

The 6th Annual World Congress on the Insulin Resistance Syndrome

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This is the third of a series of articles based on presentations at the 6th Annual World Congress on the Insulin Resistance Syndrome held 25–27 September 2008 in Los Angeles, California.

Insulin resistance epidemiology

In an update on the metabolic syndrome, Earl Ford (Atlanta, GA) discussed epidemiological relationships between metabolic syndrome and incident diabetes and compared the syndrome with risk prediction models. Over the past 3 years, more than 3,000 articles have been written about the syndrome. The 1998 World Health Organization (WHO) definition focused on glucose intolerance or insulin resistance, the 1999 European Group for the Study of Insulin Resistance required either insulin resistance or fasting hyperinsulinemia, and the NCEP/ATP III (National Cholesterol Education Program/Adult Treatment Panel III) definition in 2001 did not focus on glycemia or insulin resistance, simply requiring three of five abnormalities (abdominal obesity, low HDL cholesterol, high triglyceride levels, hypertension, and hyperglycemia), in 2002 and 2005 changing the glycemic criteria. The 2005 International Diabetes Federation (IDF) definition focused on central adiposity, giving ethnic-specific limits. The American College of Endocrinology also proposed a definition, giving a large number of possible conditions associated with insulin resistance. Using the 1999–2004 National Health and Nutrition Examination Survey data, the age-adjusted prevalence of metabolic syndrome in adults is ~35% with ATP III and 38% with IDF definitions. Based on the projected U.S. population of 218,000,000 adults in 2007, then, there are ~80,000,000 individuals with metabolic syndrome. There is heterogeneity by ethnicity and sex, with prevalence lowest

in African American men and higher in Hispanic women. With the IDF definition, prevalence of the syndrome is greater in men than women. A number of studies have analyzed the association of metabolic syndrome with cardiovascular disease (CVD) and diabetes, with meta-analysis showing a relative CVD risk of 1.5–1.8 and a threefold increase in likelihood of diabetes (1–3). In an analysis of 16 cohorts with 42,419 participants having 2,604 incident cases of diabetes over 2.3–20 years, ~1% per year, the likelihood of diabetes ranges from 2- to 11-fold in metabolic syndrome. There was heterogeneity among studies, but regardless of the definition used for diabetes, metabolic syndrome was associated with a 3.5- to 5.2-fold increase in the likelihood of diabetes. Ford pointed out that rather than comparing the reference category of three plus abnormalities with less than three abnormalities, compared with individuals having no metabolic syndrome abnormalities as the reference group, those with three abnormalities have a ninefold increase and those with four to five abnormalities have a 20-fold increase in likelihood of diabetes. The specificity of metabolic syndrome for diabetes is similar with all the definitions, although sensitivity is higher with the WHO than with the ATP III definitions. Certainly, Ford pointed out that other predictive factors are important, citing a study showing that age, sex, and family history of diabetes give additional information (4), but he suggested that this does not negate the importance of metabolic syndrome in assessing diabetes risk. Of the individual components of the syndrome, impaired fasting glucose (IFG) is most strongly and waist circumference is next most important in predicting diabetes. Whether metabolic syndrome can be taken to be an indirect measure of insulin resistance is not, however, yet clear from these studies.

