Aging and Insulin Secretion

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INTRODUCTION

This chapter reviews new and emerging information about important changes in the regulation of insulin secretion that occur during aging. Findings from animal models and from humans are presented and reviewed. In addition, this chapter links the age-related changes in regulation of insulin secretion to the high risk for development of diabetes mellitus observed in populations of older adults.

AGING, INSULIN SECRETION, AND DIABETES

Diabetes mellitus is one of the most common health problems of older adults, based on population studies in the United States and elsewhere (American Diabetes Association 2010; Chang & Halter, 2009). Figure 17.1 summarizes findings from the National Health and Nutrition Examination Survey, a population-based American study (Harris et al., 1998; Resnick et al., 2000). It demonstrates that the prevalence of known clinical diagnosis of diabetes increases from middle age to over age 60, for which the value is 11–12% of the population. In addition, equivalent numbers of people meet current criteria for diabetes diagnosis based on either fasting plasma glucose level greater than 125 mg/dl or a value exceeding 199 mg/dl 2 h after an oral glucose tolerance test (OGTT). Overall the prevalence rate of diabetes is approximately 25% of people over age 60. An additional 20% of the U.S. population meets criteria for impaired glucose tolerance (IGT), defined as a glucose level greater than 139 mg/dl but less than 200 mg/dl by OGTT and a fasting glucose level of less than 126 mg/dl. Other studies of people of older ages, including those over age 75, similarly demonstrate a prevalence rate in the 20–25% range (Chang & Halter, 2009). The prevalence rate includes people who have developed diabetes at a younger age and have survived into old age. However, the incidence rate of new diagnosis of diabetes also increases dramatically with age. The vast majority of older adults who meet criteria for diabetes have type 2 diabetes. However, some people with type 1 diabetes, characterized by severe insulin deficiency and damage to pancreatic β cells, survive to old age as well. The pathophysiology of type 2 diabetes is more complex. While circulating insulin levels may be variable, impaired insulin secretion in response to a glucose challenge is a universal finding in type 2 diabetes. Limited pathological studies have demonstrated diminished pancreatic β-cell mass (Butler et al., 2003).

Older adults who meet current criteria for diagnosis of diabetes mellitus are at substantial risk for complications of diabetes. These are largely grouped
as microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy, and macrovascular complications, which are related to high rates of atherosclerosis leading to coronary artery disease, peripheral vascular disease, and cerebrovascular disease. For example, a diagnosis of diabetes greatly magnifies the age-related increase in acute myocardial infarction rates. There is a substantial age-related increase in risk for myocardial infarction in both men and women. However, men and women with diabetes have a much greater risk for myocardial infarction at any given age. On average, people with diabetes have myocardial infarction rates similar to those of people without diabetes who are 15 years older (Booth et al., 2006). In addition to these traditional diabetes complications, older people with diabetes are at higher risk for myocardial infarction in both men and women. However, men and women with diabetes have a much greater risk for myocardial infarction at any given age. On average, people with diabetes have myocardial infarction rates similar to those of people without diabetes who are 15 years older (Booth et al., 2006). In addition to these traditional diabetes complications, older people with diabetes are at higher risk for geriatric conditions, including decline in functional status and decreased cognitive function (Chang & Halter, 2009; Maty et al., 2004; Wray et al., 2005). It is estimated that the mortality rate associated with a diagnosis of diabetes in older adults is about twofold higher than people of the same age without diabetes.

Figure 17.1 Prevalence of type 2 diabetes among elderly people in the United States according to age and American Diabetes Association diagnostic criteria, from the Third National Health and Nutrition Examination Survey (NHANES III). FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; IPH, isolated postchallenge hyperglycemia (adapted from Harris et al., 1998, and Resnick et al., 2000).

