MODY

History, genetics, pathophysiology, and clinical decision making

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Studies conducted at the University of Michigan for 60 years and at the University of Chicago for approximately 25 years form the basis of this review. As no field of study can develop or progress in isolation, we have included selected investigations performed in other centers.

EARLY HISTORY—In the academic year 1949–1950, one of us (S.S.F.), while a first-year Fellow in Endocrinology and Metabolism at the University of Michigan (Jerome W. Conn, Division Chief), initiated a prospective, long-term study on the diagnosis, natural history, and clinical genetics of diabetes. Starting with known diabetic patients from the Diabetes Clinic, I recruited their apparently healthy and asymptomatic first-degree relatives (parents, brothers, sisters, and children) for routine oral glucose tolerance tests (OGTTs). As control subjects, I recruited young individuals, many of them students, physicians, nurses, dietitians, and their spouses, who did not have a family history of diabetes or of large newborn babies. The initial objectives were *1*) to define the normal range for the OGTT, *2*) to attempt to unmask the potential diabetic subjects who manifest normal glucose tolerance by the standard OGTT and determine whether the diabetogenic activity of cortisone could be used to uncover a subclinical defect in the metabolism of glucose, and *3*) to carry out periodic follow-up over many years of the apparently healthy first-degree relatives of diabetic patients. In our first publication in 1954 (1), 19% of 152 relatives of known diabetic patients were found to have diabetes by OGTT and, moreover, some were as young as 10 years of age. The same prevalence of 19% was found when testing a larger sample of 438 relatives of known diabetic patients (2).

In 1960, we reported that mild, asymptomatic diabetes occurs in nonobese children, adolescents, and young adults. Their diabetic glucose tolerance and fasting hyperglycemia improved or normalized with the administration of sulfonylurea therapy (3–5). When I presented these results at the First International Congress of Endocrinology in Copenhagen in 1960, Professors Rolf Luft and Knud Lundbaek each remarked that they had never seen such patients and that this kind of diabetes did not exist in Europe. My response was that such diabetic subjects did not come to the physician or investigator; the investigator had to find them by testing the asymptomatic first-degree relatives of known diabetic patients.

The study of asymptomatic diabetes in young people took a new direction in 1958 when I became aware of a 70-year-old male patient who was diagnosed with diabetes at the age of 41 years (Supplementary Fig. 1, individual III-5). He was blind from diabetic retinopathy at the age of 61 years and had an amputation for peripheral vascular disease. His diabetic mother had four diabetic siblings in a sibship of nine (generation II). The proband had four diabetic siblings (in a sibship of six), the majority of whom had evidence of severe micro- and macrovascular disease as well as neuropathy. I recruited the 11 nonobese, apparently healthy and asymptomatic children of the proband for routine OGTT and thus began my studies of the RW pedigree. Seven of the 11 children, ranging in age from 11 to 30 years, were found to have abnormal glucose tolerance. The older three had fasting hyperglycemia (up to 370 mg/dL), one had a diabetic OGTT without fasting hyperglycemia, and three had impaired glucose tolerance (6–8). Subsequently, fasting hyperglycemia developed in these seven children. By prospective routine OGTTs, non–insulin-requiring diabetes was diagnosed in 11 of 21 members of generation V, all of whom were children of diabetic subjects in generation IV. Six members of generation VI have diabetes. Details of diagnosis, natural history, phenotypic expression, and treatment of members of the RW pedigree can be found in references 6–9. Repeated fluctuation between abnormal and normal glucose tolerance was shown to be part of the natural history of this type of diabetes in the RW pedigree (7).

In 1964 at the Fifth Congress of the International Diabetes Federation in Toronto, I first used the term "maturity-onset type diabetes of childhood or of the young" for this type of diabetes and emphasized its strong familial basis (10). This term was applied at that time, as the general thinking was that diabetes could be divided into two major types: juvenile-onset type (now type 1) diabetes with its explosive development to insulin dependence and occurring primarily, but not exclusively, in young people; and maturity-onset (now type 2) diabetes occurring in middle-aged and older people that could be controlled by diet and oral agents and requiring insulin only after many years.

