Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government
regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Preface

Atherosclerosis is a disease of the large arteries that is responsible for coronary artery disease and stroke, which, together, account for about half the deaths in Western populations. The single most significant risk factor in atherosclerosis is family history, implying a strong genetic component for the disease. The identification and characterization of the genes involved would have considerable clinical significance. First, it would undoubtedly provide insights into the molecular and cellular mechanisms responsible for the disease. Second, it could facilitate the development of new therapies as well as improve the targeting of therapies. Finally, it may even make it possible to predict which individuals are at high risk, allowing application of preventive measures. Although certain relatively rare single gene defects, such as mutations of the low density lipoprotein receptor which occur in familial hypercholesterolemia, result in early onset atherosclerosis, the vast majority of disease is due to a combination of more subtle genetic variations and also environmental influences. How can these genetic factors be individually identified and studied on the noisy background of multiple genetic and environmental influences?

The most powerful strategy at present appears to be what has been called the 'candidate gene approach'. This involves: first, the identification of polymorphisms of genes likely to be involved in atherosclerosis (for example, genes influencing known risk factors for the disease, including cholesterol metabolism, hypertension, and diabetes); second, testing whether such polymorphisms are associated with the risk factors in populations or families; and third, characterizing the properties of the alleles of genes that are identified. Given the large number of genes likely to be involved and the important influences of poorly understood environmental factors (diet, cigarette smoking and exercise, for example), this will certainly be a formidable and long-term endeavor, but not an impossible one.

The problem can be simplified by subdivision into genetic influences affecting the various known risk factors. Which genes contribute to hyperlipidemias and other variations of lipoprotein metabolism associated with the disease? Which genes contribute to hypertension? Which genes contribute to diabetes? Within the various risk factor categories, it may be
possible to define 'subphenotypes'. This will be of considerable importance in reducing the problem of genetic heterogeneity.

This volume focuses primarily on the role of cholesterol metabolism in atherosclerosis. The epidemiological and experimental evidence linking blood cholesterol with atherosclerosis, in both humans and animal models, is very strong. Chapter 1 by Angelo Scanu reviews this evidence, discusses lipoprotein phenotypes and subphenotypes associated with atherosclerosis, and summarizes current information on the diagnosis and treatment of lipoprotein disorders. From a clinical standpoint, it is of interest to note that, due to the fact that it is determined in large part by humoral factors, atherosclerosis, unlike most genetic disorders, is relatively accessible to dietary and drug therapy.

Among the key tools required for the identification of genes influencing risk factors in atherosclerosis are mathematical modeling approaches developed for analysis of data from nuclear families, extended pedigrees and twin studies. The uses of such methods, particularly as applied to lipoprotein variations, in both human populations and animal models, are described in Chapter 2 by Jean MacCluer. Such biometrical methodologies have provided strong evidence for the genetic determination of lipoprotein variations. Although the conclusions that have emerged from these analyses of lipoprotein variations have thus far been rather limited, they will certainly be extended considerably by the incorporation of data concerning the expression and segregation of various candidate genes.

In Chapter 3 we have compiled gene mapping results for various candidate genes involved in lipoprotein metabolism. We have constructed chromosomal 'fat maps' for both the human and mouse genes.

Chapter 4 by D. Galton and G. Ferns and Chapter 5 by Philippe Frossard and Sophia Vinogradov review approaches to the identification of genetic influences in atherosclerosis and summarize the results obtained to date. Chapter 4 focuses on candidate genes and Chapter 5 focuses on the identification of genes involved in complex disorders using DNA markers.

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Human studies of genetic influences in atherosclerosis are complicated by environmental variables and by the difficulty of detailed biochemical and genetic analyses. These problems can be largely avoided by the use of animal models. Moreover, experimental approaches in animals allows the testing of hypotheses. Chapters 6-10 review the most important
animal models for atherosclerosis. Chapter 6 by Brian Van Lenten reviews the Watanabe Heritable Hyperlipidemic (WHHL) rabbit, an animal model for familial hypercholesterolemia. The important information that has been obtained from the WHHL rabbit clearly illustrates the advantages of animal models for both basic questions pertaining to lipid metabolism and clinical questions pertaining to mechanisms contributing to atherosclerosis. Chapter 7 by Jan Rapacz and Judith Hasler-Rapacz reviews genetic studies of atherosclerosis in swine. In particular, immunogenetic studies carried out by these investigators and their collaborators over the past two decades have led to the identification of a new genetic form of hypercholesterolemia associated with accelerated atherosclerosis. Unlike individuals with familial hypercholesterolemia and WHHL rabbits, the affected swine have normal LDL receptor activity. Rather, the mutations in swine appear to involve genetically altered lipoprotein particles, and recent studies have revealed that mutations of apolipoproteins also contribute to hyperlipidemias in humans. Chapter 8 by Kathy Laber-Laird and L. Rudel reviews genetic and biochemical studies of hyperlipidemias and atherosclerosis in nonhuman primates. One criticism that has been made of the use of animal models of disease is that, due the metabolic and physiologic differences between species, the conclusions drawn from animal studies may not be applicable to humans. While this criticism does not appear to be justified in general, nonhuman primates are very similar to humans in terms of lipid metabolism and the nature of atherosclerotic lesions. Moreover, they provide advantages in that environmental variables can be controlled and that more detailed biochemical studies can be performed. Chapter 9 by Brian Ishida and Beverly Paigen reviews the mouse model for atherosclerosis. The mouse is the classical mammal for genetic studies and, as such, has several important and unique advantages for the identification and characterization of genetic factors contributing to the disease. This chapter puts to rest the notion that mice do not develop atherosclerosis; it reviews recent studies supporting the concept that high density lipoproteins protect against the disease; it summarizes information about various mutant strains of mice that may prove useful in studies of lipoprotein metabolism and atherosclerosis; and it provides a current list of resources for researchers in the field. In summary, this collection of reviews provides an overview of the
most important approaches and model systems that promise to reveal the genetic influences contributing to atherosclerosis.

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