American Diabetes Association Annual Meeting, 1997

Type 2 diabetes

ZACHARY T. BLOOMGARDEN, MD

The 1997 American Diabetes Association Annual Meeting and Scientific Sessions, held in Boston in June, included many presentations on the etiology and treatment of type 2 diabetes. Among these were the impressive Banting and Lilly lectures, which described metabolic studies that address the basic science of glucose homeostasis and the insulin-resistant state.

Metabolic Studies on Glucose Homeostasis

Alan Cherrington, Nashville, TN, gave the Banting Lecture on the role of the liver in glucose homeostasis. His work analyzes the physiology of insulin and glucagon based on hepatic catheterization studies in dogs. Peripheral insulin leads to a slower fall in hepatic glucose output (HGO) than hepatic insulin infusion. The effect of the former is partly due to decreased adipose tissue lipolysis, leading to decreased glycerol availability for gluconeogenesis, and to diversion of glycogen-derived glucose to glycolysis. The half-maximal insulin concentration needed to suppress HGO is less than the normal fasting insulin level, with a tripling of insulin completely turning off the HGO. In view of the sensitivity of the β-cell to glucose, Cherrington concluded that insulin is clearly the key minute-to-minute controller of glycemia. Increased glucagon increases the HGO, almost completely because of breakdown of glycogen, while selective glucagon deficiency decreases HGO with a marked fall in glycogenolysis. The dose-response relationship between glucagon and HGO shows a half-maximal stimulation at twice the normal fasting glucagon, so glucagon is also an important regulator of glycemia. Epinephrine and norepinephrine change little with modest changes in glucose, and suppression of catecholamines does not decrease glucose levels under basal conditions. However, an epinephrine infusion reproducing levels seen during moderate stress increases HGO, due to both glycogenolysis and gluconeogenesis, with the latter predominating after 60 min. Norepinephrine, when infused intraportally, increases HGO only because of glycogenolysis.

The liver takes up one-third of orally ingested glucose, one-third goes to muscle and fat, and the last third is used by the remainder of the body. The normal hepatic glucose uptake following oral administration of glucose is much greater than that after parenteral administration of glucose to a similar level of glycemia, suggesting the presence of additional stimulatory factors. A study from Nashville presented at the meeting showed that the gluconeogenic amino acids alanine, glutamate, and glutamine, but not other amino acids, can act as signals to the liver to enhance their own uptake, potentially increasing their gluconeogenic potential (191; references in parentheses are to abstract numbers from the Abstracts of the 57th Annual Meeting and Scientific Sessions of the ADA, *Diabetes* 46 [Suppl. 1]:1A–434). Another study confirmed the importance of the basal portal vein insulin concentration in controlling basal hepatic glucose production (192).

Gerald Shulman, New Haven, CT, discussed the cellular mechanisms of insulin resistance in the Lilly lecture. Shulman used nuclear magnetic resonance (NMR) spectroscopy of naturally occurring ^{13}C for assessment of glycogen synthesis and of ^{31}P for measurement of glucose transport and levels of high-energy glucose and glycolytic intermediates. These studies allowed assessment of the contribution of muscle glycogen synthesis to insulin-stimulated glucose disposal and of the extent to which this is affected in type 2 diabetes. Studies using somatostatin to prevent endogenous insulin and glucagon secretion kept glucose and insulin at constant levels of 10 mmol/l and 420 pmol/l, which are similar to those seen after a large meal. With the use of ^{13}C-NMR to measure calf muscle glycogen synthesis, it was determined that levels in nondiabetic subjects were twice those in patients with type 2 diabetes. Most of the infused glucose was taken up into muscle glycogen in both groups. The potential rate-limiting steps are transport of glucose by the insulin-responsive GLUT4, the hexokinase-catalyzed reaction, enzymatic phosphorylation of glucose to glucose-6-phosphate (G-6-P), and glycogen synthetase. When ^{31}P-NMR was used to measure low concentrations of intracellular metabolites, including ATP, phosphocreatinine, and basal inorganic phosphate levels, and G-6-P during the insulin/glucose infusion, G-6-P levels were found to double in nondiabetic subjects but to show virtually no change in diabetic subjects. This suggests that either glucose transport or phosphorylation is the major defect. Shulman described studies of children of two type 2 diabetic parents who themselves had normal glucose tolerance. Such children showed a similar failure to increase G-6-P levels, suggesting that these abnormalities are primary rather than acquired because of hyperglycemia.

