Neuropathy, Retinopathy, and Glucose-Lowering Treatments

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This is the seventh of a series of articles based on presentations at the American Diabetes Association (ADA) Scientific Sessions held 5–9 June 2009 in New Orleans, Louisiana. This installment pertains to neuropathy, retinopathy, and a number of innovative potential glucose-lowering therapies.

Neuropathy

Many studies presented at the American Diabetes Association (ADA) Scientific Sessions addressed aspects of neurologic disorders in diabetes. Braza et al. (abstract 569) found that 19% of 76 type 2 diabetic persons receiving metformin for >1 year had vitamin B12 levels <250 ng/ml, and 23% had levels 250–400 ng/ml. (Abstract numbers refer to the Abstracts of the 69th Scientific Sessions of the American Diabetes Association, *Diabetes*, Vol. 58, Supplement 1, 2009.) Peripheral neuropathy was present in 77 and 23% of these groups, respectively, and was found in 7% of those with normal B12 levels. Deficiency correlated neither with duration of metformin use nor with erythrocyte macrocytosis.

Abrão et al. (abstract 121) found that diabetic persons with periodontal disease or edentulism were 8.1-fold more likely to have loss of sensation to the Semmes-Weinstein 10-g monofilament. Ismail and Venkatesan (abstract 28-LB) found that diabetic versus nondiabetic persons had 94% versus 18% prevalence of sensorineural hearing loss, with mild-to-moderate hearing loss in 40% of diabetic persons with A1C <7% but in 56% of those with higher A1C levels, although noting that their findings might be explained by age differences. Bainbridge and Cowie (abstract 957) found that, among 472 diabetic participants in the National Health and Nutrition Examination Survey (NHANES), hearing impairment occurred 5.6, 5.8, and 2.7 times more often in persons with peripheral neuropathy, with coronary disease, and with A1C ≥7% than in those not having these characteristics.

Ryan et al. (abstract 101-LB) reported neuropsychological test results in 393 nondiabetic and 142 diabetic persons from 11 general medical practices, finding that 36.4% versus 45.1% had mild cognitive impairment and 3.6% versus 4.2% had dementia. Hypertension, coronary artery disease, and hypercholesterolemia were not related to risk of cognitive dysfunction. Silverstein et al. (abstract 130) administered the noncompetitive *N*-methyl-D-asparate receptor antagonist used for treatment of Alzheimer's disease immediately after subjecting rats to glucose 10–15 mg/dl for 90 min; compared with untreated rats, hypoglycemia-induced cortical neuronal damage decreased 35%.

Maués et al. (abstract 1,302) found that among 11, 28, and 29 nonobese men with no, mild, and moderate/severe obstructive sleep apnea on polysomnography, respectively, the latter group had a 68% increase in fasting plasma insulin and a 94% increase in HOMA-IR over the former, with impaired glucose tolerance in 21%. Simmons and Shaw (abstract 997) reported that, among 1,454 persons in a population survey, the red cell count was higher in those with newly diagnosed diabetes or IFG/IGT than in those with normal glucose tolerance, potentially reflecting nocturnal hypoxia from sleep-disordered breathing. Cigarette use was associated with higher hemoglobin but not with an increase in red cell count. Those with known diabetes had lower red cell count, which the authors explained as reflecting chronic kidney disease. Aronsohn et al. (abstract 684) found an apnea-hypopnea index of ≥5/h on overnight polysomnography in 47 of 54 type 2 diabetic persons, with mean A1C 6.0%, 7.7%, and 8.2% in those with no, mild-moderate, and severe obstructive sleep apnea. Maser et al. (abstract 831), however, found that a measure of autonomic neuropathy improved in nondiabetic but not in diabetic persons with sleep-disordered breathing after a 6-week period of continuous positive airways pressure nocturnal treatment.

Etropolski et al. (abstract 852) administered an extended-release form of the dual μ-opioid receptor agonist/norepinephrine reuptake inhibitor tapentadol, structurally similar to tramadol, to 588 patients with moderate-to-severe pain from diabetic peripheral neuropathy. The 392 patients who responded were randomized to active drug versus placebo for 12 weeks, with pain symptoms redeveloping in the placebo group. Side effects, however, included nausea, dizziness, somnolence, and constipation, leading to one-third discontinuing in the open-label phase and to 15% versus 8% of the placebo group discontinuing during the controlled phase of the study.