Pediatric insulin resistance

Sonia Caprio (New Haven, CT) compared the implications of IFG with those of impaired glucose tolerance (IGT) in obese adolescents, asking whether adolescents display a pattern of development of type 2 diabetes similar to that of adults. In a study involving 780 obese adolescents, 9.3% had IFG, 14.2% IGT, and 4.4% both, with IGT considerably more prevalent in female subjects. Insulin sensitivity, assessed with euglycemic clamping, was somewhat greater in those with IFG and was similar in those with IGT alone and in combination with IFG, whereas first-phase insulin secretion decreased by approximately one-third in isolated IFG or IGT and by approximately two-thirds in those with both defects (5). In a longitudinal study, Caprio followed 60 obese adolescents with normal glucose tolerance who were taking no medications. Following oral glucose tolerance tests (OGTTs) and measures of insulin sensitivity and secretion over 3 years, 46 did not progress, whereas 14 developed IGT at years 2 and 3. Fasting glucose was significantly lower in nonprogressors, with similar cytokine and insulin levels. β -Cell response was one-third lower at baseline in progressors, whose insulin sensitivity and secretion both worsened during the next 2 years, with consequent progressive reduction in the product of these indexes, the disposition index. A study of 118 obese adolescents who had OGTT and magnetic resonance imaging showed correlation between hepatic and muscle fat, with insulin resistance and prevalence of metabolic syndrome increased in those with more visceral fat (6).

Alan Sinaiko (Minneapolis, MN) assessed the relationships between development of insulin resistance and cardiovascular risk in childhood and adolescence. He reviewed the relatively poor correlations of fasting insulin (or homeostasis model assessment [HOMA], which is in essence the same measure) with clamp insulin sensitivity, in his studies in both children and adults (7), commenting that “unfortunately there’s no real easy way to measure insulin sensitivity.” Insulin resistance, measured with clamp studies, showed a lower correlation with BMI than that of fasting insulin, from

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which insulin sensitivity measures are typically derived, based on his studies of 789 normal 11- to 17-year-old children. Among 568 male and 428 female children aged 11–19 years, BMI increased similarly, blood pressure increased similarly in early adolescence, but subsequently more rapidly in male subjects, and HDL cholesterol increased in female and decreased in male subjects, with opposite changes in triglycerides (8). Insulin sensitivity was lower in girls at age 11 years, subsequently increased in girls, but decreased in male subjects, while fasting insulin did not change significantly in either sex. While insulin sensitivity decreased in male subjects, body fat also decreased, opposite to the changes in female subjects, presumably sex steroid-related, showing that fat alone is not the sole determinant of insulin sensitivity. LDL cholesterol levels were similar in male and female subjects.

Comparing those children at age 15 years in the low versus high halves of the insulin sensitivity and BMI distributions, heavier children had higher systolic blood pressure and fasting insulin but similar insulin sensitivity (9). Those in the higher versus lower half of the insulin resistance distribution similarly had no difference in BMI. Combining the two factors, fasting insulin and triglyceride levels increased and HDL cholesterol decreased stepwise going from thinner, more insulin sensitive, to thin insulin resistant, to heavy insulin sensitive, to heavy insulin resistant; an insulin resistance/cardiovascular risk score based on average z score of systolic blood pressure, triglycerides, HDL cholesterol, and fasting insulin was lowest in the thin insulin-sensitive group and highest in the heavy insulin-resistant group.

Finally, Sinaiko addressed the question of childhood factors determining risk level among adults. From age 7 to 24 years, he found a strong correlation between BMI and similarly strong correlation among systolic blood pressure, HDL cholesterol, triglycerides, and insulin resistance scores at age 13 and 23 years (10). Furthermore, the change in BMI from age 13 to 19 years predicted triglyceride levels, HDL cholesterol, and blood pressure at age 19 years, and the change in insulin sensitivity predicted blood pressure and triglyceride levels at age 19 years, independent of BMI (11). “Insulin resistance,” he concluded, “plays a very important role in addition to BMI in cardiovascular risk . . . [and is] established very early in life.”

