

**Addendum to March 26, 1999 Briefing Book**

Please note the following revisions to the March 26, 1999 Briefing Book:

<b><u>Page</u></b>	<b><u>Revision</u></b>
11	Last full paragraph: As per Dr. Watkins' update, total liver-related death, regardless of causality, is 75.
17	Change in incidence table: Line 1 – 1 in 45,000 Line 3, right column – 1 in 103,545
22	Carryover paragraph: No Rezulin-treated patients were identified in telephone survey.

# SUBMISSIONS AT MEETING

## Status of the Drug in the UK

# GlaxoWellcome

Dir Tel: 0181 990 8201  
Fax: 0181 990 8150

**GASTROINTESTINAL & METABOLIC DISEASES  
THERAPEUTIC DEVELOPMENT GROUP**

17 February 1999

Ms Kathleen R. Reedy  
Executive Secretary  
Advisors and Consultants Staff HFD-21  
Center for Drug Evaluation and Research  
5600 Fishers Lane  
Rockville, Maryland 20857  
USA

Dear Ms Reedy

Several misleading reports have appeared in the lay press suggesting that troglitazone was "banned" from sale in the UK. Glaxo Wellcome wishes to notify EMDAC of the facts concerning its decision, to suspend availability of this product in 1997.

Troglitazone was developed in Europe by Glaxo Wellcome and Sankyo, and was launched in the UK on October 1st 1997. In mid October the initial reports of hepatotoxicity began to arrive from the USA and Japan, and on October 31<sup>st</sup> a "Dear Doctor" letter was sent to UK physicians advising them of the need to monitor liver function in patients treated with troglitazone. In late November, with increasing reports of serious hepatotoxicity including death, a decision was taken by Glaxo Wellcome's Senior Medical Review Team to voluntarily suspend availability of troglitazone in the UK pending further safety evaluation and because we could not adequately quantify the risk benefit of the drug. On December 1<sup>st</sup>, following consultation with the UK Medicines Control Agency, Glaxo Wellcome and Sankyo suspended the availability of troglitazone in the UK.

In August 1998, after detailed evaluation of further safety data and review with external consultants, we concluded that the risk benefit of this drug was acceptable in certain patient populations and under certain monitoring conditions. Accordingly Glaxo Wellcome and Sankyo submitted a licence variation application to the UK Medicines Control Agency, to re-launch the product. This application is currently pending.

We would be grateful if this letter could be made available to members of the Endocrine and Metabolism Drug Advisory Committee for its meeting on March 26<sup>th</sup> 1999.

Yours sincerely,



**Dr John R. Wood**  
**Director of Therapeutic Development & Product Strategy**  
**Gastrointestinal & Metabolic Diseases**

**Glaxo Wellcome Research and Development**

Stockley Park  
Uxbridge  
Middlesex  
UB11 1BT  
UK

Telephone  
+44 (0)181 990 9876

Glaxo Wellcome Research and Development  
is a business name of  
Glaxo Research and Development Limited  
Registered in England No. 835139  
Registered Office  
Glaxo Wellcome House  
Berkley Avenue

**Written Submissions for the  
Open Public Hearing**



**DEPARTMENT OF VETERANS AFFAIRS**  
Medical Center  
1056 Clermont Street  
Denver CO 80220

January 15, 1999

In Reply Refer To:

Ms. Kathleen Reddy  
Secretary  
Endocrinologic and Metabolic Drug Advisory Committee

Fax 301 827-6776

Re: Rezulin - Committee Meeting on March 26, 1999

Dear Ms. Reddy:

I am writing this letter in support of availability of Rezulin in the armamentarium of diabetologists to treat patients with Type 2 diabetes mellitus.

Many of these individuals are insulin resistant and hyperinsulinemic and yet are treated with additional high doses of insulin. Rezulin appears to be an excellent drug to break this vicious cycle. With appropriate selection and follow-up, Rezulin is a safe choice offering substantial benefit to these patients. Our own recent research indicates that hyperinsulinemia may exert a detrimental effect. Thus, a class of drugs that lowers the levels of endogenous insulinemia would become extremely useful in these patients.

Sincerely yours,

A handwritten signature in black ink, appearing to read "B. Draznin", written over a horizontal line.

Boris Draznin, M.D., Ph.D.  
ACOS, Research & Development  
Professor of Medicine  
University of Colorado Health Sciences Center  
Denver, CO 80220

**ENDOCRINOLOGISTS:** **SHERWYN L. SCHWARTZ, M.D.** **JEROME S. FISCHER, M.D.** **MARK S. KIPNES, M.D.** **W. FERNANDO TRIGOSO, M.D.**  
**DIPLOMATE** **DIPLOMATE** **DIPLOMATE** **DIPLOMATE**  
 American Board of Internal Medicine  
 American Board of Endocrinology American Board of Endocrinology American Board of Endocrinology American Board of Endocrinology

March 22, 1999

Ms. Kathleen Reedy, RDH, MS  
 HHS/ FDA/CDER/ORM/ACS: HFD-21  
 5600 Fishers Lane, RM 1093  
 Rockville, MD 20857

Dear Ms. Reedy:

My name is Dr. Sherwyn Schwartz, the Director and Founder of the Diabetes & Glandular Disease Clinic (DGD) in San Antonio, Texas. I am writing to provide you with additional information regarding the Type II diabetes drug Rezulin® (troglitazone).

I have been an endocrinologist for the last 22 years and director of the DGD clinic for the last 20 years. During this period I have worked and continue to work as a consultant for Merck National Diabetes Advisory Board, Purdue-Pharma, Eli Lilly Device Consultants Board and Parke-Davis.

The Diabetes & Glandular Disease Clinic established an electronic patient medical record system, which is used at the point of patient care by both the physicians and the nurses. This electronic medical record allows the Center to analyze patient-level clinical data by drug therapies retrospectively and prospectively. We estimate that the clinic provides complete diabetes care for over 3000 Type II diabetics. The center is a specialist, referral and primary care clinic for various endocrine disorders.

Using our electronic medical record system we identified a total of 630 patients being treated with Rezulin® in our clinical practice and not involved in any research study whom we could fully analyze. These patients had average age of 59 and over half of this population is Hispanic. The typical patient has had Type II diabetes for an average of 13 years.