Impaired pancreatic β-cell function and the resulting decline in insulin secretion contribute to the high rate of diabetes mellitus in older adults, with multiple secondary effects of diabetes on overall morbidity and mortality. In addition, there may also be a more subtle impact of impaired insulin secretion in the aging population. Insulin is a major anabolic hormone, important for storage of fuel as glycogen and fat, but also critical for protein synthesis. Diminished protein synthesis leading to a loss of muscle mass is a common finding in aging people and an important contributing factor to frailty and other functional deficits in older adults. Thus, a decline in production of insulin below the level needed for its anabolic affects could play a role in these aspects of aging as well (Chang & Halter, 2009). However, a major challenge to testing this hypothesis is that healthy, exercising, insulin-sensitive people also have low insulin levels that are adequate to meet their metabolic and anabolic needs. As described later in this chapter, comparison of insulin levels in vivo among populations requires concomitant assessment of degree of insulin sensitivity in the same people.
REGULATION OF PANCREATIC β-CELLS AND INSULIN SECRETION

The primary source of insulin production is specialized neuroendocrine cells called β cells, which are located in collections of hormone-producing cells called islets of Langerhans, which are scattered throughout the pancreas. While an in-depth discussion of pancreatic islet structure and function is beyond the scope of this chapter, there is growing interest in understanding the factors important in regulation of β-cell turnover: differentiation of neural stem cells, proliferation, cell death, and regeneration (Bouwens & Rooman, 2005). In the past, pancreatic β cells were thought to be relatively static, with low rates of turnover and limited capacity for regeneration. However, there is increasing evidence and understanding of the capacity of pancreatic β cells to grow and proliferate under some circumstances (Bouwens & Rooman, 2005; Dor et al., 2004; Meier et al., 2008). For example, in mice pancreatic islet proliferation can be induced by partial pancreatectomy, by islet injury induced by the drug streptozotocin, by the gut hormone glucagon-like peptide-1 (GLP-1), and by pregnancy (Bouwens & Rooman, 2005; Li et al., 2003; Rankin & Kushner, 2009; Tschen et al., 2009; Xu et al., 1999). In addition, obesity is known to be associated with an increase in β-cell mass, probably due to cell proliferation (Montanya et al., 2000). Obesity develops over the life span, thereby contributing to pancreatic islet compensation for obesity-related insulin resistance. However, the mechanisms of adaptation of pancreatic β-cell proliferation to obesity are not known.

Similarly there is a large and growing literature on regulation of insulin secretion by pancreatic β cells. A complete review of this process is beyond the scope of this chapter. The glucose level is known to be a key regulator of insulin secretion (Chang & Halter, 2003, 2009). The effects of glucose appear to be multiple and complex. For example, exposure of pancreatic islets in vitro or in vivo to a constant glucose stimulus leads to a complex multiphasic hormone-secretory response. This response includes an acute phase occurring within minutes, thought to be largely due to an immediate release of preformed insulin granules that are available near the cell surface of pancreatic β cells, and a more prolonged second phase of insulin secretion that gradually increases in magnitude over time and is dependent on new protein synthesis.

In addition to being a direct insulin secretagogue, glucose can potentiate many other factors that can contribute to insulin secretion. Thus, nutrients such as some amino acids and fatty acids can stimulate insulin secretion, but only in the presence of adequate amounts of glucose. Similarly other hormones can stimulate insulin secretion in a glucose-dependent fashion. Prominent among such hormones are peptides derived from the GI tract such as a GLP-1 and gastric inhibitory peptide, also called glucose-dependent insulinotropic peptide (Chang & Halter, 2003; Korosi et al., 2001; Li et al., 2003; Xu et al., 2005). Secretion of such peptides is thought to explain observations that oral glucose administration leads to greater insulin secretion over time than the same amount of glucose administered intravenously, the so-called incretin effect. In recent years, a new class of drugs called incretins have been developed as therapeutic agents for managing hyperglycemia in people with diabetes mellitus. The incretins are agents that have GLP-1-like effects (for example, exenatide); inhibit a key enzyme that rapidly degrades exogenous GLP-1, thereby prolonging GLP-1 availability in vivo (for example, the gliptin group of drugs); or are analogs of GLP-1 that are long acting because they are resistant to degradation (for example, liraglutide).

