

## EFFECT OF TROGLITAZONE IN INSULIN-TREATED PATIENTS WITH TYPE II DIABETES MELLITUS

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FOR THE TROGLITAZONE AND EXOGENOUS INSULIN STUDY GROUP\***ABSTRACT**

**Background** Troglitazone is a new oral antidiabetic drug that increases the sensitivity of peripheral tissues to insulin. It may therefore increase the efficacy of exogenous insulin in patients with insulin-resistant diabetes mellitus.

**Methods** We studied the effect of troglitazone or placebo in 350 patients with poorly controlled non-insulin-dependent (type II) diabetes mellitus (glycosylated hemoglobin values, 8 to 12 percent; normal, 4.3 to 6.1 percent) despite therapy with at least 30 U of insulin daily. The patients were randomly assigned to receive 200 mg of troglitazone (116 patients), 600 mg of troglitazone (116 patients), or placebo (118 patients) daily for 26 weeks. Insulin doses were not increased and were reduced only to prevent hypoglycemia. Glycosylated hemoglobin, serum glucose while fasting, serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured 5 times during an 8-week base-line period and 10 times during the 26-week treatment period. Daily insulin doses were recorded during both periods.

**Results** Ninety percent of the patients completed the study. The adjusted mean glycosylated hemoglobin values decreased by 0.8 and 1.4 percentage points, respectively, in the group given 200 mg of troglitazone and the group given 600 mg of troglitazone, and fasting serum glucose concentrations decreased by 35 and 49 mg per deciliter (1.9 and 2.7 mmol per liter), respectively, despite decreases in the insulin dose of 11 percent and 29 percent ( $P < 0.001$  for all comparisons with the placebo group). Serum total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations increased slightly and serum triglyceride concentrations decreased slightly in the troglitazone-treated patients.

**Conclusions** When given in conjunction with insulin, troglitazone improves glycemic control in patients with type II diabetes mellitus. (N Engl J Med 1998;338:861-6.)

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**T**REATMENT for patients with non-insulin-dependent (type II) diabetes mellitus consists of reducing hyperglycemia through diet, exercise, and therapy with drugs or insulin.<sup>1</sup> The longer diabetes has been present, the more likely patients are to require insulin to control their hyperglycemia.<sup>2,3</sup> Despite insulin treatment,

however, hyperglycemia in these patients is often not well controlled.<sup>2</sup>

The thiazolidinediones are a class of compounds that reduce insulin resistance in animals with hyperglycemia and hyperinsulinemia.<sup>4-8</sup> These drugs have antihyperglycemic effects only in the presence of insulin<sup>9</sup> and do not cause hypoglycemia in nondiabetic animals.<sup>9,10</sup> In humans, administration of the thiazolidinedione troglitazone increased insulin-stimulated glucose disposal in obese subjects and patients with type II diabetes, demonstrating its ability to ameliorate insulin resistance.<sup>11,12</sup> It also normalized impaired glucose tolerance, thus demonstrating the potential to delay or prevent the progression of impaired glucose tolerance to diabetes<sup>13</sup>; furthermore, in preliminary studies in patients with type II diabetes, troglitazone reduced hyperglycemia and hyperinsulinemia without causing hypoglycemia.<sup>11,14,15</sup> We conducted this trial to evaluate the ability of troglitazone to improve glycemic control, as reflected primarily in changes in glycosylated hemoglobin values and fasting serum glucose concentrations, in patients who had poorly controlled type II diabetes despite insulin therapy.

**METHODS****Study Subjects**

A total of 350 patients with type II diabetes were studied. Patients were eligible for the study if they were 18 to 72 years of age, had had diabetes for less than 20 years, were receiving at least 30 U of insulin per day, and had serum glucose concentrations above 140 mg per deciliter (7.8 mmol per liter) while fasting, a glycosylated hemoglobin value between 8.0 and 12.0 percent, and residual insulin secretory capacity as defined by a fasting serum C-peptide concentration of at least 0.8 ng per milliliter (0.3 nmol per liter). The study was conducted at 22 sites in the United States in accordance with the regulatory guidelines of the Food and Drug Administration. The protocol was approved by the institutional review board at each site, and all patients gave written informed consent.

