What Is Gestational Diabetes?

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Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy. As such, GDM is the product of routine glucose tolerance screening that is currently carried out in otherwise healthy individuals. Like other forms of hyperglycemia, GDM is characterized by pancreatic β-cell function that is insufficient to meet the body's insulin needs. Available evidence suggests that β-cell defects in GDM result from the same spectrum of causes that underlie hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance. Thus, GDM often represents diabetes in evolution and, as such, holds great potential as a condition in which to study the pathogenesis of diabetes and to develop and test strategies for diabetes prevention.

DETECTION: POPULATION SCREENING FOR GLUCOSE INTOLERANCE

— The clinical detection of GDM is accomplished in different ways in different countries. In general, the approaches apply one or more of the following procedures: *1*) clinical risk assessment, *2*) glucose tolerance screening, and *3*) formal glucose tolerance testing. The procedures are applied to pregnant women not already known to have diabetes. Controversies regarding the optimal methods for detecting GDM are beyond the scope of this article. The relevant point is that the screening for GDM is the only standard medical practice that applies screening for glucose intolerance to otherwise healthy individuals. Regardless of the glucose thresholds that are used to diagnose GDM, the patients are relatively young individuals whose glucose levels are in the upper end of the population distribution during pregnancy. A small minority of those women have glucose levels that would be diagnostic of diabetes outside of pregnancy. The large majority have lower glucose levels when they are diagnosed with GDM, but they are at high risk for developing diabetes after pregnancy. Together, patients with GDM offer an important opportunity to study the evolution of diabetes and to develop, test, and implement strategies for diabetes prevention and early treatment.

GLUCOSE REGULATION IN PREGNANCY AND GDM

— Pregnancy is normally attended by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in type 2 diabetes. The insulin resistance of pregnancy may result from a combination of increased maternal adiposity and the insulin-desensitizing effects of hormones made by the placenta. Rapid abatement of insulin resistance after delivery suggests a major contribution from placental hormones. Potential mechanisms underlying the normal insulin resistance of pregnancy are reviewed by Barbour et al. (1) elsewhere in this supplement. Pancreatic β-cells normally increase their insulin secretion to compensate for the insulin resistance of pregnancy. As a result, changes in circulating glucose levels over the course of pregnancy are quite small compared with the large changes in insulin sensitivity. Thus, robust plasticity of β-cell function in the face of progressive insulin resistance is the hallmark of normal glucose regulation during pregnancy.

Like all forms of hyperglycemia, GDM results from an endogenous insulin supply that is inadequate to meet tissue insulin demands. Inadequate insulin secretion is most easily demonstrated in late pregnancy, when insulin requirements are uniformly high and differ only slightly between normal women and women with GDM (2–8). By contrast, insulin responses to nutrients are much lower in women with GDM (2,3,5–9). One potential pathophysiology for GDM is a limitation in pancreatic β-cell reserve that becomes manifest as hyperglycemia only when insulin secretion does not increase to match the increased insulin needs of late pregnancy. At first glance, studies conducted outside of pregnancy seem to support that scenario. Insulin levels are often similar between women without and with a history of GDM (3,7–11), suggesting that inadequate insulin secretion in the GDM group was limited to pregnancy. However, women with a history of GDM are usually considerably more insulin resistant than nonpregnant normal women. Thus, insulin levels would be higher in the prior GDM patients if their β-cell function were normal. The similarity of insulin levels in the face of differing insulin resistance reveals at a qualitative level a β-cell defect in women with prior GDM. The defect can be quantified by expressing insulin levels relative to each individual's degree of insulin resistance, using the hyperbolic relationship that exists between insulin sensitivity and insulin secretion (12–15). That approach reveals a large defect in pancreatic β-cell function in women with GDM both during and after pregnancy (8,10,15). Figure 1 displays data from Homko et al. (7) and data from our own group that make this point clearly. In both sets of data, differences in insulin resistance between normal and GDM groups are greatest outside of pregnancy, while differences in insulin levels or secretion are greatest during the third trimester. However, changes in insulin sensitivity and secretion occur in parallel in the two groups, albeit at lower

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Abbreviations: DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; PIPOD, Pioglitazone in Prevention of Diabetes; TRIPOD, Troglitazone in Prevention of Diabetes.

