with activity, or disease in the locomotor system requires individual assessment and tailored activity. Asymptomatic patients over 50 who are moderate or heavy smokers also fall into this category.

(5) Patients with established defects in oxygen transport who wish to improve their effort tolerance (with or without supervision) require graded, progressive exercise testing, particularly if they wish to extend their activities to a level which may be potentially harmful. This type of test permits a precise exercise prescription, which justifies its costs.

(6) Rehabilitation programs appear to be a desirable extension of our current management of many disease states. Those that care for patients with advanced disease should have advanced exercise testing capability.

An increasing number of patients will be seeking advice in this area. Their approach to exercise (and ours) needs to be liberally spiced with common sense if they are to enjoy exercise and obtain whatever other benefits await them.

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Plasma Lipids-Lipoproteins in Coronary Artery Disease
Regulation and Control

Plasma lipids, especially cholesterol and triglycerides, have long been implicated in the pathogenesis of coronary artery disease (CAD). In vivo, the water-insoluble cholesterol and other lipids are complexed with proteins (apolipoproteins) into lipoproteins for transportation and metabolism. Five main types of lipoproteins have been classified according to their size and density. These are the exogenous and endogenous triglyceride transporting chylomicrons and very low density lipoproteins (VLDL); the VLDL remnants—the intermediate density lipoproteins (IDL); the major cholesterol transporting low density lipoproteins (LDL); and the postulated tissue-cholesterol-removing high density lipoproteins (HDL). Most of the epidemiologic, experimental, clinical, and genetic studies have emphasized the role of elevated levels of LDL or the cholesterol carried in this lipoprotein fraction (LDL-C) in atherogenesis.

In general, a relatively large amount of cholesterol in the LDL fraction is regarded as atherogenic, whereas that in the LDL of familial hypercholesterolemia or "familial" type 2 disease appears to be causally related to premature CAD.

Diagnostic criteria proposed by Fredrickson et al for type 2 disease include the following: (1) elevated LDL; (2) type 2 in a first-degree relative; or (3) tendinous xanthomata. Furthermore, these patients do not exhibit a significant lowering of their LDL-C values with a standardized low-cholesterol saturated fat diet. More recently, dysfunction(s) of specific LDL cellular receptors has been reported by Brown and Goldstein in familial type 2 patients.

In view of the accelerated atherosclerosis in such patients with well-defined metabolic abnormality, most would agree that familial type 2 patients with CAD could be utilized to determine whether reduction in plasma LDL-C level by means of an effective therapeutic program could actually retard the progression or even induce regression of CAD to improve angina pectoris, prevent myocardial infarction, and reduce deaths from CAD.

Recently, an ever-increasing interest has focused on HDL. Barr et al made the early observation that the plasma alpha-lipoproteins (HDL) levels of postmyocardial infarction patients are lower than those of healthy persons. This early observation is supported by the following: (1) epidemiologic studies which indicate that high HDL concentration constitutes an independent negative risk factor for CAD; (2) clinical correlation study shows that normolipemic CAD patients frequently manifest depressed HDL; and (3) families with high HDL levels have increased longevity. Some experimental data suggest that HDL may function to facilitate removal of cholesterol from the tissues per-
haps including that from the atheromatous lesion of the vessel wall\textsuperscript{20,21}

These observations made on LDL and HDL indicate that intracellular cholesterol can be regulated by devising an intervention program which is capable of accomplishing a substantial reduction in the atherogenic LDL and VLDL fractions. A program which would reduce LDL and VLDL towards normal and would concomitantly increase the antiatherosclerotic HDL fraction will be highly desirable.

\textit{Amelioration of Atherosclerosis}

A number of experimentally induced atherosclerotic lesions in nonhuman primates have been found to regress following the removal of the atherogenic stimulus (hypercholesterolemia), with rather drastic lowering of serum cholesterol levels.\textsuperscript{22-24} Assuming that these animal studies could be extrapolated to human beings whose atherosclerosis has developed over the lifetime of the individual, the questions to be raised are: (1) Is the extent and the composition of the chronic lesion amenable to regression? (2) Could a substantial reduction in plasma cholesterol (LDL-C) concentration and increment in HDL level be achieved and maintained in man with current diet-drug therapy?