**Study Design**

The study was divided into three phases: a 2-week screening period; an 8-week single-blind, placebo base-line period; and a

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26-week double-blind, randomized comparison of troglitazone and placebo. Patients could enter the trial if they met the fasting serum glucose and glycosylated hemoglobin criteria on either of two assessments during the screening period. Patients were given recommendations for a weight-maintenance diet during this period. After completing the base-line period, the patients were randomly assigned to receive placebo, 200 mg of troglitazone, or 600 mg of troglitazone, each given once daily. The investigators were instructed not to change the insulin doses unless patients had a fasting serum glucose concentration below 90 mg per deciliter (5.0 mmol per liter) at one office visit, a concentration of 90 to 109 mg per deciliter (5.0 to 6.1 mmol per liter) on two consecutive office visits, or a concentration of less than 100 mg per deciliter (5.6 mmol per liter) on two consecutive days during self-monitoring at home. Investigators could then change insulin doses according to their clinical judgment.

### Dietary Recommendations

Dietary recommendations, provided by a registered dietitian, were based on the Harris-Benedict equation for calculating basal energy expenditure in kilocalories per day<sup>16</sup> and were consistent with the recommendations of the American Diabetes Association.<sup>17</sup> The recommended caloric intake was 1.3 times the basal energy expenditure. In calculating this value for patients with a body-mass index of more than 24 (expressed as the weight in kilograms divided by the square of the height in meters), an adjusted body weight [(actual weight - ideal weight) × 0.25 + ideal weight] was used. Dietary compliance was assessed during the study by interviews with the patients.

### Evaluation of Efficacy

Glycosylated hemoglobin and fasting serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured at 5 visits during the base-line period and 10 visits during the treatment period. Glycosylated hemoglobin was measured by high-performance liquid chromatography with the Bio-Rad Variant analyzer with an intraassay coefficient of variation of 1.2 percent (normal range, 4.3 to 6.1 percent). Fasting serum glucose was measured by the hexokinase method with a Boehringer Mannheim Hitachi automated analyzer. Serum total cholesterol and triglycerides were measured by enzymatic methods with the same automated analyzer. Serum HDL cholesterol was isolated by chemical precipitation and then measured in the same way as total cholesterol. Serum LDL cholesterol was calculated (when the triglyceride value was less than 400 mg per deciliter [4.5 mmol per liter]) with the equation of Friedewald et al.<sup>18</sup> All analyses were performed at a central laboratory.

All patients received a Life-Scan One-Touch II glucose meter and were asked to measure fasting capillary-blood glucose at least three times per week and when they had symptoms of hypoglycemia. The results were stored in the meter and downloaded at each visit. The patients recorded the time, amount, and type of each insulin dose on diary cards.

### Safety Evaluations

Safety was monitored by assessing symptoms, changes in findings on physical examination (performed by the investigators), 12-lead electrocardiograms, and the results of clinical laboratory tests (hemogram, serum-chemistry panel including liver-function tests, and urinalysis) during the base-line period and at each follow-up visit.

### Statistical Analysis

The analyses of efficacy were performed according to the intention-to-treat method and included all patients who received at least one dose of troglitazone or placebo and had at least one follow-up visit. The last observations for patients were carried

forward to impute missing values. The safety analyses also included all patients.

Statistical analyses were performed with SAS software, version 6.09. The homogeneity of treatment groups was assessed with Cochran-Mantel-Haenszel and Fisher's exact tests and F tests as appropriate. Changes from base line (the average of the five measurements during the eight-week base-line period) in glycosylated hemoglobin values and fasting serum glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride concentrations were analyzed by analysis of covariance with treatment and study center as factors and the base-line value as the covariate. We compared each troglitazone group with placebo at the midpoint of the study (average of weeks 10 and 12) and at the completion of the study (average of weeks 24 and 26) by performing step-down tests for linear trend.<sup>19</sup> Similarly, average daily insulin doses during the last two weeks of the base-line period were compared with the average daily doses between weeks 10 and 12 and weeks 24 and 26. Statistical tests for glycemic end points, lipid measurements, and insulin doses were two-sided. Exploratory analyses to investigate the effect of age, sex, and race were also conducted with analysis of covariance, with center and treatment as factors and the base-line value as the covariate.

