The European Association for the Study of Diabetes Annual Meeting, 1998

Type 1 diabetes

ZACHARY T. BLOOMGARDEN, MD

This is the last of four reports on the 34th annual meeting of the European Association for the Study of Diabetes (EASD), which was held in Barcelona, 8–12 September 1998. It deals with topics related to type 1 diabetes, including its incidence, cause, and treatment. Retinopathy and diabetes and pregnancy are also covered, and some mention is made of insulin treatment of type 2 diabetes.

THE INCIDENCE AND POSSIBLE CAUSES OF TYPE 1 DIABETES — Vaananen et al. presented a meta-analysis of 33 studies reporting the yearly incidence of type 1 diabetes (abstract 73; abstract numbers refer to the Abstracts of the 34th Annual Meeting of the EASD, *Diabetologia* 41[Suppl. 1]:A1–A380). These studies were carried out between 1960 and 1996 in 24 countries over 8–32 years. The meta-analysis shows that there has been a 2.9% yearly increase in type 1 diabetes, and the model used by these researchers predicts an incidence of 50 per 100,000 per year in Finland by the year 2010 and over 30 per 100,000 per year in many other populations. The EURODIAB TIGER Study Group (abstract 74) reported findings based on ascertainment of 97.7% of new cases of type 1 diabetes in children aged <15 years in 43 centers representing most European countries. The standardized average annual incidence rate during the period ranged from 3.2/100,000 per year in Macedonia to 40.2/100,000 per year in Finland, with an annual rate of increase of 3.6%. A particularly rapid rate of increase in type 1 diabetes in children aged <5 years was noted. Zhao et al. (abstract 323) reported the incidence of type 1 diabetes in children aged 0–14 years in the Southwest of England to be 15.4 per 100,000 per year, with an annual increase from 1975 to 1996 of 2.7% (7.7% among children aged 0–4 years, and 2% among children aged 5–9 and 10–14 years). The situation may be different among young adults, as shown by Nystrom et al. (abstract 319), who reported that from 1983–1996, the incidence of diabetes among individuals 15–34 years old in Sweden decreased by 27%, with average yearly incidence of 20.6/100,000 and 13.2/100,000 for males and females and 74.3% of cases classified as type 1 diabetes.

Other population studies sought clues to the origin of type 1 diabetes. Muntoni et al. (abstract 353) found that diabetes incidence in 43 different countries among children <15 years old correlated positively with dietary meat and milk and negatively with dietary cereal intake. In 11 European countries where the incidence of childhood diabetes increased over the last 25 years, total calorie and meat intake again correlated positively and cereal intake negatively with diabetes, which potentially helps to explain the rising incidence. In related studies, Virtanen et al. (abstract 354) followed 725 siblings of children developing type 1 diabetes in 1986–1989, 33 of whom developed diabetes through 1995, and found that consumption of more than three glasses of milk daily was associated with a 3.1-fold increase in risk, and Goisino et al. (abstract 355) reported that feeding cow's milk to Wistar rats for the first 21 days of life increased the development of hyperglycemia following administration of low-dose streptozotocin. Addressing other mechanisms potentially causing diabetes, Joner et al. (abstract 75) studied the high childhood diabetes incidence rate in Norway, where there are higher rates in the most southern counties. They examined 1,064 new cases of type 1 diabetes in children <15 years old. When they used 1 month between birth dates as the cut-off for distance in time and same municipality of residence at onset as the definition of closeness in space, the observed number of close pairs was significantly higher than expected, suggesting an etiologic role of infectious agents.

Mathieu et al. (abstract 244) reported that 1,25-dihydroxyvitamin D_3 changed cytokine profiles in a diabetes-prone mouse model. In view of this and similar studies suggesting vitamin D to be protective, the EURODIAB ACE Substudy 2 Study Group (abstract 78) assessed whether vitamin D supplementation in the perinatal and early eating period decreased rates of childhood diabetes. Data from 820 cases and 2,335 control subjects showed that vitamin D supplementation was associated with a 33% reduction in risk for type 1 diabetes.

INSULIN TREATMENT — A number of studies presented at the meeting explored new insulin treatment protocols. Fanelli et al. (abstract 268) randomly assigned 18 C-peptide–negative patients with type 1 diabetes to two 4-month periods of treatment with either a mixture of human regular and NPH insulin before dinner or to regular insulin at dinner and NPH insulin at bedtime in an open-label, crossover study. The number of incidences of nocturnal hypoglycemia was 14 vs. 3 per patient per month, fasting glucose was 8.9 vs. 7.7 mmol/l with coefficients of variation of 39 vs. 27%, and HbA_{1c} was 7.61 vs. 7.05%, suggesting the superiority of the latter approach. Pieber et al. (abstract 187) reported the effect of treatment of 333 patients with type 1 diabetes with the long-

Zachary Bloomgarden is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.