With respect to genetics, it was believed in the 1960s that diabetes was a polygenic disorder, still applicable today for type 1 and type 2 diabetes (11). However in 1974, Robert Tattersall reported a "mild" form of diabetes in three families from King's College Hospital in London and recognized that diabetes in these families had a dominant mode of inheritance (12). Tattersall thought he was dealing with a mild form of diabetes because in many patients, insulin therapy could be

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discontinued and there were fewer diabetes complications than expected, even though some retinopathy, including blindness, was described. With longer follow-up, typical severe microangiopathic and neuropathic complications developed in these families (13). Although Tattersall recognized that these patients "appeared to have maturity-onset type diabetes at an unusually early age," he did not use the term "maturity-onset diabetes of the young" (12). Robert Tattersall spent the 1973–1974 academic years with me in Ann Arbor. On the basis of the records of the prospective study that had been ongoing in Ann Arbor since 1949, we identified, in addition to the RW pedigree, 23 other families in whom our working criteria for maturity-onset type diabetes of the young applied. We were able to differentiate between the pattern of inheritance in these families from that seen in 35 families with classical juvenile-onset type (type 1) diabetes and confirmed autosomal-dominant inheritance for the former (14). In this article, we first used the abbreviation or acronym MODY for maturity-onset diabetes of the young. These two articles (12,14) provided some of the first evidence that diabetes is genetically heterogeneous, further discussed in my Banting Memorial Lecture of 1978 (6). Robert Tattersall deserves full credit for suggesting that the familial disease previously designated in 1964 as maturity-onset diabetes of the young is inherited in a dominant fashion. Tattersall quotes Cammidge who proposed, in 1928, dominant inheritance in a mild form of familial diabetes (15). This was based entirely on the finding of glycosuria, even though assays for measuring blood glucose levels had been available for approximately a decade at the time. Thus in Cammidge's pedigrees, one cannot distinguish between primary renal glycosuria or the type 3 form of MODY (MODY3 due to mutations in the gene encoding the transcription factor hepatocyte nuclear factor 1α), which is also characterized by renal glycosuria.

Since 1975, I have used autosomal-dominant inheritance consistently as one of the requirements for the definition of MODY. Although young age at diagnosis of diabetes is an important feature of MODY, age at diagnosis and time interval between diagnosis and insulin requirement should no longer be criteria for the definition of MODY as diagnosis may be made for the first time in subjects over the age of 25 years and also in subjects treated with insulin. For example, in the RW pedigree in which prospective testing started in generation IV, the mean age at diagnosis was 55 years in generations II and III, 35 years in generation IV, 20 years in generation V, and 11 years in generation VI.

PRESENTATION, PHENOTYPIC EXPRESSION, AND NATURAL HISTORY OF MODY

—MODY can be suspected and recognized if a type 2 diabetes–like condition occurs in two to three or more generations and the pattern of inheritance is consistent with autosomal-dominant inheritance (6,7). The latter is the hallmark of MODY and distinguishes it from type 2 diabetes. MODY can be diagnosed at a young age and frequently in childhood or early adolescence (9–14 years of age or earlier), particularly if sought by routine OGTT. Occasionally, MODY can also be found in type 1 diabetes–like families (16). By serial testing young members of the RW pedigree, we showed that there can be very slow progression from normal to impaired glucose tolerance, from impaired to diabetic glucose tolerance with normal fasting plasma glucose level (up to 18 years), and very slow progression from that state to fasting hyperglycemia (up to 27 years). Children and adolescents with MODY may also have fasting hyperglycemia at diagnosis and rapid progression to insulin requirement. Thus, there is a variable course in severity and rate of progression of hyperglycemia and decrease in insulin levels. Most members of MODY families are not obese, in contrast to patients with type 2 diabetes. However, this is not uniformly true, as discussed below. In many MODY families, typical microangiopathic and macroangiopathic complications occur in a frequency similar to the pattern seen in type 2 diabetic patients with similar degrees of hyperglycemia (6,7,17,18). In contrast to the clinical characteristics reported for the RW pedigree (MODY1) and families with MODY3 are subjects with glucokinase mutations (GCK-MODY, MODY2) who have mild fasting (110–140 mg/dL) and postprandial hyperglycemia from birth, lack of progression, and absence of insulin requirement and vascular complications.