During the period of time on Rezulin®, 2.7% of this group had ALT levels three times the upper limit of normal. This same set of patients experienced a 2.7% frequency of ALT levels three time the upper limit of normal prior to ever being on Rezulin®. This 2.7% of the patients on Rezulin® had the medication stopped and ALT elevation resolved over subsequent weeks. To date no serious adverse events (specifically liver failure) have occurred in our patient group on Rezulin®.

Our patients have accumulated an average one and one-third years on Rezulin®. Of these patients, 50% are being treated consistently with Rezulin® in combination with insulin and 14% treated in combination with sulphonylureas. In addition, I also have 23% being treated with off

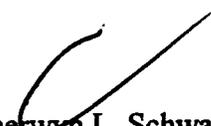


label therapy (triple therapy and in combination with metformin) and 13% with various combinations over time.

In regard to clinical outcomes in these patients treated with Rezulin®, the average glycosylated Hemoglobin (HbA1c) in these patients pre-Rezulin® was 8.8. After starting Rezulin® therapy, the average HbA1c of these patients went down 1.3 (15% decrease) units of HbA1c ( $p < .0001$ ). In addition, the 32 patients who have been treated with Rezulin® for the longest time period (longer than 2 years), have an average HbA1c of 7.4.

I find this medication to be very valuable for use in Type II diabetes mellitus patients, especially those that are obese. Insulin patients are the group that benefits the most from this medication as we have little else to offer them. This drug has also performed well in combination treatment and solo therapy. Monitoring Liver Function Tests in these patients has not been a problem for them. This is an essential drug for our clinic patients.

Sincerely,



Sherwyn L. Schwartz, M.D.

cc: Dr. Michael Friedman

William L. Isley, MD  
Plaza II, Suite 65  
4320 Wornall  
Kansas City, Missouri 64111

March 23, 1999

Kathleen Reedy  
Executive Secretary  
Endocrinologic and Metabolic Advisory Committee  
Food and Drug Administration  
Rockville, Maryland

Dear Ms. Reedy:

I would like to comment briefly on the upcoming Advisory Panel's consideration of troglitazone (Rezulin®).

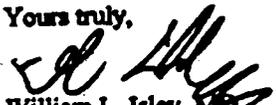
As an academic endocrinologist who spends most of his time seeing patients, I believe two issues are clear regarding this drug: 1) some patients are clearly benefited by being able to achieve glycemic control with the addition of this agent when the use of other agents in combination (including insulin) failed to afford the achievement of glycemic control; 2) a significant number of patients receiving this drug have developed liver failure causing death or requiring liver transplantation. However, these facts must be considered in context.

Most of the patients receiving troglitazone could be controlled if they were *adequately* treated with other presently available agents (including insulin). The number of patients inadequately treated with present therapies will probably decline with the advent of newer agents. Furthermore, some of the patients receiving the drug "when all else fails" do not have a significant therapeutic response. Lastly, some of the patients who have a dramatic response (reductions in hemoglobin A1c of 4-6%) gain considerable weight with subsequent deterioration of glycemic control and rise in LDL-C (perhaps conversion of small dense LDL to less atherogenic large buoyant LDL) over time, raising the question whether the patient's microvascular and macrovascular risks have been reduced significantly for "the long haul." Therefore the number of patients who have received the drug and it is the **ONLY** means for achieving lasting glycemic control is small. The vast majority of patients who take the drug are receiving it for perceived but unproved reasons to reduce macrovascular risk by reducing insulin resistance. Only a controlled clinical trial with troglitazone will show whether such a promise is true or untrue.

The liver failure problem is indeed troublesome. I know that not all cases are reported. I do not believe that the risk benefit ratio for troglitazone is acceptable in any patients except those requiring large doses of insulin who can not achieve glycemic control by any other means. However, if hepatic toxicity can not be predicted with any reasonable degree of certainty (and recent reports suggest that that may indeed be the case), then I believe that the risk benefit ratio is too high for *any* patient to take the drug, troglitazone.

Thank you for your consideration.

Yours truly,

  
William L. Isley, MD  
Associate Professor of Medicine  
University of Missouri-Kansas City School of Medicine  
Saint Luke's Lipid and Diabetes Research Center



March 24, 1999

**BY FACSIMILE**

Endocrinologic and Metabolic Drugs Advisory Committee  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**Re: Rezulin™ (troglitazone)**

Dear Members of the Endocrinologic and Metabolic Drugs Advisory Committee:

The Endocrine Society would like to thank the Endocrinologic and Metabolic Drugs Advisory Committee for the opportunity to present our views on Rezulin™ in connection with the Committee's March 26, 1999 meeting. Our membership of over 9,000 consists of over 4,500 practicing endocrinologists, the vast majority of whom regularly treat patients with type 2 diabetes mellitus and frequently prescribe therapies, including Rezulin™, to treat this life-threatening disease. As you are aware, there has been an enormous amount of publicity regarding the approval and marketing of Rezulin™ as well as post approval experience with that product. The Endocrine Society requests that during your deliberations regarding Rezulin™ at the upcoming Advisory Committee meeting you keep the following points in mind and that you ensure the continued availability of this important therapy.

First, Rezulin™ is very useful and important in the treatment of type 2 diabetic patients not otherwise well controlled by alternative treatment. Physicians and patients must have access to a variety of effective therapies to treat type 2 diabetes. Rezulin™ is critical in the treatment of a segment of patients with type 2 diabetes and its continued availability is essential to this population.

Second, the current FDA precautions and recommendations (which take the form of treatment guidelines) for Rezulin™ regarding product indications

**Endocrinologic and Metabolic Drugs Advisory Committee**

**March 24, 1999**

**Page 2**

and the necessity of liver testing are adequate and appropriate to prevent liver complications.

Third, the experience of our members indicates that weight gain and fluid retention have been neither frequent nor major problems associated with the use of Rezulin™.

Finally, we strongly urge FDA to reemphasize the current labeling requirements and continue to make the drug widely available. To that end, we request that this Advisory Committee recommend that the agency reemphasize the current labeling requirements (treatment guidelines), including the approved indications and the need for liver testing, and ensure the continued availability of this important therapy.

