both insulin users and nonusers, but such self-care behaviors only explained ~25% of the variance in glycosylated hemoglobin. Thus, other factors such as genetics, nature of the individual's diabetes, and selection bias may have a significant impact on diabetic control. But what will happen if we counsel meal skippers to mend their ways? A prospective study is needed to determine whether improved diabetic control is the consequence and not just the concomitant of recalcitrance.

Diabetes in Blacks

Diabetes in the Black population is a serious problem that needs to be addressed. This issue (p. 1139–1208) includes a symposium supplement on diabetes in Blacks that was presented at the Second National Conference on Diabetes in Blacks: Imperatives for Action that was held in Washington, DC, March 1989. The conference was attended by Dr. Louis Sullivan, Secretary of Health and Human Services, and included health-care professionals with expertise in areas ranging from the genetics of diabetes and obesity in diabetes, to the complications of the disease specifically associated with the Black population. What was actually discovered was the urgent need for the further research of diabetes in the Black population. Diabetes appears to have a greater and more serious impact on the Black population than on the White population, and we hope that this decade will see further research in this important area.

For your insulin-mixing or NPH-using patients

Humulin 70/30 makes life easier

Rapid onset and sustained duration insulin activity in a single vial

- May offer enhanced control through a more physiologic activity profile
- Accurate dosing—eliminates mixing errors
- Convenient premixed dose for better compliance
- Easy to use—for patients who find mixing difficult

Specify

Humulin® 70/30

70% human insulin isophane suspension
30% human insulin injection (recombinant DNA origin)

Humulin has just the right mix

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

Changes in refinement, purity, strength, brand (manufacturer), type (regular, NPH, Lente®, etc), species (beef, pork, beef-pork, human), and/or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage.

Leadership in Diabetes Care

Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

counter point.

point.

INTRODUCING

Glucolet® 2

Automatic Lancing Device

WITH UNIQUE FINGERSTIX™ LANCET PROTECTION

Today even taking a fingerstick blood sample can be risky business. To counter the danger of an accidental needlestick injury, new Glucolet® 2 features the unique protection of Fingerstix™ Lancet.

Lancet is encased in a rigid, *disposable* endcap to eliminate the need for loading and recapping single lancets, and to keep the lancet needle recessed both *before and after* you take your patient's blood sample.

Glucolet 2 offers you a simple, quick, and economical way to safely obtain blood samples. *We'll prove it to you.* Clip the Glucolet 2 product logo from the bottom of this ad (copies will not be accepted) and send it, with your name and address, to Glucolet® 2 Special Offer, P.O. Box 3115, Elkhart, Indiana 46515-3115. In return, we'll send you Glucolet® 2 with your first Fingerstix™ Lancet*—*at no cost*—so you can try it soon with your patients.

*Offer expires January 31, 1991. Allow 8 weeks for delivery.

Disposable Fingerstix™ Lancet

Making diabetes easier and safer to manage

Clip here

point.
Glucolet® 2
Automatic Lancing Device
counter point.

MILES

Miles Inc.
Diagnostics Division
Elkhart, Indiana 46515

Get American Diabetes Association nutrition publications at a great savings!

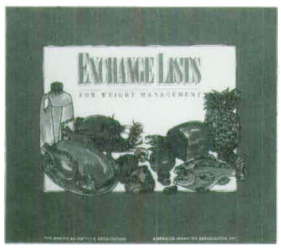
Save $5 to more than $700 when you buy bulk copies of these essential patient publications!

Exchange Lists For Meal Planning

Here's the preferred system for diabetes meal planning. Colorful charts, helpful tips on good nutrition, and the six easy-to-use food exchange lists show your patients how to balance their diets to help control their diabetes. *Regular or Large-Print Versions.*

Exchange Lists For Weight Management

It's the perfect book for any of your patients who want to get their weight under control. Help them learn the basics of good nutrition and to set goals for a good weight management program.



Guidelines For Use Of The Exchange Lists

Help your patients accomplish their special dietary goals with three new modified meal planning guides:

- *For Low-Sodium Meal Planning*
- *For Lowfat Meal Planning*
- *For Low-Sodium, Lowfat Meal Planning*

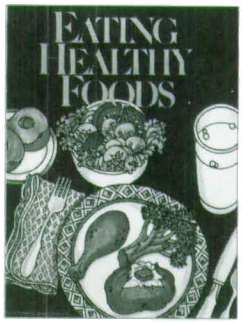
Recommended for use with the *Exchange Lists For Meal Planning.*

Healthy Food Choices

This pamphlet contains the basics of good nutrition and meal planning. Designed as an introduction to the Exchange Lists or a stand-alone product, this mini-poster is a "beginner's level" meal planning tool. *English or Spanish Versions.*

Eating Healthy Foods

Developed for people with limited reading skills, this colorfully illustrated booklet provides daily meal choices using the Exchange Lists. It's also perfect for patients needing a simplified guide to meal planning.