INSULIN SECRETION IN MODY: REPORTS BEFORE THE MOLECULAR GENETIC ERA

—In 1969, we first reported that some asymptomatic children, adolescents, and young adults with MODY had delayed and subnormal insulin responses to glucose (19). Low insulin responses to oral glucose in the RW pedigree were seen in diabetic and "nondiabetic carrier" subjects.

Long-term administration of sulfonylureas may induce increases in glucose-induced insulin secretion for up to 33 years in some subjects with MODY in the RW pedigree. However, in most, glucose-induced insulin secretion decreases over time (1–4% per year) (5). Some patients become unresponsive to sulfonylureas after 3–25 years and then have very small or no increase in glucose-induced insulin secretion and require insulin to normalize fasting hyperglycemia. The insulin and C-peptide levels can become so low in some MODY patients that they resemble type 1 diabetic patients and exhibit the same typical labile glucose levels.

In 1986, I reported two families (TE and H), each with four generations of diabetes consistent with autosomal dominant inheritance (20). Both families were studied in the 1970s and early 1980s. In contrast to the RW pedigree and most other MODY families, members of the TE pedigree had supernormal insulin responses to oral glucose, and members of the H pedigree had a delayed insulin response at 0.5 h of the OGTT and then a supernormal insulin response, as compared with 150 healthy control subjects. I suggested that these two families represented examples of the heterogeneity of insulin secretion in MODY. In retrospect, the high insulin response in the H family can be explained by mild obesity, as discussed later. The high insulin response in the TE family is unexplained. As these families are no longer available for genetic studies, we cannot present them as evidence of heterogeneity of insulin responses in MODY.

MOLECULAR GENETICS OF MODY: GENETIC HETEROGENEITY

—Genetic studies of diabetes in the RW pedigree began in 1985. Alan Permutt et al. (21) typed the insulin gene *VNTR* and showed that it did not cosegregate with diabetes. They also excluded linkage to the human insulin receptor gene in the RW and three other MODY pedigrees (including our H and TE families) in 1987 (22). The latter results were confirmed by Arthur Vinik in 1988 while on sabbatical in the laboratory of Graeme Bell, in addition to excluding the erythrocyte/HepG2 glucose transporter (GLUT1) and the apolipoprotein

B genes (23). This latter study began my collaboration with Graeme Bell, which continues more than 23 years later.

A major breakthrough in the molecular genetics of diabetes in the RW pedigree came in 1991, when after testing more than 75 DNA markers, Graeme Bell, Nancy Cox, and colleagues (24) found that a DNA polymorphism in the adenosine deaminase gene (*ADA*) on the long arm of chromosome 20 cosegregated with MODY. Although the gene responsible for MODY is tightly linked to the *ADA* gene, it was recognized that it was not the *ADA* gene itself. These results were confirmed and extended by Bowden et al. (25) who in 1992 showed linkage of MODY to the marker D20S16. It took 5 years to identify the gene responsible for MODY (now called MODY1 to distinguish from other forms of MODY) in the RW pedigree. In 1996, Graeme Bell, Kazuya Yamagata, and colleagues together with Stefan Fajans (26) identified a nonsense mutation in the gene encoding the transcription factor hepatocyte nuclear factor (HNF) 4α (gene symbol, *HNF4A*; p.Q268×) as the cause of diabetes. At the same time, this group with Andrew Hattersley and Philippe Froguel reported that mutations in the gene encoding another transcription factor, HNF-1α (*HNF1A*), were responsible for MODY3 (27). Both are transcription factors involved in tissue-specific regulation of liver genes but also expressed in pancreatic islets and other tissues.

