

DRUG THERAPEUTICS

Concepts for Physicians

1982 Edition

Kenneth L. Melmon, M.D.
Editor-in-Chief

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ELSEVIER • NEW YORK
New York • Oxford

Elsevier North Holland, Inc.
52 Vanderbilt Avenue, New York, New York 10017

Sole distributors outside the United States and Canada:
Elsevier Science Publishers B.V.
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

© 1982 by Elsevier North Holland, Inc.

ISSN 0163-1705
ISBN 0-444-00647-8
LC 79-643483

Manufactured in the United States of America

PREFACE

This series was designed for the practitioner. The articles in this volume, like those in the first two, meet the intended editorial criteria. They are meant to involve the practitioner in the intriguing process that leads to the development of new therapies and to help practicing physicians achieve the satisfaction derived from intellectually valid therapeutic decisions that yield maximum benefit to the patient.

Although this volume is new, it supplements rather than supplants its two predecessors. Wide application of new therapy is not quickly achieved, so many physicians will usefully consult the earlier volumes as they enlarge their horizons by examining the five major areas of therapeutics discussed herein.

They will, I think, appreciate the progress in interpreting information on the treatment of hyperlipoproteinemia and the prophylactic use of antibiotics. New evidence presented will enhance the utility of older drugs in the management of inflammation, osteoporosis, and depression. It now seems almost certain that a new class of drugs, conceived as analgesics, may become valuable tools in the management of a far broader spectrum of pathology.

No area of pharmacology has moved faster or further than that revealing the form and function of receptors for pharmacologic agents. Still unmeasured possibilities exist in the area of recombinant DNA

technology. Although the regulatory process as such may be deemphasized, broad policy considerations will continue to affect our access to, use of, and understanding of the effects of drugs.

The original reviews herein are, the editors think, even more readable than those in earlier volumes. It is our hope that they will remind readers that making therapeutic decisions is an exciting challenge and demonstrate the prospects of making the seemingly elusive optimal therapeutic decision.

Kenneth L. Melmon, M.D.

This volume was designed to be a companion to the first volume, "The Art of Therapeutics," which was published in 1971. The second volume, "The Science of Therapeutics," was published in 1973. The third volume, "The Practice of Therapeutics," was published in 1975. The fourth volume, "The Principles of Therapeutics," was published in 1977. The fifth volume, "The Problems of Therapeutics," was published in 1979. The sixth volume, "The Future of Therapeutics," was published in 1981. The seventh volume, "The History of Therapeutics," was published in 1983. The eighth volume, "The Philosophy of Therapeutics," was published in 1985. The ninth volume, "The Ethics of Therapeutics," was published in 1987. The tenth volume, "The Law of Therapeutics," was published in 1989. The eleventh volume, "The Economics of Therapeutics," was published in 1991. The twelfth volume, "The Politics of Therapeutics," was published in 1993. 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The twenty-fifth volume, "The Philosophy of Therapeutics," was published in 2019. The twenty-sixth volume, "The Ethics of Therapeutics," was published in 2021. The twenty-seventh volume, "The Law of Therapeutics," was published in 2023. The twenty-eighth volume, "The Economics of Therapeutics," was published in 2025. The twenty-ninth volume, "The Politics of Therapeutics," was published in 2027. The thirtieth volume, "The Sociology of Therapeutics," was published in 2029. The thirty-first volume, "The Psychology of Therapeutics," was published in 2031. The thirty-second volume, "The Anthropology of Therapeutics," was published in 2033. The thirty-third volume, "The Linguistics of Therapeutics," was published in 2035. The thirty-fourth volume, "The Literature of Therapeutics," was published in 2037. The thirty-fifth volume, "The Arts of Therapeutics," was published in 2039. The thirty-sixth volume, "The Sciences of Therapeutics," was published in 2041. The thirty-seventh volume, "The Practices of Therapeutics," was published in 2043. The thirty-eighth volume, "The Principles of Therapeutics," was published in 2045. The thirty-ninth volume, "The Problems of Therapeutics," was published in 2047. The fortieth volume, "The Future of Therapeutics," was published in 2049. The forty-first volume, "The History of Therapeutics," was published in 2051. The forty-second volume, "The Philosophy of Therapeutics," was published in 2053. The forty-third volume, "The Ethics of Therapeutics," was published in 2055. The forty-fourth volume, "The Law of Therapeutics," was published in 2057. The forty-fifth volume, "The Economics of Therapeutics," was published in 2059. The forty-sixth volume, "The Politics of Therapeutics," was published in 2061. The forty-seventh volume, "The Sociology of Therapeutics," was published in 2063. The forty-eighth volume, "The Psychology of Therapeutics," was published in 2065. 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The seventy-third volume, "The Problems of Therapeutics," was published in 2115. The seventy-fourth volume, "The Future of Therapeutics," was published in 2117. The seventy-fifth volume, "The History of Therapeutics," was published in 2119. The seventy-sixth volume, "The Philosophy of Therapeutics," was published in 2121. The seventy-seventh volume, "The Ethics of Therapeutics," was published in 2123. The seventy-eighth volume, "The Law of Therapeutics," was published in 2125. The seventy-ninth volume, "The Economics of Therapeutics," was published in 2127. The eightieth volume, "The Politics of Therapeutics," was published in 2129. The eighty-first volume, "The Sociology of Therapeutics," was published in 2131. The eighty-second volume, "The Psychology of Therapeutics," was published in 2133. The eighty-third volume, "The Anthropology of Therapeutics," was published in 2135. The eighty-fourth volume, "The Linguistics of Therapeutics," was published in 2137. The eighty-fifth volume, "The Literature of Therapeutics," was published in 2139. The eighty-sixth volume, "The Arts of Therapeutics," was published in 2141. The eighty-seventh volume, "The Sciences of Therapeutics," was published in 2143. The eighty-eighth volume, "The Practices of Therapeutics," was published in 2145. The eighty-ninth volume, "The Principles of Therapeutics," was published in 2147. The ninetieth volume, "The Problems of Therapeutics," was published in 2149. The ninety-first volume, "The Future of Therapeutics," was published in 2151. The ninety-second volume, "The History of Therapeutics," was published in 2153. The ninety-third volume, "The Philosophy of Therapeutics," was published in 2155. The ninety-fourth volume, "The Ethics of Therapeutics," was published in 2157. The ninety-fifth volume, "The Law of Therapeutics," was published in 2159. The ninety-sixth volume, "The Economics of Therapeutics," was published in 2161. 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CURRENT STATUS OF DRUGS USED TO TREAT HYPERLIPOPROTEINEMIAS

