Neuropathy, Womens' Health, and Socioeconomic Aspects of Diabetes

ZACHARY T. BLOOMGARDEN, MD

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NEUROPATHY

At a symposium on neuropathy sponsored by the University of Texas Southwestern at the American Diabetes Association meeting in San Antonio, Texas, Soroku Yagihashi (Hirosaki, Japan) discussed aspects of the pathogenesis of distal symmetric polyneuropathy. In a recent survey in Tohoku, Japan, of 32,955 individuals with diabetes, history or symptoms of neuropathy made it the most common complication, occurring in 27% of patients.

There are two major histologic findings in nerve biopsy from patients with distal symmetric polyneuropathy. Myelinated fiber density decreases, falling by approximately one-third with mild neuropathy and by two-thirds with severe neuropathy, reflecting loss of nerve fibers with degeneration of remaining fibers. There is also evidence of microangiopathy in the vasa nervosum. Nerve capillary density again decreases in proportion to the severity of the neuropathy, with capillary basement membrane area nearly doubled with mild neuropathy and tripled with severe neuropathy. The susceptibility of peripheral nerve to ischemia may be partly related to its great axon length with sparse blood supply.

As with retinopathy and nephropathy, poor glycemic control is a major cause of neuropathy, with nerves not showing insulin-mediated glucose uptake, but rather allowing direct glucose entry, which increases with hyperglycemia. In the Tohoku survey, the likelihood of neuropathy increased 2.7-, 1.7-, and 1.2-fold in individuals whose HbA_{1c} was ≥10, 7.5–9.9, and 6.5–7.49%, in comparison to those with HbA_{1c} <6.5%. In the nerve, glucose is metabolized through the polyol pathway to sorbitol via the enzyme aldose reductase (AR). Sorbitol can cause osmotic stress and can lower nerve myoinositol and taurine levels, with decreases in Na^+/K^+-ATPase, which is involved in intracellular energy homeostasis. In addition, conversion of NADPH to NADP as glucose is metabolized to sorbitol decreases availability of this substrate for the action of nitric oxide (NO) synthase in forming citrulline and NO from arginine, with potentiation of vascular dysfunction by NO deficiency. In contrast to AR, which is located within nerve fascicles, immunohistochemical staining shows that the enzyme sorbitol dehydrogenase (SDH), which metabolizes sorbitol to fructose, is present largely in epineurial arterioles and hence becomes unavailable with diabetic vasculopathy.

Yagihashi reviewed the strong relationship between AR and neuropathy, with erythrocyte AR protein levels that are similar in individuals with diabetes and in the general population, but that are lower in diabetic individuals without neuropathy than in those who have neuropathy (1). In experimental models of diabetes, AR levels in both the sciatic nerve and the renal cortex are elevated, whereas SDH levels are comparable to those in nondiabetic animals. Furthermore, AR-overexpressing transgenic mice that are made diabetic show increased nerve sorbitol in association with greater reduction in motor nerve conduction velocity (NCV) and myelinated fiber size when compared with nontransgenic mice with diabetes. Na^+/K^+-ATPase is decreased with diabetes alone, and it is further decreased in the diabetic animals overexpressing AR. Furthermore, intraneural diacylglycerol (DAG) decreases, with a fall in protein kinase C-α (PKC-α), which further decreases Na^+/K^+-ATPase activity. The diabetic mice overexpressing AR show further decreases in PKC-α. This relationship between a lowering of neural PKC-α and diabetic neuropathy contrasts with vascular smooth muscle and the endothelium, where diabetic complications appear to be mediated by increases in DAG and PKC-β.

Abnormalities of the polyol pathway may also increase production of advanced glycation end products, including the toxic intermediates 3-deoxyglucosone (3-DG), methylglyoxal, and carboxymethyl lysine (CML). The AR inhibitor epalrestat has been shown to decrease blood sorbitol and also CML and 3-DG in patients with diabetes (2). A number of such compounds have been studied. Zenarestat shows a dose-related decrease in nerve sorbitol and an increase in peroneal NCV and nerve fiber density in individuals with diabetic neuropathy (3), and fidarestat improves a number of indexes of nerve function when administered to patients for a 1-year period (4). Yagihashi concluded that with coming advances in treatment "we will have a method for the treatment and prevention of diabetic neuropathy."

Joseph C. Arezzo (Bronx, NY) discussed the role of electrophysiological testing in diabetic neuropathy. These testing modalities are of great value in multicenter studies, providing objective and specific evidence of the efficacy of new therapies. In the future, however, Arezzo pointed out that with metabolic therapies, it may be important to monitor patients' progress, particularly with "technological breakthroughs which allow measurement [of nerve conduction] at the point of care."

Electrophysiology can be used to assess abnormality of proximal and distal

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Diabetes Center, Mount Sinai School of Medicine, New York, New York.

Abbreviations: AIDA, Automated Insulin Dosage Advisor; AR, aldose reductase; CML, carboxymethyl lysine; CVD, cardiovascular disease; DAG, diacylglycerol; 3-DG, 3-deoxyglucosone; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; IRS, insulin receptor substrate; IVGTT, intravenous glucose tolerance test; LH, leutinizing hormone; MAPK, mitogen-activated protein kinase; MRFIT, Multiple Risk Factor Intervention Trial; NCV, nerve conduction velocity; NO, nitric oxide; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PKC, protein kinase C; PI, phosphatidylinositol; ROS, reactive oxygen species; SDH, sorbitol dehydrogenase; SHBG, sex hormone binding globulin; TGZ, troglitazone.

sensory and motor function. In the Diabetes Complications and Control Trial, such testing showed clear evidence that a 5-year period of intensive glycemic control was associated with a definite difference in NCV between the intervention and control groups, with accompanying differences in neuropathy symptoms and physical findings (5). In an even more dramatic study, individuals with combined kidney-pancreas transplants showed an increase of peroneal NCV by 3.8, 6.5, and 7.2 m/sec at 1, 2, and 3 years, suggesting that strict normalization may partly reverse the course of diabetic polyneuropathy (6). Other changes in nerve electrophysiology with neuropathy are a decrease in both latency and amplitude, broadening of the response time, and, ultimately, a decrease in response area among individuals as neuropathy progresses. Arezzo also pointed out that the large-diameter heavily myelinated axons are the ones assessed with standard electrophysiology, but that the more numerous small-diameter axons that mediate thermal and pain sensation, show adverse effect of diabetes, and benefit with treatment are not assessed by standard nerve testing techniques. New approaches with multichannel recording assessing a distribution of conduction velocities will allow the evaluation of function of these nerve elements.