Thank you for the opportunity to share our views with the Committee on this important matter. If you have any questions or would like additional information, please contact Susan Koppi, manager of public affairs at The Endocrine Society, at (301) 941-0252 or via email at [skoppi@endo-society.org](mailto:skoppi@endo-society.org)

Sincerely,



**Kathryn B. Horwitz, PhD**  
**President**



**Sanford R. Mallin, MD**  
**Chair**  
**Clinical Affairs Committee**

**Letters from members of the medical profession  
regarding the Citizen's Petition of  
Public Citizen's Health Research Group**



# Tulane University Medical Center

SCHOOL OF MEDICINE  
Department of Medicine SL53  
1430 Tulane Avenue  
New Orleans, Louisiana 70112-2699  
(504) 588-5441  
e-mail: vfonseca@mailhost.tcs.tulane.edu

Vivian A. Fonseca, M.D.  
Director, Diabetes Program  
Tullis-Tulane Alumni Chair in Diabetes

February 19, 1999

Dockets Management Branch  
U.S. Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville MA 20852

Re: Docket No. 98P-0622

To Whom It May Concern:

I am responding to the petition filed by Public Citizen Health Research Group regarding Rezulin® (Troglitazone tablets).

For reasons discussed below the petition should be denied.

I have been working in the field of diabetes since 1978; and now am a Professor of Endocrinology and hold a chair in diabetes. Over the last 20 years I have seen first hand the devastation caused by the complications of diabetes in many people's lives. Diabetes is a leading cause of blindness, kidney failure and amputations in the United States. Furthermore for reasons that are unclear to us (but probably related to an increase in obesity and insulin resistance) we are facing an unprecedented increase in the prevalence of this disease.

There is now very good evidence from clinical trials such as the DCCT and UKPDS that good control of diabetes decreases the development and progression of long-term complications. However, diabetes care and control remains very poor in the United States with data suggesting that the average HbA1c in the country is over 9% whereas the ADA has set a goal for most patients to be less than 7%. To some extent this reflects the lack of effective treatment that we have had until new agents have become available recently. It would be tragic therefore if effective new agents were denied to people with uncontrolled diabetes based on unscientific assessments made by public "research" groups, who have not made an attempt to scientifically assess risk benefit analysis of drugs that they wish to be banned.

There is little doubt that Rezulin® is very effective in the treatment of diabetes. The benefits are seen as monotherapy or combination with other treatments including insulin. I have personally treated several hundred patients successfully with this medication. I have also participated in clinical trials and have been an author on 4 scientifically peer-reviewed publications in leading medical journals describing results from studies with this drug. Furthermore we and others have observed not only improvement in blood glucose control but improvement in a number of other cardiovascular risk factors including hyperinsulinemia, impaired fibrinolysis, blood pressure, triglycerides, oxidation of LDL cholesterol, and vascular responses to ischemia etc. Thus Rezulin® with the potential to decrease the enormous burden of cardiovascular disease that patients with type 2 diabetes face.

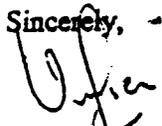
We know recognize insulin resistance (IR) as being a fundamental abnormality in the development of type 2 diabetes and that it is associated with many other risk factors that together contribute to an increase in cardiovascular disease. By addressing this fundamental problem of IR, Rezulin® may decrease the risk of cardiovascular disease. The NIH is going to do a large nine year study on the prevention of cardiovascular disease in diabetes. In that study they propose that one group of patients will receive "insulin resistance lowering treatment." It is likely that Rezulin® will be a key component of the medications used in that study. Thus, the NIH - the leading medical scientific body in this country, recognizes the importance of insulin resistance lowering medications like Rezulin®. Rezulin® is currently the only true insulin sensitizer on the market.

I am sure that the FDA will be the first to accept that every drug has side effects and the we should weigh the risks and benefits of every treatment. The efficacy of Rezulin® is now clearly established and its long-term benefit has also been established in extensions of clinical trials data from which I understand has been reviewed by the FDA. There is also data to suggest that Rezulin® may have a beneficial effect on beta cell function thus altering another fundamental abnormality in Type 2 diabetes and possibly contributing of long term control. Long term failure occurs with very high frequency with other medications and therefore the potential to alter the natural history of the disease is very important.

I recognize that there have been a number of cases of severe liver toxicity. In my own practice a few patients have had moderately severe abnormalities in liver function tests almost all which have returned to normal on discontinuation of therapy. In patients whose LFTs did not return to normal I have also found another reason such as hepatitis, gallstones etc. I know that there have been a few case of severe liver events leading to death or liver transplantation. I believe that the liver LFT monitoring instituted last summer by Parke-Davis and the FDA has resulted in a sharp decrease in the number of serious adverse liver toxicity's. This decline reflects the reversibility of the liver toxicity if detected early and the drug withdrawn. I would therefore urge you to encourage physicians to follow the monitoring guidelines rather that to simply withdraw the drug from the market.

I have read the Public Citizens Health Research Group petition carefully, as well as the response of Parke-Davis to the petition. I am struck by the fact that the Public Citizen Group led by Dr. Wolf has not done any risk benefit analysis of the drug, and does not even mention any of the problems facing people with diabetes especially the serious long-term complications. The petition therefore represents an emotional response to a rare event rather than a scientific critique and should therefore be denied.

Sincerely,

  
Vivian A. Fonseca, MD  
Director, Diabetes Program

VF/cnm

cc: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21  
5630 Fishers Lane, Rm 1093  
Rockville MD 20857



THE UNIVERSITY OF NORTH CAROLINA  
at  
Chapel Hill

Diabetes Care Center  
Division of Endocrinology  
Department of Medicine  
School of Medicine

The University of North Carolina at Chapel Hill  
CB# 7172, 647 Burnett-Womack  
Chapel Hill, North Carolina 27599-7172

Phone (919) 966-0134  
Fax (919) 966-8146

February 21, 1999

Dockets Management Branch  
U.S. Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers lane  
Rockville, MD 20852

**Re: Docket Number 98P-0622**

To whom it may concern:

I am responding to the petition filed by Public Citizens Health Research Group regarding Rezulin<sup>®</sup> (troglitazone) tablets.<sup>1</sup> I believe the petition should be denied for the following reasons.

First however, I want to disclose that the Diabetes Center at the University of North Carolina, of which I am the director, has received a several contracts from Parke-Davis to run clinical trials. Furthermore, I have received honoraria and consulting fees from Parke-Davis. This is also true of essentially every company that markets or has conducted clinical trials for diabetes related products in the U.S. in the last five years. However, I do not at all feel beholden to Parke-Davis and am writing this letter out of concern for the health of my patients.