The neuropathic foot

James A. Birke (Baton Rouge, LA) gave the Roger Pecoraro Lecture on the legacy of the National Hansen's Disease Center (Carville, LA) in the care of the neuropathic foot. Persons with Hansen's disease were forcibly quarantined at the Louisiana Leper Home in the 1890s, as the disease was essentially incurable until the first uses of sulfone drugs in the 1940s. In 1966 Dr. Paul Brand became the director of the rehabilitation program at the center, bringing out the then novel concept that repetitive walking stress was the primary cause of plantar ulceration and faulty healing in the insensate foot, implying a new approach to development of therapeutic approaches based on understanding the mechanisms of injury. Animal studies showed that local hyperthermia often appeared prior to other evidence of injury, suggesting an important approach to diagnosis. Approaches to reducing injury, particularly the use of casting and subsequent use of special footwear, were used in developing treatments. Treatment of diabetic patients at the Carville center began in the 1970s, with evidence that healing rates were sim-

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DOI: 10.2337/dc10-zb06

ilar to those of persons with Hansen's disease, contributing to the development of multidisciplinary lower-extremity amputation prevention (LEAP) programs. Approaches included annual foot screening with the 10-g monofilament to discriminate between persons at risk and those not at risk (1), ongoing patient education, scheduled follow-up based on risk, assistance for patients to obtain protective footwear, and providing easy access to prompt management of foot problems.

The Carville foot screen was adapted to provide four risk categories: 0 (no loss of protective sensation), 1 (loss of protective sensation), 2 (loss of protective sensation with either pressure callus/deformity or poor circulation), and 3 (history of plantar ulcer, Charcot foot or amputation). The essentials of patient education are straightforward: daily foot checking, promptly calling for examination with new injury, never walking barefoot or on stocking feet (even to the bathroom at night), and wearing only prescribed footwear, breaking in new shoes slowly. Birke recommended using simple devices such as soft insoles and molded depth-inlay shoes, and, when needed, walking casts, wedge shoes, and accommodative dressings (which he termed "our greatest things"), suggesting that we pay attention to patients' wishes for relatively standard-appearing footwear. "After [ulcers] close, the challenge is to keep them closed," he said, using plantar temperature measurement to determine areas at particular risk, and gradually increasing activity with appropriate footwear. Alternative methods to walking casts, which similarly result in healing of ~90% of ulcers at 6 weeks, include felt relief pads, walking splints, and "healing shoes." Such approaches have led to reduction in ulcers and hospitalizations, with consequent reduction in cost. Birke reminded the audience that Dr. Brand, referring to the terrible burden of the insensitive foot, termed pain "the gift nobody wants," and that his approach was to treat "the neuropathic foot [as] a matter of mechanics, not medicine."

Gastroparesis

Niels Ejskjaer (Aarhus, Denmark) reviewed the diagnosis and treatment of diabetic gastroparesis, suggesting that there are limits in the standard definition of delayed gastric emptying in the absence of mechanical obstruction. Indeed, although some studies suggest that about half of type 1 diabetic persons have evidence of the condition (2), other studies show, paradoxically, that fewer than half of diabetic persons with symptoms compatible with gastroparesis, such as early satiety, pain, bloating, nausea, and vomiting, have evidence of delayed gastric emptying. Ejskjaer noted that poor glycemic control may be the only sign in some patients, although hyperglycemia in itself will delay gastric emptying (3), leading to an indeterminate direction of causality. Severe cases may lead to weight loss, electrolyte derangement, and recurrent swings between ketoacidosis and hypoglycemia. Gastroparesis may also be associated with dysmotility of the esophagus, gallbladder, and biliary tract, and with pancreatic exocrine dysfunction and nocturnal diarrhea. Diagnosis requires careful history, examination, endoscopy, and gastric emptying tests in excluding other causes. Gastroparesis may be brought about by a combination of autonomic neuropathy, glucose toxicity, connective tissue degeneration, advanced glycation end product (AGE) formation, and perhaps autoimmunity. There is histological evidence of smooth muscle degeneration and fibrosis as well as of abnormal vagal nerve fiber density in gastroparesis (4), suggesting elements of both gastromyopathy and neuropathy in the condition. In a study comparing 15 type 1 diabetic patients with 12 normal control subjects, an endoscopic technique found increased pain threshold in diabetic patients, but larger referred pain areas from such stimuli, suggesting central neuronal changes in the pathophysiology of diabetic gastroparesis, evidence of involvement of a "third neuron" in the brainstem and thalamus (5). Gastric emptying tests include scintigraphy and ultrasound, giving information more about retention than emptying of gastric contents, and electrogastrography and breath and paracetamol (acetaminophen) tests.