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

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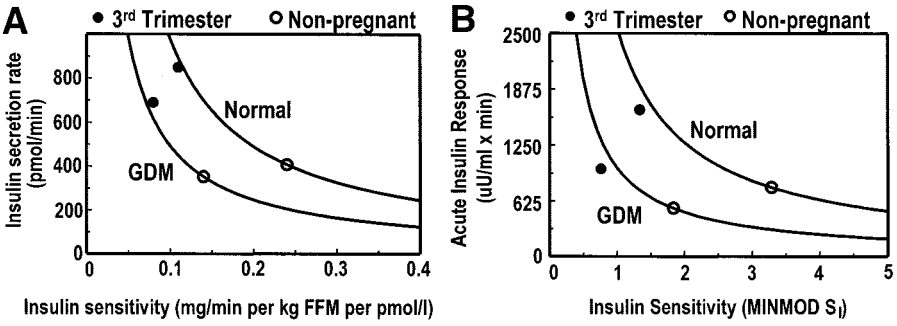

Figure 1—A*: Relationships between prehepatic insulin secretion rate calculated from deconvolution of C-peptide levels and insulin sensitivity calculated as steady-state glucose utilization divided by steady-state insulin levels, both during steady-state hyperglycemia (3 h, 180 mg/dl). Data are from seven women who had GDM and eight women who maintained normal glucose tolerance during pregnancy, all studied by Homko et al. (7). Figure is reproduced from Buchanan (15).* B*: Relationships between acute insulin response to intravenous glucose (AIRg, incremental insulin area during first 10 min after glucose injection) and insulin sensitivity measured by the minimal model (min^{-1} per $\mu U/ml \times 10^4$) in 99 Hispanic women who had GDM and seven Hispanic women who maintained normal glucose tolerance during and after pregnancy. For both studies, tests were performed in the third trimester and again remote from pregnancy. Curved lines represent insulin sensitivity-secretion relationships defined by the product of insulin sensitivity and secretion in nonpregnant women.*

overall insulin levels in the GDM groups. β-Cell compensation for insulin resistance is reduced to a similar degree during and after pregnancy in both studies (by 39 and 47%, respectively, in the Homko study and by 69 and 62%, respectively, in our study). These findings, which are consistent with the earlier studies of Catalano et al. (3,9), provide evidence that GDM represents detection of chronic β-cell dysfunction, rather than development of relative insulin deficiency as insulin resistance increases during pregnancy. Thus, the routine glucose screening that is conducted during pregnancy serves as a useful tool for detection of women with chronic and, as we will see below, often worsening β-cell dysfunction.

While the full array of causes of β-cell dysfunction in humans remains to be determined, clinical classification of diabetes outside of pregnancy is based on three general categories of dysfunction: *1*) occurring on a background of chronic insulin resistance, *2*) autoimmune, and *3*) monogenic. There is evidence that each of these three categories contributes to β-cell dysfunction in cases of GDM, a fact that is not surprising given that GDM is detected by what amounts to population screening for elevated glucose levels in young women.

GDM on background of chronic insulin resistance

During pregnancy, when GDM is diagnosed, insulin sensitivity is quite low in normal women and in women with GDM. Nonetheless, precise measures of insulin sensitivity applied in the third trimester have revealed slightly greater insulin resistance in women with GDM than in normal pregnant women. The additional resistance occurs for insulin's actions to stimulate glucose disappearance (2,3) and to suppress both glucose production (2,3) and fatty acid levels (2). Abatement of the physiological insulin resistance of pregnancy after delivery leads to a greater increase in insulin sensitivity in normal women than in women with GDM. In other words, the abatement reveals a separate chronic form of insulin resistance in the women who had GDM. This finding of greater insulin resistance in women with prior GDM has been consistent across studies in which whole-body insulin sensitivity has been measured directly (8,10,11,16–19). It indicates that most, although probably not all (see below), women who develop GDM have chronic insulin resistance. Serial measurements of insulin sensitivity starting before pregnancy have documented insulin resistance before conception and at the beginning of the second trimester in women with GDM (3,9).