Phillip A Low (Rochester, MN) discussed the variety of syndromes of diabetic neuropathy, with a myriad of differing mechanisms, including macro- and microvascular disease and metabolic effects on nerves and their supporting cells. Chronic distal sensory neuropathy is the most common type, occurring in approximately one-quarter of individuals with diabetes before 10 years, in half of those between 10 and 20 years, and in three quarters of those after 20 years. Most are asymptomatic, although the majority have abnormal findings on electrophysiological evaluation of either autonomic or peripheral nerves. About one-tenth of individuals with diabetes have the clinical syndrome of painful peripheral neuropathy, and an equal number have clinical evidence of autonomic dysfunction, an underappreciated component of which, Low pointed out, is the finding of abnormal sweating patterns. He expressed the opinion that evaluation of these patients, including nerve conduction measurement, is important, not in the least to exclude etiologies other than diabetes itself, which he stated is seen in ~4% of patients. For management, he urged consideration of local treatment modalities, including "cold soaks," particularly in the evening, and the use of massages, which may help the patient's symptoms and are unlikely to cause harm. For individuals under age 60 years requiring pharmacological treatment, he suggested the tricyclics amitryptiline or nortryptiline at dosages of 25–75 mg at bedtime. Because of the propensity of the tricyclics to cause cognitive dysfunction, he recommended the use of gabapentin in older patients, suggesting the need for doses of 1,800–3,600 mg daily for adequate effect (although one should note that this may also cause sedation).

Acute or subacute distal diabetic neuropathy, sometimes referred to as "insulin neuritis," is typically seen in individuals with type 1 diabetes who are rapidly coming under tight glycemic control. Despite minimal sensory loss and weakness, often with normal NCV, these patients display burning, aching, and stabbing dysesthesias as well as contact allodynia. Increased limb blood flow is demonstrable, suggesting a form of autonomic dysfunction, perhaps with acute institution of glycemic control leading to a vasodilatory effect of insulin through arteriovenous shunts, with resultant nerve hypoxia. An alternative hypothesis is that absolute or relative hypoglycemia is responsible for the nerve dysfunction, so that avoidance of hypoglycemia may be useful in management. The syndrome usually shows full recovery within 6 months.

Diabetic radiculopathy is infrequently diagnosed, with the patient typically complaining of deep, aching pain in a radicular distribution, perhaps reflecting pain in the nerve trunk. There is distal symmetric polyneuropathy in most of these patients, and, conversely, the finding of radicular involvement is common in diabetic polyneuropathy, being found in one-quarter of patients when carefully sought. Topical treatment with a lidocaine patch may be effective in these patients, who also respond to amitryptiline and gabapentin.

Diabetic autonomic peripheral neuropathy involves small nerve fibers, with a distal distribution overlapping with chronic distal sensory neuropathy, initially with evidence of autonomic overactivity, with coldness and sweating, and later with warm, dry, hyperpigmented skin. There is a similar evolution of distal sensory symptoms, initially with a burning or prickling discomfort, and later a dull constant aching with sensory loss. Orthostatic hypotension, gastroparesis, constipation or diarrhea, erectile dysfunction, and neurogenic bladder are also common findings with autonomic dysfunction. Low pointed out that a complication of sildenafil treatment is the exacerbation of orthostatic falls in blood pressure. There may be an autoimmune component to autonomic neuropathy, with antibodies to the neuronal nicotinic acetylcholine receptor seen particularly in patients with subacute onset and titer correlating with severity (7).

Proximal diabetic neuropathy is a syndrome with subacute onset and progression, showing a greater degree of motor loss than of sensory loss. Pain is common, with severe, deep, and dull symptoms arising from the nerve trunk, often with marked weight loss, with autonomic dysfunction seen in the majority of these patients. Nerve conduction studies show evidence of both axonal degeneration and demyelination, with both found on nerve biopsy, and also with inflammatory infiltrate. For this reason, particularly when symptoms are severe and bilateral, Low suggested that consideration be given to treatment with corticosteroids, intravenous immunoglobulin, or plasma exchange in these patients. Another autoimmune neuropathy that may occur in patients with diabetes is chronic inflammatory demyelinating polyradiculopathy (CIDP), a more diffuse condition affecting both large and small fibers, both proximally and distally, with similar findings on nerve conduction and biopsy studies. Immunosuppressive treatment is useful in these patients and is often required for extended periods because the axonal degeneration suggests that clinical response may not be seen for up to 6 months after initiation of treatment.

GASTROPARESIS

Moore et al. (241-OR) found stimulated and unstimulated saliva flow rates of 0.88 and 0.22 ml/min, respectively, in 262 patients with type 1 diabetes vs. 1.02 and 0.28 ml/min in 183 healthy control subjects, showing an association with diabetic neuropathy as well as with cigarettes and candidal infections, although there was negative association with alcohol use

(abstract numbers refer to the Abstracts of the 61st Annual Meeting of the American Diabetes Association, *Diabetes* 50 [Suppl. 2]:1–A649). Also, 16 vs. 10% of diabetic patients vs. control subjects reported dry-mouth symptoms. Samsom et al. (322-PP) reported that 34 of 124 patients with diabetes not selected on the basis of upper gastrointestinal symptoms, 83% of whom had HbA_{1c} <9%, had a >2 SD delay of gastric emptying compared with 26 healthy volunteers, without association with fasting glucose, glycohemoglobin, type of diabetes, age, or body weight. Samsom et al. (1539-P) performed gastric emptying tests in 124 patients with diabetes, showing delay in 27%, with nausea, fullness, and upper abdominal pain correlating positively and hunger and desire to eat correlating negatively with the half-time for gastric emptying.