There is considerable interest in pharmacologic treatment approaches. A number of prokinetic agents have been usedfor the treatment of gastroparesis, including dopaminergic antagonists such as metoclopramide and domperidone; motilin agonists such as erythromycin; the serotonergic agonists cisapride, tegaserod, renzapride, mosapride, and ATI-7505; the muscarinic agonist bethanechol; the acetyl cholinesterase inhibitors physostigmine and neostigmine; the H2 receptor antagonist nizatidine LR; the cholecystokinin receptor antagonists loxiglumide and dexloxiglumide; the opiod receptor antagonist alvimopan; and a number of ghrelin receptor agonists. Ghrelin is a 28-amino acid peptide produced in the gastric mucosa, with a number of studies showing an effect in increasing gastric emptying. Ejskjaer reviewed his study of ten patients treated with a ghrelin receptor agonist, with gastric emptying normalized in three and significant improvement of emptying in all, and a mean 37% decrease in the severity of postprandial fullness (6). A number of surgical treatments are also used. Gastrostomy can be performed endoscopically, while jejeunostomy, requiring surgical placement, may be more effective, although still associated with very high complication rates due in large part to the severity of underlying illness of many persons with the condition (7). Total parenteral nutrition is occasionally needed but may be associated with adverse outcome as well (8). Gastrectomy, pyloroplasty, and gastrojejeunospomy have also been used. Gastric pacing may lead to improved outcome, reducing the requirement for parenteral nutrition and hospitalization (9). Ejskjaer's studies have shown improvement in symptoms at 1 and 2 years, although without evidence of improved gastric motility, contractility, or function.

Peripheral neuropathy

David N. Herrmann (Rochester, NY) discussed diabetic sensory neuropathy, reviewing the classification of peripheral sensory fibers into large myelinated A-α/β, smaller myelinated A-β, and unmyelinated C fibers serving mainly nociceptive sensations. Nerve conduction studies measure function of the myelinated fibers. Different patterns of distal sensory neuropathy may be seen, with small fiber neuropathy associated with pain, dysesthesia, and paresthesia, typically with physical findings restricted to mild pin or thermal sensation loss and with normal electrophysiological tests, while large fiber loss leads to tight, wrapped band-like sensations, abnormal electrophysiological tests, impairment of vibration and proprioceptive sensation, loss of reflexes, and positive Rhomberg sign or ataxic gait. Often there is a mixed presentation with abnormalities of both small and large fibers.

The classic staging system of diabetic distal symmetric polyneuropathy ranges from asymptomatic mild findings to increasing degrees of symptomatic neuropathy, but this relies particularly on

assessment of large fiber function. Medial plantar nerve action potential measurement (10) may detect early distal large fiber involvement, but there is a prominent age effect, the studies are technically difficult, and local foot trauma may lead to abnormalities. In a study of 108 control subjects and 133 patients with clinical distal sensory neuropathy, using age-based normative data, sural nerve potential was abnormal in only 27% of persons with large fiber neuropathy and in 9% with small fiber neuropathy, while the medial plantar nerve action potential was abnormal in 69 and 11%, respectively. Other medial plantar nerve conduction studies suggest that this is a reproducible test that may be more useful than sural nerve conduction studies in persons with mild symptomatic diabetic neuropathy (11).