## RESULTS

### Characteristics of the Treatment Groups

The base-line demographic and disease-related characteristics and the degree of glycemic control were similar in the three treatment groups (Table 1). Eighty-seven percent of the patients were taking intermediate-acting and short-acting insulin twice daily. Eighty-five percent of the patients took their assigned study medication for 24 or more weeks of the planned 26-week study. A total of 314 of the 350 patients (90 percent) completed the study.

### Glycemic Control

The mean glycosylated hemoglobin values, fasting serum glucose concentrations, and daily insulin doses during the study are shown in Figures 1, 2, and 3, respectively. In the troglitazone groups, the glycosylated hemoglobin values reached a nadir at about 16 weeks (Fig. 1), whereas fasting serum glucose values reached a nadir at 4 to 8 weeks (Fig. 2). The decreases in glycosylated hemoglobin values, fasting serum glucose concentrations, and insulin doses were dose-related and were statistically significant for both troglitazone groups as compared with the placebo group ( $P < 0.001$ ) at both the midpoint and the end of the study (Table 2). The reductions in glycosylated hemoglobin values and fasting serum glucose concentrations in the troglitazone groups occurred while insulin doses were decreasing. In contrast, the insulin dose in the placebo group did not change (Fig. 3). The dose-related effect of troglitazone was similar in men and women and among patients of different ages and racial or ethnic groups (data not shown).

### Serum Lipid Concentrations

Serum total cholesterol, LDL cholesterol, and HDL cholesterol concentrations increased slightly

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS WITH TYPE II DIABETES MELLITUS TREATED WITH TROGLITAZONE OR PLACEBO.\***

CHARACTERISTIC	200 mg OF TROGLITAZONE (N = 116)	600 mg OF TROGLITAZONE (N = 116)	PLACEBO (N = 118)
Sex — no. (%)			
Men	54 (47)	53 (46)	60 (51)
Women	62 (53)	63 (54)	58 (49)
Race or ethnic group — no. (%)			
White	81 (70)	78 (67)	82 (69)
Black	18 (16)	24 (21)	18 (15)
Hispanic	14 (12)	12 (10)	16 (14)
Other	3 (3)	2 (2)	2 (2)
Age — yr	56±9	56±9	56±10
Body-mass index	34.8±6.3	35.1±5.5	35.0±6.3
Weight — kg	98.4±20.5	100.7±17.9	100.6±19.3
Duration of diabetes — yr	10±5	10±5	10±4
Duration of insulin therapy — yr	5±5	5±4	5±4
Total daily insulin dose — units†	72±36	70±30	75±37
Glycosylated hemoglobin — %	9.5±1.1	9.3±1.1	9.4±1.1
Fasting serum glucose — mg/dl	214±45	215±49	219±46
Fasting serum C peptide — ng/ml	1.6±0.6	1.7±0.6	1.7±0.6

\*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100. Base-line glycosylated hemoglobin, fasting serum glucose, and serum C-peptide values are the average of values collected every two weeks during the base-line period. To convert values for glucose to millimoles per liter, multiply by 0.056. To convert values for C peptide to nanomoles per liter, multiply by 0.33.

†Total daily dose is the mean of recorded daily insulin doses for the last two weeks of the base-line period.

during treatment in the troglitazone groups (Table 3). The mean serum triglyceride concentrations decreased slightly in all groups.

#### Body Weight

The mean weights at base line, week 8, week 16, and week 26 were 100.5, 100.5, 100.5, and 102.0 kg, respectively, in the placebo group; 98.6, 99.5, 100, and 100.5 kg in the group given 200 mg of troglitazone; and 100.9, 103.2, 104.5, and 104.5 kg in the group given 600 mg of troglitazone. The small increases in body weight at 26 weeks in the troglitazone groups were statistically significant ( $P < 0.001$ ) as compared with the placebo group.