Abell et al. (414-PP) reported the effect of treatment in 17 patients with diabetes and severe gastroparesis with neurostimulator pacing leads implanted in the stomach. At baseline, these patients vomited ~25 times/week, with a decrease to 6 and 7 episodes/week after 6 and 12 months of treatment, respectively. There was improvement in the "total symptom score" and in a quality of life index as well. Of the 17 patients with diabetes and an additional 16 with idiopathic gastroparesis treated with the procedure, 5 were discontinued, 2 because of infection, 1 because of lead perforation, 1 due to pregnancy, and 1 because the subject died. Mccallum et al. (504-P) investigated the effects of high-frequency gastric electrical stimulation with a similar surgically implanted pulse generator in 15 patients with severe gastroparesis refractory to standard medical therapy, showing a decrease in gastric retention at 4 hours, from 44% initially to 29 and 27% at 3 and 6 months, respectively, with a 35 and 34% decrease in symptoms of nausea and vomiting, respectively.

FOOT CARE

Caravaggi et al. (62-OR) enrolled 82 patients with foot ulcers in a randomized controlled clinical trial of hyaluronan-based dermal and epidermal autologous grafts, showing 65 vs. 42% healing at week 11, with an estimated time to complete healing of 57 vs. 77 days. Pearson and Albert (64-OR) analyzed osteomyelitis of the foot in 63 patients, 92% of whom had diabetes, showing resolution in 4 of 8 patients treated with antibiotics for 6 weeks, but in none treated for <6 weeks. Altogether, 59 patients had antibiotics plus surgery, ranging from toe to below-knee amputation, with 85% responding to treatment, suggesting the benefit of resection of the involved bone over antibiotic treatment alone. Piaggesi et al. (65-OR) reported a marked decrease in histological evidence of inflammation and an increase in granulation tissue in 10 patients with neuropathic ulcer treated with total contact cast, in comparison to 10 comparable patients without pressure relief.

Abouaesha et al. (927-P) reported that ultrasound measurement of plantar tissue thickness in the forefoot during weight bearing showed good correlation with foot pressures at the metatarsal heads among 157 patients with diabetic neuropathy without peripheral vascular disease. Tissue thickness of less than 11.05, 7.85, 6.65, 6.55, and 5.05 mm at the 1st-5th metatarsal heads predicted plantar pressure at those sites with a sensitivity of 73–97% and a specificity of 52–84%. Van Schie et al. (937-P) from this group compared 14 individuals with diabetes and Asian ethnicity with 14 Europid patients matched for age, sex, and neuropathy, without history of foot ulcer, showing that plantar thicknesses at the 5 sites was ~2 mm greater in the former group, with considerably lower peak pressures, perhaps explaining their relatively low risk of foot ulceration. Armstrong et al. (928-P) and Caselli et al. (929-P) from the same group reported that patients with high peak plantar pressure showed particular benefit from injected liquid silicone in the forefoot, and that the peak forefoot plantar pressure was disproportionately increased with severe neuropathy and was significantly associated with foot ulceration in a group of 238 patients followed for 30 months.

PREGNANCY AND DIABETES

At the Council on Diabetes in Pregnancy, Ulf J. Eriksson (Uppsala, Sweden) discussed approaches to reducing congenital anomaly risk. Of ~1.2 million Swedish births screened during 1987–1997, 3,864 infants with preexisting diabetes and 8,688 with gestational diabetes mellitus (GDM) had respective congenital malformation rates of 9.5 and 5.7%, compared with the population rate of 5.7% (8). Malformations discovered during pregnancy and leading to pregnancy termination were not included in the survey. Malformations included orofacial clefts, cardiovascular defects, esophageal/intestinal atresia, hypospadias, limb reduction defects, spine malformations, and polydactyly. Neural tube defects were not found in this list, perhaps because of screening. GDM did not show increased overall risk, although there was increase in risk of certain malformations; however, in mothers with GDM, there may be a subgroup with increased risk for diabetic embryopathy, perhaps due to preexisting undetected type 2 diabetes.

Eriksson commented that some studies may have had less complete ascertainment of malformation frequencies, but he reviewed the available recent literature. In a survey of 691 diabetic pregnancies from 1988 to 1997 and 729 retrospective control subjects, risks were 4.2 and 1.2% (9). Women with HbA_{1c} values of 5.6–6.8% (2.0–5.9 SD above normal) showed a relative risk of 3.0, suggesting increased risk even with slightly raised glycemic levels. Another study of outcome of 462 pregnancies in 355 women with type 1 diabetes from 10 maternity units during 1990–1994 found that there were 78 spontaneous abortions, 9 stillbirths, and 24 terminations, 9 for congenital anomalies (10). In comparison to the nondiabetic rates, pregnancy loss occurred in 25 vs. 5 of 1,000 live births, the infant mortality rate was 19.9 vs. 6.8 of 1,000 live births, and the malformation rate was 94 vs. 9.7 of 1,000 live births. In a report of 4,180 diabetic pregnancies, 3,764 with GDM and 416 with type 2 diabetes, increasing hyperglycemia at diagnosis was associated with increased risk of anomalies (11). Major malformations occurred in 3.4%, minor malformations in 2.7%, and "genetic" malformations in 0.2% of pregnancies, with the malformations including cardiac (37.6%), musculoskeletal (14.7%), neurological (9.8%), and multiple organ systems (16%) defects. Another study of 332 infants of women with type 2 diabetes found 11.7 and 5.1% major and minor malformation rates, which were associated with both maternal HbA_{1c} at presentation and age at onset of diabetes (12).

In the absence of special preconception care, type 2 diabetes is therefore associated with very high risk. In type 1 and type 2 diabetes, the malformation risks are ~8–12%. Eriksson characterized

these rates as constituting "treatment failure" and stated that treatment to reduce malformations should include optimized metabolic control, preconception advice, and embryo-fetal monitoring. He reviewed a report from a center in which instituting strict preconceptional glucose control reduced the rate of malformations from 14 to 2.2% (13).