Troglitazone is clearly one of the most important products to be developed for the treatment of diabetes since the disease was first described thousands of years ago. Its efficacy in combination therapy of diabetes is unparalleled, particularly in the treatment of very obese patients. There is a substantial portion of patients in my practice (~20%) who simply could not achieve near normal or even acceptable glucose control without troglitazone therapy. Because of its greater expense and the more rigorous monitoring necessary with troglitazone therapy, most patients in whom I have prescribed it have exhausted other alternatives. Withdrawal of the agent from the U.S. market based on the current concern regarding liver toxicity would be premature (as I will discuss below) and would clearly negatively affect the lives of hundreds of thousands to millions of people with diabetes nationwide and at least 500 of my personal patients. And again, at least for my patients, there is no alternative treatment except to accept sub-optimal glycemic control.

<sup>1</sup> <http://www.citizen.org/hrg/publications/1449.htm>

Perhaps more importantly, troglitazone's true benefit in the therapy of insulin resistance is just now beginning to be understood. I suspect that it will be an even more important weapon in the fight against heart disease than it is in the management of diabetes due to its effects on the biology of vascular disease. There are initial Japanese studies that demonstrate significant reduction in carotid intimal thickness within two months of therapy.<sup>2</sup> It clearly is of benefit in the therapy of polycystic ovarian syndrome<sup>3</sup> and impaired glucose tolerance<sup>4</sup>. I await the results of ongoing and planned studies in regards to these important clinical problems for which Parke-Davis does not yet have indications for therapy but for which troglitazone is clearly a potential therapeutic agent, again with no acceptable alternatives for many patients.

Regarding the issue of troglitazone safety, there are two levels of concern. First, relates to more minor side effects. Arguably, troglitazone is the single best tolerated drug for the therapy of diabetes. There is no agent with a lower patient withdrawal rate or with a better side effect profile. When dealing with a disease like diabetes with extreme morbidity as the consequence of inadequate control, the availability of any agent that is well tolerated and easy to administer is important.

The second level of concern regarding complications of therapy relates to potentially lethal complications of therapy. My understanding of available data is imperfect, but it is my impression that there have been less than 40 deaths or liver transplants associated with troglitazone therapy. There are apparently approximately three cases who developed extreme liver disease (death or need for liver transplant) who had completely appropriate liver monitoring and follow-up. Parke-Davis has estimated the overall risk of extreme liver events as 1/44,000 in the pre-monitoring era and 1/100,000 in the post-monitoring era. To put this in perspective, the risk of death from metformin induced lactic acidosis<sup>5</sup>, from sulfonylurea induced hypoglycemia<sup>6</sup>, from penicillin associated anaphylaxis, from poisoning, from drowning and from fires are each in the 1 per 50,000 to 100,000 range. Those risks and the risk of troglitazone related extreme liver toxicity pale in comparison to the annual risk of death due to motor vehicle accident (about 1/6,100)<sup>7</sup> and the annual death rate among patients with diabetes (about 1/30). In the grand scheme of things, life is a fatal condition and life with diabetes a more rapidly deadly form of life. Troglitazone is not clearly more dangerous than the major alternative therapies for the treatment of diabetes or treatments or lifestyle choices that are widely regarded as safe. Outcomes studies with troglitazone have not been completed, but it seems likely that patients with diabetes treated with troglitazone would likely live longer than either those left untreated or those who were less well treated as a result of withdrawal of troglitazone from the U.S. market.

The final issue, which I think is worthy of mention with regards to this debate, is the notion that there are safer alternatives just around the corner. I am a consultant to Takeda-Lilly and have been a consultant to SmithKline Beecham in regards to their development of thiazolidinediones. I do not think that I am breaching any confidentiality agreement in stating that there is likely to be less liver toxicity associated with rosiglitazone or pioglitazone than with troglitazone. However, the three compounds are dramatically

<sup>2</sup> Minamikawa J, Tanaka S, Yamauchi M, Inoue D, Koshiyama H. Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *Journal of Clinical Endocrinology & Metabolism* 83(5):1818-20, 1998.

<sup>3</sup> Reviewed in: Sattar N, Hopkinson ZE, Greer IA. Insulin-sensitising agents in polycystic-ovary syndrome. *Lancet* 351(9099):305-7, 1998.

<sup>4</sup> Antonucci T, Whitcomb R, McLain R, Lockwood D, Norris RM. Impaired glucose tolerance is normalized by treatment with the thiazolidinedione troglitazone. *Diabetes Care* 20(2):188-93, 1997.

<sup>5</sup> Campbell IW. Metformin and the sulfonylureas: the comparative risk. *Horm Metab Res* 17(suppl 15): 105-110, 1985.

<sup>6</sup> Bailey CJ, Nattrass M. Treatment-metformin. *Baillieres Clin Endocrinol Metab* 2:455-476, 1988.

<sup>7</sup> <http://hazmat.dot.gov/riskcompare.htm>

different in their interaction with their proposed receptor whose function is the regulation of transcription. Available clinical trial data documents that there are differences in the various agents with regards to efficacy in different clinical scenarios, differences in their lipid effects and differences in other side effects. As a result, and because we still do not fully understand the basic biology of thiazolidinedione drug effects, it would be exceptionally premature to feel confident that the newer agents will be safer compounds. In two to three years, we may know that to be true. For now, the toxicity associated with troglitazone therapy is minimal and the benefits significant with over one million people treated. It will be some time before we will be able to say that the same is true of the newer thiazolidinediones.

I believe it would be detrimental to health of our nation to have troglitazone withdrawn from the U.S. market. I believe further restriction on its use is unnecessary. I applaud the Food and Drug Administration and Parke-Davis for their efforts to make sure that the medical community is aware of the risks and benefits of troglitazone therapy and monitoring techniques to minimize that risk. There has been tremendous harm done to thousands of patients with diabetes due to unbalanced reporting of the concerns regarding troglitazone. What we need in the U.S. is more aggressive treatment of diabetes in response to public awareness of the huge risk that patients with diabetes face, not reasons for patients and practitioners to fear each therapy. Since diabetes and impaired glucose tolerance/insulin resistance is a major contributor to cardiovascular and cerebrovascular disease in approximately 50% of cases, arguably, troglitazone is a therapy for a family of disorders whose negative impact on the health of the nation is unparalleled with regards to expense, morbidity and mortality.