Pancreatic islets are also known to be under neural control. Insulin secretion can be activated by parasympathetic neural stimulation and influenced by sympathetic neural system stimulation as well. The sympathetic nervous system effects are complex in that β-adrenergic stimulation enhances insulin secretion, while α2-adrenergic stimulation inhibits insulin secretion (Halter et al., 1984; Metz et al., 1978; Morrow et al., 1993). Thus during activation of sympathetic control of islet cells there is overall some inhibition of glucose-stimulated insulin secretion, but at the same time tonic enhancement mediated by β-adrenergic stimulation. Thus, when sympathetic stimulation stops, the pancreatic islets are prepared to increase insulin secretion dramatically. During stressful situations, when there is a dramatic activation of sympathetic nervous system activity, hyperglycemia develops because of multiple neural effects that increase glucose production and diminish utilization, while insulin secretion is inhibited. This hyperglycemia rapidly resolves when the sympathetic nervous system activity returns to normal as insulin secretion responds dramatically (Halter et al., 1984). Interest in α-adrenergic inhibition of insulin secretion has grown from findings that one experimental mouse model of diabetes appears to be a result of overexpression of α2-adrenergic receptors on pancreatic islets. This type of diabetes can be prevented by knockout of the α2-adrenergic receptors. Furthermore, in human populations an α2-adrenergic receptor gene variant is associated with risk for type 2 diabetes (Rosengren et al., 2010).

Overall physiologic regulation of insulin secretion is most apparent in humans in response to ingestion of a meal. Meal ingestion provides a complex set of signals to pancreatic islets including an increase in glucose level, increase in other nutrients, release of GI peptides, and activation of neural signals. The net
result is a finely regulated insulin secretory response that minimizes postmeal hyperglycemia under physiologic conditions as well as any overshoot and subsequent hypoglycemia. However, the complexity of these signals makes it difficult to use insulin levels after a meal as an indicator of pancreatic β-cell function in any given individual or in pathologic states. For example, one person may have a small increase in insulin levels in response to a meal, despite high postmeals glucose levels, because of impaired β-cell function. Another person may have similarly low insulin levels after a meal, but with normal β-cell function that is responding appropriately to low postmeal glucose levels and other meal-related signals. Even when a more simple stimulus is provided, such as oral glucose (e.g., OGTT), multiple neural and endocrine signals are generated in addition to the glucose level itself, and of course all of these signals, including the glucose level, are changing over time. Thus, the circulating insulin response during an OGTT is also difficult to interpret as a measure of pancreatic β-cell function.

Insulin secretion patterns after a meal are complex, but even in the absence of a major event such as meal ingestion, circulating insulin levels in vivo are challenging to interpret. One problem is that much of the secreted insulin is removed by the liver during initial delivery of insulin via the portal vein and never gets to the peripheral circulation. Under most physiological circumstances, peripheral insulin levels provide a good estimate of pancreatic secretion. However, variation of liver insulin extraction among individuals can complicate comparisons. Measurement of C-peptide levels can provide a solution to this problem. C peptide is the part of the proinsulin molecule that is cleaved off as proinsulin is converted to insulin in β-cell secretory granules. C peptide is cosecreted with insulin, but is not removed by the liver. The combination of measurement of circulating C-peptide levels with mathematical modeling of C-peptide kinetics by deconvolution analysis has provided a validated estimate of insulin secretion rate in vivo (Chang & Halter, 2003). Another problem with interpretation of insulin levels in vivo is that, as has been observed for a number of other hormones, normal basal secretion of insulin occurs in a pulsatile manner. There are rapid, low-amplitude pulses occurring every 8–15 min and in addition pulses with a longer duration of 60–140 min and larger amplitude (Chang & Halter, 2003; Matveyenko et al., 2008). Such endogenous variability of basal insulin secretion can be magnified by infusion of glucose to achieve a constant glucose level that is above normal. Thus, measurement of a single insulin level, even in the fasting state, can provide only a rough estimate of basal rates of secretion in a given individual.

A key determinant of the rate of basal insulin secretion and insulin responses to challenge such as a meal in a given individual is that individual’s sensitivity to the metabolic effects of insulin. There appears to be an adaptive response to changes in body sensitivity to metabolic effects of insulin, leading to an increase in pancreatic β-cell mass, as described above, and rates of insulin secretion. The most common example of such β-cell adaptation is the response to simple obesity-related insulin resistance.