The etiology of malformations, which occur mainly during the first 7 weeks of gestation, is hyperglycemia, perhaps with hydroxybutyrate and branched-chain amino acids also contributing to teratogenesis. Mechanisms include reactive oxygen species (ROS) excess, inositol deficiency, and arachadonic acid deficiency. The relationship between ROS and glucose-induced embryonic dysmorphogenesis has been studied whereby addition of the antioxidants superoxide dismutase, catalase, or glutathione peroxidase reduced teratogenesis (14). In vitro studies of cultured bovine aortic endothelial cells show that high glucose concentration increases ROS and activates PKC, increasing formation of AGEs and increasing flux in the polyol pathway. Normalizing levels of mitochondrial ROS with manganese superoxide dismutase prevented these consequences (15).

A study in which 283 women with increased risk for preeclampsia were randomized to either placebo or 1 g vitamin C plus 400 units vitamin E daily at 16–22 weeks showed a 76% reduction in risk of preeclampsia, suggesting this to be a potential approach (16). A randomized controlled trial of these vitamins is planned in 800 women with type 1 diabetes to assess preeclampsia as a primary objective. The study plans to initiate treatment after conception, so the potential decrease in malformation rates may not be recognized. Eriksson emphasized the need for preconception counseling for women of childbearing age with diabetes. Two-thirds of all pregnancies in the U.S. are unplanned, including those for women with diabetes, and efforts to increase preconception planning to date have been largely unsuccessful.

Lois Jovanovich (Santa Barbara, CA) gave the Norbert Freinkel lecture, pointing to his concept that fuel-mediated teratogenesis underlies diabetic fetopathy. She stressed the importance of "obsessing about glucose" in treating diabetic women during pregnancy. In studies of hourly glucose measurement in nondiabetic pregnant women, the fasting glucose level was 55–65 mg/dl, and no whole-blood glucose level exceeded 120 mg/dl, with 24-h mean levels of ~80 mg/dl. Women with diabetes, however, had marked fluctuation in glycemia. The use of home glucose monitoring showed that fasting and 1-h postprandial glucose sufficed to assess glycemia in women treated with diet, with both preprandial and 1-h postprandial glucose monitoring needed in women treated with insulin.

Using a diet with 30 kcal/kg present pregnancy weight in normal-weight women and 24 kcal/kg in obese women as well as reducing carbohydrate to one-third of dietary calories, with at least 3 insulin injections daily, Jovanovich found it possible to normalize maternal glucose. Insulin requirements for optimal treatment increase during pregnancy, with 0.7, 0.8, and 1.0 units $\cdot kg^{-1} \cdot day^{-1}$ at the end of the 1st and 2nd trimesters and at term, respectively.

In studies of diabetes in early pregnancy, there was a close relationship between hyperglycemia and risk of spontaneous abortion (17). Fetal malformation is also decreased by good glycemic control. Comparing 347 diabetic and 389 control women who enrolled in a study within 21 days of conception and 279 diabetic women who entered later, major malformations were found in the infants of 4.9% of the early-entry diabetic women, 2.1% of the control subjects, and 9.0% of the late-entry diabetic women, suggesting benefits of efforts to achieve good metabolic control around the time of conception (18). A subsequent evaluation of 84 women with diabetes recruited prior to conception, with mean glucose levels during embryogenesis and organogenesis within 3.3–7.8 mmol/l in 50% of preconception subjects and exceeding 10 mmol/l in only 6.5%, showed only one major congenital anomaly, whereas 12 anomalies occurred among infants of 110 already-pregnant women with diabetes referred at 6–30 weeks' gestation (19).

For GDM, the treatment of choice is lifestyle modification. Exercise may be particularly useful, with studies suggesting that this may improve glucose levels (20) and also reduce macrosomia rates. If the peak postprandial glucose exceeds 120 mg/dl, insulin administration is needed. Insulin lispro appears to have ideal characteristics for the approach to optimal glycemia. New approaches with continuous glucose monitoring may allow further improvement in outcome.

At a symposium on current issues in GDM, Oded Langer (New York, NY) discussed glyburide as an alternative to insulin treatment in the pregnant diabetic patient. "The gold standard is obviously the use of insulin," he commented, pointing out that pregnancy is associated with insulin resistance and increased insulin secretion. The group of women who are unable to increase insulin secretion are those who develop GDM, which may be regarded as "the same disease in an early stage" as type 2 diabetes, a view that can lead to better overall treatment for these patients.

Langer showed that it is often possible to markedly improve glycemia and decrease insulin resistance with diet therapy. Failure to control the diabetes with diet, he suggested, can be determined by fasting, 1-h, and 2-h glucose exceeding 95, 140, and 120 mg/dl, respectively, or by the finding of increased fetal abdominal circumference. For those patients failing to show adequate control with diet, "intensified therapy," with goals of maintaining postprandial glucose levels at $<$120 mg/dl, leads women with GDM to have outcomes similar to those of women without GDM, whereas treatment with lesser treatment goals leads to worse outcome, similar to that of no treatment at all (21).

A study performed in South Africa reported no adverse effects of glyburide and metformin given during pregnancy to a small group of women (22). There is no reason, Langer stated, to believe that treatment started during the second trimester would lead to congenital anomalies, and, indeed, studies comparing women with type 2 diabetes treated with diet, insulin, or sulfonylureas prior to pregnancy have not shown differences in outcome, whereas greater blood glucose and maternal age are clearly associated with anomalies. Glyburide treatment was highly effective during the first few years of the U.K. Prospective Diabetes Study (UKPDS), with 70% of patients achieving good initial control. In a study of maternal-fetal transfer of glyburide, there is no evidence that measurable levels cross the placenta.

Langer addressed the hypothesis that glyburide can replace insulin, with comparable pregnancy outcome, and that it may be more acceptable to women. He

discussed his study of patients with GDM enrolled with fasting glucose levels of <140 mg/dl. They were treated with diet alone if the fasting glucose could be maintained at <96 mg/dl, and the remaining 404 women were randomized to insulin or glyburide (23). The dose of glyburide was started at 2.5 mg and increased to a maximum of 20 mg daily, with eight glyburide patients (4% of the group) requiring a change to insulin. Glycemic control was identical in the glyburide and insulin groups; neonatal cord insulin levels were the same, suggesting that the fetal islets were not stimulated; and high-pressure liquid chromatography did not show glyburide in the fetal circulation. There was no evidence of more macrosomia or anomalies, no metabolic difference for the neonates, and no difference in neonatal respiratory function, time in intensive care, or any other outcome of pregnancy.