Thank you for taking my thoughts into consideration and feel free to call, write, or page me if you have questions, concerns or issues with which you think I might be of help.

Sincerely,

  
John B. Buse, MD, PhD, CDE  
Associate Professor of Medicine  
Director, Diabetes Care Center

Cc: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21  
5630 Fishers Lane, Room 1093  
Rockville, MD 20857



*The University of Oklahoma*  
*Health Sciences Center*

ENDOCRINOLOGY, METABOLISM AND HYPERTENSION SECTION

March 1, 1999

RE: Docket Number 98P-0622

Dockets Management Branch  
U.S. Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, Maryland 20852

To Whom It May Concern:

As a clinician who has been intensively involved in the care of patients with diabetes for almost 20 years, I am compelled to rebut the petition submitted by Sidney Wolfe and his organization "Public citizen Health Research Group" to withdraw Troglitazone ("Rezulin") from the market. Over the course of my 20 years of practice, it has been obvious to me that Type 2 diabetes was a progressive disease requiring escalation of therapy every year or so in an attempt to get once controlled diabetes back under control. I have come to appreciate that this was due to the fact that none of the agents we had available for the therapy of Type 2 diabetes prior to 1997 addressed the underlying pathophysiology, insulin resistance years prior to the availability of Rezulin. As a diabetologist, the in vitro and animal data suggesting that troglitazone would improve the metabolic responses to insulin made me anxious to add this drug to the limited armamentarium available to me to try to control hyperglycemia in these difficult patients. Since the introduction of troglitazone in 1997, I have not been disappointed in the influence this agent has had on my ability to get previously uncontrollable patients controlled. As more data has been available on attenuation of the associated co-morbidities of increased blood pressure, elevated triglycerides and low HDL cholesterol, I have come to appreciate that this agent is the first specific therapy we have had for Type 2 diabetes. It is now obvious to me that the thiazolidenediones should be the cornerstone of our therapy of Type 2 diabetes with other agents used as adjuvants in those patients who can not be managed with monotherapy as they function at other sites of the pathophysiology, primarily at the acquired relative insulin deficiency. Excitingly the most recent data of improved  $\beta$  cell function after therapy with troglitazone, a shift in the pattern of LDL particles from the most atherogenic, small dense LDL (Pattern B) to the larger, lighter (Pattern A), reductions in fibrinogen and PIA-1 as well as reduction in the intimal-medial thickness of carotid arteries, portend even greater cardiovascular benefit with this agent than would be predicted by comparable metabolic control achieved by other agents.

Dr. Wolfe's position fails to put into perspective the mortality of untreated Type 2 diabetes in 2,000 deaths/100,000 patients years or that even with therapy, 150,000 of the 16 million patients with diabetes die from this disease and its associated complications each year. This is a life-threatening disease and a certain level of toxicity has to be acceptable we would have few approved therapies for this deadly disease. While the liver in

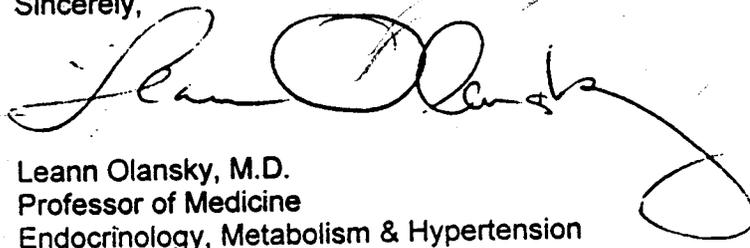
jury of troglitazone can be life-threatening, it fortunately has been rare (one in forty thousand patients) if none on the currently recommended monitoring is undertaken, I find that Parke-Davis has taken a very responsible and ethical position in warning practitioners to monitor ALT levels monthly for the first 8 months, then every 2 months for the rest of the first year. It is my understanding that this has brought the hepatic-related deaths to under one per 100,000 patients. Not only have their representatives repeatedly reminded me and other practitioners to do this but the company has given unequivocal guidelines about levels of ALT above which the agent should not be started, as well as what action to take if ALT rises about 1.5 x ULN and recommending discontinuation if ALT exceeds 3 x the ULN and advises physicians not to rechallenge patients who have reached these levels. This is much more than the "Dear Doctor" letter sent when the issue of liver injury from NSAIDs was again addressed after Duract had entered the market and demonstrated this toxicity shared with other agents of this class. It is true that Duract was withdrawn but the other members of this class remaining share the potential for severe liver injury, even death or the need for liver transplant yet this important class of agents capable of relieving considerable human suffering has not been withdrawn; some members are even over the counter medications. Undoubtedly, not every elevation of ALT more than 3X the upper limit of normal seen in patients on troglitazone is hepatic toxicity capable of causing liver failure, but the recommendations are conservative and made to minimize the risk to patients.

I am of the opinion that Dr. Wolfe is in error in his estimate that only 10% of severe adverse reactions are reported to the FDA. This may be true of older drugs, especially when the specific adverse has been fairly well established. With new agents, the opposite is likely true. Toxicity is often attributed to the newest agent added by the potential for over-reporting. This patient population is rarely on a single agent. Fatty liver is a common concomitant condition. The media spotlight on this agent generated in part by Dr. Wolfe and his organization assures that any hepatic failure a patient on Troglitazone will be reported.

I do not wish to minimize the seriousness of even one iatrogenic patient death, but it is most important that the committee put the rather rare occurrence (reduce further reduced by the pharmaceutical company guidelines for liver monitoring) in the perspective of the very serious life-threatening disease treated by this agent. There are patients likely dying daily due to lack of aggressive therapy of this disease. I plead with the committee not to withdraw this important weapon we have recently acquired in our fight against this terrible disease.

Thank you for your attention in this most important matter.

Sincerely,



Leann Olansky, M.D.  
Professor of Medicine  
Endocrinology, Metabolism & Hypertension



Thomas  
Jefferson  
University

Jefferson  
Medical  
College

Department of Medicine  
Division of Endocrinology  
and Metabolic Diseases

211 South 9th Street, Suite 601  
Philadelphia, PA 19107  
(215) 923-1718  
Fax (215) 928-3160

March 10, 1999

Dockets Management Branch  
US Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, MD 20852

**Docket Number 98P-0622**

To whom it may concern:

I am responding to the petition filed by Public Citizen Health Research Group regarding Rezulin ® (troglitazone) Tablets.