Nonalcoholic fatty liver disease

Arun Sanyal (Richmond, VA) discussed nonalcoholic fatty liver disease, focusing on characteristics allowing one to recognize the 15% of individuals with the condition who are at risk of progression to cirrhosis. In a study of 150 patients undergoing serial biopsy, of those with no or just mild fibrosis, a substantial number progressed over 3–4 years, whereas regression was seen in some of those with more severe baseline disease (12). Sanyal pointed out that this may in part represent the potential error from single small biopsy specimen. Risk factors for advanced fibrosis are increased age, race/ethnicity/genetic background (with higher risk among Hispanics and lower among African Americans), weight gain, fat distribution, insulin resistance, activation of the innate immune system, and environmental toxins, such as hydrocarbons (13). Once cirrhosis develops, the rate of progression to liver failure is less than that with hepatitis C, with hepatocellular carcinoma developing after 5 years in ~15% versus 35%. Risk factors for nonalcoholic steatohepatitis (NASH) are present in many patients with hepatocellular carcinoma, suggesting this to be a more important cause than generally realized (14), with such patient candidates for transplantation despite the risk of NASH recurring in the transplant.

Sanyal recommended that biopsy be performed for patients with persistently abnormal enzymes, persistent hepatomegaly, or abnormal hepatic imaging because the indirect markers of hepatic fibrosis are “all in their relative infancy,” with low sensitivity and specificity. He suggested that biopsy be performed only when it would lead to a change in treatment, as would be the case if another cause of liver disease were found, so that he tended to use the presence of metabolic syndrome as a rationale for not performing biopsy (15), although noting that approximately one-quarter of patients typically will be found to have other causes.

The National Heart, Lung, and Blood Institute guidelines for NASH management recommend lifestyle modification for all patients. As NASH involves oxidative stress and mitochondrial injury, leading to inflammation and apoptosis, Sanyal considered metformin to be not promising, whereas pioglitazone appears to be potentially beneficial (16), although “its long-term value remains debated.” Another option for suitable candidates with

BMI >35 kg/m² is bariatric surgery (17). Drugs being studied include pentoxifylline, probiotics, silencing mir34a and 451, and rimonabant.

Insulin resistance and polycystic ovary syndrome

Ricardo Azziz (Los Angeles, CA) stressed the importance of hyperandrogenism and insulin resistance in polycystic ovary syndrome (PCOS). It is interesting that most studies of PCOS use the insulin level and related measures such as HOMA to assess insulin sensitivity, given Sinaiko’s explanation of the inadequacy of this approach. Based on fasting insulin level, two-thirds of women with PCOS have insulin resistance (18), with higher insulin levels seen in women with more PCOS features (19). More precise approaches, such as the use of disposition index, have shown evidence of insulin resistance among women with PCOS both with or without obesity (20). Azziz suggested that PCOS is typically caused by insulin resistance that leads to hyperinsulinemia, acting with luteinizing hormone to cause ovarian theca cells to hypertrophy causing hyperandrogenism. He commented that elevations in insulin also reduce hepatic sex hormone-binding globulin production, exacerbating hyperandrogenism.

Insulin action is reduced in adipocytes of women with PCOS (21), whose tissues show decreased glucose transport, with a reduction in autophosphorylation of fibroblast insulin receptors. Adipocytes of women with PCOS have abnormal cytokine secretion, with increased proinflammatory factors and decreased adiponectin. Some of this involves cross talk between adipocytes and inflammatory cells, with cultured resident adipose tissue macrophages from women with PCOS suppressing adiponectin to a greater extent than do macrophages from control women.

Interestingly, polycystic ovaries themselves do not predict the metabolic or reproductive phenotype, whereas androgen levels and the presence of hirsutism are strong markers (22). PCOS leads to a doubling of type 2 diabetes risk (23,24), and obesity and PCOS are additive in increasing the risk of glucose intolerance (25). Among women with PCOS, as would be expected, positive family history of diabetes increases the risk of diabetes and IGT (26). It has been somewhat difficult to demonstrate an increase in cardiovascular risk in women with PCOS, but low HDL cholesterol occurred in

15%, high LDL cholesterol in 8.5%, and high triglyceride levels in 2.5% of 398 patients studied (27); event rates are low (28), although this represents in part the relative youth of affected women, and a study of postmenopausal women who had a history of PCOS suggested a reduction in cumulative cardiovascular event-free survival (29).