Noting that fasting free fatty acid (FFA) levels are strong predictors of insulin resistance, Shulman reviewed the Randle hypothesis that FFAs compete for oxidation with glucose and so contribute to insulin resistance. He used a heparin/lipid infusion to increase FFA levels in normal subjects. The glucose infusion rates required to maintain euglycemia decreased to levels similar to those in severe insulin resistance, with a 50% fall in muscle glycogen synthesis and a fall below baseline in muscle G-6-P suggesting an action at the glucose transport or hexose kinase step. Conversely, in studies of insulin-resistant children of type 2 diabetic parents, insulin-stimulated glucose metabolism increased >40% after a 6-week exercise training program, although not to the level seen in nonrelatives, who also doubled their glycogen synthesis rate. Interestingly, the increment in G-6-P in insulin-resistant offspring, although less than normal before

Zachary Bloomgarden is a practicing endocrinologist in New York City.

exercise, was greater than normal after exercise, so an additional, more distal abnormality in glycogen synthetase must also be present. Thus, in diabetes there is a defect in muscle glycogen synthetase due to decreased glucose transport and phosphorylation. This may be a primary pathogenic defect in view of its presence in insulin-resistant offspring. It is perhaps due to increased FFA levels and may be susceptible to improvement with exercise training. The liver is the major gluconeogenic organ and is perhaps involved in an important way with the hyperglycemia of type 2 diabetes. With the use of ^{13}C-NMR to measure directly hepatic glycogen, it is possible to document glycogenolysis during fasting to assess directly its contribution to glucose production. Shulman showed that in patients with type 2 diabetes, basal hepatic glycogen content during a 22-h fast is half that in nondiabetic subjects, despite which glucose production is increased because of gluconeogenesis.

Other studies presented at the meetings addressed related topics. Kruszynska et al. (195) confirmed the importance of fatty acid suppression on the normal metabolism of an oral glucose load by showing that heparin plus lipid infusions resulted in hyperinsulinemia and decreased glucose utilization. Meyer et al. (90) showed evidence that the kidneys account for a substantial proportion of FFA disposal, suggesting a potential role in the development of insulin resistance. Matsuda and DeFronzo (265), studying insulin-resistant individuals, and Eriksson et al. (260), studying individuals with normal glucose tolerance having two relatives with type 2 diabetes, showed adipocyte insulin resistance for FFA disposal. The latter study also showed increased muscle sympathetic nerve activity, suggesting a possible role of the sympathetic nervous system. Mau et al. (550) presented data indicating that decreased physical activity levels are of more importance than increased dietary intake as causes of diabetes. Interestingly, Leite et al. (220) showed that individuals at risk for type 2 diabetes appear also to have decreased exercise capacity as measured by maximal oxygen consumption. These results may mean that there are a multiplicity of causes of type 2 diabetes.

Other Perspectives on Insulin Resistance and the Causes of Type 2 Diabetes

Insulin resistance and the causes of type 2 diabetes were studied from a variety of other perspectives as well. Day et al. (301) showed that a polymorphism at position 238 of tumor necrosis factor-α (TNFα) is associated with increased insulin sensitivity independent of differences in BMI, suggesting a role of this circulating factor in the pathogenesis of the insulin-resistant state. Furthermore, Ventre et al. (327) reported that genetic ablation of TNFα in mice results in lower triglyceride levels and improved insulin sensitivity under conditions of experimental obesity. Dunaif and Diamanti (91) showed data obtained by percutaneous muscle biopsy during insulin infusion of women with the polycystic ovary syndrome. A defect was seen in the early steps of insulin receptor signaling consistent with the inhibition of insulin receptor tyrosine kinase activity by serine phosphorylation that had been identified in cell-free systems and intact fibroblasts of women with the syndrome. The defect was independent of obesity and was found to occur in the absence of type 2 diabetes.