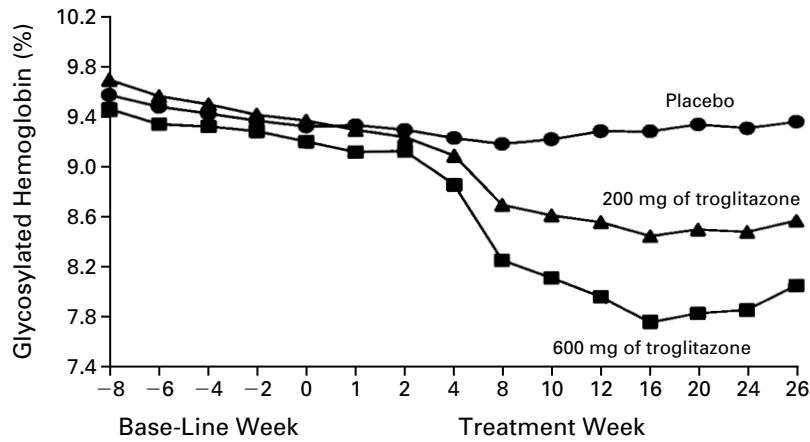
#### Adverse Events

Troglitazone was well tolerated. Overall, the incidence and types of adverse events were similar in all three groups, with 94 percent of patients in the combined troglitazone groups and 97 percent of patients in the placebo group reporting at least one adverse event.

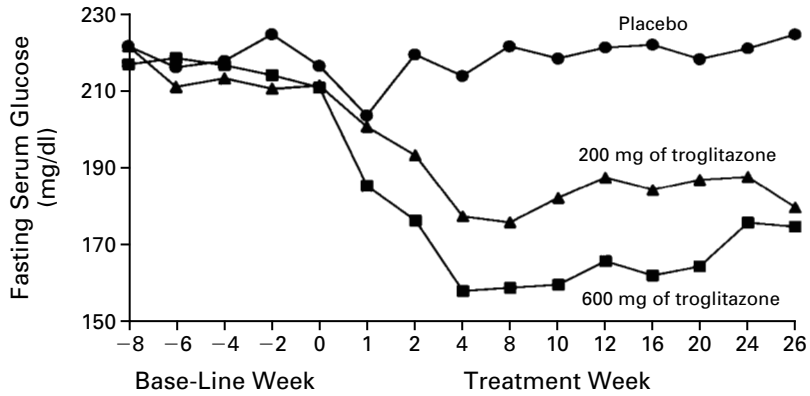
Symptoms of hypoglycemia occurred in 41 percent of the patients in the placebo group, 45 percent of those given 200 mg of troglitazone, and 62 percent of those given 600 mg of troglitazone and were associated with concurrent capillary-blood glucose readings of  $\leq 50$  mg per deciliter (2.8 mmol per liter) in 8 percent, 14 percent, and 23 percent of the patients in the respective groups. Of the entire capillary-blood glucose data base of over 30,000 measurements per group, only 0.21 percent of the values in the placebo group were  $\leq 50$  mg per deciliter; the respective values in the group treated with 200 mg of troglitazone and the group treated with 600 mg of troglitazone were 0.26 percent and 0.53 percent. The hypoglycemic events tended to occur early in the course of troglitazone treatment and decreased in frequency after the insulin dose was reduced: 33 episodes and 30 episodes of symptomatic hypoglycemia were reported during the first two weeks of treatment in the group given 200 mg of troglitazone and the group given 600 mg of troglitazone, respectively, as compared with reports of 14 episodes and 17 episodes in the same two groups during the last two weeks of treatment. Except in one patient who lost consciousness and was treated with intravenous glucose, all episodes of symptomatic hypoglycemia were successfully treated with food or glucose tablets. No patient was withdrawn from the study because of hypoglycemic symptoms.

In the group given 600 mg of troglitazone, the mean red-cell count, hematocrit, and hemoglobin values decreased by 5 percent, 5 percent, and 4 percent, respectively, but the values remained within the normal range. These decreases occurred soon after treatment was begun; thereafter, the mean values did not change, and in most patients the values subsequently increased. The values did not change significantly in the other two groups.