American Diabetes Association.

Bulk Prices	10-99	100-499	500-999	1,000+
Exchange Lists For Meal Planning				
Regular	$1.05	$1.00	$ .90	$ .75
Large Print	$2.15	$2.00	$1.75	$1.50
Exchange Lists for Weight Management	$1.05	$1.00	$ .90	$ .75
Guidelines For Use of the Exchange Lists (pkg. of 10)				
For Low-Sodium Meal Planning	$5.00	$4.80	$4.20	$3.60
For Lowfat Meal Planning	$5.00	$4.80	$4.20	$3.60
For Low-Sodium, Lowfat Meal Planning	$5.00	$4.80	$4.20	$3.60
Healthy Food Choices (pkg. of 25)				
English	$6.75	$6.25	$5.50	$4.75
Spanish	$6.75	$6.25	$5.50	$4.75
Eating Healthy Foods	$1.70	$1.60	$1.40	$1.20

YES! Please send me the following publications:

Qty.		Total
_____	*Exchange Lists for Meal Planning* #CELMP	_____
_____	*Exchange Lists for Meal Planning* (large print) #CELPML	_____
_____	*Healthy Food Choices* #CELHFC	_____
_____	*Healthy Food Choices* (spanish) #CSHFC	_____
_____	*Exchange Lists for Weight Management* #CELWM	_____
_____	*Eating Healthy Foods* #CELEHF	_____
_____	*Guidelines: For Low-Sodium* (pkg. of 10) #CELGLS	_____
_____	*Guidelines: For Lowfat* (pkg. of 10) #CELGLF	_____
_____	*Guidelines: For Low-Sodium, Lowfat* (pkg. of 10) #CELGLSLF	_____
	($5 minimum order required) Publications Total	_____
	VA Residents Add 4.5% Sales Tax	_____
	Add Shipping & Handling (see chart)	_____
	TOTAL	_____

Shipping and Handling Chart
(calculate using publications total)
up to $5.00.....add $1.75
$5.01 - $10.00.....add $3.00
$10.01 - $25.00...add $4.50
$25.01 - $50.00...add $5.50
over $50.00.....add 10% of order

Name_____

Address_____

_____

City_____ State____ Zip_____

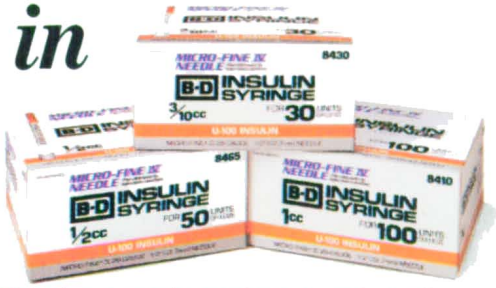
CS5911C

Send your check or money order payable to the **American Diabetes Association, 1970 Chain Bridge Road, McLean, VA 22109-0592.** Allow 6-8 weeks for domestic delivery. Add $3.00 to shipping and handling for each additional "ship to" address. Add $15.00 to shipping and handling for air shipped orders outside the U.S. Prices subject to change without notice.

The ultimate in injection comfort promises the ultimate in patient compliance.

The B-D MICRO-FINE® IV is so sharp, so superbly lubricated, no other needle even comes close for comfort.

The ultimate in comfort leads to the ultimate in patient compliance with your insulin injection instructions. One more reason physicians, nurses and hospitals use B-D syringes more than any other brand.



We back up our comfort promise to your patients with a money-back guarantee on every box of B-D syringes. It's our way of assuring them they will receive the ultimate in injection comfort.