Several population studies shed light on the genetics of type 2 diabetes. Levy et al. (524) showed that among siblings of individuals with type 2 diabetes, obesity, high triglycerides, and low HDL cholesterol were not only increased in frequency, but also were found to occur most frequently in individuals whose siblings had these disorders. From 47 to 59% of the variance in these conditions was explained by family history. In the Atherosclerosis Risk in Communities (ARIC) study of 9,564 whites and 2,608 blacks, black women and men had a 63–67% greater diabetes risk, even after adjusting for family history of type 2 diabetes, BMI, waist-to-hip ratio, and sports activity, suggesting that there are independently acting inherited characteristics. Similarly, Bonora et al. (525) reported prevalence rates of insulin resistance associated with impaired glucose tolerance, type 2 diabetes, hypertension, dyslipidemia, and hyperuricemia among 888 subjects aged 40–79 years participating in the Bruneck Study. Insulin resistance was strongly associated with hypertriglyceridemia and low HDL cholesterol. Insulin deficiency was also associated with type 2 diabetes. Wareham et al. (78) reported that in a prospective study of 723 volunteers who had a nondiabetic initial oral glucose tolerance test, baseline amylin concentration, a potential marker of islet dysfunction, predicted change in glucose tolerance.

The Global Burden of Diabetes

Aubert (536) discussed anticipated trends in the global burden of diabetes over the coming three decades. In 1995, it was estimated that there were 135 million people with diabetes, and it is anticipated that this will increase to 154 million in the year 2000 and to 300 million in the year 2025. Currently, 75% of people with diabetes are in developing countries, and this will increase to 83% in the year 2025. The frequency of diabetes will increase 170% in developing countries but 42% in developed countries.

Nigam (381) discussed a presentation of diabetes more common in the developing world, that with BMI <18.5 kg/m^2 without evidence of malnutrition. Of a series of 906 consecutive patients presenting in Jaipur, India, 16.4% showed this pattern. Patients presented with fatigue and weight loss averaging 2.9 kg. Central obesity was seen in 20.8%, and ketonuria was present only in 8.5% of patients in association with stress. At entry, 10.2% of patients required insulin, but at 5 years, 41.6% required this treatment. Peripheral neuropathy was the most common complication and pulmonary tuberculosis, the most common infection.

Minerals and Diabetes

A number of studies addressed the effect of the minerals vanadium, magnesium, and chromium on diabetes. Cusi et al. (131) administered vanadyl sulfate, 150 mg daily for 6 weeks, to 12 patients with type 2 diabetes. Fasting glucose decreased from 191 to 155 mg/dl and fructosamine from 359 to 291 μmol/l, with a fall in total and LDL cholesterol and hepatic glucose production and an increase in insulin-mediated glucose uptake. Aharon et al. (375) found a decrease in HbA_{1c} from 8.1 to 7.6% with a dosage of 100 mg daily in five patients with type 1 diabetes, without change in glucose disposal during a euglycemic-hyperinsulinemic clamp. Lu and Fantus (590) studied the mechanism of action of vanadium in vitro in rat adipocytes. They showed that depletion of cellular levels of the antioxidant glutathione increased insulin resistance and increased sensitivity to vanadium, suggesting that the effect of this agent might be particularly manifest under conditions of increased oxidative stress. Kao et al. (76) reported that in a prospective survey of 12,172 individuals, the ARIC study, the incidence of type 2 diabetes showed an inverse relationship with serum magnesium levels among whites, with twice the risk in those with serum

magnesium <1.4 than in those with levels >1.7 mg/dl. Cefalu et al. (216) reported on a randomized double-blind trial of chromium picolinate at a dosage of 1,000 μg daily for 8 months in 26 moderately obese nondiabetic subjects. Insulin sensitivity increased significantly with treatment, without significant change in serum insulin or in intra-abdominal fat measurements.