Lifestyle modification may be extremely helpful for patients with PCOS (30); Azziz suggested that metformin not be given routinely to women with PCOS, rather reserving the agent for those women at particular risk, and reviewed a meta-analysis of 31 trials with 4,570 participants followed for 8,267 patient-years to suggest that glycemic abnormality or family history of diabetes be used as criteria for use of this agent (31), whereas hirsutism and acne do not respond to metformin, which acts indirectly and is only modestly effective in improving ovulation and reducing metabolic complications. Thiazolidinediones may also be useful in treatment of PCOS. In assessing glycemia, fasting glucose alone is insufficient for distinguishing IGT from diabetes (25), and Azziz suggested that insulin levels might be additional useful measures, although he recognized that no clinical evidence exists for such an assertion. Certainly, it is reasonable for OGTT to be performed regularly in women with PCOS (32).

Insulin resistance and dementia

Suzanne Craft (Seattle, WA) reviewed the role of insulin resistance in brain aging and dementia. Alzheimer's disease (AD) is the most common form of dementia, affecting 4,000,000 individuals in the U.S., approximately half of those aged ≥ 85 years, defined by a defect in memory as well as in at least one other area of cognitive function. AD is progressive, associated with cerebral volume loss, histological evidence of atrophy, and the presence of neurofibrillary tangles composed of hyperphosphorylated tau and neuritic plaques composed of aggregated β -amyloid ($A\beta$).

Insulin plays a role in normal brain function and cognition, whereas dysregulation of insulin increases the likelihood of cognitive impairment and AD. Insulin receptors are distributed in the hippocampus and entorhinal cortex, areas involved in memory, and the frontal cortex, suggesting roles in cognition as well as in controlling food intake. Insulin crosses the blood-brain barrier (BBB) and

increases glucose utilization and levels of certain neurotransmitters, enhancing memory and other aspects of cognition at optimal levels in healthy physiology (33). Insulin also regulates $A\beta$, with one of the major proteases degrading $A\beta$, the insulin-degrading enzyme, so that when insulin levels are increased, $A\beta$ degradation is reduced. Insulin resistance, hyperinsulinemia, and type 2 diabetes are associated with increased risk of AD (34–37); potential mechanisms reduced brain insulin uptake and signaling as a result of downregulation of insulin crossing BBB, reduced brain glucose metabolism, disrupted regulation of $A\beta$ trafficking and clearance, and increased inflammation. AD is associated with reduction in brain glucose metabolism, particularly in the parietal and temporal regions. In newly diagnosed mild type 2 diabetes, without dementia, fluorodeoxyglucose positron emission tomography shows significant hypometabolism in the temporal and parietal lobes and the frontal cortex, similar to the pattern in early AD. The degree of hypometabolism appears to worsen with increasing levels of glycemia. There are two $A\beta$ isoforms: $A\beta_{42}$, which is neurotoxic and memory inhibiting, and $A\beta_{40}$, which deposits in cerebral vessels and impairs vascular function. Craft suggested that these effects are analogous to those of islet amyloid polypeptide on β -cell function. In animal models of AD, insulin resistance increases amyloid burden and impairs memory (38). In humans, hyperinsulinemia appears to increase brain $A\beta$ levels and inflammation. During a hyperinsulinemic-euglycemic clamp, spinal fluid $A\beta_{42}$ levels increase in subjects aged ≥ 70 years, whereas interleukin-1 α and -6 and tumor necrosis factor- α levels and F2-isoprostane double regardless of age, with the latter being brain derived, suggesting intrinsic inflammation. In the ≥ 70 -year-old group, the change in F2-isoprostane correlated with the increase in $A\beta$, further suggesting that inflammation is linked to the insulin effect. Craft noted that lipid plus heparin infusion also increases $A\beta$ levels—further evidence of the linkage to insulin resistance.