Z.B. is or has been an investigator in studies of HOE 901 insulin, nateglinide, glimepiride, sildenafil, and troglitazone.

Abbreviations: ACEI, ACE inhibitor; DCCT, Diabetes Control and Complications Trial; EASD, European Association for the Study of Diabetes; ESRD, end-stage renal disease; IGFBP, IGF binding proteins; SIK, simultaneous islet and kidney transplant; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

lasting insulin HOE 901 at bedtime or NPH insulin at bedtime or at breakfast and bedtime, as well as preprandial regular insulin. With HOE 901, fasting glucose was 10.1 vs. 12.0 mmol/l in clinic and 7.1 vs. 7.9 mmol/l on home self-monitoring, with fewer nocturnal hypoglycemic episodes than seen with bedtime-only NPH and with a 0.14% lower HbA_{1c} at 4 weeks. Matthews et al. (abstract 948) administered HOE 901 to 136 patients with type 2 diabetes whose HbA_{1c} was >7% on treatment with sulfonylureas, either alone or with acarbose or metformin. NPH insulin was given to 68 patients. HbA_{1c} fell similarly by 0.8%, but 7.3 vs. 19.1% of patients developed overnight symptomatic hypoglycemic episodes on HOE 901 versus NPH. Sinha et al. (abstract 188) reported on another long-acting insulin analog, NN304, which is formed by attachment of a free fatty acid to the insulin molecule. They observed a less pronounced peak effect than for NPH insulin and action through a 6-h, although not through a 12-h, period. Lindholm et al. (abstract 185) showed improved postprandial glycemia with insulin aspart, a rapid-acting insulin analog, versus regular insulin.

Inhaled insulin

Skyler et al. (abstract 169) compared 35 patients with type 1 diabetes treated with subcutaneous insulin with 35 treated with bedtime ultralente plus a dry powder insulin formulation delivered before meals by aerosol inhalation for 3 months. HbA_{1c}, body weight, and hypoglycemia were similar, but a patient satisfaction questionnaire showed that patients significantly favored the inhaled insulin treatment. There was no adverse effect on pulmonary function. Cefalu et al. (abstract 872) reported results of a similar treatment trial of insulin-treated patients with type 2 diabetes and observed similar glycemic outcome, although the patients treated with inhaled insulin showed 0.4 kg weight loss in comparison to a 1.1 kg gain with conventional insulin treatment. Patient satisfaction was again greater with inhaled insulin, and pulmonary function was again unchanged. Berger et al. (abstract 873) studied 60 patients with type 2 diabetes and HbA_{1c} >8% despite doses of sulfonylurea equivalent to ≥5mg glyburide daily or of >1,500 mg metformin daily. These patients were randomly assigned to continued oral agent treatment or to the addition of inhaled insulin. The latter group had a fall in HbA_{1c} from 10.2 to 8.3%, while those on oral agents alone had a fall from 10.1 to 9.6%. Severe hypoglycemia was not seen.

Lispro

Robinson-Pleadwell et al. (abstract 53) showed less glycemic excursion after exercise with lispro than with regular insulin in a randomized open-label crossover trial of 20 patients with type 1 diabetes. Rabasa-Lhoret et al. (abstract 54), in a similar study, showed that a 75%, but not a 50%, decrease in premeal lispro dosage reduced the risk of exercise-induced hypoglycemia while maintaining postprandial glycemic control. Lalli et al. (abstract 181) reported that 28 patients with type 1 diabetes receiving bedtime NPH insulin who were randomly assigned to receive preprandial lispro, compared with 28 treated with regular insulin, showed 3.9 vs. 6.7 hypoglycemic episodes per patient per month, although they required addition of NPH insulin at each meal to attain HbA_{1c} levels of 6.36 vs. 6.72%. Hypoglycemic awareness and counterregulation were better in the lispro-treated group. Schernthaner et al. (abstract 182) showed similar glycemic control and hypoglycemia frequency with lispro administered immediately before or shortly after meals in 30 patients with type 1 diabetes. Trautmann et al. (abstract 183) compared three treatments in 423 patients with sulfonylurea failure: sulfonylurea plus preprandial lispro; sulfonylurea plus bedtime NPH insulin; and preprandial lispro plus bedtime NPH insulin without sulfonylurea. These researchers observed a fall in HbA_{1c} from 9.8 to 8.4–8.7% and similar hypoglycemia frequencies on the three regimens, although with lower fasting and higher postprandial glucose levels in the group treated with sulfonylurea plus bedtime NPH insulin and complete avoidance of nocturnal hypoglycemia with sulfonylurea plus preprandial lispro. Ilic et al. (abstract 184) showed that 35 women with gestational diabetes attained somewhat better glycemic control with fewer hypoglycemic events with preprandial lispro than with preprandial regular insulin treatment.