BETTER B-D DIABETES CARE

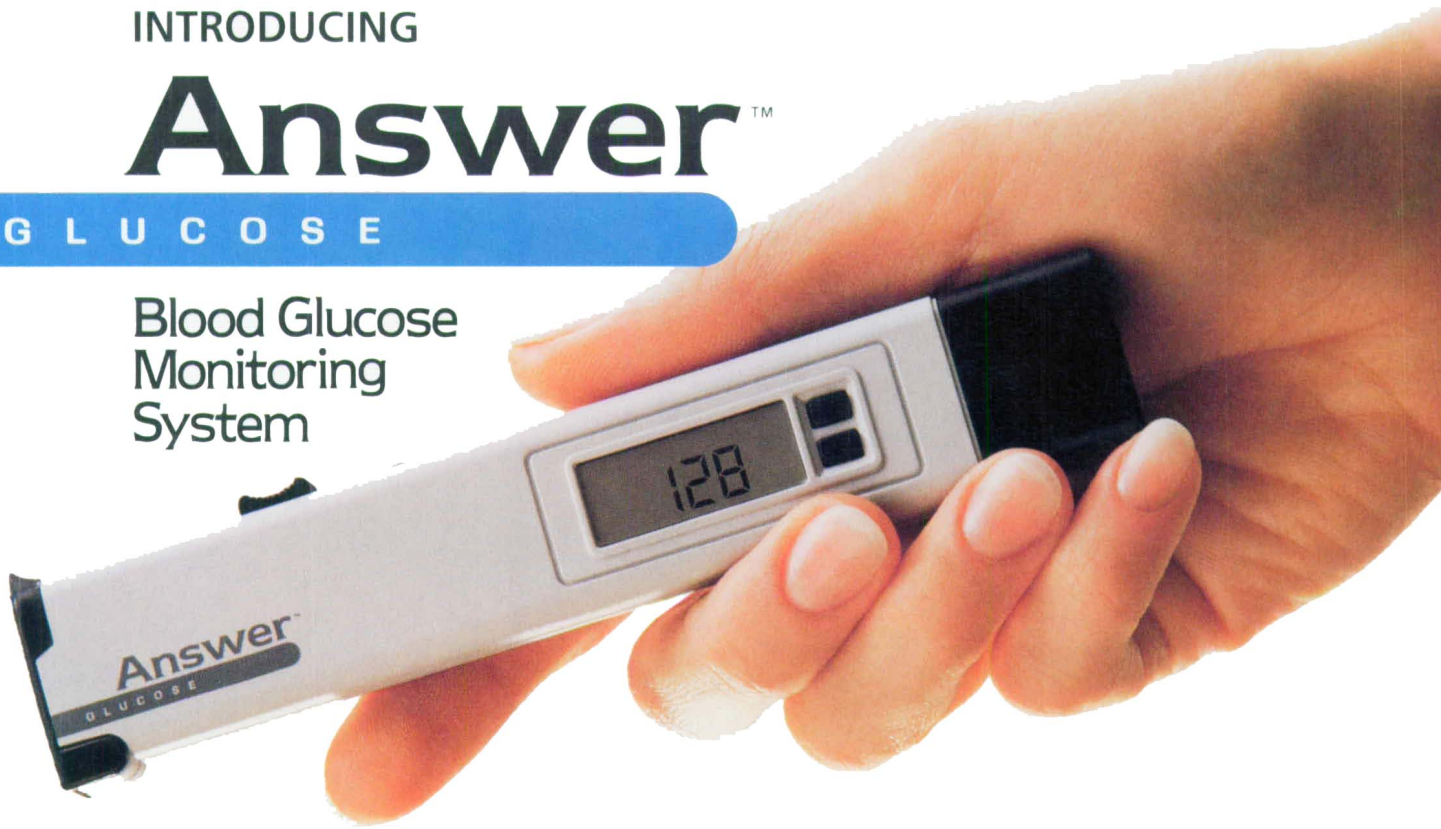
Look for 38th Postgraduate Course registration information in this issue.

INTRODUCING

Answer™

GLUCOSE

Blood Glucose Monitoring System

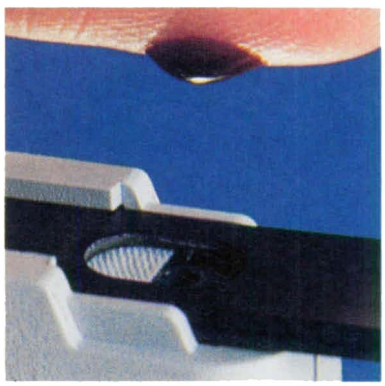


A better response to your patients' self-monitoring questions

The convenience of a lancing device that's *built-in*

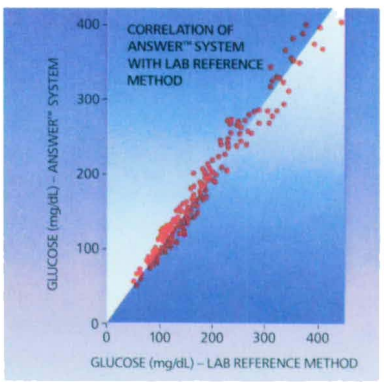
The Answer™ Meter is the *only* one with an integral lancing device. And that means greater convenience for your diabetic patients.