Philippe Froguel and Alan Permutt (28), and independently Andrew Hattersley (29), and their colleagues showed linkage of the glucokinase gene on chromosome 7 with MODY, suggesting that mutations in this candidate gene were another cause of MODY. Subsequently, Nathalie Vionnet, Philippe Froguel, and colleagues in collaboration with Graeme Bell identified mutations in the glucokinase gene (*GCK* and MODY2) (30). These latter studies highlighted the key role of glucokinase as the glucose sensor of the β-cell and its regulation of glucose-stimulated insulin secretion.

Doris Stoffers and Joel Habener in 1997 reported a five-generation Virginia family in which MODY cosegregated with a frame-shift mutation (p.P63fsX60) in the gene encoding another β-cell transcription factor, insulin promoter factor 1 (*IPF1*), termed MODY4 (31). The proband in that family was an infant with pancreatic agenesis, neonatal diabetes, and pancreatic exocrine dysfunction who was homozygous for this mutation. A Michigan–Kentucky family with the same mutation and which shared a common ancestor with the Virginia family was reported by us in 2010 (32). Also in 1997, Graeme Bell, Yukio Horikawa, and colleagues reported a mutation in the gene encoding the transcription factor HNF-1β (*HNF1B*) in a patient with MODY and early-onset kidney disease (MODY5) (33).

Genetic studies have revealed that MODY is not a single genetic entity but can have many causes. Online Mendelian Inheritance in Man lists 11 forms of MODY (Supplementary Table 1). The most common causes of MODY are mutations in *HNF1A* and *GCK*, and less commonly *HNF4A*, *HNF1B*, and *INS* (34). Mutations in the other genes listed in Supplementary Table 1 are quite rare. As there are families with a MODY-like phenotype of unknown cause, we anticipate that ongoing genetic studies will identify additional genes.

PATHOPHYSIOLOGICAL STUDIES OF MODY IN THE MOLECULAR GENETIC ERA

—Prior to the identification of the genes responsible for MODY, we had suggested that MODY was a primary genetic disorder of the β-cell (19,35). The genetic studies mapping the MODY1 gene to the region of *ADA* allowed us to identify carriers and thus examine insulin secretion and action directly in patients with MODY1 (36).

Using the frequently sampled intravenous glucose tolerance test and Bergman's minimal model, as well as Polonsky's low-dose prolonged glucose infusion to measure insulin secretion rate (ISR) and pulse analysis (36), we (in collaboration with Kenneth Polonsky and Jeffrey Halter) showed that nondiabetic carriers had normal sensitivity to insulin and normal acute insulin response to intravenous glucose. However, the same subjects had decreased mean plasma C-peptide concentrations and reduced absolute amplitude of insulin secretory oscillations during prolonged glucose infusion. These responses were similar to those observed in diabetic carriers. Thus, deranged and deficient insulin secretion, and not insulin resistance, appears to be the genetic or the primary abnormality that characterizes nondiabetic carriers in the RW pedigree. Diabetes becomes manifest when additional superimposed environmental factors supervene (e.g., physiological decrease in insulin sensitivity with growth and puberty) (6,7).

Again in collaboration with Kenneth Polonsky and his colleagues, we examined the dose–response relationship between plasma glucose concentration and ISR during a graded intravenous glucose infusion (37). Nondiabetic MODY1 subjects had a defective insulin secretory response to an increase in plasma glucose concentration, and this response differed from nondiabetic MODY2 and MODY3 subjects (37–40). These series of studies led us to propose that MODY is a primary genetic disorder of the pancreatic β-cell with mutations in different genes affecting glucose-stimulated insulin secretion (40).