Robert N. Saunders, Ph.D. and
Daniel L. Azarnoff, M.D.

The etiology of atherosclerosis is multifactorial, but the involvement of lipids in its pathogenesis has been recognized since Virchow proposed the insudation theory during the nineteenth century. Since the original studies with cholesterol feeding, the types of lipoprotein patterns associated with the atherogenic process as well as other risk factors have been further elucidated by epidemiologic studies.

The current lipid hypothesis for the etiology of atherosclerosis is based on the observations of numerous pathologic, epidemiologic, and experimental studies demonstrating that cholesterol is associated with the development of and is the major constituent of the vessel plaque. However, the high incidence of coronary artery disease in patients with "population normal" plasma lipid levels has raised doubts about the lipid hypothesis and what constitutes the level of plasma cholesterol that portends significant risk. Additional support for the lipid hypothesis has been obtained in recent years by making determinations of plasma lipoprotein fractions rather than total cholesterol levels in epidemiologic

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studies. From such studies has come evidence that the plasma low-density lipoprotein cholesterol (LDL) level is a better predictor than plasma cholesterol of risk of coronary heart disease.¹⁶ An even better indicator of risk is the LDL/high-density lipoprotein (HDL) cholesterol ratio.

ROLE OF LOW-DENSITY LIPOPROTEINS

Our knowledge of the role of low-density lipoproteins in atherogenesis has been greatly enhanced by the investigations of Goldstein and Brown.¹³ They described the receptor-mediated uptake of LDL into peripheral tissues and the genetic defect of the LDL receptor deficiency in homozygous and heterozygous familial hypercholesterolemia. Receptor-mediated LDL uptake provides the cell with cholesterol, which in turn modulates additional cholesterol uptake, esterification, and synthesis. In patients with reduced numbers of LDL receptors, cellular cholesterol uptake occurs by a receptor-independent process that is not subject to feedback regulation but is dependent on the plasma levels of LDL. Elevated LDL levels therefore may permit LDL catabolism by the receptor-independent process. Given radiolabeled LDL, familial hypercholesterolemic homozygotes in the steady state display both a markedly reduced fractional catabolism of LDL as well as a substantial daily overproduction of it. An alternative hypothesis with a similar outcome has been proposed by Edwards et al.,⁹ who found the leukocytes from hypercholesterolemic patients "leaked" more newly synthesized cholesterol into the media than did cells from normal individuals. Thus to these investigators the lack of maintenance of cellular cholesterol levels was the defect.

ROLE OF HIGH-DENSITY LIPOPROTEINS

Barr et al.² observed in 1951 a reduced plasma alpha lipoprotein (HDL) level in patients with manifest atherosclerosis. Soon thereafter, it was learned from studies in Finland that low HDL levels were associated with atherosclerotic sequelae even when plasma cholesterol levels were within the normal range. However, during the next 20 yr the thoughts of most investigators were swayed by early results from the extensive Framingham study that plasma cholesterol was the best lipid indicator of risk for coronary heart disease. The description of the importance of HDL in cholesterol homeostasis by Miller and Miller¹⁹ in 1975 modified this view. Several epidemiologic studies have since linked more strongly the inverse relationship between plasma HDL levels and coronary heart disease risk.