Heinemann et al. (abstract 935) reported the effects of 1:1 and 1:3 lispro:NPL (a protamine-retarded lispro formulation) in six patients with type 1 diabetes. Maximal metabolic activity was seen at 113 and 123 min, with action for up to 15 h. Holleman et al. (abstract 937) compared 1:1 mixtures of lispro:NPL and regular insulin:NPH in nine patients with type 1 diabetes. Maximal insulin concentrations were seen at 52 and 137 min with the two preparations, although with glucose nadirs at similar times of 210 and 203 min. Gentile et al. (abstract 941) randomly assigned 47 patients with type 2 diabetes and stable cirrhosis to receive lispro or regular insulin before meals. Glycemic control was similar, but lispro was associated with two versus seven hypoglycemic episodes per 2-month treatment period. Hoekstra et al. (abstract 965) studied lispro versus regular insulin with an insulin-dosing nomogram by which the number of units of insulin used was (glucose in mmol/l −6) · BMI · 0.04 for incidental glucose levels ≥14 mmol/l at 9:00 P.M. in hospitalized patients with type 2 diabetes. In the study, 64 insulin dosages were administered to 37 patients, with glucose testing at 0, 120, 180, and 240 min. With lispro, 16 of 29 dosages resulted in adequate glycemia after 120 min, a significantly better response than to regular insulin, for which 7 of 35 dosages resulted in adequate glycemia after 120 min. Similar 19 and 23 dosages achieved adequate glycemic levels at 240 min, and three and two episodes of hypoglycemia were seen with the two agents. Fever decreased the fall in blood glucose, while physical activity led to a greater fall. Taboga et al. (abstract 936) reported that glycemia was greater and total plasma radical-trapping parameter levels were lower after regular insulin versus lispro following a standard meal in 17 insulin-requiring patients with type 2 diabetes. These data suggest that during meals, free radical production is linked to the level of postprandial hyperglycemia.

Pramlintide

Ratner et al. (abstract 233) randomly assigned 539 obese patients with type 2 diabetes to receive placebo or the amylin analog pramlintide at doses of 30, 75, or 150 μg three times daily for 52 weeks. The resulting falls in HbA_{1c}, from levels of 9.0–9.3%, were 0.2, 0.3, 0.5, and 0.6%, the latter two being significantly greater than the placebo effect. Fineman et al. (abstract 653) reported that 12 patients with type 2 diabetes treated with insulin and 12 treated with oral agents alone showed greater suppression of glucagon after a 4-h placebo infusion and a standardized meal than after pramlintide and a standardized meal. Denaro et al. (abstract 718) showed that in a rat model, pramlintide delayed gastric emptying, decreased gastric acid secretion, and decreased

exocrine pancreas lipase and amylase secretion, which with decreased postprandial glucagon secretion, contributed to the glycemic benefit.