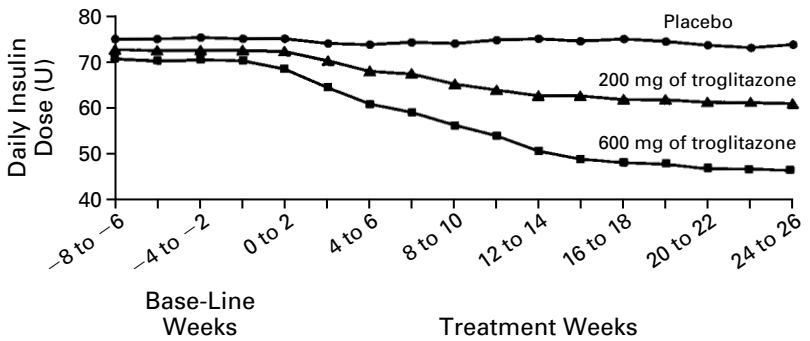
Eight patients (two in the group given 200 mg of troglitazone, three in the group given 600 mg of troglitazone, and three in the placebo group) had serum aminotransferase concentrations that were more than three times the upper limit of the normal range during the 26-week treatment period. Treatment was discontinued in two of the patients in the group treated with 600 mg of troglitazone, because of jaundice and hyperbilirubinemia in one (the patient subsequently recovered) and because of concomitant congestive heart failure in the other. The serum aminotransferase concentrations returned to normal in the third patient in this group during continued therapy. The concentrations returned to normal in the two patients in the group treated with 200 mg of troglitazone after therapy was interrupted. In the three patients in the placebo group, serum aminotransferase concentrations subsequently returned to base-line values without interruption of treatment.



**Figure 1.** Mean Glycosylated Hemoglobin Values in Patients with Type II Diabetes during the Base-Line Period and during Treatment with Troglitazone or Placebo.



**Figure 2.** Mean Serum Glucose Concentrations during Fasting in Patients with Type II Diabetes during the Base-Line Period and during Treatment with Troglitazone or Placebo. To convert values for glucose to millimoles per liter, multiply by 0.056.



**Figure 3.** Mean Daily Insulin Dose in Patients with Type II Diabetes during the Base-Line Period and during Treatment with Troglitazone or Placebo.

**TABLE 2.** ADJUSTED MEAN CHANGES FROM BASE LINE IN GLYCOSYLATED HEMOGLOBIN VALUES, FASTING SERUM GLUCOSE CONCENTRATIONS, AND DAILY INSULIN DOSE AFTER 24 TO 26 WEEKS OF TROGLITAZONE THERAPY IN PATIENTS WITH TYPE II DIABETES.\*

VARIABLE	200 mg OF TROGLITAZONE	600 mg OF TROGLITAZONE	PLACEBO
Glycosylated hemoglobin (percentage points)	-0.8†	-1.4†	-0.1
Fasting serum glucose (mg/dl)‡	-35†	-49†	+0.8
Daily insulin dose (% change)	-11†	-29†	+1

\*Values were adjusted for study center and base-line value.

†P<0.001 for the comparison with placebo.

‡To convert values for glucose to millimoles per liter, multiply by 0.056.

**TABLE 3.** MEAN SERUM CHOLESTEROL AND TRIGLYCERIDE CONCENTRATIONS AT BASE LINE AND AFTER 24 TO 26 WEEKS OF TROGLITAZONE THERAPY IN PATIENTS WITH TYPE II DIABETES.\*

VARIABLE	200 mg OF TROGLITAZONE	600 mg OF TROGLITAZONE	PLACEBO
Serum cholesterol (mg/dl)			
Base line	217±38	208±40	210±56
End of study	224±45†	220±52†	210±40
Serum LDL cholesterol (mg/dl)			
Base line	135±34	125±34	122±48
End of study	144±38†	139±38†	125±51
Serum HDL cholesterol (mg/dl)			
Base line	39±9	38±9	38±9
End of study	41±10	41±11‡	38±9
Serum triglycerides (mg/dl)			
Base line	222±112	239±175	263±364
End of study	209±141	203±150	240±183

\*Values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglycerides to millimoles per liter, multiply by 0.011.

†P<0.05 for the comparison with base line.

‡P<0.001 for the comparison with base line.