Insulin resistance disrupts neurovascular unit function even without cerebrovascular disease. The neurovascular unit, composed of blood vessels and perivascular neurons, couples neuronal activity with regional brain blood flow regulating BBB transport (39), with insulin appearing to have beneficial regulatory effects. Microvascular lesions in small arterioles

are markers of vascular pathology; a neuropathological analysis of 180 brains from a longitudinal cohort of autopsies of subjects (mean age 86 years) showed microvascular lesions to increase both with diabetes and with dementia and particularly in subjects with both conditions.

Given the evidence of association of insulin resistance with AD and dementia, Craft reviewed evidence that measures to improve insulin action may benefit these conditions. Brain gray and white matter volume increased in the elderly after a 6-month aerobic exercise program (40), and other studies showed that aerobic exercise improved recall and verbal fluency. A recent 4-month study showed that pioglitazone improves memory in nondemented adults, with increase in brain glucose metabolism on positron emission tomography scan, and two studies have shown benefit of rosiglitazone in nondiabetic individuals with AD (41,42). Intranasal insulin flows along the olfactory or trigeminal nerves to bypass BBB in rapidly delivering insulin to the brain, with some evidence of slower axonal insulin transport through olfactory neurons. In a study of intranasal insulin, improvement in memory was seen, although not in subjects with the $\epsilon 4$ polymorphism of apolipoprotein E (43). The Study of Nasal Insulin to Fight Forgetfulness (SNIFF) showed improved memory and attention in 25 adults with early AD who received intranasal insulin 20 units twice daily for 21 days, and further studies of this approach are being carried out.

Pharmacological approaches to insulin resistance

Colin Fishwick (Leeds, U.K.) discussed the early stage of drug discovery in the development of agents to address aspects of insulin resistance. Most medications affect specific molecular targets, usually proteins, with key steps—the identification of a target and validation of a therapy—directed at it, often involving systematic screening of thousands or millions of compounds, with expansion of identified molecules and devising variants to optimize to clinical candidates, subsequently devising clinical trials. In an illustration of the traditional approach, for one target, 3,870,000 compounds were screened, with 879 potential compounds having 87 unique structures, leading to just three potential series of compounds. This may not be cost-effective given that the “small molecule diversity space” is so large and random

high-throughput screening is very inefficient. Of the 10^{60} potential molecules that one could imagine, only a very small number are present in a screening “library” of compounds. An alternative approach is to use the X-ray structure or model of an enzyme to design a molecule that would “fit” as an inhibitor or activator and then design molecules with “virtual high-throughput screening” that can be synthesized and assayed in actual screening. Fishwick described use of a *de novo* molecular design computer program that analyzes protein structures, identifies binding regions, and suggests small structures suitable as ligands. An example of the use of this approach is the study that analyzed the structure of D-alanine:D-alanine ligase, an essential enzyme of *Escherichia coli* cell-wall synthesis, and designed a molecule binding to the active site (44). Currently, Fishwick’s group is attempting to develop antithrombotic agents inhibiting factor XIIIa, which renders blood clots resistant to fibrinolysis by cross-linking fibrin chains. Virtual screening allowed selection of 10 of ~100,000 compounds, one of which was found to be moderately active in actual testing—an increase in efficiency of screening by a factor of 10,000.

Steve Shoelson (Boston, MA) discussed an anti-inflammatory approach to treating type 2 diabetes and cardiometabolic syndrome. Shoelson reviewed a report from 1876 that showed that type 2 diabetes treatment with 5 g sodium salicylate daily effectively reduced glycosuria, finding that occasional reports appeared subsequently, with a study in 1901 showing that aspirin in a dosage of 5–8 g daily had similar effects (45). Note that salicylate does not inhibit cyclooxygenase as does acetyl salicylate; its metabolic target is, instead, nuclear factor- κ B (46), which has a number of effects to reduce insulin action (47–49). If salicylates reverse aspects of the molecular pathogenesis of insulin resistance, then, might these agents offer a potential treatment to lower the blood glucose level in subjects with diabetes? In a study of 8.5 g aspirin daily, glucose levels decreased with improvement in insulin sensitivity (50). A 4-week trial of salsate (disalcid), a dimer of salicylic acid not associated with gastric irritation (4.5 g daily), showed lower blood glucose, triglycerides, free fatty acid, and C-reactive protein, while increasing adiponectin levels (51). Potential mechanisms of salicylate action in type 2 diabetes, beyond inhibition of nuclear