Despite the aforementioned reservations, a number of investigators have designed studies to determine whether there is evidence for atherosclerosis regression in man. Buchwald and associates\textsuperscript{25} have reported that ileal bypass operation can achieve substantial lowering of plasma cholesterol in hyperlipidemic patients to either reduce the rate of progression or to induce regression of angiographically documented CAD in 77 percent of 22 patients. Brandt et al\textsuperscript{26} have employed a precise and reproducible angiographic technique to show a positive correlation between regression of early femoral lesion and significant reduction in plasma LDL and VLDL concentration. Kuo and associates\textsuperscript{27} report that progression of angiographically documented CAD can be arrested for several years in a series of type 2 patients when their plasma cholesterol or LDL-C and their serum triglyceride-VLDL levels could be substantially reduced and maintained at low levels by combined low cholesterol-low saturated fat-low simple carbohydrate diet and bile acid sequestrating resin-colestipol therapy. Nikkila and associates\textsuperscript{28} also found that progression of CAD in patients with type 2 disease is reduced more dramatically in those who show the greatest amount of serum cholesterol lowering.

Thus, evidence is accumulating to suggest that in most cases, human CAD is potentially regressible or stabilizable, if plasma cholesterol and LDL-cholesterol concentrations are vigorously reduced to more "ideal" levels—<220 mg/dl and <150 mg/dl, respectively. Since plasma triglyceride or VLDL levels are also involved in lipoprotein metabolism and implicated in CAD,\textsuperscript{3} simultaneous suppression of hypertriglyceridemia has been shown to contribute toward regression of early femoral arterial lesion.\textsuperscript{28}

\textit{Other Effects of Lipid-Lipoproteins on Atherosclerosis and its Complications}

The diet-colesterol treatment has no effect upon HDL-cholesterol (HDL-C) concentration of type 2 patients.\textsuperscript{27} Although there is no absolute increase in HDL, the HDL-C/LDL-C ratio is increased as the result of LDL-C reduction. Thus, the possibility that a relative HDL increase may also contribute to the observed beneficial clinical response cannot be ruled out.

Several investigators and ourselves\textsuperscript{29,30} have used nicotinic acid to enhance the hypolipemic effect of diet-resin therapy. Besides its hypolipemic effect, nicotinic acid in pharmacologic doses of 3 to 6 g per day has been shown to increase HDL-C and to alter the major apoprotein composition of HDL. The drug raises Apo A-I while it lowers Apo A-II content of HDL. Shepherd and his associates\textsuperscript{31} postulated that such changes induced by nicotinic acid in lipoprotein metabolism has prophylactic value for prevention of CAD.

The complex relationships of platelets and cholesterol to atherosclerosis have been investigated in patients with familial type 2 disease. These studies have demonstrated that platelets from type 2 persons show increased sensitivity to epinephrine, ADP, and collagen, accompanied by several fold increases in nucleotide release.\textsuperscript{32} In composition, these hypersensitive platelets from type 2 patients are found to exhibit elevated free cholesterol content and a C/P ratio 8 percent greater than platelets from normolipemic subjects.\textsuperscript{33,34} Further elucidation of lipid-induced abnormal platelet activity to enhance thrombotic complications and premature CAD in type 2 disease may provide an insight on the lipids-platelet interaction in the progression of arterial disease and the development of acute vascular complications. Indeed, Bizios et al\textsuperscript{35} and Tremoli et al\textsuperscript{36} have reported that patients with familial type 2 hyperlipoproteinemia may manifest an increased production of platelet thromboxane A\textsubscript{2}, a potent proaggregatory and vasoconstricting agent.

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