PANCREAS TRANSPLANTATION — Reinhard Bretzel, Giessen, Germany, analyzed current approaches to pancreatic islet transplantation. He pointed out that although our current strategy is to replace islets at the very late stage of renal failure with either simultaneous pancreas-kidney or pancreas after kidney transplantation, "the (goal) perspective of islet transplantation is to treat very early." Possible occasions for islet transplantation would include the onset of microalbuminuria, or of difficulty achieving adequate glycemic control without severe hypoglycemia, or of excessive weight gain in trying to become euglycemic. More radically, one could imagine eventual islet transplantation in the >90% of patients with type 1 diabetes who cannot achieve true euglycemia with intensive treatment. Bretzel emphasized that the aims of islet transplantation are metabolic improvement, outcome improvement, and quality of life improvement. Through the end of 1997, 325 islet transplants had been performed, mainly after 1990 when improved methods of islet isolation were developed that allow one pancreas to produce sufficient islets for many transplants. The main centers (and the number of islet transplants that have been performed there) are Giesen (56), Minneapolis (31), Pittsburgh (25), Milan (20), Miami (17), and St. Louis (14). Since 1990, however, only 32 of 235 transplant patients have achieved insulin independence, 17 of 209 within 1 year of transplantation. The remainder requiring more than 1 year for the very slow development of exogenous insulin independence. Islet autografts have also been performed, in 35 patients requiring pancreatectomy for nonmalignant conditions, with 63% of these patients being insulin independent at 1 year. An additional 40% of 15 patients receiving islet allograft transplants after pancreatectomy for malignancy are insulin independent at 1 year. This suggests, Bretzel pointed out, that there may be accelerated or additional immune rejection in patients with underlying type 1 diabetes because of recurrence of their autoimmune islitis, a problem for which new treatments to induce tolerance are just beginning to be developed. The goal is to avoid lifelong immunosuppression, a necessity if islet transplantation alone is ultimately to be considered. Additionally, existing immunosuppressive agents may have adverse effects on the islets. A number of clinical points are related to success in islet transplantation. Appropriate donor selection is important, with the use of very lean donors not leading to good results, and organ procurement requires cold ischemia of <8 h. Considering the autoimmune islitis problem, patients with high titer anti-islet antibodies might be expected to do poorly. Indeed, graft survival was worse among 12 islet cell antibody–positive then among 11 islet cell antibody–negative patients. Interestingly, this phenomenon may be less important with whole-pancreas transplantation. At Giessen thus far, 20 of the 56 transplants have been of islets after a kidney transplant, 30 have been simultaneous islet and kidney transplants (SIKs), and 5 have been islet transplants alone; 1 islet transplant was performed in a patient with type 1 diabetes who had previously required a liver transplant. Giessen has also begun collaborations to isolate islets to be transplanted at other institutions. Inclusion criteria currently recommended for islet after kidney (or other organ) transplant are that the patient be aged 18–50 years, without residual C-peptide for >10 years, without portal hypertension or hepatitis, and with creatinine clearance >60 ml/min unless a SIK is planned. A wait of ≥6 months is required to overcome the majority of rejection problems. Psychological assessment of patients is also required. Islets are infused intraportally using a catheter placed after computed tomography–guided percutanous transhepatic catheterization in the left lobe. Strict euglycemia with glucose levels <120 mg/dl is maintained during the transplant, with a post-transplantation protocol of continuous insulin infusion to maintain glucose levels at ≤140 mg/dl. Patients are kept in the hospital for at least 25 days after the transplantation for immunosuppression.

Of the 20 patients who received islet after kidney transplants, 8 have C-peptide function at 1 year, and the time to insulin independence is 280–400 days in successful cases. A C-peptide level >1.0 ng/ml is a good predictor of success, but the time needed to determine whether a given patient will become insulin independent is not yet known. Of SIK patients, 15 of 20 have some islet function, with 4 followed for at least 1 year being insulin independent; 15 of 17 have survived for 1 year, and 14 of these have ongoing renal survival. There is some evidence that patients with partial islet function have some benefit as well. The insulin requirement decreased by 16–40 U/day and HbA_{1c} is 1% lower in patients with islet function, who show average C-peptide levels of 1.6 ng/ml. No patient has had severe hypoglycemia after islet transplantation, a marked contrast to pretransplantation status and "a real advantage." Bretzel pointed out that some studies show very high mortality in patients with hypoglycemia unawareness, and his group has begun a study of five such patients who received islets alone, with immunosuppression for only 30 days. During this period, hypoglycemic symptoms have improved and the patients' catecholamine response to hypoglycemia, but, interestingly, not their glucagon response, has returned. Bretzel noted that there is some evidence that C-peptide may have a physiological role in upregulating Na-K ATPase and may play a role in hypoglycemia awareness, autonomic neuropathy, and albuminuria, further suggesting the potential clinical benefit of functioning islets. Saudek et al. (abstract 17) reported the results of 106 combined pancreas and kidney transplants performed since 1983 in uremic patients with type 2 diabetes at the Institute for Clinical and Experimental Medicine, Prague. Current 1-year patient and pancreas graft survival rates are 90 and 76%. Of 30 patients followed for at least 1 year with full function of both grafts, 18% had improved grade of diabetic retinopathy, in comparison to none of the 10 recipients with pancreatic graft failure and none of the 18 type 1 diabetic recipients of kidney transplant alone. Clinical neurologic assessment improved in 96% of patients with pancreas and kidney function, but in 65% of the other groups. Smets et al. (abstract 18) reported that mortality was 50% lower after simultaneous pancreas-kidney transplantation in 85 patients compared with 330 patients after transplantation of a kidney alone, with the groups similar at baseline because of governmentally regulated regional allocation, suggesting the former to be the preferred approach for patients with end-stage renal disease (ESRD).