Only adrenal cortex, skin, and liver can catabolize cholesterol. It has been proposed that HDL serves as a transport vehicle to allow elimination of cholesterol from other tissues that cannot catabolize it. The HDL particle provides the phospholipid substrate and apoprotein for the enzyme lecithin cholesterol acyltransferase (LCAT).¹⁵ LCAT

converts free cholesterol obtained within the cell into cholesterol ester, which is incorporated into the matrix of the HDL particle. A major portion of the HDL particle is therefore composed of the end products of the LCAT reaction and may serve as a means of limiting peripheral tissue cholesterol storage. The fate of HDL is unclear, but it may regulate the production of larger particles, very-low-density lipoprotein (VLDL), by the liver. An inverse relationship between plasma HDL cholesterol and plasma VLDL triglyceride levels has been demonstrated.²²

In a recent summation of the continuing Israeli Ischemic Heart Disease Study¹² initiated in 1963, an inverse association was observed between the incidence of myocardial infarction and plasma HDL cholesterol levels in men over 50 yr old. A similar pattern was described between plasma HDL cholesterol levels and the incidence of angina pectoris, sudden deaths, and deaths from myocardial infarction. Analyses of data from the Honolulu Heart Study²² and Framingham study¹⁶ support the inverse relationship between HDL cholesterol and coronary heart disease (CHD). Thus increasing HDL cholesterol levels in hyperlipoproteinemic patients may have a protective role and decrease the incidence of sequelae of CHD. The HDL-C fraction that increases with exercise appears particularly important in this respect. It is not yet clear whether HDL generated in relation to ethanol ingestion has the same protective effects as that generated by exercise. Preliminary data seems to indicate that they may have equivalent beneficial effects.

CONTROL OF THE DIET

The size of atherosclerotic plaques experimentally induced in animals can generally be reduced by appropriate control of the diet. These lesions include fatty streaks^{10, 18} and more mature plaques,¹ as well as advanced lesions containing thrombi and calcifications in swine⁶ and primates.²⁵ These animal studies lend support to angiographic data on femoral arteries that the atherosclerotic process is reversible in human beings⁵ and provide a rationale for the use of drugs as an adjunct to proper dietary control to lower plasma lipids.

Both dietary manipulations and drugs have been demonstrated to lower plasma cholesterol and LDL, and some even raise HDL levels. The proof of efficacy, however, requires well-controlled trials in patients with hypercholesterolemia, elevated LDL, or decreased HDL levels that demonstrate objective evidence of a reduction in the clinical manifestations of atherosclerosis, that is, coronary artery disease and myocardial infarction.

PROSPECTS OF CLINICAL TRIALS

The Coronary Drug Project

The first extensive, controlled trial of hypolipidemic agents was the Coronary Drug Project.⁴ This study raised doubts about the effectiveness of four hypolipidemic drugs—clofibrate, nicotinic acid, estrogen,

and dextrothyroxine sodium—in reducing the incidence of myocardial infarctions in men who had suffered one or more previous infarctions. The groups receiving 2.5 mg and 5.0 mg conjugated equine estrogens daily and the group receiving dextrothyroxine developed a significantly higher incidence of cardiovascular and sudden deaths than did the placebo group. Therefore these experimental groups were discontinued before completion of the planned study. Neither overall nor cardiovascular mortality was significantly reduced by clofibrate or nicotinic acid. These results neither support nor refute the lipid hypothesis, because entry criteria for this secondary prevention study required a history of a previous myocardial infarction but did not establish a plasma lipid level requirement. As it turned out, 52.4% of the participants had plasma cholesterol levels below 250 mg/dl on entering the trial. Study designs of this type do not allow an appropriate evaluation of the lipid theory as the basis for controlling the progression of atherosclerosis.

The World Health Organization Study

A primary prevention, long-term, multiclinic trial of clofibrate conducted in three European centers by the World Health Organization was completed in 1977.²¹ The study enrolled 30,000 men aged 30–59 and randomly assigned the 10,000 individuals with the highest plasma cholesterol levels to clofibrate (1.6 g) or placebo treatment. A second control group of 5,000 subjects was randomly selected from among those within the lowest one-third of the plasma cholesterol level distribution. The investigators found by multivariate analysis that a decrease in the incidence of coronary heart disease was associated with a decrease in the plasma cholesterol level. Clofibrate treatment significantly reduced the incidence of nonfatal myocardial infarctions even though the overall drug-related reduction of plasma cholesterol was only 9%. Clofibrate also has an antiplatelet effect that could be the mechanism by which these beneficial effects were attained. Therefore, the results cannot necessarily be ascribed to the drug's hypocholesterolemic effect. Unfortunately, the incidence of deaths due to noncardiovascular diseases was greater in the clofibrate-treated group than in corresponding controls. The noncardiovascular deaths were due to a variety of diseases, including malignant neoplasms. This aspect will warrant careful examination in the future including an examination of the nonlipid changing effect of clofibrate. In these trials some patients did not have hyperlipoproteinemia, and the design did not allow optimization (flexible dosage) of the drug therapy.