Approaches with evaluation of both small and large fibers may allow earlier recognition of diabetic peripheral neuropathy, perhaps improving selection of persons for clinical trials. Herrmann noted that studies of persons with more advanced disease may address a population with irreversible damage. Diabetic persons previously thought not to have neuropathy may have subtle abnormalities with patch skin biopsy, which allows immunohistochemical staining of epidermal nerve fibers to measure fiber density and to examine morphological abnormalities, a measure of small nerve fibers (12,13). Such studies compare favorably with nerve conduction measurement in assessment of diabetic neuropathy (14), and may show greater sensitivity than sural nerve biopsy in the measurement of peripheral small fiber loss (15), correlating with clinical neuropathy severity (16). The medial plantar nerve action potential becomes abnormal later than skin biopsy in persons with normal routine nerve conduction studies (17), with skin biopsy nerve fiber density potentially having a role in early diagnosis of diabetic peripheral neuropathy (18). Another approach to early diagnosis is the use of confocal microscopy to show evidence of corneal denervation (19).

Pathogenesis of neuropathy

Angelika Bierhaus (Heidelberg, Germany) discussed inflammation in diabetic neuropathy, noting the importance of pain in the recognition of heat, cold, and inflammation, with well-recognized molecular mechanisms, but pointing out that pain also occurs in a variety of metabolic disturbances, in particular diabetes, with uncertain mechanisms. Hyperglycemia appears to be related to the development of pain, but evidence that improvement of glycemia reduces such symptoms is lacking, suggesting that other factors may be involved. It is interesting that pain and dysesthesias may precede the development of type 2 diabetes, and that with hyperglycemia or elevated free fatty acid levels there is increased flux through the mitochondrial respiration chain leading to increased oxidant stress, with elevated levels of superoxide production, and a consequent increase in production of metabolites such as dihydroxyacetone phosphate, which is converted into the AGE precursor methylglyoxal (MG). A number of factors increase MG production, which directly and via its metabolites may produce vascular and neuronal inflammation, in part involving prostaglandin E2 and nuclear factor (NF)-κB (20). MG is physiologically degraded by glyoxalase (GLO)-1 and -2, reduced activity of which will increase AGE production, leading Bierhaus to suggest that the loss of these MG-detoxifying mechanisms may contribute to diabetic neuropathy. She pointed out that a compound similar to MG is present in horseradish and wasabi, resulting in the "burning" taste associated with these two foods, and this may be relevant to some symptoms of painful neuropathy.

Studies of the nematode *Caenorhabditis elegans* overexpressing the homolog of GLO show reduction in damage associated with elevated glucose levels, leading to increased life span and to prevention of neuronal damage (21). In a mouse model, diabetes was associated with a reduction in GLO activity and an increase in MG levels. Sciatic nerve GLO activity was particularly low, even more so in diabetic mice, suggesting greater risk of AGE accumulation in peripheral nerves. In an animal model, diabetes decreased GLO to a level similar to that in mice with one copy of an inactive gene, with increased MG levels, and evidence of hyperalgesia with a "hotplate" stimulus. A GLO inhibitor also increased MG levels and led to hyperalgesia, while GLO overexpression reduced hyperalgesia. It appears that a voltage-gated sodium channel, Nav1.8, plays a role in the increased pain response, and that inhibiting the sodium channel with ambroxol or reducing expression of Nav1.8 reduced the degree of MG-dependent hyperalgesia. MG binds to arginine residues in Nav1.8, opening the channel and leading to greater pain perception, suggesting potential therapeutic approaches. In a pilot study, plasma MG levels were higher in diabetic persons with painful neuropathy.

The accumulation of MG leads to increased AGE formation (22) and to NF-κB activation with loss of neuronal function (23,24). Interestingly, receptor for AGE (RAGE) deficiency partially protects mice from diabetes-mediated inhibition of GLO-1 expression and neuropathic pain. Bierhaus concluded that there is a relationship of MG with pain in early diabetes and with loss of pain perception in the later stages of diabetic neuropathy.