In related studies, Kunt et al. (abstract 687), noting that C-peptide increases glucose uptake in muscle cells, with improvement of renal and nerve function and increased capillary blood flow, showed that C-peptide increases endothelial nitric oxide

synthase in aortic endothelial cells in association with increased calcium influx, perhaps explaining its vasodilating effect. Sima et al. (abstract 688) showed that C-peptide enhances the insulin-stimulated tyrosine kinase activity of partially purified human insulin receptors and that rat fibroblasts expressing the human insulin receptor incubated with C-peptide for a period of 30 min prior to insulin stimulation showed a marked increase in tyrosine phosphorylation of the β-subunit of the insulin receptor. This may explain studies that demonstrate that short-term infusion of C-peptide improves glucose utilization and reduces glomerular hyperfilteration in type 1 diabetes.

INSULIN PUMP THERAPY

— Jean-Louis Selam, Paris, France, discussed insulin pump treatment with both external and implantable pumps. Portable pumps are used today by at least 4,000 patients in Germany, 3,000 in France, 1,200 in Sweden, and 900 in Holland. He addressed the question of whether pumps are definitely beneficial in comparison to multiple daily insulin injections, in terms of hypoglycemia prevention, glycemic control, and quality of life. Pumps, he said, have "suffered the lack of good data with randomized studies." In the Diabetes Control and Complications Trial (DCCT), 40% of intensively treated patients used pumps and 60% used multiple injections, with 0.5% lower HbA_{1c} but more hypoglycemia in this nonrandomized and highly motivated group. Average HbA_{1c} levels at Selam's center are 8.7% among patients using pumps, with reported levels of 7.1% in a survey of device manufacturers and even lower in statements made by some enthusiasts. A realistic appraisal, Selam stated, is that the A_{1c} difference with pump therapy is "not large enough to influence the degree of microangiopathy." In terms of quality of life, 40–50% of patients discontinue use of pumps within 2 years, suggesting that "it all depends upon the selection in the beginning" but that a majority probably does not feel a major improvement with pumps. There is no consensus, then, as to indications for pump therapy, such as brittle diabetes and overly frequent hypoglycemia. For that matter, what constitutes brittle diabetes and overly frequent hypoglycemia are subject to debate. Selam feels that the reported frequency of subcutaneous insulin resistance varied so greatly from center to center that it is more a subjective than a real phenomenon, often related to patient manipulation of their insulin treatment for secondary gain, in which case insulin pump treatment will be completely unsatisfactory. Some centers do and some do not use pumps for children or adolescents. Overall, recommendations have been for use in as few as none to as many as 10% of type 1 diabetic patients.

Cost is an important issue, and studies suggest that the pumps require monthly expenditure of around $65 for physician follow-up visits (not including 24-h emergency diabetologist availability, which some, although not all, centers feel is necessary), of around $35 for administrative costs, of around $55 initially and $8 subsequently for nursing treatment, and of around $250 for disposables and for amortization of the pump cost. Home glucose monitoring should be performed at least four times per day, potentially adding cost. The multiple-rate pumps are two to three times more expensive, but a higher early morning basal rate may lead to less late-morning hyperglycemia, although this probably applies only to the one-third of patients who show a marked "dawn phenomenon." Particularly in children, this dawn phenomenon varies from day to day, so variable rates can increase the risk of hypoglycemia. Another use of multiple basal rates is in the avoidance of 10:00 P.M. to 2:00 A.M. hypoglycemia. A number of factors change glucose levels in the morning. Levels rise and fall with increased size of the nighttime meal and nighttime alcohol ingestion, and it is convenient for patients to program multiple basal rates for use with various evening patterns.