Therapeutic Approaches to Type 2 Diabetes

The short-acting insulin secretagogue repaglanide was studied by a number of investigators. Pamsbo et al. (132) showed data suggesting the agent to be optimally effective when given three times, rather than twice, daily. Moses et al. (365) studied combination treatment with repaglanide plus metformin at a dosage of 1–3 g daily in 83 patients with type 2 diabetes who had failed to show adequate glycemic control. HbA_{1c} fell 1.41% and fasting blood glucose 2.18 mmol/l with the combination while not changing significantly with either agent alone. Repaglanide and metformin monotherapy led to similar degrees of glycemic control, although repaglanide was not associated with gastrointestinal side effects. Hatorp et al. (584), recognizing that the average half-life of repaglanide is 0.5 h, investigated the use of flexible regimens in patient eating at irregular times. Glycemic control was similar whether the drug was given on a fixed schedule or on a flexible schedule, omitting or taking an extra dose with missed or extra meals. Finally, Landgraf et al. (626) reported a 14-week double-blind comparative study showing that glycemic control was similar with repaglanide or glyburide.

Raskin et al. (633) studied BTS 67582, another oral short-acting nonsulfonylurea insulin secretagogue, in 258 patients with type 2 diabetes with fasting glucose levels of 140–230 mg/dl on diet therapy. Patients were randomly assigned to receive placebo or 100, 250, or 500 mg of BTS 67582 twice daily for 3 months. Fasting glucose and HbA_{1c} decreased 30 mg/dl and 1.3% at the two higher doses, with symptomatic hypoglycemia in 8.7% and 9.8% of patients. De Souza et al. (925) presented data on a third rapid-onset short-acting insulin secretagogue, A-4166, in a rat model of type 2 diabetes. With this agent, they detected rapid insulin secretion after meals with a lower degree of postprandial hypoglycemia than seen with glyburide, glipizide, or repaglanide.

Deems et al. (589) presented data on a new agent, SDZ PGU 693, which increases adipocyte and myocyte glucose uptake and utilization and decreases hepatocyte glucose production in vitro by mechanisms distinct from those of troglitazone (TGZ) and metformin. In rodent and primate type 2 diabetes models, glucose levels decreased and insulin sensitivity increased with this agent.

Gerstein et al. (642) investigated the use of hydroxychloroquine at 300 mg twice per day in 135 obese type 2 diabetic subjects who had not responded well to sulfonylurea (glycated hemoglobin >11%) on glyburide at a dosage of 10 mg twice daily. Compared with the results of treatment with glyburide alone, glycohemoglobin decreased 0.9% at 3 months and 1.7% at 15 months, with lower triglyceride and LDL cholesterol levels. By 18 months, 95.5% of placebo patients, but 77% of those on hydroxychloroquine plus glyburide, were withdrawn because of poor control, suggesting that with this degree of hyperglycemia more potent glucose-lowering treatment is ultimately required.

Several studies investigated new aspects of sulfonylurea treatment. Edwards et al. (176) treated 7 type 2 diabetic patients with glipizide GITS, 20 mg daily, and 7 with metformin, 2.5 g daily, for 6 weeks, after which all 14 patients were given combination treatment for 12 weeks. On combination treatment, HbA_{1c} fell 2.2 to 3.1%. In vitro binding to arterial proteoglycans of LDL isolated from the patients was less than that seen with either agent alone, presumably due to the improved glycemic control. Another study of glipizide GITS, by Blonde et al. (612), showed that 393 treated patients had a 0.87% fall in HbA_{1c} but did not show weight gain, although a 5.66-lb weight loss was seen in 201 patients treated with placebo, who had a 0.57% increase in HbA_{1c}. No adverse effect was seen on lipid levels. Riefflin et al. (620) measured C-peptide secretion in patients with type 2 diabetes treated with placebo or glyburide, 2.5 mg twice daily, during hyperinsulinemic clamps at 72, 144, and 216 mg/dl blood glucose levels. C-peptide secretion increased at higher glucose levels, but at each level the increase with glyburide was similar. The investigators suggested that the proportionally greater β-cell stimulatory effect at normal glucose concentrations may add to the tendency of glyburide to cause hypoglycemia. Bogaty et al. (982) addressed the phenomenon of ischemic preconditioning, wherein exercise-induced myocardial ischemia can be attenuated with repeated exercise. Activation of vascular ATP-sensitive potassium channels might affect this, and in view of the potential interaction of glyburide with these cellular structures, 10 diabetic subjects with stable angina treated with glyburide in a dosage of at least 10 mg daily were studied during two successive exercise tests. The degree of attenuation of myocardial ischemia with repeated exercise was similar to that seen in nondiabetic subjects. Either the K_{ATP} channel is not involved in this form of ischemic preconditioning or the degree of interaction of glyburide with the K_{ATP} channel is not sufficient to increase ischemia in patients with stable angina.