Langer concluded, "Why not give glyburide instead of insulin if I can get the same result?" The U.S. Food and Drug Administration classifies glyburide and metformin as class B agents for pregnancy, at low to moderate risk, so although these are not specifically deemed unsafe for use during pregnancy, there remain concerns. Would glyburide "cause increased stress on the pancreas" and increase risk of subsequent diabetes? "We have to follow them for many years to know," Langer stated. He noted that women with existing type 2 diabetes who wished to become pregnant would still, in his practice, be changed to insulin so as not to expose the fetus to oral agents during the period of organogenesis. Asked about combination treatment, he recommended against this. He agreed that metformin may be more logical in view of the insulin resistance underlying the disease, but he stressed the need for clinical trials with this agent.

Thomas Buchanan (Los Angeles, CA) discussed prevention of diabetes after pregnancy. He noted that GDM, diagnosed with fasting, 1-, 2-, and 3-h postload glucose exceeding 105, 190, 165, and 145 mg/dl, respectively, affects 4.5% of the women in his clinic, an important group for prevention of diabetes, with 10% developing type 2 diabetes annually. He pointed out that there is a curvilinear relationship between insulin secretion and insulin resistance, and he speculated that failing β-cell secretion in the setting of insulin resistance underlies the development of diabetes. Women who have GDM have approximately one-third the insulin secretory capacity of those who do not develop diabetes during pregnancy, and after pregnancy they can be shown to have insulin resistance as well.

Buchanan hypothesized that women who have had GDM "have β-cells that fail in the setting of insulin resistance," and asked whether it is possible to delay or prevent the onset of diabetes by addressing this mechanism. In a 3-month study of women who had had GDM and were given 400 mg troglitazone (TGZ) daily, insulin resistance improved, and patients stayed "on the curve" of insulin sensitivity versus insulin secretion, leading to decreased insulin secretion, which he described as "afterload reduction for the β-cell."

The Troglitazone in the Prevention of Diabetes (TRIPOD) study of women characterized by Buchanan as having a 70% risk of diabetes over the subsequent 5 years followed 235 nonpregnant women who had had GDM, two-thirds with impaired glucose tolerance (IGT) at baseline, who were treated for a mean of 30 months with TGZ versus placebo. Weight gain was similar in the placebo and active treatment groups. The placebo group developed diabetes at rate of 12.3%/year, whereas TGZ decreased the risk of development of diabetes by 56%.

Insulin sensitivity did not change with placebo, and it increased 66% with TGZ, whereas the insulin area during an intravenous glucose tolerance test (IVGTT) decreased, without a change in the rate of fall in glucose during IVGTT. There was a similar degree of protection in individuals with lower and higher glucose during glucose tolerance testing, but women whose insulin sensitivity did not improve showed no decrease in the rate of development of diabetes, and those with greater improvement in insulin sensitivity during TGZ treatment (and hence a larger fall in insulin secretion) had lower rates of development of diabetes, suggesting that decreasing the insulin secretory "burden" associated with insulin resistance was related to the protection from subsequent development of diabetes.

Only 1 of 41 women treated with TGZ developed diabetes during 8 months of follow-up after the treatment was stopped, suggesting that "we stopped the underlying decompensation that leads to diabetes." Buchanan recommends thiazolidinedione treatment for all women who have had GDM, and the patients in both the TGZ and placebo groups have now all been placed on rosiglitazone.

After GDM, the high risk of diabetes, Buchanan concluded, is due to β-cell failure worsened by insulin resistance. These patients require regular follow-up. If the fasting glucose increases (even in the normal range), "they've lost a lot of β-cell function," and Buchanan noted that if the fasting glucose exceeds 120 mg/dl, there is increased risk of fetal malformation, so that prepregnancy treatment is required. The acute insulin response and the degree of insulin compensation for insulin resistance show a heritability of ~60%, whereas insulin resistance itself only has a heritability of 33%, further supporting this double-defect model of the causation of GDM. Although TGZs should not be used during pregnancy without additional information showing safety, insulin treatment and exercise should be effective and should promote β-cell rest. Although metformin is an attractive option, Buchanan pointed out that if it crosses the placenta, we need to know not only about perinatal outcome but also about long-term development of the offspring.

STUDIES OF GDM

Hattersley et al. (15-OR) studied the outcome of 60 live births in 30 women with GDM secondary to a heterozygous glucokinase mutation, of whom there were 31 offspring who had the mutation. Unaffected offspring had higher birth weight (4.1 vs. 3.3 kg), greater head circumference (35 vs. 33 cm), and higher placental weight (762 vs. 611 g), suggesting that reduced fetal insulin secretion results in reduction in growth.

Ferrara et al. (17-OR) reported changes in the prevalence of GDM among 271,023 pregnant women aged 15–49 years without overt diabetes in a managed care organization in northern California from 1991 to 1999. A 50-g 1-h oral glucose tolerance test (OGTT) that was followed, if abnormal, by a 100-g 3-h OGTT was performed in 64% of women in 1991, increasing to 96% in 1996, and staying around this level since then. Among the women who were screened, the prevalence of GDM increased from 3.4% in 1991–1995 to 6, 4.8, and 5.4% in 1997, 1998, and 1999, respectively, providing evidence of an increase in prevalence.