The relationship between insulin secretion and insulin sensitivity has been studied in detail in experimental animals and in humans. Among populations with varying degrees of insulin sensitivity (as quantitated by a number of methods in vivo), a surprisingly consistent relationship between insulin secretion rate and degree of insulin sensitivity has been documented (Kahn et al., 1993). As illustrated in Figure 17.2, this relationship is hyperbolic, both in humans and in rodents (Matveyenko et al., 2008). The simplest mathematical model that fits these data is the product of a measure of β-cell function and a measure of insulin sensitivity (Kahn et al., 1993). This product has been termed the Disposition Index. Thus, across a population of normal people with varying degrees of insulin resistance and appropriate compensation of insulin secretion, the Disposition Index will have the same value. A given individual may move down the hyperbolic curve by reducing weight, improving insulin sensitivity by adapting by downregulating insulin secretion or move back up the curve with increased weight, worsening insulin resistance, and adaptation by increasing insulin secretion. In either case, the product of insulin secretion times insulin resistance will remain unchanged.

This type of analysis has been used to identify individuals who fail to adapt normally to changes in insulin resistance by secreting inadequate amounts of insulin and have a lower product or Disposition Index. Disposition Index has been used as a way of comparing individuals who have different degrees of insulin sensitivity to identify those with poor β-cell function, in the sense of poor adaptation to changes of insulin resistance. Thus, individuals who appear to be predisposed to the development of diabetes such as women who have previously had gestational diabetes or family members of people with diabetes have been shown to have a lower Disposition Index compared with normal (Utzschneider et al., 2004).

A number of studies have demonstrated a decline in β-cell function and insulin secretion with age in rodents. To understand mechanisms of this age-related decline in function, studies have focused on pancreatic islet cell proliferation and β-cell turnover...
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Figure 17.3 demonstrates a modest decline in islet proliferative capacity with age in normal mice age 2 to 19 months (Rankin & Kushner, 2009). This aging effect is much more dramatic when the proliferative response of older animals to partial pancreatectomy, streptozotocin, and exendin-4 (a GLP-1 agonist) is compared to the robust responses observed in young animals. A decline in response is evident by 8–12 months of age and response is almost undetectable by 14–19 months of age. Similarly, 1- to 2-month-old mice increase islet mass and β-cell proliferation in response to high-fat diet, but 7- to 8-month-old mice cannot (Tschen et al., 2009). This study also found a lack of an islet proliferative response to streptozotocin and exendin-4 in 7- to 8-month-old mice. Thus, loss of islet proliferative capacity appears to occur early in life in rodents and perhaps would make them susceptible to impaired glucose regulation if there is future injury to islets or accelerated loss of β cells over time. Exposure to high concentrations of glucose in vitro can lead to apoptosis of β cells, evidence of glucose toxicity. Islets from adult 7- to 8-month-old Sprague–Dawley rats appear to be more sensitive to glucose-induced apoptosis (Maedler et al., 2006).

Pancreatic β-cell proliferation appears to be p0145 dependent on cell cycle regulation (Kushner et al., 2005; Park et al., 2004). Study of the cell cycle inhibitor p16 has led to some new insights on aging and...
regulation of islet growth (Krishnamurthy et al., 2004, 2006). As illustrated in Figure 17.4, there is a substantial increase in expression of the cell cycle regulator p16 in islet tissue from mice age 15–18 months (Krishnamurthy et al., 2006). Increased p16 expression is associated with a substantial age-related decline in islet proliferation. Overexpression of p16 markedly reduces islet proliferation in younger mice to a level similar to that observed in older mice, and knockout of p16, thereby preventing p16 from increasing with aging, appears to reverse the age-related decline in islet cell proliferation in this model. In this context it is of great interest that p16 is one of the proteins produced from the CDKN2a gene locus (Krishnamurthy et al., 2004). Genetic variation at this locus has emerged as a consistent association with type 2 diabetes risk from genome-wide scanning studies in humans (Saxena et al., 2007; Scott et al., 2007; Steinthorsdottir et al., 2007; Zeggini et al., 2007). Thus, increased p16 production with aging is linked with decreased islet proliferation with aging, and alterations in its expression through the CDKN2a locus may contribute to the risk for type 2 diabetes.

### PANCREATIC β CELL FUNCTION AND AGING—HUMAN STUDIES

Limited access to human pancreas tissue has allowed only limited exploration of regulation of pancreatic β cells in vitro, and studies of human β-cell turnover...
are also very limited. However, findings from humans appear to parallel age-related changes observed in rodents, including diminished insulin secretion in vitro, diminished proliferative capacity, and increased sensitivity to apoptotic effects of high glucose exposure (Butler et al., 2003; Ihm et al., 2006).

