It’s Time To Be Practical

THE DISCOVERY AND TREATMENT of hyperlipidemia is now an established part of the practice of preventive cardiology. Definitive proof is still lacking that the resulting change in lifestyle for many people will be rewarded by a decrease in the risk of premature ischemic heart disease. The circumstantial evidence for a probable benefit to many is overwhelming, however, and this risk factor deserves the attention it is now receiving. Because the number of subjects who may be screened for hyperlipidemia is potentially enormous and because a clear or well ratified set of explicit criteria for screening are lacking, there is concern that screening will impose a heavy burden upon physicians and increase the cost of primary health care. Specialists in hyperlipidemia are in short supply and the subdiscipline is awash in eddies and cross-currents of uncertainty because knowledge is growing, yet incomplete. Specifically, something needs to be said about the current place of lipoprotein phenotyping by electrophoresis in the management of hyperlipidemia by the physician who is not a specialist in lipid disorders.

The detection of hyperlipidemia is relatively simple. It requires a blood specimen — ideally, but not absolutely, one that has been drawn in the fasting state — and determination of cholesterol and triglyceride concentrations. With the automated methods now in use, a cholesterol above 250 mg/100 ml or a (fasting) triglyceride over 200 mg/100 ml provides a definition of hyperlipidemia that is reasonable and conservative. Upon finding a subject with hyperlipidemia, the physician is likely to wonder if he should now obtain a lipoprotein electrophoretic analysis. At present, my answer, directed to the generalist, is negative.

Ten years ago, we recommended in this Journal the use of lipoprotein patterns for the identification of different groups of familial hyperlipidemia. Electrophoresis, a technique already well developed at the time, was adapted to replace the largely inaccessible ultracentrifuge and recommended as a preliminary method for providing lipoprotein patterns. With the addition of quantitation (which many unfortunately chose to overlook) a taxonomy was developed and the classification of hyperlipidemia in terms of types of hyperlipoproteinemia became, and still is, an exceedingly popular practice. Initially, there were five, then six, types. These provide convenient shorthand designations indicating the elevation of one or more lipoprotein families. The patterns encompass the lipoprotein abnormalities that may occur in nearly all patients with hyperlipidemia. Their use sharpens the focus upon the diversity of metabolic abnormalities that underlie hyperlipidemia. As was stressed initially, the types of hyperlipoproteinemia are not diseases, but groups of disorders similarly affecting the concentrations of particular lipoproteins. A given pattern may be primary (often familial) or secondary to other diseases. Each type is associated with particular clinical features that are useful to know. Irrespective of etiology, each type tends to respond better to a specific therapeutic approach. The general validity of this approach has not changed.

In two respects, the typing system has fallen short. One of these, particularly germane to primary care practice, is a technological lag that has prevented general access to the accurate assignment of lipoprotein patterns. When hyperlipidemia is of modest proportions, an accurate distinction between types 2 and 4, which make up the vast majority of patients detected upon screening for hyperlipidemia, is depen-
dent upon quantitation of low density lipoproteins (LDL). Electrophoretic methods have been recently developed that are capable of quantitative analyses in a large volume of samples, but commercial laboratories, which necessarily must be concerned with the costs of a given test, cannot provide this service.

The diagnosis of type 3 hyperlipoproteinemia requires substantiation by chemical measurement of the composition of very low density lipoproteins (VLDL). The necessity of preparative ultracentrifugation has been emphasized in a retrospective analysis of our experience with many of the patients with this lipoprotein pattern followed up to 10 years. Evidence is stronger than ever that they are a distinctive group among all patients with hyperlipidemia, but electrophoretic techniques cannot provide a reliable separation.

A second failing of the typing system is its limited value in genetics. This comes as no surprise. It was early emphasized that no type of hyperlipoproteinemia should be considered genotypic. In patients with severe forms of familial hyperlipidemia, differences among disorders tend to be stark and the patterns relatively stable. When lipoprotein analyses were extended to larger populations, which contained a high proportion of more moderate abnormalities, the distinctions became less clear. The patterns were observed to be less stable; concentrations of LDL or VLDL might cross arbitrary limits of abnormality from day to day. More important was the increasing evidence of heterogeneity in lipoprotein patterns in affected relatives within a hyperlipidemic family. The best example, and most pertinent to cardiologists, was that provided by the Seattle study, in which affected relatives of many hyperlipidemic survivors of myocardial infarction were found to have type 2a, type 2b and type 4 patterns in about equal numbers! In these families heterogeneous lipoprotein patterns appear to be different manifestations of a single abnormal gene and the disorder has been called "familial combined hyperlipidemia" by Goldstein and co-workers. It is likely that "combined hyperlipidemia" will be encountered often in screening for hyperlipidemia. There is no specific biochemical test to establish the diagnosis of this inheritable disorder and a probable diagnosis can be obtained only by extensive family screening.

Said once again for emphasis, neither lipid determinations nor the full range of lipoprotein analysis can provide the diagnosis of a specific genetic disorder in a single patient. This fact must not discourage the screening of relatives of hyperlipidemic subjects, for they will have a much greater likelihood of being hyperlipidemic than members of the general population.

Most patients with primary hyperlipidemia fall into three large groups. Except in the relatively few with type 3, neither chylomicrons nor chemically abnormal lipoproteins (as far as we know today) are present. Thus, the majority of patients with hyperlipidemia can be detected, sorted and managed by lipid analyses alone. A detailed set of suggestions for estimating lipoprotein patterns from cholesterol and triglyceride concentrations has appeared elsewhere. The three groups include patients with hypercholesterolemia alone, hyperglyceridemia alone, and a combination of the two. It is easy enough to classify pure hypercholesterolemia as type 2a and pure hyperglyceridemia without chylomicrons as type 4. The therapeutic approaches to either are fairly straightforward and lipoprotein electrophoresis adds no important information.

Mild to moderate excesses of cholesterol and triglycerides can be generally considered as mixed hyperlipidemia. Either types 2b, 3 or 4 may be represented. Mixed hyperlipidemia is not to be confused with combined hyperlipidemia, for the latter is meant to refer to the particular genetic abnormality mentioned above, in which any of several lipid or lipoprotein patterns may appear in different members of the same family. The therapy of any patient with moderate mixed hyperlipidemia can begin with prescription of a diet that is weight controlling, low in saturated fats and cholesterol and avoids excesses of simple sugars and alcohol. Within a month of good attention to this diet, the response will dictate whether one of two further actions is required. If the triglycerides remain over 300 mg/100 ml, a trial of clofibrate may be instituted. If triglycerides have declined leaving a clearcut excess in cholesterol, more severe restriction of cholesterol and saturated fat intake and, possibly, the use of a bile acid-binding resin may be necessary.

Encounters with patients who have triglyceride concentrations above about 1000 mg/100 ml will be rare. In such cases it is useful for the physician to look for the characteristic collar of chylomicrons on the standing plasma, which is a possible harbinger of pancreatitis and an urgent reminder to restrict fat in the diet. The separation of the rare type 1 from the more common type 5s (or severe type 4s) is an exercise for which cooperation with the specialist is recommended.

New knowledge will progressively supply specific biochemical markers for the identification of different causes of hyperlipidemia. Until this inevitable and desirable transition has been completed, the conversion of lipid concentrations to patterns of

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hyperlipoproteinemia offers the clearest view of physiological mechanisms and metabolic derangements alike. Nevertheless, there are practical limits to obtaining this illumination that must now be noted.

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References

It's time to be practical.
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