Alawi (1595-P) presented a nonran-

domized comparison of insulin lispro versus human regular insulin among 59 pregnant women with type 1 diabetes and 63 with GDM. HbA_{1c} was 0.7% lower with lispro in both groups, with 1-h postprandial glucose that was 48 mg/dl lower in the type 1 and 28 mg/dl lower in the GDM patients treated with lispro. Altogether, 10 and 9% of women treated with regular insulin were hypoglycemic during weeks 31–40, as opposed to 6 and 4% treated with lispro, and glucose levels <30 mg/dl were seen in 12 and 16% of infants whose mothers were treated with regular insulin, but 5 and 5% of those whose mothers received insulin lispro. Garg et al (1602-P) compared outcomes of pregnancy of 60 women treated with lispro and 33 with human regular insulin, showing lower HbA_{1c} throughout pregnancy, fewer severe hypoglycemic episodes, and reduced need for caesarian section, without evidence of adverse consequence for the fetus.

POLYCYSTIC OVARY SYNDROME

Roger Lobo (New York, NY) discussed the pathophysiology of the polycystic ovary syndrome (PCOS). He noted that the ovarian morphology of PCOS can be seen in many other conditions, including hypothalamic amenorrhea, and in up to 25% of the normal population. Thus, morphology should be dissociated from the "key features, which are clinical," including hyperandrogenism and oligo- or amenorrhea, so that he prefers to call the syndrome hyperandrogenic anovulation. At a 1990 consensus conference, it was agreed that if you can "exclude other causes and have hyperandrogenism and anovulation, that's enough for the diagnosis." In fact, Lobo pointed out that some women with normal ovulatory function and hyperandrogenism actually may have the syndrome as well. He noted that PCOS affects between 6 and 8% of the population, and it shows strong association with IGT, diabetes, hypertension, and cardiovascular disease (CVD). Elevated leutinizing hormone (LH) was thought to be a criterion in the past, but it is present in only two-thirds of the cases. Elevated estrone is frequent, and because of the low sex hormone binding globulin (SHBG) level, the free estradiol plus estrone puts most patients chronically at a follicular phase level and may be associated with endometrial hyperplasia and increased risk of endometrial and ovarian cancer.

There appears to be early evidence of abnormal ovarian morphology at and prior to menarche, suggesting underlying ovarian susceptibility. Hirsutism is not seen in all women with PCOS because of different levels of skin 5-α reductase, leading to differences in androgen effects.

Insulin resistance was initially observed in PCOS ~20 years ago, particularly with obesity, but also in lean individuals with the syndrome. Complete anovulation tends to be associated with lower insulin sensitivity. IGF-I binding protein is low, so that free IGF-I is elevated. Both IGF-I and insulin stimulate ovarian androgen production, suggesting this to be the primary cause of the syndrome. These observations have led to the concept that hyperinsulinemia underlies the hyperandrogenemia, abnormal ovarian morphology, and other features of the syndrome, with dyslipidemia caused partly by hyperandrogenemia as well, and all of the abnormalities are compounded by obesity. There is a 30-fold increase in sleep-disordered breathing in PCOS, particularly in women with hyperinsulinemia. Women with PCOS have increased risk of hypertension and diabetes, particularly seen after menopause, with a 7-fold increase in calculated risk of myocardial infarction.

Andrea Dunaif (Chicago, IL) further discussed the relationship of the syndrome to insulin resistance, which was first understood with appreciation of the relationship between syndromes of extreme insulin resistance and PCOS. Recent studies of animal models of insulin resistance have further shown its relationship to the reproductive abnormalities. The degree of insulin resistance is similar to that seen in type 2 diabetes, and evidence of abnormal β-cell function can be shown even without IGT. IGT and diabetes are seen in 31 and 7% of patients with PCOS, respectively, and these rates are approximately four times greater than in control populations. Epidemiological studies have shown that women whose menstrual cycle length exceeds 40 days have a twofold increase in risk of developing diabetes.

The mechanism of insulin resistance has been studied with muscle biopsy, showing decreased phosphatidylinositol (PI)-3 kinase phosphorylation in women with PCOS, without a decrease in the abundance of insulin receptor substrate-1 (IRS-1) or PI-3 kinase, whereas the abundance of IRS-2 is actually increased, a finding not present in type 2 diabetes. The mechanism of the signaling defect was studied in skin fibroblast cultures. Insulin-stimulated tyrosine phosphorylation decreases, whereas constitutive serine phosphorylation increases. Extracts from cells cultured from women with PCOS duplicate this pattern, which Dunaif suggested might be mediated by an extrinsic factor. The metabolic pathways of insulin response show decreased activity, whereas the mitogen-activated protein kinase (MAPK) pathway is intact, perhaps leading to increased ovarian androgen secretion. In cultured skeletal muscle from women with PCOS, the MAPK pathway actually shows increased activity, compatible with a stimulatory factor, which Dunaif suggested might be related to abnormal levels of or response to free fatty acids.

Dunaif suggested that insulin resistance alone is not sufficient to cause PCOS, pointing out the infrequency of the syndrome among the very insulin-resistant Pima Indian population, and noting that features of PCOS, including hyperandrogenism and oligomenorrhea, are commonly found in siblings of patients. Studies of family members suggest that abnormal genes in the region of the insulin receptor gene may be involved in the syndrome.

Maria Iuorno (Richmond, VA) discussed the role of insulin-sensitizing therapy in PCOS. There is evidence that hyperinsulinemia increases ovarian thecal cell androgen production and decreases levels of SHBG, which in turn increases free testosterone levels, causing disordered LH release and pulsatility, all contributing to the illness. PCOS shows features of the dysmetabolic syndrome, with increased risks of hypertension, dyslipidemia, diabetes, and atherosclerosis. The converse finding that type 2 diabetes is frequently associated with menstrual abnormality is now also being appreciated (24).

Lowering insulin levels with administration of diazoxide for a brief period reverses many of the abnormalities of PCOS, lowering free testosterone and raising SHBG levels (25). Subsequent trials with metformin decreased circulating insulin, LH, and free testosterone, with increased SHBG levels (26). In a further

study by this group, metformin increased ovulation to 36% from a placebo rate of 4% after 39 days, with the addition of clomiphene increasing ovulation to a greater extent in patients who had been given metformin than in those receiving placebo (27). Moghetti et al. (28) recently reported a 6-month placebo-controlled trial, followed by a 1-year open-label trial. Menstrual cyclicity improved, although without change in hirsutism. Insulin-stimulated glucose uptake increased, free testosterone decreased, and HDL cholesterol increased with treatment. Iuorno commented that her current approach is to use metformin doses of 2 g daily for optimal effect.