In the 1960s, we demonstrated that amino acids and proteins are potent stimuli to insulin secretion (41). Among amino acids, arginine is the most potent stimulus to insulin and glucagon secretion. To ascertain the effects of arginine on insulin and glucagon secretion in MODY1 (42), we studied nondiabetic noncarriers, nondiabetic carriers, and diabetic carriers in the RW pedigree. There was a decrease in insulin secretion in the nondiabetic carriers in response to a constant arginine infusion that was exacerbated during the hyperglycemic clamp and in diabetic carriers. Glucagon secretion at basal glucose concentration was also decreased in both the nondiabetic and diabetic carriers. We also observed that nondiabetic carriers had a reduced amylin response to arginine that was proportional to the deficit in insulin secretion (43). There was also reduced pancreatic polypeptide (PP) secretion in diabetic and nondiabetic carriers (43). Thus, mutations in *HNF4A* appear to confer a generalized defect in pancreatic islet cell function involving β-, α-, and PP-cells. This generalized defect could either be due to defects in common signaling pathways, to an overall reduction in the mass of pancreatic islet cells, or a combination of both (43).

PREDICTIVE BIOMARKERS FOR MODY

—HNF-1α and HNF-4α were initially identified in the liver, where they regulate the expression of a large number of genes encoding serum proteins, including clotting factors and apolipoproteins, among others. Thus, we and others have searched for serum markers to identify patients with MODY due to *HNF4A* and *HNF1A* mutations. With George Brownlee, we measured factor IX levels in plasma and found no significant difference between carriers with MODY1 (RW pedigree) and controls (G. Brownlee,

S.F.F., and G.I.B., unpublished data). In contrast, triglyceride and apolipoprotein C-III levels are significantly reduced (44,45). Moreover, the levels of apolipoproteins A-II and C-III, lipoprotein (a), and triglycerides were significantly reduced in carriers in the RW pedigree whether diabetic or nondiabetic (45), indicating that HNF-4α deficiency rather than hyperglycemia is the primary cause of these decreases. Although the levels of triglycerides and apolipoproteins are significantly decreased in *HNF4A* mutation carriers, there is still substantial overlap between groups, which limits their usefulness as biomarkers to identify individuals who would benefit from genetic testing.

Apolipoprotein M levels are reduced in *HNF1A* mutation carriers but are not a useful predictive marker (46). However, Anna Gloyn and her colleagues have recently shown that high-sensitivity C-reactive protein (hs-CRP) is lower in HNF1A-MODY than in other forms of diabetes, and measurement of hs-CRP may be useful as a prescreening tool to identify patients for genetic testing (47).

PHENOTYPIC HETEROGENEITY IN MODY—The clinical phenotype of patients with the same form of MODY can vary, as can the phenotype of individuals within a family who share the same mutation (48,49). This reflects differences in the effect of the mutation on protein functions as well as the modifying effect of environmental factors (diet, exercise, and other nongenetic factors) on genetics. This is illustrated for MODY1 by a male carrier in the RW pedigree, who at 44 years of age had normal glucose levels in all OGTTs, an age by which all other carriers had developed diabetes (26). Obesity can also modify the phenotype of carriers (32). Finally, the clinical progression can vary within MODY families and can include neonatal hypoglycemia in some subjects with MODY1 (50,51).

BODY WEIGHT AND MODY—The majority of subjects with MODY are not obese. In the past, the presence of obesity in a diabetic subject was considered to be evidence against MODY. In 2010, we described a five-generation Michigan–Kentucky pedigree (32), ascertained through a proband with neonatal diabetes and pancreatic agenesis, that was homozygous for the *IPF1* mutation p.P63fsX60 (31). By family history, we ascertained 110 individuals in this pedigree. Diabetic and nondiabetic subjects were genotyped and phenotyped where possible. There were 16 diabetic subjects who carried the *IPF1* mutation and 4 in whom it could be presumed to be present. There were eight diabetic subjects who did not carry the mutation and had type 2 diabetes. Both MODY4 and type 2 diabetes in this pedigree are associated with obesity and hyperinsulinemia. Obesity and hyperinsulinemia have also been observed sporadically in MODY1, MODY3, and MODY6 subjects, and hyperinsulinemia may be a clinical feature when obesity occurs together with MODY (32). Thus, genetic testing for MODY should be considered in multigenerational families, even in the presence of obesity, especially if such families contain young diabetic members.