factor- κ B, include reduction in inflammation, increased insulin sensitivity, increased circulating insulin levels as a result of impaired renal insulin clearance, and increased first-phase insulin response to glucose, with reduction in circulating triglycerides, possibly associated with increased energy expenditure and improvement in endoplasmic reticular stress.

The Targeting Inflammation with Salsate in Type 2 Diabetes (TINSAL-T2D) trial is being carried out in two stages. The initial randomized controlled trial of 108 type 2 diabetic patients treated with 0, 3.0, 3.5, and 4.0 g salsate daily, showed 0–2 dropouts in each group, although one patient had to stop the agent because of exacerbation of chronic tinnitus, which became an exclusion for the subsequent stage 2. A1C fell from baseline 7.4–7.9 by 0.4–0.5%, with hypoglycemia in sulfonylurea-treated patients. Triglyceride levels decreased somewhat, with possible mild improvement in cystatin C, a measure of the glomerular filtration rate, but LDL cholesterol increased modestly, and there were signals of increase in body weight and blood pressure. There was a modest decrease in leukocytes, compatible with anti-inflammatory effect. The TINSAL-CVD study is being carried out and will enroll 900 patients randomized to salsate, placebo, and lifestyle, with computed tomography angiography for a 30-month trial.

Peter Grant (Leeds, U.K.) presented what he termed “lessons from the glitazones.” The development of type 2 diabetes follows a prodromal phase of worsening insulin resistance with compensatory increase in insulin secretion, leading to secondary β -cell failure with consequent hyperglycemia. Insulin resistance, in part caused by obesity, occurs in metabolically active tissues, hepatocytes, adipocytes, and myocytes. Insulin resistance also affects cardiac myocytes, endothelial cells, macrophages, and platelets, leading to cardiovascular disease, making insulin resistance a valid target for both prevention and treatment of diabetes and CVD. Insulin resistance regulates nitric oxide production, controlling blood flow and vascular tone, moderates platelet reactivity, and affects intrinsic repair mechanisms. There are also changes in thrombosis and inflammation that link insulin resistance with CVD, with C-reactive protein altering endothelial cell function and increasing thrombus formation and increased clotting factor levels and

inhibition of fibrinolysis and platelet function, all leading to insulin resistance as an “inflammatory atherothrombotic syndrome,” so that treatment targeting insulin resistance may not only improve diabetes but also CVD.

Peroxisome proliferator-activated receptor (PPAR) α and PPAR γ have lipid- and glucose-lowering effects, respectively, PPAR α causing fatty acid oxidation and PPAR γ affecting adipogenesis and lipogenesis, increasing tissue glucose uptake. Pioglitazone appears to activate both of the nuclear receptors, whereas rosiglitazone is more specific for PPAR γ . When a ligand binds to PPAR γ , a dimer with the retinoid X receptor and retinoic acid is formed, binding to a PPAR response element to cause gene transcription, changing transcription of a wide range of proteins.