The risk of ketoacidosis with pump use is currently 3–6% per patient per year, considerably lower than in early experience when catheter obstruction with unbuffered insulin preparations was more frequent. Indeed, although he treats some 100 patients, Selam stated that he has not had cases of this for several years because of better patient selection and education. Currently used pumps give a battery alarm at 5–72 h, to minimize this danger. Both high and low ambient temperatures can increase insulin precipitation, and pumps should generally be used at a temperature of ~20°C. An advance has been the realization that even buffered regular insulin preparations show less stability and more precipitation over several days than lispro, which Selam considers the insulin of choice, although "the results are positive but not ecstatic." Somewhat less hypoglycemia and better HbA_{1c} have been reported with lispro. Because of the short duration of action of lispro, higher basal and lower bolus doses may be required, and rather than 30 min preprandially, boluses should be given immediately preprandially as with subcutaneous lispro.

Selam concluded that the pump should be regarded as just part of an overall program of management of type 1 diabetes. "The danger," he explained, "is when the patient thinks that the pump is everything and forgets diet, home glucose monitoring, and returning to the doctor!" He suggested that pumps were indicated for patients with HbA_{1c} >8% who have made earnest prior efforts at diabetes self-management, as well as for those whose HbA_{1c} was <8% but who had frequent hypoglycemia. Ideal patients are young, intelligent, educated, physically active, and somewhat obsessive. He also discussed implantable pumps, which have been used in treating 933 patients in 56 centers, initially in 1983–1984 with another peak of interest in 1990–1993, after which problems with insulin preparation stability leading to catheter obstruction decreased use. With current, more stable preparations, the major impediment to the use of implantable pumps is now cost, which is more than three times that of external pumps. Battery life should be 3–4 years, although the need to refill pumps monthly rather than every several months because of precipitation of insulin in the catheter has led to a battery life of only 2–3 years. Pump implantation is a surgical procedure requiring general anesthesia, and catheter repair and local inflammatory complications require laparascopic surgery in around 20% and around 6% of patients annually. Despite these concerns and the visible abdominal bulge, however, the more physiological intraportal delivery approach may decrease hypoglycemia, so the implantable pump approach remains of interest.

RETINOPATHY

— Ronald Klein, Madison, WI, spoke on the prevention and treatment of retinopathy. "The gatekeeper is hyperglycemia," he explained, with glycation, protein kinase C activation, production of vasoproliferative substances, free radical damage, and increased aldose reductase activity all contributing to subsequent development of retinal damage. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), proliferative retinopathy affected 11% of type 1 and 2% of type 2 diabetic patients over 4 years,

with higher levels in those with longer diabetes duration. Modifiable risk factors are the degree of hyperglycemia, blood pressure, and lipid levels. There is a stepwise increase in the risk of progression with increasing HbA_{1c} levels, particularly for proliferative retinopathy (1). Similar data on the relationship of glycemia to retinopathy have been shown in the DCCT (2) and other studies (3) of type 1 diabetes and in the Kumamoto study of type 2 diabetes (4). Klein pointed out that only 40% of type 2 and 20% of type 1 patients achieve HbA_{1c} levels ≤7%. Higher baseline diastolic blood pressure was also a significant predictor of total and of proliferative retinopathy among type 1 diabetic patients in WESDR. Addressing the question of whether treatment with ACE inhibitors (ACEIs) is beneficial, Klein referred to the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus substudy of 354 patients with retinal examinations before and after treatment with lisinopril or a control: The rate of progression of retinopathy decreasing by half with treatment (5). He emphasized the need for additional studies, to include patients with type 2 diabetes. In terms of lipid effects, WESDR showed a 50% increase in hard exudate for every 50 mg/dl increase in total cholesterol levels (6). Similar data from the Early Treatment Diabetic Retinopathy Study showed around 50% increased risk of visual loss with total cholesterol levels >240 vs. ≤240 (7). A study is underway with atorvastatin to address this. No relationship was found in WESDR of retinopathy with cigarette or alcohol use, with physical activity, or with the degree of obesity. Klein stressed the need to educate patients about the importance of glycemic control and of having dilated eye examinations, and to overcome economic barriers to these. He also spoke of new developments in retinopathy research, including the use of protein kinase C inhibitors and vitamin E and other antioxidants and treatment to prevent vascular proliferation.