Five studies have been published with TGZ, the largest with 410 women treated with 0, 150, 300, and 600 mg daily, showing improvement in insulin sensitivity, lowering of testosterone, and, at the 600-mg dose, improvement in hirsutism (29). D-chiro-inositol is a member of a new class of insulin sensitizer, a stereoisomer of inositol phosphoglycans, which is cleaved from cell membrane sites, mediating insulin action when insulin binds to the insulin receptor. The conversion of myoinositol to D-chiro-inositol may be decreased in diabetes. Administration of the agent decreases total and free testosterone and increases ovulation in women with PCOS.

Iuorno concluded with a discussion of administration of metformin to women with PCOS during pregnancy. Early fetal loss occurs commonly in women with the syndrome, and the use of metformin appears to prevent these events, extending studies suggesting safety of metformin treatment during pregnancy to a new concept that this may actually improve outcome.

STUDIES OF BEHAVIOR AND EDUCATION

Schlaefer et al. (309-PP) studied 424 Medicaid beneficiaries with diabetes who filled at least 1 prescription for a glucose-lowering medicine in 1999. The number of refills was inversely associated with the number of hospitalizations and ER visits, suggesting a potential strategy for improving outcomes. Although on average there were 6 office visits per patient per year, 19% of the patients did not see a health care provider (other than the pharmacist) in 1999. Sabbah et al. (148-OR) noted that individuals with diabetes 18–64 years of age lose 8.3 days of work per year, compared with 1.7 days for those without diabetes. A total of 74 patients, half with diabetes, participated in a 6-month 5-site controlled trial of the impact of a cardiovascular risk reduction program directed by a clinical pharmacist. At 6 months follow-up, the intervention group had 35 mg/dl lower fasting plasma glucose, 1.2% lower HbA_{1c}, 9 mmHg lower systolic blood pressure, 6 mmHg lower diastolic blood pressure, and 4.8 mg/dl higher HDL levels. Lorenzi et al. (146-OR) described the MediCal Type 2 Diabetes Project treating 186 individuals with type 2 diabetes for ≥1 year and HbA_{1c} ≥7.5% with "individualized case management assistance" in addition to primary care. HbA_{1c} decreased from 9.5 to 8.3, 8.2, and 7.9% at 6, 12, and 24 months, respectively, but from 9.7 to 9.0, 8.9, and 8.7% among 172 control subjects, suggesting that this may be a useful approach for the Medicaid population.

Maryniuk et al. (300-PP) assessed the time spent by 33 nurses and dietitians employed as diabetes educators in 14 locations in the U.S., concluding that 4.1 h of patient care was scheduled and 3.5 h actually spent on patient care on a typical day, with an additional 5.2 h spent on non–patient care activities. Gary et al (1637-P) reported a meta-analysis of 62 randomized controlled trials of educational and behavioral interventions to improve diabetic control in 8,076 diabetic patients over a median of 4 months with 6 months follow-up, showing a fall in HbA_{1c} of 0.4%. They concluded, "Currently employed educational/behavioral interventions in patients with type 2 diabetes produce measurable, albeit modest, improvements in glycemic control."

Surwit et al. (340-PP) reported that a 2-SD increase in the hostility score on a standardized interview (the Cook-Medley hostility scale) of 273 women and 326 men at age 50 was associated with a 2.9-fold increase in risk of diabetes, as well as a 1.5-fold increase in risk of myocardial infarction, at follow-up at age 70.

Tatti and Lehmann (103-OR) compared 12 patients with type 1 diabetes educated using the Automated Insulin Dosage Advisor (AIDA; available online at http://www.2aida.org/aida/lehmann.htm), a program simulating effects of changes in insulin treatment, and 12 patients educated with conventional lessons initially and with AIDA after 10 weeks. HbA_{1c} decreased from 7.2 to 6.4% in those using the simulation program initially, but it decreased from 7.1 to 7.0 with conventional lessons, with a subsequent decrease to 6.8%. Hypoglycemia decreased by half in both groups after the use of AIDA.

Egede and Zheng (858-P) reported that 57 and 42% of Caucasian adults with diabetes reported having been administered influenza and pneumococcal vaccinations in the 1999 Behavioral Risk Factor Surveillance System random-digit-dialing telephone survey, whereas these vaccines were reported as being received by 44 and 22% of African-Americans with diabetes. Singh et al. (30-LB) studied 55 men with diabetes, showing that the 11 who drank some alcohol, but no more than one drink daily, showed greater verbal fluency and mental flexibility than the 44 who did not drink at all, suggesting benefit of moderate alcohol consumption. Finally, Miller et al. (299-PP) used the Vanderbilt Television News Archives to track nightly broadcasts from 1991 to 2000 on stations ABC, NBC, and CBS. There were 68, 1,295, and 2,151 broadcasts mentioning diabetes, cancer, and CVD, respectively, suggesting that diabetes news coverage is substantially less than that given to other chronic diseases.

SOCIOECONOMIC ASPECTS OF DIABETES

Nichols and Brown (3-OR) analyzed annual health care costs among 16,180 individuals with diabetes in a health maintenance organization. CVD was present in 29% of patients but in only 16% of age- and sex-matched control subjects, with an annual additional cost of $6,449 in those with and $4,697 in those without diabetes. At age <45, 45–54, 55–64, 65–74, 75–84, and >84 years, the annual cost for those with diabetes and CVD was $7,878, $10,142, $12,105, $10,951, $10,259, and $9,529, whereas for those with diabetes but no CVD, the annual cost was $3,558, $3,815, $4,289, $4,826, $5,250, and $4,684, respectively. Bagust et al. (6-OR) modeled the lifetime health cost of patients with versus without diabetes, estimating these costs at $209,000 vs. $116,000 for men and $274,000 vs. $161,000 for women, with the largest element (45%) of extra cost hospital being inpatient care.