The α-glucosidase inhibitors acarbose and miglitol were studied by a number of investigators. Frank et al. (361) administered 100 mg of acarbose to 26 patients with type 1 diabetes prior to a standard breakfast given in a single feeding or as two partial feedings separated by 120 min. Acarbose prevented the hyperglycemia seen with the single feeding, giving a glycemic pattern over 210 min similar to that with the split meal. Blood glucose at 90 min was lower with acarbose and a single meal than with placebo and the split meal. Mertes (362) presented an assessment of the efficacy and safety of acarbose in 2,035 patients with type 2 diabetes over a 2-year period. Fasting and 1-h glucose levels decreased by 43 and 65 mg/dl, and HbA_{1c} decreased by 1.1%. Only 2.5% of patients discontinued the treatment, suggesting it to be a useful therapeutic agent. Lopez et al. (370) presented an interesting assessment of type 2 diabetic subjects with fasting glucose exceeding 160 mg/dl despite treatment with chlorpropamide, 500 mg, and metformin, 1500 mg daily. Acarbose at a dosage of 300 mg daily was added for 17 patients, and NPH insulin at bedtime was added for 12 patients. The latter proved more efficacious, with HbA_{1c} falling from 11.1% to 10.3% with acarbose but from 11.7% to 9.4% with insulin. Buse et al. (392) described a prospective dose-titration study of acarbose in 2,139 patients with type 2 diabetes. One-hour postprandial glucose levels fell by 46 mg/dl and HbA_{1c} fell by 0.8%, with larger reductions in patients with higher baseline glycohemoglobin levels. However, 41% of patients experienced flatulence, diarrhea, or abdominal pain. Lee and Morley (987) presented data analyzing weight change in obese type 2 diabetic patients during a 6-month period of treatment with acarbose at a dosage of 300 mg daily in relationship to

baseline dietary carbohydrate content. Those individuals consuming >50% of dietary calories as carbohydrate lost 4.8 kg, while those consuming less carbohydrate had a 1.0-kg weight increase. The former group showed a fall in HbA_{1c} as well. Studies by Johnston et al. (602,610) assessed the effect of miglitol. The first study involved 345 African-American patients and demonstrated a 0.53% fall in HbA_{1c} with miglitol at a dosage of 100 mg three times per day, in comparison to a 0.66% increase with placebo. Fasting and 2-h postprandial glucose levels fell 6 and 23 mg/dl with treatment, while both rose 30 mg/dl with placebo. Flatulence, soft stools, and diarrhea, were the major side effects, leading to withdrawal of 8% of patients. In the second study, 411 type 2 diabetic subjects over age 60 on diet treatment alone were treated with placebo, miglitol at dosages of 25 or 50 mg three times per day, or glyburide at a mean dosage of 3.75 mg daily. The HbA_{1c} fell 0.50% and 0.41% in the two miglitol groups and 0.93% with glyburide while not changing with placebo. There were decreases in fasting and postprandial insulin levels in the two miglitol groups but an increase with glyburide. Body weight decreased by 1.07, 2.61, and 1.55 kg with placebo and the two miglitol dosages, but increased 2.31 kg with glyburide, and episodes clinically suggestive of hypoglycemia occurred at the placebo level with miglitol but in 46% of glyburide-treated patients.

