Preface
Alan J. Garber

Pathogenesis of Type 2 Diabetes Mellitus
Ralph A. DeFronzo

This article provides an overview of the pathogenesis of type 2 diabetes mellitus. Discussion begins by describing normal glucose homeostasis and ingestion of a typical meal and then discusses glucose homeostasis in diabetes. Topics covered include insulin secretion in type 2 diabetes mellitus and insulin resistance, the site of insulin resistance, the interaction between insulin sensitivity and secretion, the role of adipocytes in the pathogenesis of type 2 diabetes, cellular mechanisms of insulin resistance including glucose transport and phosphorylation, glycogen and synthesis, glucose and oxidation, glycolysis, and insulin signaling.

The Metabolic Syndrome
Alan J. Garber

This article provides an overview of the metabolic syndrome, a collection of cardiovascular risk factors that denote a high-risk, multifactorial, adverse cardiovascular state, which is largely the result of obesity and resulting insulin resistance. Treatment for the metabolic syndrome should be focused primarily on modifying lifestyle, with reduction of the underlying obesity and insulin resistance. A combination of chemoprevention and lifestyle modification may prevent many if not most cases of diabetes if treatment is instituted early.

Oral Antidiabetic Agents: 2004
Harold E. Lebovitz

The appropriate management of patients with type 2 diabetes presents many challenges to health care providers. The first several years of type 2 diabetes are likely to be unrecognized and untreated. The pathophysiology of type 2 diabetes dictates that treatment of insulin resistance should be an early and central focus.
for every therapeutic program. The pharmacologic tools currently available are capable of allowing most patients with type 2 diabetes to achieve good metabolic control. Implementation of early combination therapy is essential if glycemic targets are to be met.

**Insulin Therapy in Type 2 Diabetes**

Trent Davis and Steven V. Edelman

Unlike type 1 diabetic patients, who have no significant insulin secretion and require insulin therapy from the disease onset, a prominent feature in the early stages of type 2 diabetes is insulin resistance with hyperinsulinemia. Therefore, improving insulin sensitivity by diet, exercise, and weight management will benefit type 2 diabetic patients. When these measures fail, glycemic goals may be achieved with oral agents. However, at the late stage of disease, most patients require exogenous insulin therapy to achieve optimal glucose control. The American Diabetes Association recommends that the objective of normalizing glycemia and glycated hemoglobin concentrations for patients with type 2 diabetes should be similar to that for type 1 diabetes.

**Dyslipidemia in Type 2 Diabetes**

Ronald M. Krauss and Patty W. Siri

Type 2 diabetes mellitus is associated with a cluster of lipid abnormalities: elevated plasma triglycerides, reduced high-density lipoprotein cholesterol, and smaller and denser low-density lipoproteins, which have been associated with an increased risk of cardiovascular disease. Insulin resistance may contribute to dyslipidemia associated with type 2 diabetes by increasing hepatic secretion of large, triglyceride-rich very low-density lipoprotein particles and by impairing the clearance of lipoprotein particles from plasma. Lifestyle interventions may be effective in improving the diabetic dyslipidemia syndrome. For patients who do not respond to lifestyle changes, pharmacologic therapies (lipid-lowering medications and anti-diabetic agents) are available. Clinical trials demonstrate that the use of such pharmaceutics to treat diabetic dyslipidemia concomitantly reduces the risk of coronary artery disease.

**Endothelial Dysfunction and Hypertension in Diabetes Mellitus**

Paresh Dandona, Ajay Chaudhuri, and Ahmad Aljada

Although the net balance between vasoconstriction and vasodilation determines the tone of the blood vessel, the vasodilatory–vasoconstrictive response following a challenge may also be determined by the intrinsic mechanical and biological properties of the vascular smooth muscle. This article reviews the action of nitric oxide, acetylcholine, and insulin; the effects of hyperglycemia, increase in free fatty acids, diabetes, and obesity on the vasculature; treatment of hypertension in diabetes; the benefits of lowering blood pressure and intensity of blood pressure control; and compares specific antihypertensive therapies on cardiovascular outcomes. The effects of
antihypertensive therapy on microvascular complications, choice of antihypertensive regimen, antioxidant and anti-inflammatory effects of antihypertensive drugs, and the potential role of antidiabetic drugs in the treatment of hypertension are also presented.