Retinopathy

Several studies presented at the ADA meeting addressed aspects of diabetic retinopathy. Gong et al. (abstract 97) presented microvascular outcome results of a 20-year follow-up of 566 of the original 577 participants in the Chinese Da Qing study of lifestyle intervention for prediabetes; after 20 years, severe retinopathy decreased 46%. Saaddine et al. (abstract 382) reported retinopathy prevalences of 34.2% among 349 persons with known diabetes (10.5% had moderate or severe nonproliferative retinopathy, 2.8% had proliferative retinopathy, and 4.1% had clinically significant macular edema), 12.9% among 45 with previously undiagnosed diabetes, and 8.9% among 361 with fasting plasma glucose ≥100 and <126 mg/dl in the 2005–2006 NHANES. Retinopathy prevalences were higher with longer duration of diabetes, with higher A1C, and among persons treated with insulin. Weinrauch et al. (abstract 867) treated 71 type 1 diabetic persons with diabetic retinopathy and nephropathy with glomerular filtration rate (GFR) ≥30 ml/min to weekly pulsatile insulin infusion versus multiple daily insulin dose treatment alone. Benefit had previously been shown in preservation of renal function, but this was not demonstrated for retinopathy; there was a trend to reduced progression. Lee et al. (abstract 945) reported that, among 1,241 type 2 diabetic patients, there was no association of alcohol use with the presence of diabetic retinopathy, but that regularly drinking alcoholic beverages was associated with a 1.6- and 2.6-fold increase in risk of deterioration of visual acuity over mean 5.5-year follow-up among Caucasian and non-Caucasian participants, respectively.

Approaches to glucose-lowering

Current treatments. Willis et al. (abstract 171) assessed cost-effectiveness of the 2008 ADA/European Association for the Study of Diabetes (EASD) consensus statement approach for type 2 diabetes at a goal A1C of 7% versus 8%. Following a protocol of treatment with metformin, then metformin plus sulfonylurea, then metformin plus basal insulin, then adding prandial insulin three times daily, Willis et al. calculated cost to be $3,610 higher with the 7% target and a $52,000 cost per quality-adjusted life-year gained. Sensitivity analysis showed "the 7% threshold strategy would be more cost-effective if treatment intensification occurred with therapies with better side-effect/tolerability profiles." Schramm et al. (abstract 89) assessed 9,808 cardiovascular deaths among 100,206 persons with diabetes living in Denmark initiating oral agent monotherapy from 1997–2006. Compared with metformin, mortality increased among persons receiving glimeperide, glibenclamide, glipizide, and tolbutamide, trending to higher levels with gliclazide and acarbose, and trending to lower levels in persons treated with repaglinide. Jackness and Tamler (abstract 49-LB) created a list of the ten most-prescribed medications in 2005–2006 among patients with diabetes from a database of 91 health plans with 52 million participants: metformin, statins, lisinopril, thiazolidinediones, furosemide, hydrochlorothiazide, insulin glargine, amlodipine, and atenolol. For most of these, 2- to 10-fold reductions in cost were found in discount stores and mail-order companies in comparison to neighborhood retailers and convenience store chains. Mathew et al. (abstract 532) intensely treated 30 type 2 diabetic persons, showing that insulin treatment reducing fasting glucose from 164 to 89 mg/dl and A1C from 9.0 to 7.3% was associated with a 40% reduction in hepatic steatosis, with no change in total body or intramyocellular fat.

Peroxisome proliferator–activated receptor–directed treatments. Gupta et al. (abstract 8) found that peroxisome proliferator–activated receptor (PPAR)-γ signaling upregulated cultured islet glucose-dependent insulinotropic peptide (GIP) receptor mRNA and protein and increased in vivo GIP-induced insulin secretion. Reaven et al. (abstract 15-LB) treated 393 persons with impaired glucose tolerance with pioglitazone 45 mg daily versus placebo for 39 months, finding a 0.006 versus 0.009 mm/year increase in carotid intima-media thickness.