Among the presentations were reports on a number of studies of insulin therapy and combination therapy in type 2 diabetes. Perriello et al. (363) compared responses to 3-month periods of bedtime insulin versus a multiple-injection regimen in 14 patients who had failed to respond to sulfonylurea. Fasting glucose and hepatic glucose production decreased similarly, but the mean 24-h glucose concentration and HbA_{1c} were 52 mg/dl and 1.4% lower with the multiple-dose regimen without differences in 24-h mean insulin concentration, body weight, or insulin sensitivity. Brabant et al. (371) studied nine patients who had failed to respond to sulfonylurea and compared data before and after 10 days of treatment with preprandial boluses of regular insulin or lispro. Mean 24-h serum proinsulin and C-peptide decreased and the endogenous insulin response to meals and to hyperglycemia was restored following short-term insulin treatment to levels comparable to those of healthy subjects. Perriello et al. (593) compared 100 type 2 diabetic subjects treated with insulin plus sulfonylureas or insulin plus metformin for 6 months. In nonobese patients, glycemic control was similar with the two regimens, but there was a 2.6-kg greater weight gain with sulfonylureas. In obese patients, glycemic control was better with the metformin regimen, which was associated with a 1-kg weight loss, in comparison to the 2.3-kg weight gain with sulfonylurea plus insulin. McNulty et al. (622) compared metformin 850 mg three times per day with gliclazide 160 mg twice per day in combination with daily NPH insulin in 41 type 2 diabetic subjects whose blood glucose levels were inadequately controlled with oral agents. Both approaches decreased HbA_{1c}, by 1.54% with metformin and 2.1% with gliclazide, but there was a 2-kg greater weight gain and a 10-fold greater frequency of hypoglycemia with the latter. Schernthaner et al. (643) studied 134 patients who had not been responsive to sulfonylurea on treatments with sulfonylurea plus metformin, sulfonylurea plus bedtime NPH insulin, 70/30 insulin twice daily, or 70/30 insulin twice daily plus metformin. Addition of metformin was not as effective as addition of insulin at bedtime, and administration of 70/30 twice daily led to greater improvement in HbA_{1c}, particularly if metformin was also administered. BMI increased by 0.5 to 1.3 kg/m^2 in all groups.

Troglitazone (TGZ)

At a symposium on TGZ, Bruce Spiegelman, Boston, MA, spoke on the mechanisms of action of thiazolidinediones (TZDs). In 1990, a genetic enhancer element involved in adipocyte regulation was discovered. This element was later found to be identical to the nuclear peroxisome proliferator activated receptor-γ (PPARγ), which forms a heterodimeric complex with several nuclear proteins and leads to adipocyte differentiation. PPARγ was found to bind thiazolidinediones and is expressed mainly in adipocytes, although expression in skeletal muscle is seen at a level 3–5% of that in adipocytes. Because there is a perfect match between the binding affinity of TZDs to PPARγ and their efficiency in decreasing insulin resistance, PPARγ seems to be the binding site of TZDs. There is evidence that a natural ligand is what Spiegelman characterized as an obscure prostanoid, 15-deoxyΔ12,14PG J2, but this may not be present at sufficient levels in vivo to act on the PPARγ binding sites. TZD binding may improve insulin sensitivity by increasing adipocyte differentiation to produce a larger number of small adipocytes, which are more insulin-sensitive, assuming no increase in total adipocyte mass. Alternatively, PPARγ activation in muscle and liver may explain the action of TZD on these tissues. A final possibility is that PPARγ activation may alter adipocyte signaling by changing the production of TNFα or leptin or by altering fatty acid levels. Adipocytes secrete the cytokine TNFα, which can cause insulin resistance both in vivo and in vitro. TNFα levels are increased in many animal models of obesity and in obese humans. Neutralization of TNFα with a soluble TNFα receptor lowers blood glucose in Zucker fatty rats with insulin-resistant diabetes. Similarly, TNFα-knockout mice have decreased insulin resistance in a variety of experimental obesity models. TNFα interferes with the tyrosine phosphorylation of the insulin receptor and increases the opposing pathway of serine phosphorylation, causing insulin resistance. TZDs and 15-deoxyΔ12,14PG J2 have been shown to antagonize the effect of TNFα on adipocytes, but several hours are required for the effect to become manifest, suggesting a requirement for nuclear synthesis.