For reasons discussed in the attached response, the petition should be denied.

Sincerely,

Jeffrey L. Miller, M.D., F.A.C.P., F.A.C.E.  
Director of Clinical Endocrinology

Cc: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21  
5630 Fishers Lane, Room 1093  
Rockville, MD 20857

## Rezulin ® (troglitazone)

Type 2 diabetes is a fatal disease accounting for some 150,000 deaths annually in the United States of America. 75% of these deaths are due to atherosclerotic cardiovascular disease. One of the primary target organs for insulin action is adipose tissue. In obesity, excessive amounts of adipose tissue result in excessive beta cell function in an attempt to maintain normoglycemia. There is a host of data, including amongst others the Paris prospective study linking endogenous hyperinsulinemia to coronary heart disease.

In order to decrease the ravages of this disorder on the macrovascular system, the obvious ideal pharmacological agent would be an agent that minimizes this insulin resistance and decreases beta cell function, thus allowing a lesser amount of endogenous insulin to be more effective and minimizing the ravages of this condition on the vascular system. In this regard Rezulin ® (troglitazone) is the forerunner of an exciting new category of compounds (thiazolidenediones) one of whose sites of action is to minimize beta cell function and thus minimize the atherosclerotic potential of this disorder. To this end Rezulin ® (troglitazone) has numerous cardiovascular benefits which is unique to this compound and this has put this agent in a class of its own. These benefits include, but are not limited to (1) antioxidant activity ①, (2) conversion of atherogenic to nonatherogenic LDL ② (3) decrease in PAI-1 ③, (4) increase in lipoprotein a ④ (5) an acute decrease in carotid arterial thickness ⑤ (references enclosed). Rezulin ® (troglitazone) has gone beyond conventional diabetes management (blood sugar, hypertension and lipid control) towards cardiovascular risk reduction to minimize the complications of this disorder on the cardiovascular system as enumerated above. To this end it has no equal, as it goes beyond all other agents which treat blood sugar. Diabetes is no longer a metabolic, glucose disorder but rather a vascular disease and Rezulin ® (troglitazone) is the first in the category of thiazolidenediones to effectively afford any risk reduction in this arena. Rezulin ® is proven to be effective as monotherapy, and to be the ultimate synergistic agent in combination with insulin, sulfonylureas and metformin.

-With these enormous benefits of Rezulin ®, what are the risks? The idiosyncratic hepatocellular injury attendant with this agent has not been problematic in my own large diabetic population. To date, with extensive experience in the use of Rezulin ® (troglitazone) in a few thousand patients, my incidence of adverse reaction has been much lower than the 1.9% rise in ALT published in clinical trials, and I have been fortunate enough not to be involved in any significant hepatic injury, and thus have been very comfortable with this agent in terms of its side effect profile. Personally, I do believe the media hype on the liver damage assessed with Rezulin ® in December of 1997 played well into Glaxo-Wellcome Pharmaceutical's decision to withdraw troglitazone from the UK market. Glaxo-Wellcome has its own non-glitazone PPAR-gamma agonist, and in addition at that time was courting another pharmaceutical company that has its own soon to be released glitazone category of agent, and thus this news was timely for Glaxo-

Wellcome to remove troglitazone, to entertain its own forthcoming compound as well as the possibility of the other glitazone. When the pharmaceutical merger broke off; Rezulin was back in trials in the UK!

Rezulin ® (troglitazone) has been a boon to my large diabetic population both in terms of blood glucose, hypertension and lipid control; but more specifically reduction in insulin resistance and all the cardiovascular benefits as enumerated above. I do believe this is the single greatest advance we've had in the pharmacotherapy of insulin resistant diabetes in the last 40 to 50 years, and I see this agent as the pioneer in the field to take diabetes into the new millenium. The benefits of this agent far outweigh the risks, and there are currently in the USA no comparable oral diabetic agents available which afford such dramatic cardiovascular risk reductions.

## References

1. Cominacini L, Young MMR, Capriati A, et al. Troglitazone increases the resistance of low density lipoprotein to oxidation in healthy volunteers. *Diabetologia*. 1997; 40:1211-1218. **Troglitazone exhibited antioxidant activity and reduced LDL oxidation products in healthy subjects.**
2. Cominacini L, Garbin U, Pasini AF, et al. Troglitazone reduces LDL oxidation and lowers plasma E-selectin concentration in NIDDM patients. *Diabetes*. 1998; 47:130-133. **Troglitazone reduced LDL oxidation products in NIDDM subjects.**
3. Fonseca VA, Reynolds T, Hemphill D, et al. Effect of troglitazone on fibrinolysis and activated coagulation in patients with NIDDM. *J Diab Comp*. 1998; 12:181-186. **Troglitazone treatment was related to a decrease in plasma PAI-1 concentrations and may thus have a positive effect on fibrinolysis.**
4. Matsumoto K, Miyake S, Yano M, Ueki Y, Tominaga Y. Increase of lipoprotein with Troglitazone. *Lancet*. 1997; 350:1748-1749. **Troglitazone (400 mg/d for 4 weeks) increased levels of lipoprotein (a), an important risk factor for coronary heart disease, in NIDDM patients.**
5. Minamikawa J, Tanaka S, Yamauchi M, et al. Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *JCEM*. 1998; 83:1818-1820. **Troglitazone was associated with a decrease in carotid arterial intimal and medial complex thickness after as little as 3 months of treatment.**



DEPARTMENT OF MEDICINE  
SCHOOL OF MEDICINE

March 11, 1999

VETERANS ADMINISTRATION HOSPITAL  
3350 LA JOLLA VILLAGE DRIVE  
LA JOLLA, CALIFORNIA 92161

Dockets Management Branch  
U.S. Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, Maryland 20852

Docket Number 98P-0622

To Whom It May Concern:

I am responding to the petition filed by Public Citizen Health Research Group to remove Rezulin (Troglitazone) from the market. As a specialist in the management of diabetes mellitus and its complications and a primary care provider for many patients with type 2 diabetes, I believe that such a decision by the FDA would be a major mistake. Although I am a speaker and consultant for many pharmaceutical companies, including Parke-Davis, who are involved with marketing medications for the treatment of diabetes, I am expressing my concern solely because of the effect such an action would have on the type 2 diabetic population.