A number of studies suggest that IGF-1 antagonists may be useful in the treatment of proliferative retinopathy. Burgos et al. (abstract 61) measured vitreal levels of IGF-1 and IGF binding protein (IGFBP)-1 and IGFBP-3 in diabetic patients with retinal neovascularization and in nondiabetic patients at the time of vitrectomy. When adjusted for total vitreal protein to assess the contribution of serum diffusion, IGF-1, but not the binding proteins, showed significantly increased levels that suggest synthesis. Spranger et al. (abstract 62) performed a similar study and found a less marked increase in IGF-1, which could be entirely explained on the basis of diffusion across the blood-retina barrier, and also showed that the increase in binding protein level was proportional to total vitreal protein level. However, Giannini et al. (abstract 63) presented tissue culture studies of human retinal endothelial cells suggesting that the cells are capable of producing IGFBP-2, -3, -4, and -5 and that in vitro, growth can be stimulated by IGF-1, fibroblast growth factor, and platelet-derived growth factor but not by insulin or growth hormone. IGF-1 increased levels of IGFBP-5, which in turn potentiates IGF-1 action, while IGF-1 decreased levels of IGFBP-4, which inhibits IGF-1 action. IGFBP-4 and −5 mRNA levels were not changed, suggesting that there are other forms of regulation. Aziz et al. (abstract 64) found increased levels of transforming growth factor-β receptor in the plasma of 11 diabetic patients with background retinopathy but normal levels in plasma and vitreous of 11 patients with proliferative retinopathy who were undergoing vitrectomy. Plasma vascular endothelial growth factor levels were normal in both groups, but vitreous vascular endothelial growth factor was increased in patients with proliferative retinopathy, suggesting that this plays a role later in the syndrome.

PREGNANCY — Jack Kitzmiller, U.S., discussed pregnancy in the type 1 diabetic woman with late complications from the perspective of a perinatology specialist obstetrician. Such pregnancies should be considered "an episode, hopefully a happy episode, in a lifelong disorder," so that not only pregnancy outcome but also long-term patient outcome after pregnancy must be considered. He pointed out that even "stage 1" nephropathy with hyperfiltration may predispose to preeclampsia, seen in 9% of diabetic versus ~6% of nondiabetic pregnancies. Preeclampsia is associated with increasing blood pressure and is diagnosed when urine protein levels (albumin comprises only around one-quarter of this during pregnancy) exceed 300 mg/(24 h). Normal urine albumin excretion during pregnancy is 9–13 mg/(24 h), and levels exceeding 30 mg/(24 h) are associated with 11–30 and 22% risks of preeclampsia and preterm delivery. In 12 studies of 146 women with >1 g/(24 h) proteinuria, creatinine clearance <80 ml/min or serum creatinine >1.2 mg/dl was seen in 32% during the first trimester, hypertension was seen in 42%, 46% had hematocrit <28%, and 56% had proliferative retinopathy. By the end of pregnancy, 36% had >5 g/(24 h) proteinuria, with many patients developing severe edema, one of the few indications for diuretic treatment during pregnancy. Proteinuria tended to decrease postpartum but remained >5 g/(24 h) in 23%. The glomerular filtration rate worsened during pregnancy in 26%, and hypertension worsened to >140/90 mmHg in 72%. ESRD developed in 31% of these patients within 3 years postpartum, and in 49% of the subgroup with mild renal insufficiency prepartum. Although this may be similar to the natural history of the disease without pregnancy, Kitzmiller stated that a creatinine clearance <40 ml/min should be regarded as a contraindication to pregnancy, and that women with this degree of renal insufficiency wanting to become pregnant first require transplantation. Both the patient and husband need to be counseled about this, as well as about the 3-year mortality of ~7.5%, which again is similar to that in patients with this severity of illness who do not become pregnant. In a study presented at the meeting, Rossing et al. (abstract 22) evaluated the long-term impact of pregnancy on renal function and survival in all 94 women with type 1 diabetes developing diabetic nephropathy between 1970 and 1989 at the Steno Diabetes Center, who were followed until death or 1996. Of these women, 25 became pregnant on average 5 years after the onset of nephropathy and had no difference in loss of kidney function as determined by linear regression on reciprocal serum creatinine values, time of doubling of serum creatinine (seen in 28% of those who did and those who did not have a pregnancy), or development of ESRD, suggesting that with current treatment approaches pregnancy has no adverse long-term impact on renal function. After an average follow-up period of 14 years, mortality was 28 and 26% for the two groups. Thus, Kitzmiller stated that although the prognosis is not good "in the aggregate," there is no adverse effect of pregnancy per se on nephropathy.