There is a substantial amount of information about glucose tolerance and insulin secretion as a function of age in humans (Chang & Halter, 2003). The age-related decline in glucose tolerance in nondiabetic humans has been observed in many studies (Chang & Halter, 2003; Chen et al., 1985, 1987) and is illustrated in Figure 17.5. Insulin levels have been measured during such studies of glucose tolerance. However, as indicated above, the insulin levels are very difficult to interpret because of the complexity of the stimulus and the change in glucose levels over time that is not matched between young and older subjects. This difficulty is further compounded by the challenge of studying older individuals, who often are relatively insulin resistant because of age-related obesity, decreased physical activity, and possibly other factors, but are compared to younger, more insulin-sensitive individuals. One approach to this challenge is to measure both insulin secretion under standardized conditions and insulin sensitivity in older and younger subjects and use the Disposition Index as a way of adjusting for group differences in insulin sensitivity. Multiple studies have now demonstrated that Disposition Index values are lower in older adults than in younger adults (Basu et al., 2003; Kahn et al., 1992; Szoke et al., 2008; Utzschneider et al., 2004). This indicates that overall $\beta$-cell function, at least as assessed in response to the degree of insulin sensitivity, is diminished in older people.

Another approach is to carry out controlled studies in older and younger subjects matched for degree of insulin sensitivity. In one such study, a controlled glucose stimulus was provided by varying the glucose infusion during the study to achieve a standardized rate of increase of the glucose level over time in healthy young and older subjects matched for degree of insulin sensitivity (Chang et al., 2006). Subjects meeting the criteria for diabetes were excluded. As illustrated in Figure 17.6, insulin secretion rate, estimated by deconvolution of C-peptide kinetics, increased gradually over time as the glucose level was increased by glucose infusion. Healthy older people with no abnormality of glucose tolerance had significantly lower insulin secretion in response to this same glucose challenge compared to the younger individuals. Older individuals who met the criteria for IGT, and thus may have been at risk for developing diabetes, demonstrated a further reduction in insulin secretion response. In this type of procedure with a gradual increase in glucose level in the physiologic range, people with overt type 2 diabetes would show no increase in insulin secretion. Thus, even healthy older people with normal glucose tolerance appear to demonstrate an age-related deficit of glucose-induced insulin secretion. This impairment is worse in people with IGT. The same study subjects were treated with nicotinic acid, to induce insulin resistance, for 2 weeks or with matching placebo. In response to nicotinic acid-induced insulin resistance, younger subjects consistently increased the insulin secretion response to a glucose challenge, whereas older patients with IGT were not able to do so. The Disposition Index fell slightly in all groups with nicotinic acid but the decline was greatest in the older subjects. Thus, short-term induction of insulin resistance led to expected islet function adaptation in younger subjects, but older people were less able to adapt.
Another study used deconvolution of C-peptide kinetics to study pulsatile insulin secretion in healthy older adults and older adults with type 2 diabetes in comparison to healthy younger people (Meneilly et al., 2005). Impairments of pulsatile insulin secretion were observed in both elderly groups and were most severe in those with diabetes. Infusion of GLP-1 partially reversed the impairments in the diabetes patients.

There has been substantial interest in the relationship between insulin signaling pathways and longevity since the unexpected findings initially from yeast and worm studies that genetic disruption of insulin and insulin-like signaling pathways can lead to a substantial increase in longevity (see Chapter 2 of this book). Additional work in Drosophila and some work in rodents has further demonstrated that multiple interventions to change insulin and insulin-like signaling pathways throughout life can prolong life span. However, this work is complicated by the fact that this signaling pathway is activated by a receptor mechanism that responds both to insulin and to growth factors such as insulin-like growth factor-1. In fact, in rodent models of aging it appears as though the growth effects are most important, as various models of growth deficiency are associated with longevity. The finding that impaired insulin signaling is associated with longevity and health seems at odds with findings in humans that insulin resistance and impaired insulin secretion, both leading to reduced overall insulin signaling, result in diabetes and its associated increased morbidity and mortality. This is
obviously an area of great interest that requires substantial further investigation.