Contrary to the statements made in the petition, I strongly believe many patients will suffer and ultimately develop complications and possibly die if this drug is removed from the market. It seems clear to me that while use of Rezulin can be associated with a rare severe idiosyncratic hepatocellular toxicity, this compound has truly transformed the lives of many type 2 diabetics by improving glycemic and metabolic control to a degree not achievable with other available medications.

This rare hepatotoxicity from Rezulin is even further reduced when liver function tests (ALT, AST) are monitored according to the current recommendations. The adverse effects, both in terms of morbidity and mortality, of inadequate treatment of type 2 diabetes is far greater than the toxicity of this compound and results in a risk-to-benefit ratio that I believe strongly favors continued availability of Rezulin.

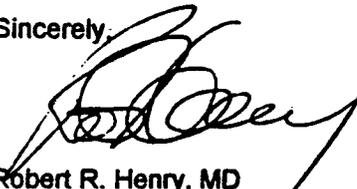
In my clinical experience, there are many circumstances when addition of troglitazone to a failing diabetic treatment regimen has led to dramatic improvement in metabolic control. The additional benefits of this compound, on the classic diabetic dyslipidemia of high triglycerides, low HDL cholesterol and increased concentrations of small, dense, LDL particles is truly unique. This effect, combined with early, but provocative, evidence of potential cardiovascular benefits, is further compelling grounds to retain this compound in the therapeutic armamentaria of type 2 diabetes.

Finally, I take issue with the petition statement that actual cases of hepatotoxicity are probably underreported. I believe this to be unlikely, and suspect rather, that adverse hepatic events may be over-reported in view of the extensive recent press and television publicity. Furthermore, many of the reported cases of hepatotoxicity may be guilty by association, rather than causal in nature.

The petition filed by Public Citizen Health Research Group has been a disservice to many patients with type 2 diabetes who, out of fear from the exaggerated publicity, have discontinued this medication unnecessarily and have had deterioration in metabolic control.

The availability of Rezulin has improved the lives of many patients with type 2 diabetes. It would be a regressive step to withdraw this medication and I trust that the committee and the FDA will see fit to deny the petition.

Sincerely,



Robert R. Henry, MD  
Professor of Medicine, UCSD  
Chief, Section of Endocrinology, Diabetes, & Metabolism  
VA San Diego Healthcare System

RRH/srw

Cc: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21n  
5630 Fishers Lane, Rm 1093  
Rockville, MD 20857



Department of Obstetrics & Gynecology  
 Division of Reproductive Endocrinology

Penn State College of Medicine  
 The Milton S. Hershey Medical Center  
 Department of OB/GYN, H103  
 500 University Drive  
 Hershey, PA 17033-2390

(717) 531-8478  
 (717) 531-1540

3/17/99

Dockets Management Branch  
 U.S. Food and Drug Administration  
 Department of Health and Human Resources  
 Room 1061, HFA-305  
 5630 Fishers Lane  
 Rockville, Maryland 20852

To whom it may concern:

I am responding to the petition filed by the Public Citizen Health Research Group regarding Rezulin (troglitazone) Tablets. I am a reproductive endocrinologist with a large clinical practice and research interest in polycystic ovary syndrome. I have recently participated as a principal investigator in a multi-center randomized controlled trial sponsored by Parke-Davis of the use of troglitazone in women with polycystic ovary syndrome. The final results of this trial are unknown to me. I am writing to underscore the importance of research into safe and effective treatment of this condition.

Polycystic ovary syndrome is thought to be one of the most common endocrine abnormalities affecting women and somewhere between 5 -10% of women are affected with excess androgen and menstrual irregularity. The cause of this condition is unknown. Women most commonly present to the gynecologist with complaints of infertility (due to infrequent ovulation), bleeding complaints (ranging from absent menses to unpredictable heavy menses), and hirsutism. Currently, there is no medication that addresses all of these concerns simultaneously.

I, and more importantly the women who are my patients, desperately are seeking treatment which would allow spontaneous ovulation and conception, regular menstrual cycles, and decreased body hair. Clinical trials of interventions, that enroll adequate numbers of women to answer the questions of therapeutic benefit and risk, are essential to guiding our treatment of these women. Unfortunately treatment of polycystic ovary syndrome currently is very much based on the hunch of the individual physician.

Thank you for the opportunity to address the importance of this condition as a common and debilitating health problem in women and one in need of further study, especially large scale clinical trials of new therapeutic agents.

Sincerely,

Richard S. Legro, M.D.

Asst Professor of Obstetrics and Gynecology



March 19, 1999

Dockets Management Branch  
US Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, MD 20852

**Docket Number 98P-0622**

To Whom it May Concern:

I would like to express my strong opposition to the petition filed by Public Citizen Health Research Group regarding Rezulin® (troglitazone) tablets and urge that the petition be denied for the reasons outlined below.

First, Rezulin is a unique and highly effective oral medication for the treatment of type 2 diabetes mellitus that has already benefited over one million patients with this common and devastating disease. It is the first drug of its class, the thiazolidinediones, to be made available for clinical use and its unique mechanism of action to reduce insulin resistance gets at the core defect in the vast majority of people with type 2 diabetes. In carefully conducted clinical trials it has been shown to be effective in improving glycemic control and reducing insulin resistance in patients with type 2 diabetes when used either alone as monotherapy (Maggs et al, Ann Intern Med 1998; 128:176-185) or when used in combination with sulfonylureas (Horton et al, Diabetes Care 1998; 21:1462-1469), Metformin (Inzucchi et al N Engl J Med 1998; 338:867-872), or insulin (Schwartz et al, N Engl J Med 1998; 338:861-866).

Second, we have learned from the United Kingdom Prospective Diabetes Study (UKPDS) that type 2 diabetes is a progressive disease that requires an aggressive stepped-care approach using a combination of lifestyle modification and multiple pharmacological interventions to achieve and maintain currently accepted levels of glycemic control with the goal of preventing or reducing long term complications (UKPDS Group, Lancet 1998; 352:837-853). No single medication used in this landmark study was able to provide sustained glycemic control, resulting in the need for combination therapy in the majority of patients. This is also the common experience of clinicians in the United States and has led to the use of two or more different classes of oral medications having

Page Two

different mechanisms of action or the combination of oral agents plus insulin to achieve and maintain glycemic targets in patients with type 2 diabetes. Rezulin has proven to be an extremely valuable agent in this regard because of its efficacy and unique mechanism of action.