The perinatal outcome of women with nephropathy has improved somewhat. However, comparing two series from 1981–1988 and 1990–1996 of 90 and 175 infants, fetal survival was 94.4 and 96.6%, 13 and 15% were small for gestational

dates, 58 and 65% required preterm (<37 week) delivery, the major cause of which was preeclampsia/hypertension, 69 and 74% required Cesarean section, one-quarter of both groups had respiratory distress syndrome, and 7.8 and 7.7% of both groups had major congenital malformations. "At the same time," Kitzmiller stated, "there have been multiple reports that if you do good glycemic control before and during very early pregnancy, anomalies are seen in ≤2%. We have a lot of work to do in that area." He gave two major goals: *1*) to attain completely normal glucose levels, both before and following meals, since "all studies that show improved postnatal outcomes use postprandial values," and *2*) to control blood pressure, recommending a goal of 130/85 mmHg, although many obstetric studies of preeclampsia alone begin treatment at 150/100 mmHg, since this protects the health of the mother as well as that of the fetus. There are a limited number of drugs suitable for blood pressure treatment during pregnancy, however. Methyldopa is the agent with which obstetricians have had the most experience. Diltiazem may decrease albuminuria, in comparison to the dihydropyridine calcium channel blockers, although there are no controlled studies. Several studies do suggest fetal limb defects with use of diltiazem in early pregnancy, so Kitzmiller does not recommend this during the first 12 weeks of pregnancy. β-Blockers have a role, although caution is needed in terms of hypoglycemia, and there are some studies suggesting more fetal growth restriction with these agents. Finally, prazocin and either oral or transcutaneous clonidine have been shown to be safe. ACEIs must be avoided. "Unfortunately, during pregnancy," Kitzmiller explained, "it can kill the fetal kidney." Indeed, he recommended that every woman treated with an ACEI should be asked whether she takes a contraceptive. He referred to a study of eight women withdrawn from ACEI treatment just prior to pregnancy. Creatinine clearance did not worsen and preeclampsia developing in three, not an unexpected frequency. Thus, along with intensive control, withdrawal from ACEIs is an important aspect of preconception management. He recommended a 60–80 g protein diet, pointed out that calcium treatment is not required and that aspirin is ineffective in decreasing preeclampsia, advised adequate iron with administration of erythropoietin for hematocrit levels <26%, and stated that an important aspect to treatment may be bed rest. He feels that having the woman lie (on her side) during most of the day contributes to improved outcomes. In terms of the important issue of distinguishing preeclampsia from worsening nephropathy, clinical features include thrombocytopenia (although this may be seen during pregnancy alone), abnormal liver chemistries, features of disseminated intravascular coagulation, and the development of seizures, which are used to define eclampsia (unless the patient has an independent seizure disorder). Intravenous magnesium sulfate treatment is effective for preeclampsia, with Caesarian section sometimes required.

Turning to retinopathy, Kitzmiller stressed that all women must have ophthalmologic evaluation at first evaluation and during pregnancy, even when the initial examination is negative. An analysis of reports of 228 pregnant women with type 1 diabetes showed that 27% had no retinopathy, 38% had minimal or mild background retinopathy, 22% had moderate to severe background retinopathy, and 13% had proliferative retinopathy. Retinopathy develops in 26% of those with negative initial evaluation and worsens in 55–70% of those with mild background changes, 5% of whom develop proliferative retinopathy. With moderate to severe retinopathy, 19–47% develop proliferative retinopathy. "Retinopathy is a big risk," Kitzmiller explained, "and there's going to be a lot of laser done." There is not, however, increased risk of blindness in 5–10 years of follow-up postpartum. In the DCCT, the rate of retinopathy progression from 1 year postpartum was similar to that in control populations. There is also evidence that good prepartum glycemic control is associated with less deterioration of retinopathy during pregnancy. Risk factors include rapid improvement in glycemic control and high HbA_{1c} at baseline, as well as hypertension. In a brief discussion of cardiac disease, a relevant study examined women of childbearing age preparing for renal transplant. Nonsmokers with normal baseline electrocardiogram and diabetes duration of <25 years all had negative coronary angiography. However, if the patient has any evidence of cardiovascular disease, Kitzmiller recommended that CABG be performed prior to conception. Untreated cardiovascular disease, along with renal failure, should be regarded as contraindications to initiating or continuing pregnancy for women with type 1 diabetes.

Vitamin E supplementation may be important. An interesting study during pregnancy in rats with diabetes by Bonet et al. (abstract 224) showed frequencies of malformations of 44, 12, and 7% among animals with diabetes with and without vitamin E supplementation and among animals without diabetes. Hepatic oxidant markers increased. Cederberg and Eriksson (abstract 225) found similar benefit of vitamin E without additional effect of adding vitamin C.

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