MACROSOMIA AND TRANSIENT NEONATAL HYPOGLYCEMIA IN MODY1—In 2007, Ewan Pearson, Andrew Hattersley, and colleagues reported a remarkable and previously unrecognized feature of the natural history of MODY1 (50). In a comparison of 54 mutation carriers (from 15 pedigrees with 12 different mutations) with noncarrier family members, they found a significant increase in median birth weight (790 g) with a 56% prevalence of macrosomia in carriers versus 13% in noncarriers. Transient neonatal hypoglycemia was reported in 8 of 54 neonates. Three of these infants had hyperinsulinemia.

We examined macrosomia and neonatal hypoglycemia in the RW pedigree (51). In 34 mutation carriers, birth weight was increased by a median of 751 g as compared with noncarriers. Macrosomia occurred in 59% compared with 8% in noncarriers. In both the subjects studied by Pearson et al. (51) and in the RW pedigree, macrosomia was inherited from mother (64 and 68%, respectively) and father (46 and 47%, respectively). There were only two instances of neonatal hypoglycemia in the RW pedigree. Thus, the natural history of MODY1 includes hyperinsulinemia in fetal and neonatal life, progressing to insulin-deficient diabetes in later years. The molecular basis for the differential effects of HNF-4α deficiency on β-cell function and insulin secretion in neonates and later in life and the exact timing of the switch from hyperinsulinemia to hypoinsulinemia are unknown. In this regard though, a male carrier with macrosomia had, at age 3 years, a normal OGTT but a low-normal insulin response to glucose (51).

Further analysis of macrosomia of MODY1 infants has revealed no effect of parental origin of the *HNF4A* mutation on birth weight and no effect of severity of macrosomia on age of diagnosis of subsequent diabetes (E.R. Pearson, S.S.F., G.I.B., and A.T. Hattersley, unpublished observations).

Macrosomia and neonatal hypoglycemia have not been associated with *HNF1A* mutations (50). This raises the question as to which genes are regulated by *HNF4A* but not by *HNF1A* in β-cell development.

MODY AND THE GENETICS OF TYPE 2 DIABETES—As predicted by J.V. Neel in the premolecular genetic era (11), type 2 diabetes is a polygenic disease with superimposed precipitating environmental factors. We began our studies of MODY with the expectation that the identification of the genes responsible for MODY would provide insight into the genetics and pathophysiology of type 2 diabetes. Common variants in *HNF1A* and *HNF1B* affect risk of type 2 diabetes in large-scale meta-analyses, and common variants in *HNF4A* may also be associated with type 2 diabetes, at least in some populations (52,53). Despite the lack of evidence that mutations in MODY-related genes are responsible for the development of type 2 diabetes in the majority of cases, the molecular mechanisms by which variants in these genes lead to hyperglycemia may be relevant to the pathophysiology of the β-cell defects in type 2 diabetes. In this regard, defects in the metabolism of glucose in the pancreatic β-cell may be responsible, at least in part, for the impaired insulin secretion seen in patients with type 2 diabetes as it is in MODY. Thus, lessons learned from studies of MODY may improve our understanding of type 2 diabetes. Resequencing of the various MODY genes as well as the genes responsible for other monogenic forms of diabetes (dominant and recessive, syndromic and nonsyndromic) is a goal of the National Institutes of Health–funded T2-GENES Consortium, and these studies will help elucidate the role of monogenic diabetes genes in the etiology of type 2 diabetes.