The simplicity of a no wipe, no blot procedure



We know that you want your patients' glucose testing to be as simple and accurate as possible. The Answer™ System helps minimize procedural errors because it requires no wiping, no blotting, no timing ...just "touch" the sample to the test strip!

The assurance of results that are consistently reliable

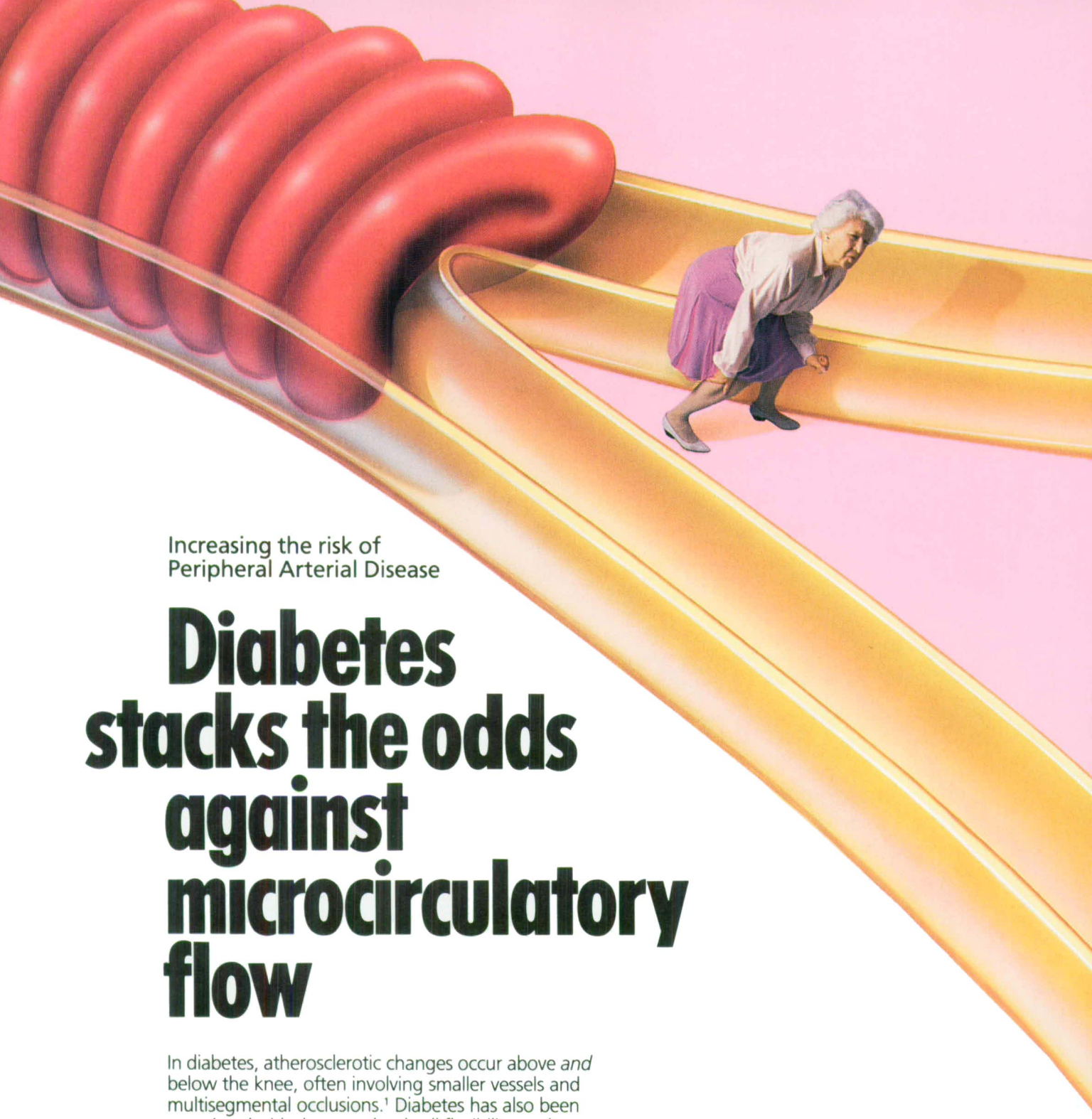


Laboratory tests demonstrate correlation of the Answer™ System with the YSI Analyzer of >0.98.* That means a level of accuracy and dependability you and your patients can feel good about.