Perreault et al. (abstract 364) showed greater improvement in insulin sensitivity and in serum triglyceride and HDL cholesterol levels in obese, insulin-resistant adult rhesus monkeys receiving the balanced pan PPAR agonist indeglitazar than with pioglitazone, without the weight gain seen with the latter agent. Delmedico et al. (abstract 365) administered the PPAR -δ and -γ agonist DB959 in animal models of diabetes, reporting comparable glycemic effect to that of rosiglitazone. DePaoli et al. (abstract 117) treated 69 type 2 diabetic persons with INT131, a selective PPAR-γ modulator, for 4 weeks, showing a 30 mg/dl reduction in fasting glucose with less weight gain and without the hemodilution-related fall in hematocrit seen with thiazolidinediones. D'Ardhuy et al. (abstract 924) administered the PPAR-α/γ agonist aleglitazar 0–900 g daily for 6 weeks to 71 type 2 diabetic persons not receiving oral hypoglycemic agents, finding dose-dependent improvement in glucose tolerance and fasting glucose, insulin, triglyceride, and HDL cholesterol levels. Henry et al. (abstract 917) administered aleglitazar, pioglitazone, or placebo to 332 type 2 diabetic persons for 16 weeks, finding dose-dependent improvement in A1C, triglyceride, and LDL and HDL cholesterol; edema was seen at higher aleglitazar doses. Yamaaki et al. (abstract 921) administered both bezafibrate and fenofibrate to 10 dyslipidemic type 2 diabetic patients, with both agents reducing triglyceride and increasing HDL cholesterol, but only bezafibrate increasing adiponectin, reducing γ-glutamyl transpeptidase, and improving glycemia, the authors speculating it to be a dual α/γ agonist.

Shi et al. (abstract 517) analyzed the effect of warnings about thiazolidinedione use in 2007 on 13,293 type 2 diabetic patients treated mainly with rosiglitazone in the Veterans Affairs Health System. A1C increased 0.3% in the 5,999 patients discontinuing use of these agents, with 75% of these patients failing to take another agent. Wang and Pugh (abstract 657) studied cardiovascular risk among 16,751 type 2 diabetic patients treated in the Veteran's Affairs system, finding no evidence of harm with combined use of rosiglitazone and insulin, indeed with reduction in cardiovascular risk among some subgroups. Ma et al. (abstract 574) reported lower costs of care for 407 persons treated with addition of rosiglitazone versus 723 with addition of a sulfonylurea to metformin. Use of at least 80% of the amount of medication prescribed was demonstrated in 38% versus 27%. Simpson et al. (abstract 1,013) reported that mortality among 297 and 906 diabetic persons treated with metformin plus pioglitazone versus rosiglitazone was 1.22- and 0.68-fold that of 1,902 diabetic persons treated with metformin plus sulfonylurea; neither of the risk ratios was, however, significantly different from unity.

Lavery et al. (abstract 125) found 73, 50, and 12% greater foot, ankle, and hip fracture rates in 45,319 diabetic than in 616,921 nondiabetic patients. Schwartz et al. (abstract 985) compared fracture risk among 520 women with versus 7,397 without self-reported type 2 diabetes, followed for 5 years, with 256 confirmed hip fractures. A T-score of −2.5 was associated with a 6.1% 5-year fracture risk among nondiabetic women at age 75, but among diabetic women, the equivalent risk was seen with a T-score of −2.0, suggesting that this threshold be used for the diagnosis of osteoporosis in diabetic patients. Aubert et al. (abstract 501) analyzed a pharmacy and medical claims database of 13 million persons, with information on 69,047 persons receiving a thiazolidinedione and 75,352 comparators, taking metformin, exenatide or a sulfonylurea. Controlling for age; for diagnoses of COPD, asthma, osteoporosis, and stroke; and for prior fracture, fractures were 55% more likely for women and 26% more likely for men treated with a thiazolidinedione, without difference between rosiglitazone and pioglitazone.