Third, Rezulin is very well tolerated by the vast majority of patients who are taking it. Except for the rare cases of hepatotoxicity, there are very few side effects. Since its release in March 1997, we have prescribed Rezulin for over 2000 patients at the Joslin Clinic in Boston, MA. An occasional patient has experienced some fluid retention which has usually responded promptly to diuretics, some patients have gained 5 to 10 pounds in weight associated with improved glycemic control and only a very few have experienced asymptomatic increases in hepatic transaminases that have returned to normal when the medication was discontinued. We have not had any patient develop severe hepatotoxicity leading to jaundice or liver failure, consistent with the much larger data base gathered nationally that demonstrates that the current guidelines for monitoring liver function in patients treated with Rezulin do, in fact, work well.

Based on the above, I believe it is clear that the benefit to risk ratio is very favorable for Rezulin and that with proper monitoring of liver function tests the rare cases of severe hepatotoxicity have been and will continue to be reduced to an acceptable level. The available data already demonstrate that the monitoring program currently in place is effective and has resulted in a marked reduction of severe adverse events in patients treated with Rezulin. Therefore, Rezulin should not be banned for use in the treatment of type 2 diabetes mellitus as petitioned by Public Citizen Health Research Group but should continue to be made available to the many millions of people with type 2 diabetes who will benefit from it.

Sincerely yours,



Edward S. Horton, MD  
Vice President & Director of Clinical Research  
Joslin Diabetes Center  
Professor of Medicine  
Harvard Medical School

CC: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21  
5630 Fishers Lane, Room 1093  
Rockville, MD 20857

rezulinpet



BRIGHAM AND  
WOMEN'S HOSPITAL

75 Francis Street  
Boston, Massachusetts 02115

E-mail: adunaif@bics.bwh.harvard.edu  
Tel: 617 732-8798, Fax: 617 264-5210

Andrea Dunaif, M.D.  
Director, Women's Health

March 23, 1999

Dockets Management Branch  
U.S. Food and Drug Administration  
Department of Health and Human Resources  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, Maryland 20852

Docket Number 98P-0622

To Whom It May Concern:

I am responding to the petition filed by Public Citizen Health Research Group regarding Rezulin® (troglitazone) Tablets.

Polycystic Ovary Syndrome is considered the most common endocrinopathy affecting premenopausal women. Recent Nurses Health Study data indicates the prevalence to be approximately 7% of this population. PCOS is characterized by hyperandrogenism and chronic anovulation and is also associated with profound insulin resistance, and hyperinsulinemia. Consequently women with PCOS are considered to be at increased risk for type 2 diabetes and cardiovascular morbidity.

Insulin resistance is a unique feature of PCOS, not found in ovulatory hyperandrogenic women (1). My colleagues and I have also found that insulin-stimulated glucose utilization is decreased by 35-40% in women with PCOS, independent of obesity (2). This decrease is similar to that seen in type 2 diabetes (3). Several studies have shown prevalence rates of glucose intolerance to be as high as ~40% in obese women with PCOS (1,2,4-6). While most of these women are in their third and fourth decade of life, IGT and type 2 diabetes have also been documented in adolescents with PCOS. Thus, PCOS appears to be a major risk factor for type 2 diabetes in women, regardless of age.

Agents that decrease circulating insulin levels have been studied in women with PCOS because they may improve several of the metabolic derangements associated with the syndrome. The insulin-sensitizing agent troglitazone has been shown to improve oral glucose tolerance and insulin resistance in individuals with IGT (7,8).

My colleagues and I have documented that administration of troglitazone to women with PCOS has resulted in improved insulin sensitivity and decreased androgen excess (9). In addition, it was concluded that troglitazone improves total body insulin action, resulting in lower circulating insulin levels and that troglitazone may provide a novel therapy for PCOS.

Due to the fact that troglitazone may address both the short term symptoms as well as the long term metabolic consequences of PCOS, it is my opinion that additional research should be pursued and that the petition to ban troglitazone should be denied.

Sincerely,

*Andrea Dunaif* EJR

Andrea Dunaif, MD  
Chief, Division of Women's Health



A Teaching Affiliate  
of Harvard Medical School

PARTNERS HealthCare System Member

Cc: Kathleen Reedy, RDH, MS  
HHS/FDA/CDER/ORM/ACS: HFD-21  
5630 Fishers Lane, Rm 1093  
Rockville, MD 20857

John D. Dingell  
Michigan 16<sup>th</sup> Congressional District  
Washington, DC  
Room 2328  
Rayburn House Office Building  
Washington, DC 20515  
(202)225-4071

Henry A. Waxman  
California 29<sup>th</sup> Congressional District  
Washington DC  
2204 Rayburn House Office Building  
Washington, DC 20515  
(202)225-3976

References:

1. Dunaif A, Graf M, Mandeli J, Laumas V, Dobrjansky A. 1987 Characterization of groups of hyperandrogenic women with acanthosis nigricans, impaired glucose tolerance and/or hyperinsulinemia. *J Clin Endocrinol Metab.* 65:499-507.
2. Dunaif A, Segal K, Futterweit W, Dobrjansky A. 1989 Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes.* 38:1165-1174
3. Yki-Jarvinen H, Koivisto VA. 1983 Effects of body composition on insulin sensitivity. *Diabetes.* 32:965-969.
4. Modan M, Harris MI, Halkin H. 1989 Evaluation of WHO and NDDG criteria for impaired glucose tolerance. *Diabetes.* 38:1603-1635.
5. Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A. 1992 Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. *Diabetes* 41:1257-1266.
6. Dunaif A, Sorbara L, Delson R, Green G. 1993 Ethnicity and polycystic ovary syndrome are associated with independent and additive decreases in insulin action in Caribbean Hispanic women. *Diabetes* 42:1462-1468.
7. Dunaif, Finegood 1996  $\beta$ -cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 81:942-947.
8. Cavaghan M, Ehrmann D, Byrne M, Polonsky K. Treatment with the oral antidiabetic agent troglitazone improves  $\beta$ -cell responses to glucose in subjects with impaired glucose tolerance. *J Clin Invest.* In press.
9. Nolan J, Ludvik B, Beardsen P, Joyce M, Olefsky J. 1994 Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *N Engl J Med.* 331: 1188-1193.
10. Dunaif A, Scott D, Finegood D, et al. 1996 The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 81: 3299-3306.