Bagust et al. (838-P) used a computer model of type 2 diabetes progression and

U.S. Census Bureau projections to suggest that by 2050, although total population will grow 47%, there will be 112% more diagnosed diabetic people, with the number of individuals having blindness in either eye increasing from the current 217,000 to 336,000, end-stage renal disease increasing from 556,000 to 1,050,000, foot ulcers and amputation increasing from 656,000 to 945,000, stroke increasing from 346,000 to 509,000, and coronary disease increasing from 1,227,000 to 1,681,000. The total cost of health care for patients with diabetes will, they predicted, increase from $38 to $94 billion. They noted that the working-aged (20–60 years) population will only increase by 28% during this time, implying that consideration be given to the potential burden of diabetes care funding. Boyle et al. (839-P) used a similar approach and estimated a 165% increase in the number of individuals with diabetes by 2050, with a 173% increase in direct medical expenditures. Among men aged >75 years, they predict that the number of individuals with diabetes will increase more than fourfold.

George A Kaplan (Ann Arbor, MI) addressed the topic of "Upstream and Downstream Approaches to Inequalities in Health: the Case of Diabetes." The number of human genes mapped, he stated, has increased dramatically, leading politicians to tell us that "victory over disease and disability" is at hand. There is, however, tremendous inhomogeneity in life expectancy in different communities in the U.S., with up to 30-year differences between areas. It is unlikely that molecular biology will be helpful in addressing this. Obesity and diabetes are increasing progressively (30,31) in a fashion suggestive of an infectious disease. We need, Kaplan stated, to address social and economic policies, institutions, neighborhoods/communities, living conditions, social relationships, individual risk factors, genetic factors, and pathophysiology. He pointed out that socioeconomic inequality is widespread, affecting all age groups and affecting multiple organ systems and risk factors for disease, exemplified by the fatality rates for women passengers on the Titanic of 3, 16, and 45% in first, second, and third class. "These patterns are not," he stated, "fixed in time or place, indicating that there must be some things we can do."

The relationship between socioeconomic position and health outcomes has been widely studied over the past 2 decades. In 1992 Rogot studied >1 million people selected from U.S. Census data, showing that among white and African-American men and women, mortality decreases as annual household income increases from <$5,000 to >$50,000. In the Multiple Risk Factor Intervention Trial (MRFIT) (32), median family income showed a dramatic correlation with mortality, which increased from 51.4 to 91.8 deaths per 10,000 individuals, moving from the highest to lowest income group. Men in Canada similarly show gradation in survival corresponding to economic status. Data from the National Health and Nutrition Examination Survey (NHANES) shows consistently greater frequency of height below the 5th percentile in poorer children aged 2 through 17 years. Pregnancy outcome is again dramatically improved with higher socioeconomic status, even in countries such as Sweden, which has high availability of health care.

The MRFIT study shows lower social class to be associated with increased death rates for a variety of illnesses. Chronic conditions more common in individuals with lower socioeconomic status, using education as a marker, include arthritis, psoriasis, visual loss, hearing loss, asthma, and diabetes. Carotid intima-media thickness increases with lower education and with lower income. In the Kuopio Ischemic Heart Disease Risk Factor study, education shows a strong inverse relationship with cigarette use, alcoholism, and sedentary behavior. The same pattern is seen with psychosocial factors, such as the condition of "hopelessness." This marker of depression is about five times more frequent in the lower third than in the upper third income group. LDL cholesterol, systolic blood pressure, and fasting blood glucose show similar increases with decreasing income.

Studies of diabetes from Alameda County from 1965 to 1998 showed a 31% increase from the lowest to highest income quartile. Those who did not finish high school have more than twice the risk of those with college education, and those living in poverty areas have almost twice the risk. In NHANES III, diabetes was seen in 9.5 vs. 4.7% of those with 9–11 vs. 12 years of education. Both men and women show increased diabetes mortality in the lowest income quartile. In MRFIT, diabetes mortality differences between Caucasian and African-American men were 2.6-fold greater when adjusted for age, but when adjusting for income the increase is 1.4-fold, suggesting that at least 75% of the increase in risk is related to income differences. Income inequality similarly shows strong correlations with the rate of diabetes.

What "upstream processes" might, Kaplan asked, reduce diabetes risk? He suggested better health and education for children, building healthy neighborhoods, addressing cumulative effects of stress, and improving access to care. In *Paradise Lost* Milton pointed out that "the childhood shows the man, as the morning shows the day." Maternal education shows strong correlation with birth weight. There is a strong relationship between birth weight and risk for diabetes, measured decades later, with an almost 3-fold difference in diabetes prevalence between the highest and lowest birth weight quartile (33). Individuals whose fathers performed unskilled manual labor had 2.5-fold greater risk of diabetes than those in higher social classes. High school students currently attend physical education classes less frequently, and as the percentage of low income students increases, the proportion of schools without physical activity opportunities increases. An important factor is the "commercialization" of school food programs. Ventures such as Channel One TV, seen daily by 40% of American teenagers, with the percentage higher among poorer children, promote "junk food" and soda consumption, which leads the children to the vending machines now prominently located in most school cafeterias.

The neighborhoods in which people live are also very important. Mortality rates are 50% higher in poverty areas of Alameda County. Those who lived in these areas had a greater decrease in physical activity and a greater increase in depression over a 9-year period of follow-up. Middle-income areas have more restaurants, whereas low-income areas have more "fast-food" and liquor stores. We need to think on an even larger scale of the way our neighborhoods are structured. The "new urbanism" promotes small self-contained neighborhoods with walking and improved public transit, but this is currently being applied only to wealthier regions. If these approaches are

not applied equally, they will increase inequality of health.

One of six families in the U.S. are now "working poor." Job uncertainty, nonstandard work hours, stress, and lack of control over work threaten health. Compared with families in the top income quartile, those in the lowest quartile are twice as likely to lack sick leave or family leave for sick children, leading to increased levels of stress, which may act via glucocorticoids to the development of diabetes and its complications. Lack of access to health care for the poor is another association that explains adverse outcomes. Kaplan concluded that understanding the socioeconomic causes of diabetes and reducing these inequalities is possible, offering us the ability to treat "the causes of the causes."

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