A number of studies presented at the meeting added to our understanding of the mechanism of action of TZDs. Eckel et al. (575) reported that TGZ antagonized the effect of hyperglycemia in activating protein kinase C, which reduces the kinase activity of the insulin receptor. Okuno et al. (329) reported that in the Zucker fatty rat model of insulin-resistant diabetes, TGZ reduced glucose and insulin levels in association with decreased expression of TNFα by white adipose tissue, which showed increased cell number with decreased size and triglyceride content and unchanged tissue mass, whereas brown adipose tissue mass increased. Paulik et al. (357) also suggested that brown adipocyte differentiation, perhaps in association with expression of uncoupling protein and increased β_3-adrenergic sensitivity, may underlie the antidiabetic effect of TZDs. Park et al. (85) reported that in skeletal muscle from patients with type 2 diabetes and from nondiabetic obese subjects, TGZ increases glucose transport and that this increase is associated with increased expression of mRNA for GLUT1 and GLUT4. Furthermore, TGZ activates glycogen synthase in skeletal muscle in association with specific

expression of PPARγ mRNA in myocytes. Finally, Buckingham et al. (638) showed prevention of degenerative changes in β-cells in the Zucker fatty rat model after long-term treatment with the TZD BRL 49653, and Smith et al. (577), from the same group, showed prevention of the onset of diabetes and of proteinuria. Fujiwara et al. (291) reported a similar effect of TGZ in this model.

Randall Whitcomb, Ann Arbor, MI, gave a review of safety data pertaining to TGZ. The drug was approved in February 1997 and launched 1 month later. Close to 200,000 patients have been treated, in addition to more than 2,000 patients who were treated in clinical trials, almost 1,000 for more than 1 year and more than 500 for more than 18 months. No major adverse effects were noted. There was a transient increase in measurements of liver chemistry (>3 times normal) in 1–2% of patients. An increase in cardiac index in association with decreased blood pressure and decreased peripheral resistance was seen, and there was a 0.4 mg/dl fall in hemoglobin in association with a 5–7% increase in plasma volume, without frequent findings of peripheral edema or dizziness. No adverse changes in cardiac mass or function were reported in a study by Driscoll et al. (574) on 154 patients treated with TGZ at a dosage of 800 mg daily or with glyburide at a dosage up to 20 mg daily. The two treatments resulted in similar glycemic control, with lower blood pressure and lipids and improvement in echocardiographic left ventricular function indices at 96 weeks in the TGZ-treated group.

Kenneth Polonsky, Chicago, IL, spoke on the effects of TGZ in patients with impaired glucose tolerance (IGT). In a study of 14 patients treated with 400 mg daily, and compared with 7 controls, there was no weight change, and glucose tolerance improved with TGZ while insulin levels fell and insulin sensitivity improved, although not to normal levels. Glycohemoglobin fell from 6.4% to 6.0% with treatment but did not change with placebo. A larger, multicenter study showed progressively greater increase in peripheral glucose disposal rate in patients with mild diabetes treated with 100, 200, and 400 mg TGZ daily. With a dosage of 600 mg daily, hepatic glucose output also showed a fall, suggesting hepatic effects to be less sensitive than those in the periphery, predominantly in skeletal muscle. Polonsky also pointed out that when corrected for increased insulin sensitivity, there is evidence of some improvement in insulin secretion as well. In a study of women with the polycystic ovary syndrome and IGT, TGZ similarly improved glucose tolerance and insulin sensitivity, with, in addition, a fall in androgen levels. Levels of plasma activator inhibitor-1, a prothrombotic factor, also showed a fall in this group.