*Data on file, Wampole Laboratories

Wampole Laboratories
Div. of Carter-Wallace, Inc.
Cranbury, NJ 08512

Customer Support: 1-800-525-6718

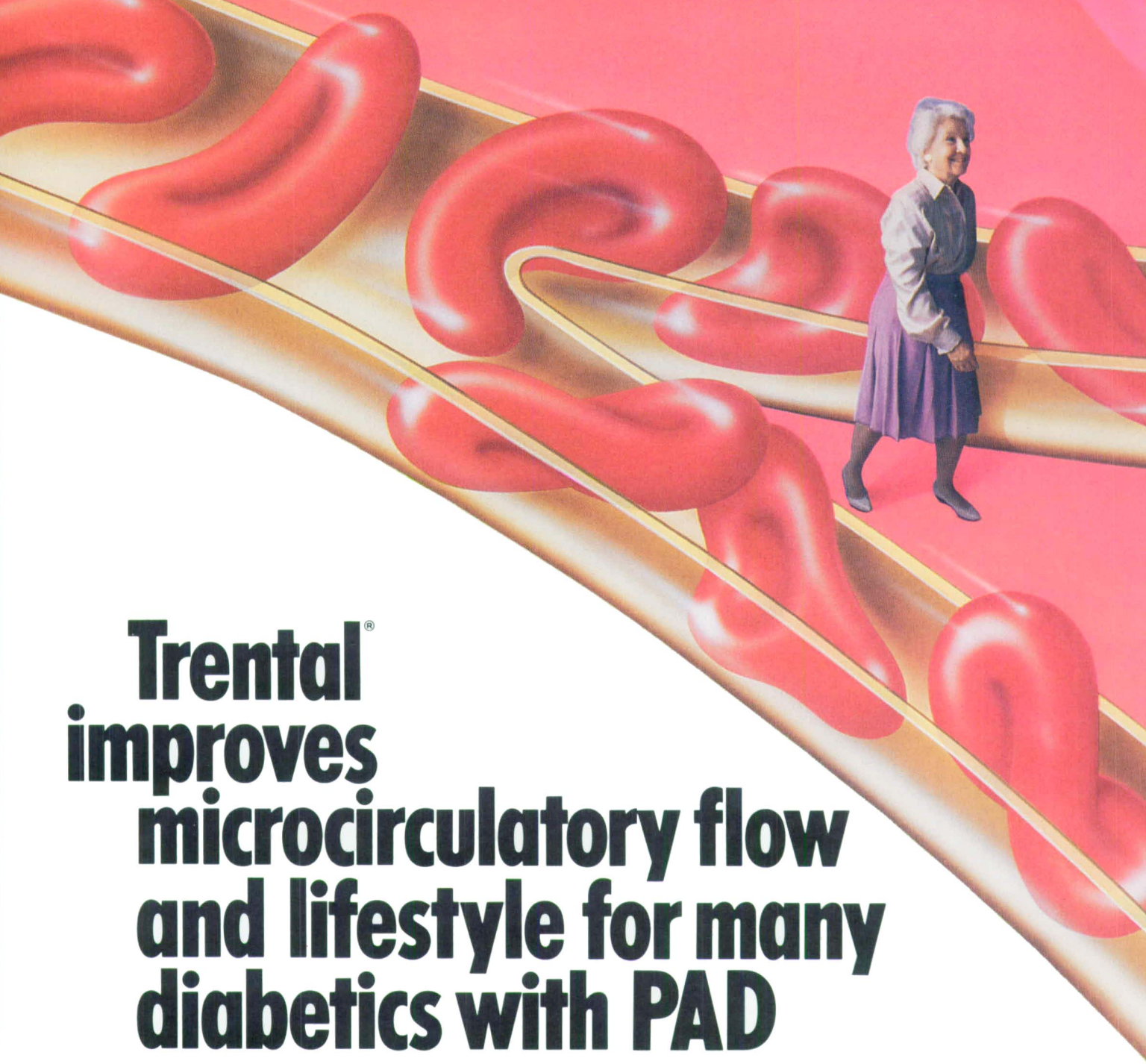


Increasing the risk of
Peripheral Arterial Disease

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 flexibility[2] while decreasing elevated plasma fibrinogen levels,[3] aggregation of platelets[4] 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