Gonadal and Erectile Dysfunction in Diabetics
Rabih A. Hijazi, Marion Betancourt-Albrecht, and Glenn R. Cunningham

The high prevalence of erectile dysfunction in patients with diabetes is caused mainly by vascular and neurological conditions; nevertheless, hypogonadism may also contribute to erectile dysfunction and to changes in mood, libido, body composition, and bone density. Age, obesity, and the assay used to measure testosterone will affect the diagnosis of hypogonadism. This article focuses on the interaction of these conditions and attempts to explain possible mechanisms for observations reported in the literature.

Diabetic Neuropathies
A.I. Vinik and Anahit Mehrabyan

Diabetic neuropathy (DN) is a common complication of diabetes that often is associated with considerable morbidity and mortality. The epidemiology and natural history of DN is clouded with uncertainty because of confusion regarding the definition and measurement of this disorder. The recent resurgence of interest in the vascular hypothesis, oxidative stress, the neurotrophic hypothesis, and the possibility of the role of autoimmunity has opened up new avenues of investigation for therapeutic intervention. The ability to manage successfully the many different manifestations of diabetic neuropathy depends ultimately on success in uncovering the pathogenic processes underlying this disorder.

Diabetic Nephropathy and Retinopathy
Ali Jawa, Juanita Kcomt and Vivian A. Fonseca

Diabetic nephropathy and retinopathy are arguably the two most dreaded complications of diabetes. Together they contribute to serious morbidity and mortality. As they progress to end-stage renal disease and blindness, they impose enormous medical, economic, and social costs on both the patient and the health care system. Because nephropathy and retinopathy are frequently linked in patients, this article reviews their common and individual aspects of pathophysiology, clinical features, and management.

Ischemic Heart Disease and Congestive Heart Failure in Diabetic Patients
W.H. Wilson Tang, Anjli Maroo, and James B. Young

Ischemic heart disease and heart failure are major contributors to the morbidity and mortality associated with diabetes mellitus. With growing knowledge of how the metabolic derangements of diabetes
contribute to the pathogenesis of cardiovascular disease, we must continuously refine our understanding of optimal screening and strategies for prevention and treatment for these interlinked disorders. This article summarizes our current understanding of ischemic heart disease and heart failure in patients with diabetes mellitus, highlighting gaps in our knowledge about the relationship between diabetes and cardiovascular disease. Special consideration is given to new strategies for treating the adverse effects of abnormal glucose metabolism on the cardiovascular system.

Acute Hyperglycemic Crisis in the Elderly
Jason L. Gaglia, Jennifer Wyckoff, and Martin J. Abrahamson

The geriatric population is at particular risk for developing hyperglycemic crises with the development of diabetes. With increasing age, insulin secretory reserve, insulin sensitivity, and thirst mechanisms decrease. The elderly are particularly vulnerable to hyperglycemia and dehydration, the key components of hyperglycemic emergencies. If recognized early, hyperglycemia can frequently be treated in the outpatient setting even with moderate or large ketonuria, provided patients can take fluids, monitor blood glucose frequently, and follow standard “sick day rules.” With increased diabetes surveillance and aggressive early treatment of hyperglycemia and its complications, morbidity and mortality from acute diabetic crises in the geriatric population can be greatly reduced.

In-Hospital Management of Type 2 Diabetes Mellitus
Lillian F. Lien, M. Angelyn Bethel, and Mark N. Feinglos

The increasing prevalence of type 2 diabetes brings with it a need to understand the particular impact of hospitalization in this patient population. Type 2 diabetes has been shown to increase length of stay, infection, and mortality rates. To optimize inpatient care, it is important to understand target glycemic goals as well as in-hospital glucose monitoring and diabetes management goals. A practical review of regimens for subcutaneous insulin administration, intravenous insulin infusion, and inpatient use of oral agents is presented. Methods for achieving adequate preparation and education of the patient and family for discharge to the outpatient setting are also discussed.

Hypoglycemia in Type 2 Diabetes
Salomon Banarer and Philip E. Cryer

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes and a barrier to true glycemic control and becomes a progressively frequent clinical problem in advanced type 2 diabetes mellitus. As patients approach the insulin-deficient end of the spectrum of type 2, hypoglycemia results from the interplay of therapeutic insulin excess and compromised physiologic and
behavioral defenses against falling plasma glucose concentrations. By practicing hypoglycemia risk reduction, applying the principles of aggressive glycemic therapy, and considering conventional risk factors and those indicative of compromised glucose counter-regulation, it is possible to minimize the risk of hypoglycemia and improve glycemic control. Nonetheless, people with diabetes need better treatment regimens.