Novel treatments. Huffman et al. (abstract 326) studied HNGF6A, an analog of Humanin, which has been evaluated for neuroprotection in studies of Alzheimer's disease–related neurotoxicity in ZDF rats. HNGF6A improved insulin sensitivity and lowered blood glucose levels. Scranton et al. (abstract 481) assessed the effect of rapidly absorbed bromocriptine versus placebo in 113 thiazolidinedione-treated patients with A1C >7.5%, finding a 0.7% versus 0.6% A1C reduction over 52 weeks. Gumbiner et al. (abstract 11-LB) administered MB07803, a fructose-1,6-bisphosphatase inhibitor, to 42 type 2 diabetic persons with baseline A1C 8.8% and fasting glucose 221 mg/dl for 14 days, demonstrating 16, 58, and 55 mg/dl reductions in fasting glucose with 50, 200, and 400 mg daily, respectively. One-third

of those receiving 200 mg had nausea, and half of those receiving 400 mg developed vomiting, with one person developing nonsustained lactate >4.5 mmol/l. Migoya et al. (abstract 116) administered the glucokinase activator MK-0599 in doses of 25, 50, and 100 mg three times over a 1-day period to nondiabetic persons, finding dose-related glucose-lowering but with hypoglycemia at two higher doses.

Glucocorticoid antagonism. Rosenstock et al. (abstract 7-LB) administered the 11-β-hydroxysteroid dehydrogenase type 1 inhibitor, INCB13739, to metformin-treated type 2 diabetic patients, finding no change in A1C in 28 patients receiving placebo, but 0.6% and 0.5% reductions in 54 patients receiving 100 and 200 mg daily, respectively. Plasma ACTH increased but remained within the normal range, and cortisol levels were unchanged, suggesting that adrenal insufficiency would not occur frequently with this agent (but that it could occur). Asagami et al. (abstract 92-LB) administered a selective glucocorticoid antagonist, ADS108297, not affecting progesterone action, to mice in a diet-induced obesity model, showing prevention of weight gain and a similar improvement of insulin resistance to that seen with rosiglitazone administration. Gross et al. (abstract 97-LB) administered the glucorticoid receptor antagonist mifepristone 600 mg daily or placebo to 60 persons treated with risperidone 1.5–2.0 mg twice daily, finding a 2.3 versus 4.2 kg weight gain at 28 days with prevention of increased fasting insulin and triglyceride levels.

Anti-inflammatory treatments. Donath et al. (abstract 113) showed a 1.1% A1C reduction at 3 months in type 2 diabetic patients following a 0.1 mg/dl single infusion of the high-affinity anti-interleukin-1β antibody XOMA 052. Owang et al. (abstract 310) reported similar effects in a high-fat/high-sucrose diet diabetic mouse model. Boaz et al. (abstract 1,724) compared 100 type 2 diabetic patients who had lost weight with 102 patients who had no weight loss history, finding that 89% versus 72% had taken anti-inflammatory agents, with exposure to these agents more than doubling the likelihood of weight loss. Goldfine et al. (abstract 115) treated 108 type 2 diabetic persons having A1C 7.0–9.5% with the NF-κB inhibitor salsalate, 3, 3.5, or 4.0 g three times daily, finding placebo-adjusted 0.5–0.6% reduction in A1C, 27–32 mg/dl reduction in fasting glucose, 31–49 mg/dl reduction in triglyceride, and 1.7–2.8 μg/ml elevation in adiponectin, with hypoglycemia in patients receiving concomitant sulfonylureas; 20% versus 11% of placebo-receiving patients developed tinnitus. Han et al. (abstract 360) administered 600 mg/day of α-lipoic acid intravenously for 14 days to 10 overweight persons with IGT and 6 with normal glucose tolerance, showing improvement in insulin sensitivity and β-cell function with treatment. Schwartz et al. (abstract 362) administered the antioxidant bardoxolone to 57 diabetic persons with chronic kidney disease, showing a 0.3% reduction in A1C from a baseline of 7.6%.