DECISION MAKING IN MODY—When a patient who appears to have type 2 diabetes but also has a family history of multigenerational diabetes, particularly when early-onset, MODY should be suspected (see Supplementary Data, Summary of Clinical Issues in MODY). Most

patients with MODY are lean, but obesity should not exclude a diagnosis of MODY. Likewise, but less commonly, when a young diabetic patient resembling type 1 diabetes is islet autoantibody negative and has measurable C-peptide levels, MODY should be suspected. Under these circumstances, genetic testing is indicated. Genetic testing will disclose whether MODY is present and will distinguish between subtypes of MODY, and thereby give clues to prognosis and treatment. Once a diagnosis for MODY is made, other family members, both diabetic and nondiabetic, should be screened for the family-specific mutation and possible abnormalities of carbohydrate metabolism. Such screening procedures are as follows, listed in ascending order of sensitivity: hemoglobin A1C (A1C), fasting plasma glucose, 2-h postglucose levels, 1-h postglucose levels, and OGTT (most sensitive) (54). Genetics counseling should be provided, especially in children.

The most common causes of MODY are mutations in *HNF1A* and *GCK*, and mutations in these two genes account for 80% (*HNF1A*, 58%; *GCK*, 22%) of cases in the U.K. (the relative frequency of *GCK* is higher in cases ascertained through pediatric clinics, whereas the frequency of *HNF1A* is higher in cases from adult clinics) (34,55). Mutations in *HNF4A* account for ~5% of cases and *HNF1B* (renal cysts and diabetes syndrome) for 2%. Mutations in other genes are very rare causes of MODY. We focus our genetic testing on mutations in *HNF1A*, *GCK*, and *HNF4A* and *HNF1B* if there is evidence of renal cysts or abnormal kidney or genital tract development.

Patients with a genetic diagnosis of *HNF1A*- or *HNF4A*-MODY can often be treated with sulfonylureas with good glycemic control. There is usually progressive deterioration in pancreatic β-cell function and/or mass in patients with these two forms of MODY (5). Our experience suggests that good control slows this decline, but there are no controlled trials to prove this and such studies are needed. A low carbohydrate diet might be helpful along with exercise to increase insulin sensitivity. Glinides may be considered in the patients with *HNF1A*-MODY, as this class of sulfonylureas is shorter acting and has lower risk of reactive hypoglycemia (56).

Patients with GCK-MODY generally need no treatment. In patients with gestational diabetes, treatment is required. If A1C levels are >6.5% or fasting blood glucose >126 mg/dL, some clinicians have suggested that Metformin may reduce fasting blood glucose levels. However, we have seen MODY2 patients with fasting plasma glucose in the 140–150 mg/dL range who have not progressed or developed complications for up to five decades. Otherwise, insulin is the only established treatment because both insulin secretion and hepatic glucose production are abnormal.

In the future, glucokinase activator class of drugs might be useful in GCK-MODY. Whether agonists for other gene mutations might be helpful is speculative. In *Pdx1*-deficient mice that develop MODY4-type diabetes, an experimental procedure has been discovered that prevents apoptotic and necrotic β-cell death and diabetes (57). Whether this procedure will be applicable to humans and other forms of MODY remains to be determined.

CONCLUDING REMARKS—When we began our studies of MODY 60 years ago, very little was known about the genetics and pathophysiology of diabetes. Patients with diabetes were described as having juvenile-onset or maturity-onset diabetes. These terms have evolved to type 1 and type 2 diabetes, with insulin-dependent and non–insulin-dependent also being briefly used as the diabetes community struggled and continues to struggle with how best to define the various forms of diabetes. Monogenic forms of diabetes including MODY are now recognized as a discrete class of diabetes (58,59). MODY was initially thought to be a rare form of diabetes. We now know that MODY is very common, masquerading as type 1 diabetes or, more commonly, type 2 diabetes. The frequency of MODY among patients with diabetes is estimated to be 1–2%. The majority of MODY patients are undiagnosed or missed (34). Genetic testing for MODY is now routine and can affect correct diagnosis and treatment (60). MODY has entered the mainstream.

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