#### Withdrawal Due to Adverse Events

Five patients in the placebo group, one in the group given 200 mg of troglitazone, and six in the group given 600 mg of troglitazone were withdrawn from the study because of adverse events. The causes of withdrawal were stroke, metabolic myopathy, unintended pregnancy, transient ischemic attack, and exacerbation of depression in the placebo group; myocardial infarction two days before drug treatment was begun in the group given 200 mg of troglitazone; and myocardial infarction, coronary artery disease, congestive heart failure, forgetfulness and lack of concentration, exacerbation of gastric reflux, and jaundice and hyperbilirubinemia in the group given 600 mg of troglitazone.

#### DISCUSSION

Chronic hyperglycemia in patients with type II diabetes occurs because of resistance to the action of insulin and decreases in insulin secretion. Insulin resistance is a prominent feature, if not the primary defect, in these patients; in some of them insulin-stimulated uptake of glucose is decreased by 60 to 80 percent.<sup>20</sup> The results of prospective epidemiologic studies indicate that insulin resistance is detectable before glucose tolerance deteriorates.<sup>21-26</sup>

Patients with type II diabetes are often treated according to a stepped progression, starting with a regimen of nutrition and exercise and progressing to therapy with a sulfonylurea drug, metformin, or acarbose, alone or in combination. These therapies are often ineffective, and up to 60 percent of patients eventually require insulin,<sup>2</sup> often in high doses.

In our study of patients with poorly controlled type II diabetes who were receiving insulin therapy, troglitazone resulted in a significant dose-related decrease in glycosylated hemoglobin values and fasting serum glucose concentrations. The effect of troglitazone on fasting serum glucose concentrations was evident within 4 weeks after treatment was begun and its effect on glycosylated hemoglobin values was maximal at 16 weeks, and the improvement was sustained for the remainder of the study. This improvement occurred despite decreases in the insulin dose of 11 percent in the group given 200 mg of troglitazone and 29 percent in the group given 600 mg of troglitazone. Our study, as well as smaller studies of patients with type II diabetes treated with troglitazone alone, thus demonstrates a significant antihyperglycemic effect of troglitazone.<sup>14,15</sup> The 1.4 percent absolute decline in glycosylated hemoglobin values in the group treated with 600 mg of troglitazone represents a decline of approximately 15 percent from the base-line value. If we assume that data from the Diabetes Control and Complications Trial (DCCT) are applicable to patients with type II diabetes, this 15 percent decline translates to a reduction in the risk of progression of diabetic retinopathy of approximately 60 percent.<sup>27</sup>

We did not study the possibility that an increase in the insulin dose or a change in the insulin regimen to multiple injections of insulin (as in the intensive treatment regimen used in the DCCT) would have improved glycemic control in these patients. However, in most patients in the United States with type II diabetes who are treated with insulin, the disease remains uncontrolled despite the use of large insulin doses.<sup>2</sup>

Troglitazone was well tolerated, and most adverse events were considered to be related to the underlying diabetes. Several patients had abnormalities in liver function, but therapy was permanently discontinued for this reason in only one patient.

Most of the patients were obese, with a base-line mean body-mass index of about 35. The troglitazone-treated patients had small dose-related increases in body weight. They were instructed to follow a weight-maintenance diet, rather than a weight-reduction diet, so that any improvement in glycemic control induced would not be confounded by the effects of weight loss.

The ratio of serum HDL cholesterol to total cholesterol, a marker of cardiovascular risk, did not change in the patients — the troglitazone-associated increase in serum HDL cholesterol concentrations offset an increase in serum total cholesterol concentrations. Serum triglyceride concentrations decreased slightly in the patients who were treated with troglitazone.

We conclude that the administration of troglitazone results in sustained improvement in glycemic control when given as an adjunct to insulin therapy in patients with type II diabetes. These results are consonant with the findings of physiologic studies that troglitazone increases the sensitivity of peripheral tissues to insulin.

Supported by Sankyo U.S.A., New York, and Parke-Davis Pharmaceutical Research, Division of Warner-Lambert, Ann Arbor, Mich. Drs. Schwartz, Raskin, and Fonseca have served as consultants for Parke-Davis.

## APPENDIX

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