Trental (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:
1. Levin ME, Sicard GA: Evaluating and treating diabetic peripheral vascular disease, Part I. *Clinical Diabetes* May/Jun 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. **3.** Perego MA, Sergio G, Artale F: Haemorrheological aspects of the pathophysiology and clinical features of peripheral occlusive arterial disease. *Pharmatherapeutica* 1983;3(1):91. **4.** Seiffge D: *IRCS Med Sci* 1980;8:727. **5.** 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. **6.** Ehrly AM: Effects of orally administered pentoxifylline on muscular oxygen pressure in patients with intermittent claudication. *IRCS Med Sci* 1982;10:401. **7.** 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 × 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		Used only for Controlled Clinical Trials	
	Trental®	Placebo	Trental®	Placebo
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
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. **Hoechst**
Somerville, New Jersey 08876

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

Q73224-190

Patience pays off when you start a patient on Trental®

Trental® therapy can make a dramatic difference to your patients – increasing their mobility and independence, enhancing their participation in social and professional activities, and giving them a fresh outlook on life. But, the physical improvement behind these benefits doesn't happen overnight. It's a gradual process.

3x3=success with Trental® treatment

To start patients off on the right foot with Trental®, follow the 3×3 formula for success.

3 tablets a day, with meals

The usual dosage of Trental® is one 400 mg tablet taken 3 times a day, with a full meal.

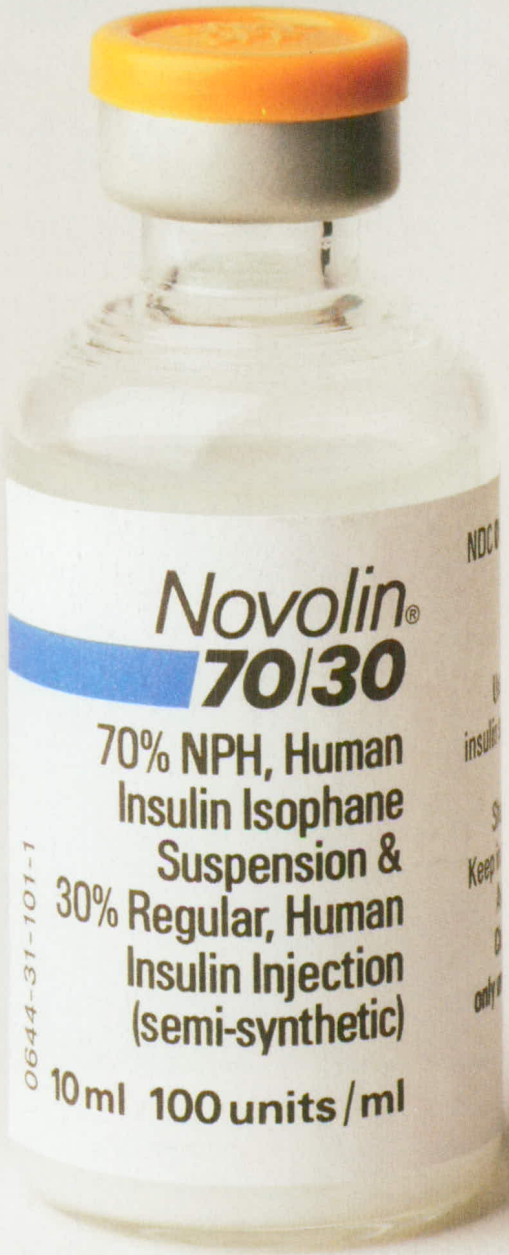
3-month initial trial, evaluate, then continue

While patients might feel somewhat better within weeks, at least 3 months' therapy is generally required before the full effectiveness of Trental® becomes evident. To sustain improvement, therapy must be continued.

Trental® 400 mg Tablets
(pentoxifylline)

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

From the worldwide leader in diabetes care.



Novolin® 70/30 (70% NPH human insulin isophane suspension & 30% regular human insulin injection [semi-synthetic]): The world's first commercially available human premixed insulin is structurally identical to endogenous human insulin.

- STABLE — Precise, premixed ratio consistently maintained
- ACCURATE — Eliminates mixing errors
- EFFICACIOUS — Helps promote good glycemic control[1]

Human insulin that helps eliminate human error

Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.
The worldwide leader in diabetes care

[1] Roland JM: Need Stable Diabetics Mix Their Insulins? *Diabetic Medicine* 1985;2:51-53.