Given that GDM represents a cross section of glucose intolerance in young women, mechanisms that lead to chronic insulin resistance in GDM are likely as varied as they are in the general population. Obesity is a common antecedent of GDM, and many of the biochemical mediators of insulin resistance that occur in obesity have been identified in small studies of women with GDM or a history thereof. These mediators include increased circulating levels of leptin (20) and the inflammatory markers tumor necrosis factor-α (21) and C-reactive protein (22), decreased levels of adiponectin (23,24), and increased fat in liver (25) and muscle (26). In vitro studies of adipose tissue and skeletal muscle from women with GDM or a history thereof have revealed abnormalities in the insulin signaling pathway (27–30), abnormal subcellular localization of GLUT4 transporters (31), decreased expression of peroxisome proliferator–activated receptor-γ (27), and overexpression of membrane glycoprotein 1 (29), all of which could contribute to the observed reductions in insulin-mediated glucose transport. To date, studies of cellular mechanisms of insulin resistance in GDM have been small, and it is not clear whether any of these abnormalities represent universal or even common abnormalities underlying the chronic insulin resistance that is very frequent in GDM.

The data presented in Fig. 1 and serial studies of insulin sensitivity and secretion before and during pregnancy (3,9) reveal that many women with GDM have the ability to change their insulin secretion reciprocally to short-term changes in insulin sensitivity. However, they do so along an insulin sensitivity-secretion relationship that is ~40–70% lower (i.e., 40–70% less insulin for any degree of insulin resistance) than the relationship in normal women. Thus, many women with GDM do not have a fixed limitation in their insulin secretory capacity. Rather, they have insulin secretion that is low relative to their insulin sensitivity, but acutely responsive to changing sensitivity. It is important to distinguish these short-term relationships between insulin sensitivity and secretion, which occur over several months, from changes that occur over the course of years (Fig. 2). The short-term changes reflect normal physiology, albeit offset to insulin levels that are lower than normal for the degree of insulin resistance. The long-term changes often reflect progressive loss of β-cell compensation for insulin resistance (Fig. 2*A*), a loss that leads to progressive hyperglycemia and diabetes (Fig. 2*B*). Routine blood glucose screening during pregnancy appears to identify women with declining β-cell function at a time when they may be amenable to interventions to slow or stop progression to diabetes (see below).

The etiology of falling β-cell function

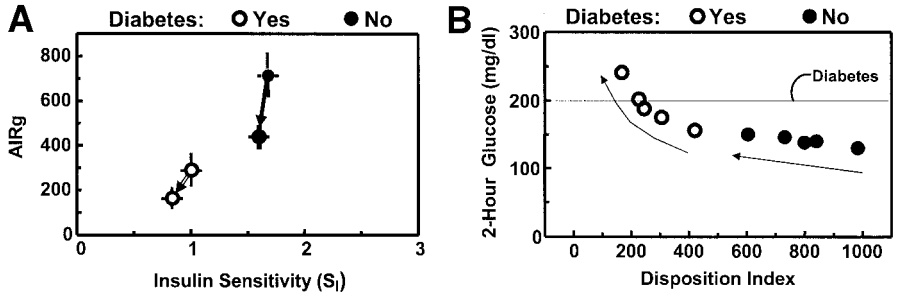

Figure 2—A: *Coordinate changes in S_I and AIRg, as defined in Fig. 1, in 71 nonpregnant Hispanic women with prior GDM. Intravenous glucose tolerance tests (IVGTTs) were performed after index pregnancies at 15-month intervals for up to 5 years or until fasting glucose exceeded 140 mg/dl. Symbols are mean (± SE) at initial and final visits, during median follow-up of 44 months in 24 women who had diabetes at one or more evaluations (diabetes = yes), and during median follow-up of 47 months in 47 women who were not diabetic at any evaluation (diabetes = no).* B: *Coordinate changes in β-cell compensation for insulin resistance (disposition index, the product of S_I and AIRg) and 2-h glucose levels from 75-g oral glucose tolerance tests in the same 71 women. Symbols represent mean data at 15-month intervals, ordered relative to final visits. Arrows denote direction of change over time. The mean disposition index in Hispanic women without a history of GDM was 2,018. Adapted from Xiang et al. (57).*