Bile acid–directed treatments. Beysen et al. (abstract 476) performed glucose turnover studies in 55 type 2 diabetic persons randomized to colesevelam 3.75 g daily or placebo, showing 0.5% and 20 mg/dl differences in A1C and fasting glucose after 12 weeks. Insulin levels did not change, glucose production increased with placebo while not changing with colesevelam, and glucose clearance increased with colesevelam while not changing with placebo, suggesting this to be the mechanism of the glucose-lowering effect of the agent. Brufau et al. (abstract 498) studied bile acid pool sizes and synthesis rates in 12 normal and in 12 type 2 diabetic persons before and after an 8-week period of administration of colesevelam. At baseline, the diabetic patients had higher cholic acid synthesis rate, higher deoxycholic acid input rate and pool size, higher percent contributions to the total bile acid pool and lower chenodeoxycholic acid pool sizes. Colesevelam reduced A1C by 0.65% and increased the cholic acid pool size in the diabetic patients, leading to increased hydrophilicity of the bile acid pool and, presumably, to reduced susceptibility to gallstone formation. Triglyceride levels increased 40 mg/dl, correlating with the increase in cholic acid synthesis, and LDL cholesterol decreased 11 mg/dl. Takebayashi et al. (abstract 503) compared effects of colestimide 3.0 g and rosuvastatin 2.5 mg daily in 40 type 2 diabetic persons with dyslipidemia, finding the former to reduce A1C from 8.8 to 7.9%, as well as urinary levels of 8-iso-prostaglandin F2α and monocyte chemoattractant protein-1, without influencing insulin sensitivity, adiponectin, or retinol binding protein-4 levels. Henry et al. (abstract 13-LB) treated 64 type 2 diabetic patients with nonalcoholic fatty liver with 6-ethyl chenodeoxycholic acid, INT-747, a potent farnesoid-X receptor (FXR) agonist, 25 or 50 mg daily for 6 weeks. Glucose disposal rate decreased 6% with placebo, whereas it increased 20–30% with low-dose insulin and 10–20% with high-dose insulin; liver chemistries improved; and LDL increased with a reduction in HDL cholesterol and triglyceride levels. One should note the paradox that bile acid sequestrants, by lowering bile acid levels, reduce their activation of FXR, and hence reduce FXR activation, which has been thought to lead to lower glucose levels (25), yet the modified bile acid, which activates FXR, was demonstrated to have a glucose-lowering effect as well.

Treatments increasing glycosuria. Wilding et al. (abstract 482) treated 71 insulin-requiring type 2 diabetic patients with placebo versus dapagliflozin. Dapagliflozin blocks renal glucose reabsorption by selectively inhibiting sodium-glucose cotransporter 2. Administration of dapagliflozin resulted in an A1C reduction of 0.1% versus 0.6% with weight loss of 1.9 versus 4.4 kg over 12 weeks. Chari et al. (abstract 110) normalized glucose with use of phlorizin to produce glycosuria in a streptozotocin-diabetic rat model, showing restoration of response to mediobasal hypothalamic hypoglycemia, with the glial isoform of GLUT1 reduced by 50% with hyperglycemia and returning to normal levels with treatment.

Pramlintide. Lutz et al. (abstract 579) and Pencek et al. (abstract 580) presented observational open-label 6-month studies of the effects of pramlintide in 541 type 1 and 364 type 2 diabetic persons receiving prandial insulin (70% of those beginning the studies). Type 1 diabetic patients completing the study reduced prandial insulin by 14%, increased long-acting insulin 8%, lost 2.8 kg weight, and had a 0.3% reduction in A1C. Type 2 diabetic patients completing the study increased insulin 16%, lost 1.9 kg weight, and had a 0.5% reduction in A1C. Hypoglycemia requiring assistance occurred at rates of 33% and 8% per year during 0–3 and 3–6 months, respectively, in type 1 diabetic patients and at rates of 19% and 2% per year in type 2 diabetic patients.

Acknowledgments— Z.T.B. has served on speaker's bureaus of Merck, Novo Nordisk, Lilly, Amylin, Daiichi Sankyo, and GlaxoSmithKline; has served on advisory panels for Medtronic, Takeda, Merck, AtheroGenics, CV Therapeutics, Daiichi Sankyo, BMS, and As-

traZeneca; holds stock in Abbott, Bard, Medtronic, Merck, Millipore, Novartis, and Roche; and has served as a consultant for Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, and Nastech. No other potential conflicts of interest relevant to this article were reported.

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