Another possible link between glucose regulation, pancreatic islet function, and longevity is the well-known effect of caloric restriction (CR) over the life span to improve longevity. Studies of CR rodents clearly demonstrate that improved glucose regulation, reduced obesity, and lower insulin levels are part of the CR phenotype (see Chapters 1 and 21). However whether these changes in glucose and insulin during caloric restriction are critical factors that contribute to longevity effects are not known. Most recently, initial CR studies in nonhuman primates have demonstrated some possible enhanced longevity, but also clear improvements in age-related changes in glucose and insulin regulation (Colman et al., 2009). Furthermore, dramatic prevention of age-related development of abnormalities of glucose metabolism was observed.

These observations also seem to be at odds with the findings that impaired insulin signaling throughout life improves longevity. However, insulin sensitivity is usually defined in relationship to metabolic effects of insulin, not its growth effects. It is thus conceivable that these two actions could be dissociated. For example, Masoro has proposed that improved sensitivity to the metabolic effects of insulin during CR leads to appropriate downregulation of insulin secretion. Low insulin levels during CR result in low insulin signaling at other sites, such as the brain, which may lead to growth retardation as a proximate cause for the enhanced longevity of CR animals (Masoro, 2009).

There is also great interest in the TOR signaling pathway as a potential mechanism by which caloric restriction leads to enhanced longevity (Kapahi & Vig, 2009; and see Chapter 9). Suppression of the TOR pathway by the drug rapamycin, even when administered to mice in middle age, enhances longevity (Harrison et al., 2009). There is evidence that a downstream ribosomal protein S6 kinase may be a key part of this pathway, and a knockout of this kinase also enhances longevity in female mice (Selman et al., 2009). Interestingly, such mice have lower body weight, less accumulation of body fat than wild-type animals, better insulin sensitivity, and improved glucose tolerance. Thus, this longevity phenotype has characteristics similar to those of caloric restriction that involve insulin regulation and its signaling pathways.

A conceptual model for the high rate of age-related diabetes in humans is illustrated in Figure 17.7 (Chang & Halter, 2003). This model hypothesizes that dual factors interact to lead to the development of hyperglycemia in aging: insulin resistance and decreased insulin secretion. Insulin resistance to the metabolic effects of insulin with aging appears to reflect predominantly lifestyle factors leading to increased adiposity and diminished physical activity (note that mechanisms for insulin resistance may be different for these two causal factors). Independent age effects on insulin action may also contribute, but the magnitude appears to be small. There may be genetic factors contributing to insulin resistance with
aging, although these have not yet been identified. In some elderly patients, coexisting stressful illness leading to sympathetic nervous system activation and use of medications such as glucocorticoids can directly contribute to resistance to insulin action (Supiano et al., 1993). As outlined in this chapter there are aging effects on β-cell proliferation, and probably on susceptibility to apoptosis, which contribute to diminished β-cell mass and decreased insulin secretion capacity with aging. Functional defects in pancreatic β-cell function may also contribute to the observed age-related impairment of insulin secretion. As described earlier, sympathetic nervous system activation from coexisting illness can also contribute to impaired insulin secretion, and there is evidence for increased sympathetic nervous system activity overall in aging people even in the absence of acute illness (Supiano et al., 1990).

Finally, multiple genetic risk factors have been identified, such as the genes regulating p16 expression and the α2-adrenergic receptor, which appear to influence diabetes risk primarily by effects on pancreatic β-cells. However, the identical and very high concordance rate for type 2 diabetes observed in both fraternal and identical twins suggests that important nongenetic factors, possibly early in life, contribute to diabetes risk (Poulsen et al., 2009). The earliest defect in pancreatic insulin secretion that is detected appears to be impaired adaptation to concomitant insulin resistance, leading to IGT and ultimately to type 2 diabetes as the age-related decline in pancreatic β-cell function and adaptation both worsen. This overly simplistic model implies that the pancreatic islet adaptation is the same regardless of the mechanisms contributing to insulin resistance. However, this hypothesis needs to be tested. The substantial preventive effects of lifestyle interventions described earlier on this progressive course appear to be due to improvement of the degree of insulin resistance, thereby reducing the need for insulin production from β cells limited by age-related changes in mass and function.

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