that occurs on a background of chronic insulin resistance is unknown. Small-scale genetic studies comparing frequencies of alleles known to be associated with diabetes outside of pregnancy or to be involved in glucose metabolism have revealed small but statistically significant differences between normal women and women with GDM for variants in the promoter of the glucokinase gene that is relatively specific for β-cells (32), in the *calpain-10* gene (33), in the gene for the sulfonylurea receptor 1 (34), and in the gene for the β-3 adrenoreceptor. Insulin resistance was not characterized in these studies, so it is not clear whether the findings are specifically relevant to evolving type 2 diabetes. Observations by our group in Hispanic women with prior GDM indicate that they develop progressive loss of β-cell function as a result of high insulin secretory demands. Reducing the secretory demands by treating insulin resistance with the thiazolidinedione compound, troglitazone (35), preserved β-cell function and reduced the risk of progression to type 2 diabetes. We have recently observed the same phenomenon using another thiazolidinedione drug, pioglitazone (36). These findings suggest that Hispanic women who develop GDM do not tolerate high levels of insulin secretion for prolonged periods of time. The biology underlying poor tolerance of high rates of insulin secretion is speculative at this time, but could include susceptibility to β-cell apoptosis induced by islet-associated amyloid polypeptide (37,38), oxidative stress (39), or stress to the endoplasmic reticulum (40) .

GDM and autoimmune β-cell dysfunction

A small minority (≤10% in most studies) of women with GDM have circulating antibodies to pancreatic islets (anti-islet cell antibodies) or to β-cell antigens such as GAD (anti-GAD antibodies) (2,41–46). Although detailed physiological studies are lacking in these women, they most likely have inadequate insulin secretion resulting from autoimmune damage to and destruction of pancreatic β-cells. They appear to have evolving type 1 diabetes that comes to clinical attention through routine glucose screening during pregnancy. Whether pregnancy can actually initiate or accelerate islet-directed autoimmunity is unknown. The frequency of anti-islet and anti-GAD antibodies in GDM tends to parallel ethnic trends in the prevalence of type 1 diabetes outside of pregnancy. Patients with anti-islet or anti-GAD antibodies often, but not invariably, are lean. They can have a rapidly progressive course to overt diabetes after pregnancy (43).

GDM and monogenic diabetes

Monogenic forms of diabetes outside of pregnancy can result from variants in autosomes (autosomal dominant inheritance pattern, commonly referred to as "maturity-onset diabetes of the young" or "MODY" with genetic subtypes denoted MODY1, MODY2, etc.) and from variants in mitochondrial DNA (maternally inherited diabetes, often with distinct clinical syndromes such as deafness). The age at onset tends to be young relative to other forms of nonimmune diabetes, and patients tend not to be obese or insulin resistant. Both features point to abnormalities in the regulation of β-cell mass and/or function that are severe enough to cause hyperglycemia in the absence of insulin resistance. Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes for glucokinase (MODY2) (42,47–49), hepatocyte nuclear factor 1α (MODY3) (42), and insulin promoter factor 1 (MODY4) (42). Mitochondrial gene mutations have also been found in small numbers of patients with GDM (50). These monogenic forms of GDM appear to account for only a small fraction of cases of GDM (42,47–50). They likely represent examples of preexisting diabetes that is first detected by routine glucose screening during pregnancy.

GDM: AN OPPORTUNITY FOR THE STUDY OF EVOLVING DIABETES AND FOR DIABETES PREVENTION

— GDM is a form of hyperglycemia that is detected at one point in a woman's life. Some women have hyperglycemia that is already in the range that would be diagnostic of diabetes outside of pregnancy. The rest have glucose intolerance that could be *1*) limited to pregnancy, *2*) chronic and stable, or *3*) a stage in progression to diabetes. As recently reviewed by Kim et al. (51), long-term follow-up studies reveal that most, but probably not all, women with GDM go on to develop diabetes outside of pregnancy, especially during the first decade after the index pregnancy (Fig. 3). Thus, in most women, GDM is a stage in the evolution of diabetes, leading to recommendations that women with GDM be tested for diabetes soon after pregnancy and periodically thereafter. Optimal timing of such testing has not been established. Diabetes prevalence rates of ~10% in the first few months postpartum (52) support testing at that time. Diabetes incidence rates in the range of 5–10% per year support annual retesting. Oral glucose tolerance testing is more sensitive in detecting diabetes, as it is currently defined, than is measurement of fasting glucose levels (53).