What Grant termed “lesson 1” is the recognition that the glitazones modulate the expression of dozens of genes in many cell types, so that unintended side effects are inevitable. The system works over time with diurnal variation, further adding complexity. His “lesson 2” is that insulin resistance is a complex phenotype regulated by transcriptional activation and circadian variation in PPAR expression, with short-term insulin resistance presumably physiological and potentially beneficial, whereas long-term insulin resistance is pathological and harmful. Our understanding of the insulin resistance phenotype and its management is, Grant noted, incomplete, and chronopharmacology may be an issue that we currently do not fully understand. The clinical case for managing insulin resistance and risk clustering has been shown in many studies. In A Diabetes Outcome Progression Trial (ADOPT), use of rosiglitazone reduced the risk of monotherapy failure to a level one-third lower than with metformin and two-thirds lower than with glyburide. Hence, Grant termed “lesson 3” the recognition that glitazones effectively produce sustained reduction in glucose and A1C in a dose-related fashion additive to other agents. PPAR agonists have potentially beneficial effects on adiponectin, resistin, leptin, and other adipocytokines; shift fat from visceral to subcutaneous depots; improve free fatty acid metabolism; and increase adipocyte insulin sensitivity. In the macrophage, there may be induction of the adiponectin receptor, suppression of cytokines such as tumor necrosis factor and interleukin-6, and decrease in CD26 expres-

sion. The agents reduce C-reactive protein, adhesion molecules, plasminogen activator inhibitor-1, and fibrinogen levels.

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), 5,238 high-risk type 2 diabetic subjects were randomized for 3 years to pioglitazone or placebo, with what Grant termed weak evidence of benefit and a nonsignificant reduction in primary end point. A meta-analysis of rosiglitazone by Nissen suggested increased myocardial infarction risk, although Grant suggested this appeared on close analysis to be “a statistical quirk.” Subsequent randomized controlled trials, including DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication), ADOPT, RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease—Preterax and Diamicron Modified Release Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial), appear to refute Nissen’s finding, which Grant termed “lesson 4,” that rather than there being increase in risk of ischemic CVD, the glitazones appear to have a minor beneficial effect on outcomes, with both PPARs having beneficial effects on cardiovascular surrogates. Adverse events, however, have been found with the glitazones, with weight gain, a portion of which is due to edema appearing to be mediated by Na retention from direct PPAR γ effect on the collecting tubule, leading to increased risk of heart failure, although not associated with increasing mortality. The agents also increase risk of fracture that affected ~10% of female and 4% of male subjects in ADOPT, occurring in peripheral locations, as a result of conversion of cells that may become osteoblasts into adipocytes. Grant’s “lessons 5” is the development of edema, heart failure, and small bone fracture as unintended consequences of PPAR γ agonist treatment.

There is currently a “pharmaceutical crisis” of rising drug development cost but decreased remuneration, with drugs vulnerable to attack and industry not well able to effectively respond. Reliance on small numbers of high-selling drugs leaves pharmaceutical companies highly vulnerable to rapid downturn in their prospects. Grant recalled the British Prime Minister Harold Macmillan’s response to a journalist when asked what

was most likely to blow governments off course: “Events, dear boy, events,” in summarizing the rapid reversal of rosiglitazone’s prospects.

- 23 May 2007: meta-analysis
- 31 May 2007: shares in GlaxoSmithKline dropped 13%, a loss of £9,000,000,000 in value
- June 2007: Lehman slashed GlaxoSmithKline share target
- February 2008: GlaxoSmithKline pre-tax profits were down £300,000,000
- June 2008: GlaxoSmithKline dismissed 350 scientists
- June 2008: rosiglitazone vindicated by the ACCORD and VADT randomized controlled trials at the American Diabetes Association meeting

The pharmaceutical response is to broaden portfolios to include larger numbers of drugs with smaller sales across a wide range of conditions, with less reliance on blockbusters, expanding into nontraditional markets and building closer links with academic science to exploit strengths in developing targets. The academics, the journals, the medical profession, and the media were complicit in generating what he considered a panic response. Grant’s “lesson 6,” then, is that the blockbuster is a high-risk strategy and that the glitazone story argues strongly for closer links between pharmaceutical and academic medicine to facilitate drug development—a position that he termed precisely opposite to “the developing tide of medical opinion.”

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