Jerrold Olefsky, San Diego, CA, also spoke on the effects of TGZ in patients with diabetes. The drug lowers glucose and insulin levels in a variety of animal models of diabetes and obesity. In type 2 diabetes, there is a 40 mg/dl fall in fasting blood glucose in association with a fall in insulin and hepatic glucose production levels. About 20–30% of patients fail to respond, but both responders and nonresponders tend to have similarly increased insulin sensitivity. In a 6-month study of 390 insulin-treated diabetic patients given placebo or 200 or 600 mg TGZ, fasting blood glucose fell from 210 to 175 mg/dl and to 160 mg/dl with the two TGZ dosages. HbA_{1c} fell from 9.3 to 8.5 and to 7.9%, and there was an average decrease of 15 and 42% in insulin dosages, which averaged 75 U/day. Eleven percent of placebo-treated patients, 30% of those receiving 200 mg of TGZ, and 57% of those receiving 600 mg of TGZ achieved HbA_{1c} <8.0%. In a 6-month study of 402 diet-treated diabetic patients, TGZ dosages of 100, 200, 400, and 600 mg daily lowered fasting glucose levels 11, 42, 51, and 60 mg/dl in comparison to placebo. Insulin and free fatty acid levels fell, triglyceride levels fell 40–50 mg/dl, HDL rose only at the highest dosage, and LDL levels rose 4–8 mg/dl, although without a rise in apolipoprotein B levels, suggesting increased LDL size and decreased atherogenicity. In a study of the combination of micronized glyburide at a dosage of 12 mg daily with TGZ, there was no significant change in patients whose glyburide was replaced with TGZ at 400 or 600 mg, although glucose levels rose when only 200 mg of TGZ was given without the glyburide. When TGZ was added to the glyburide, the blood glucose fell 40 mg/dl with dosages of 200 and 400 mg and 80 mg/dl with a dosage of 600 mg, with falls in HbA_{1c} of 0.8% and 1.4% with the higher TGZ dosages. Olefsky recommended continuing prior treatment with insulin or sulfonylureas and only cautiously decreasing these once the glycemic target is attained.

In another report, Valiquett et al. (168) presented a study of 392 patients treated with TGZ dosages of 100 to 600 mg daily. In comparison to the placebo group, fasting blood glucose levels at 6 months fell 42, 51, and 60 mg/dl with 200, 400, and 600 mg TGZ daily, HbA_{1c} fell by 0.4, 0.7, and 1.1%, and triglyceride levels fell by 58, 57, and 72 mg/dl. A number of studies addressed the use of TGZ in combination with other agents for type 2 diabetes. Inzucchi et al. (134) studied 28 patients with type 2 diabetes treated with 400 mg of TGZ daily or 2 g of metformin daily. Fasting glucose levels fell 17 and 19% at 3 months, with additive glucose-lowering effect when the two agents were combined for an additional 3-month period. Insulin sensitivity, as measured by glucose infusion rates during a hyperinsulinemic euglycemic clamp, increased 20 and 43% with metformin and TGZ, with further improvement when the two agents were combined. Ghazzi et al. (169) reported a study of 541 patients with type 2 diabetes and with fasting serum glucose over 140 mg/dl on treatment with 12 mg daily of micronized glyburide. These subjects were randomly assigned to continue receiving glyburide or to receive placebo with addition of TGZ in dosages of 200, 400, and 600 mg daily. HbA_{1c} increased 1% with 200 mg TGZ alone, was stable with the 400- and 600-mg dosages, and decreased 1.6%, 1.8%, and 2.7% in patients treated with glyburide plus the three TGZ dosages. Fasting glucose levels were similarly affected, rising 20 mg/dl with 200 mg daily TGZ alone, falling 2 and 12 mg/dl with the 400- and 600-mg dosages, but decreasing 54, 61, and 79 mg/dl in patients treated with glyburide plus TGZ at the three dosages. Finally, Raskin and Graveline (170) reported on a study of 351 patients with type 2 diabetes receiving insulin in dosages of at least 30 U daily, who were randomly assigned to the addition of placebo or TGZ in a dosage of 200 or 600 mg daily. HbA_{1c}, fasting glucose, and insulin dosage were unchanged with placebo, but HbA_{1c} decreased 0.8% and 1.3%, fasting glucose decreased 29 and 43 mg/dl, and the mean insulin dosage decreased 10 and 22 U/day with the 200- and 600-mg TGZ dosages.