The types of diabetes that develop after GDM have generally not been investigated. However, the causes and contributions of insulin resistance and poor insulin secretion that occur in GDM (see above) are likely to be involved in diabetes that occurs after GDM as well. Type 2 diabetes almost cer-

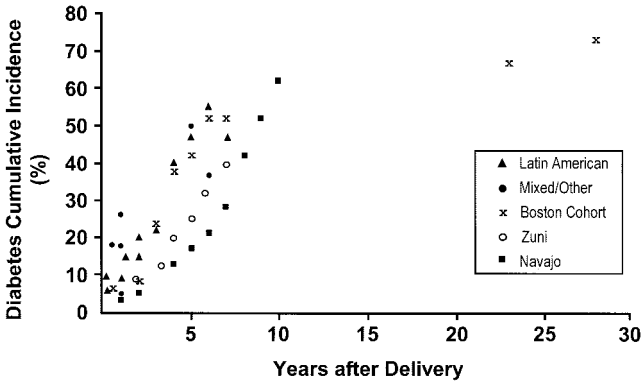

Figure 3—*Cumulative incidence of diabetes after GDM in five studies (59–65). Adapted from Kim et al. (51).*

tainly predominates, given the overall prevalence of the disease in relation to other forms of diabetes and the fact that risk factors such as obesity and weight gain are shared between GDM and type 2 diabetes. However, immune and monogenic forms of diabetes occur as well. These latter subtypes of diabetes should be considered in women who do not appear to be insulin resistant (e.g., lean patients). Anti-GAD antibodies can identify women who may have evolving type 1 diabetes. While there is no specific intervention to delay or prevent that disease, patients should be followed closely for development of hyperglycemia, which may occur relatively rapidly after pregnancy (43). Clinical testing for variants that cause monogenic forms of diabetes is becoming available, but interpretation of the results can be complicated, and consultation with an expert in monogenic diabetes is advised. Early-onset diabetes with an appropriate family history—autosomal-dominant inheritance for MODY, maternal inheritance for mitochondrial mutations—may provide a clue to the presence of those diseases. Like autoimmune diabetes, there is no specific disease-modifying treatment for these forms of diabetes, although patients with MODY due to mutations in hepatic nuclear factor 1α appear to respond well to treatment with insulin secretagogues (54). Genetic counseling may be appropriate for patients with monogenic diabetes and their families.

Results from the Diabetes Prevention Program (DPP), the Troglitazone in Prevention of Diabetes (TRIPOD), and Pioglitazone in Prevention of Diabetes (PIPOD) studies reveal approaches that can be used to delay or prevent diabetes in women whose clinical characteristics suggest a risk of type 2 diabetes. In the DPP (55), intensive lifestyle modification to promote weight loss and increase physical activity resulted in a 58% reduction in the risk of type 2 diabetes in adults with impaired glucose tolerance. GDM was one of the risk factors that led to inclusion in the study. Protection against diabetes was observed in all ethnic groups. Treatment with metformin in the same study also reduced the risk of diabetes, but to a lesser degree and primarily in the youngest and most overweight participants. Analysis of data from parous women who entered the DPP with or without a history of GDM (B. Ratner, personal communication) revealed that *1*) the women with prior GDM were younger than women with no history of GDM, *2*) the women with prior GDM had a 60% greater cumulative incidence of diabetes after 3 years of follow-up, *3*) intensive lifestyle modification reduced the risk of diabetes by a similar degree in women with and without prior GDM, and *4*) metformin was more effective in reducing the risk of diabetes in women with a history of GDM than in women who gave no such history (50% vs. 14% risk reductions, respectively). In the TRIPOD study, assignment of Hispanic women with prior GDM to treatment with the insulin-sensitizing drug troglitazone was associated with a 55% reduction in the incidence of diabetes. Protection from diabetes was closely linked to initial reductions in endogenous insulin requirements (Fig. 4) and was ultimately associated with stabilization of pancreatic β-cell function (35). Stabilization of β-cell function was also observed when troglitazone treatment was started at the time of initial detection of diabetes by annual glucose tolerance testing (56). In the PIPOD study, administration of another insulin-sensitizing drug, pioglitazone, to the same high-risk patient group revealed stabilization of previously falling β-cell function (57) and a close association between reduced insulin requirements and a low risk of diabetes (Fig. 4). The DPP, TRIPOD, and PIPOD studies support clinical management that focuses on aggressive treatment of insulin resistance to reduce the risk of type 2 diabetes. Glycemia should also be monitored to evaluate success (i.e., stable or falling glycemia) and to detect failure (rising glycemia and/or diabetes if it develops).