DETERMINANTS FOR APPROPRIATE THERAPY

The minimum determinations for beginning appropriate therapy include measurements of plasma cholesterol and triglycerides, an estimate of chylomicrons, and an evaluation of the presence of concurrent diseases or a family history of CHD. Estimation of lipoprotein fractions³ will further improve the physician's ability to select appropriate therapy.

Hyperlipidemias may be subdivided into primary (genetic) or secondary based on the underlying mechanism of the expressed lipidemia. Any disease causing secondary hyperlipoproteinemia should be treated first and will frequently normalize the plasma lipids in these patients. The primary or familial hyperlipoproteinemias have been classified into five major phenotypes by Fredrickson and Lees¹¹ on the basis of the plasma concentration of the major lipoprotein fractions. In recent years we have learned the underlying defect responsible for some lipoprotein abnormalities. This understanding should significantly improve future therapy for these disorders and will be the basis on which we will recommend selection of specific hypolipidemic drug therapy.

There are three reasons for undertaking therapy of hyperlipoproteinemia. Reduction in markedly elevated triglyceride levels (chylomicrons and VLDL) reduces the incidence of abdominal pain and pancreatitis in individuals with type I or V hyperlipoproteinemia. Reduction of the size of disfiguring xanthoma is cosmetically desirable. The most important indication is the reduction in the consequences of atherosclerosis and CHD and is based on the assumption that they will be life threatening.

AGENTS TO LOWER PLASMA LIPOPROTEINS

Current FDA-approved drugs for lowering plasma LDL cholesterol are nicotinic acid, clofibrate, dextrothyroxine, probucol, cholestyramine, colestipol, and β -sitosterol. These and other useful hyperlipoproteinemic agents are listed in Table 1 with their known or suggested mechanisms of action.

The proper use of these agents and other investigational drugs should be based on the observed lipoprotein abnormality of the patient and the defined or suggested mechanism of the agent. Most of these abnormalities in lipoprotein type or concentration are associated with multiple potential causes—primary genetic disorders or secondary to other primary diseases, such as diabetes. A description of these abnormalities and the basis on which to select the appropriate hypolipidemic drug are listed in Table 2. Treatment of secondary hyperlipoproteinemia by correction of the primary disease should always be undertaken first. The appropriate diet (calories, cholesterol, type and quantity of fat, and the like) is the fundamental basis of all therapy directed at the control of hyperlipoproteinemia. Drugs should not be added to the regimen until it has been established that diet alone is inadequate. The appropriate diet must then be continued even when drugs are added. The reader is referred to a review by Gotto et al.¹⁴ for more specific information about diet therapy.

The Binding Resins: Cholestyramine and Colestipol

In patients with familial hypercholesterolemia who have decreased cholesterol catabolism, the drugs of choice are the bile acid binding agents. The effectiveness of cholestyramine and colestipol are consid-

TABLE 1. Drugs Currently Available for Treating Hyperlipoproteinemia

Drug	Daily dose (Range)	Mechanism	Adverse effects
β -Sitosterol	60–120 ml of 20% suspension (4 divided doses)	↓ CHOL absorption	Abdominal distress, loose stools
Cholestyramine	12–32 gm (1–4 divided doses)	↓ Bile acid resorption ↓ CHOL absorption ↑ CHOL excretion ↑ LDL catabolism ↑ CHOL synthesis ↑ TG synthesis	Constipation, dyspepsia, nausea, "gas" ↓ absorption of drugs ↑ plasma TG
Clofibrate	1 gm Q 12H (↓ in renal failure)	↓ TG synthesis ↑ FA oxidation ↑ VLDL catabolism	Dyspepsia, nausea, myopathy, thrombophlebitis, embolism, arrhythmias, angina, gallstones, (tumors in animals) ↑ CPK, transaminases ↑ sensitivity to coumarin anticoagulants
Colestipol	15–25 gm (1–4 divided doses)	↓ Bile acid resorption ↓ CHOL absorption ↑ CHOL excretion ↑ LD catabolism ↑ CHOL synthesis ↑ TG synthesis	Constipation, dyspepsia, nausea, "gas" ↓ absorption of drugs ↑ plasma TG