SUMMARY AND FUTURE DIRECTIONS

— The full array of causes of hyperglycemia in GDM is not

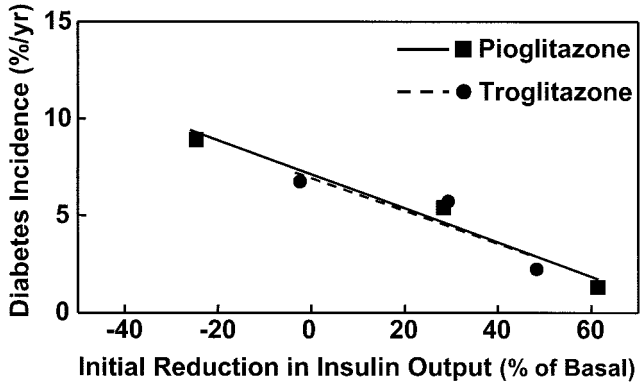

Figure 4—*Relationship between initial fractional reduction in insulin output and corresponding diabetes incidence rates during drug treatment in the troglitazone arm of the TRIPOD study (●, median duration of treatment = 31 months) and in the PIPOD study (■, median duration of treatment = 35 months). Insulin output was assessed as the total area under the insulin curve during 4-h, tolbutamide-modified intravenous glucose tolerance tests. Reductions in insulin output were calculated between enrollment into each study and the initial on-treatment IVGTT, which occurred after 3 months in TRIPOD and after 1 year in PIPOD. Symbols represent the low, middle, and high tertile of change in each study. Lines represent best linear fits of data for each study. Reproduced from Xiang et al. (36).*

known. However, available data suggest that GDM results from a spectrum of metabolic abnormalities that is representative of causes if hyperglycemia is in relatively young individuals. In many, perhaps most, women with GDM, the abnormalities appear to be chronic in nature, detected by routine glucose screening in pregnancy. They are frequently progressive, leading to rising glucose levels and eventually to diabetes. Thus, GDM can be viewed largely as diabetes in evolution that provides important research and clinical care opportunities. Regarding research, GDM offers a strong opportunity to study the early biology of diabetes. Cross-sectional studies could identify metabolic abnormalities in different subsets of prior GDM, including important ethnic differences in contributions of obesity, adipose tissue biology, insulin resistance, and β-cell dysfunction to the pathogenesis of nonimmune diabetes. Longitudinal studies could identify analogous contributions to evolving hyperglycemia and diabetes. Genetic studies may identify genetic determinants of prediabetic phenotypes before metabolic decompensation obscures genotype-phenotype relationships. Careful attention to gene-environment interactions and to ethnic differences may be particularly important and potentially rewarding in such studies. As reviewed by Ratner (58) in this supplement, GDM offers an important opportunity for the development, testing, and implementation of clinical strategies for diabetes prevention. Some progress has already been made in this area, but no intervention has been uniformly effective or durable, so there is much room for advancement. Combining clinical trials with physiological, genetic, and pharmacogenetic investigations may help to define mechanisms for diabetes prevention (and, thus, for diabetes itself) that could differ between or among ethnic groups. All of these efforts will require an interdisciplinary approach if we are to gain a full understanding of the causes of GDM, its relation to diabetes after pregnancy, and methods to reduce the frequency of both problems in a world of increasing hyperglycemia.

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