Some Observations on Hyperlipoproteinemias and their Classification

The time has come when we as practitioners must make our peace with the lipoproteins. Important new evidence has accumulated during the past decade firmly establishing hyperlipoproteinemia as a risk factor in atherosclerosis. This includes not only additional epidemiologic correlations but also, most importantly, several studies in which favorable effects on morbidity and mortality were observed as a result of dietary or drug treatment of hyperlipoproteinemia. Criticisms of one sort and another can be leveled at these studies individually, and the book has by no means been closed; additional clinical research and further field trials are needed. Nevertheless, the impact of the intervention trials already completed is such that best medical practice now certainly calls for correction of frank hyperlipoproteinemia. The questions of when to treat (How shall we define the upper limits of normal?) and how to treat (What is the best diet in each case? When are drugs indicated and which?) are only partially answered by available objective data. As is so often the case, the physician is ultimately called upon to exercise his judgment on a case-by-case basis. In order to reach wise decisions on these questions as new information becomes available, the physician will need to be conversant with the system of lipoprotein macromolecules that carry cholesterol, triglycerides, and phospholipids in the plasma compartment. The most widely accepted system for classifying the hyperlipoproteinemias is that introduced by Fredrickson, Levy, and Lees. A panel of the World Health Organization has now adopted this system with certain modifications, and its proposal is reproduced in this issue of Circulation. The WHO Memorandum is introduced in the hope that it may provide "... an internationally acceptable provisional classification ... to facilitate communication ..." (italics ours). We agree that it does that. In using it, however, we should be clearly aware of its strengths and weaknesses, its scope and limitations.

Classification systems in medicine tend to be both a blessing and a curse. To the extent that they clarify diagnosis, lead to an understanding of pathophysiology and prognosis, and assist in designing therapeutic approaches, they can be a blessing. To the extent that they tend to rigidify thinking about underlying causes of disease or discourage further investigation, they can be a curse. In modern medicine our goal must be the definition of disease in terms of specific pathogenetic mechanisms whenever possible. In the case of inherited disorders the goal must be the definition of specific proteins or protein enzymes that are deleted or defective. Classification based empirically on clinical or chemical syndromes, if not directly related to the underlying gene defect, can obscure heterogeneity.

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Circulation, Volume XLV, February 1972
Gout, for example, was once considered to be an entity defined by hyperuricemia. More sophisticated metabolic studies show us that a variety of single or multiple genetic errors may underlie the gouty syndrome. Similarly, one suspects that what we now call "diabetes mellitus" may ultimately be resolved into subcategories based on deeper understanding of pathogenesis. Conversely, the same genetic error may express itself differently, and overclassification may obscure relationships. Nevertheless, one must start somewhere, using whatever clinical and biochemical guideposts are available to define probable—or at least possible—phenotypes. As discussed below, pragmatic advantages may stem from even such a tentative grouping. Validation, however, rests on pursuit of the ultimate definition of mechanism and genotype.

At the present time there is only one form of familial hyperlipoproteinemia in which the probable enzyme defect has been identified and that is familial hyperchylomicronemia, one of the rarest forms of hyperlipidemia. Rather good evidence has been presented in this case for an inherited deficiency in lipoprotein lipase.7 The molecular basis for the other inherited forms of hyperlipoproteinemia remains unknown although some insights are developing at least with regard to the general nature of the metabolic errors involved.8–10 The WHO classification is therefore fundamentally a classification by phenotype, essentially a description of the patterns of lipoprotein elevations observed. Now the concentrations and patterns of lipoproteins are by no means invariant and immutable. For example, both in normal individuals and in patients with dyslipoproteinemia, diet will have a profound effect. This brings us to one aspect of the classification that deserves emphasis. One of the important "ground rules" set forward by Fredrickson and collaborators6 and reemphasized in the WHO Memorandum is that the blood sample for analysis must be drawn when the subject has been maintaining a steady body weight, when he has been on a diet of "usual" composition (see below), and when he has been fasting for 10–14 hours.

The plasma of a normal individual drawn several hours after a fat-rich meal will show elevated concentrations of triglyceride and an increase in pre-β-lipoprotein concentration. Such a plasma is said to show a type IV pattern, but the subject does not necessarily have type IV hyperlipoproteinemia. Normal subjects taking diets containing inordinately large amounts of carbohydrate (70–80% of calories) may show an increase in pre-β-lipoprotein concentration even in the fasting state, but again they should not be for that reason classified as having type IV hyperlipoproteinemia. Normal subjects may be hyperlipoproteinemic during a period of positive caloric balance but normolipemic during steady state before, and again after, weight gain. There is a rough analogy between the use of the glucose tolerance test in the diagnosis of diabetes mellitus and the use of the lipoprotein pattern in the diagnosis of hyperlipoproteinemias. In both cases the diet of the patient during the days prior to testing must be taken into account and the timing of the test or test sample must be specified, the fasting state being the most readily standardized reference point in the diurnal cycle.

Lipoprotein patterns are also importantly altered as a secondary response in a number of disease states. Consequently, as in the differential diagnosis of hyperglycemia, the first concern on encountering any hyperlipoproteinemia is to rule out the disease states that may underlie it, i.e., rule out secondary hyperlipoproteinemia. Thus, for example, a patient has the pattern of type IV hyperlipoproteinemia if his plasma (drawn after an overnight fast and when the patient is on a diet containing usual amounts and kinds of fats) shows an elevation in the concentration of pre-β-lipoproteins (very low-density lipoproteins) and no increase in the concentrations of other classes of lipoproteins. This same type IV pattern may, however, be encountered in patients with hypothyroidism, uncontrolled diabetes, nephrotic syndrome, pancreatitis, dysglobulinemia, and perhaps other primary disease states. With correction of the underlying disease the type IV pattern may revert to
a normal pattern—the patient had type IV hyperlipoproteinemia secondary to “X.” Each one of the six lipoprotein patterns defining the basic types of hyperlipoproteinemia can be encountered secondary to one or more underlying disease states, and these must be carefully ruled out before the designation of primary hyperlipoproteinemia is warranted. The WHO group also proposes inclusion under “primary” those hyperlipoproteinemic states due to diet (including alcohol intake) or due to drugs (including estrogenic and steroid hormones) when the genesis is “through an unknown mechanism.” The rationale for this is unclear. Is a woman whose lipoprotein pattern is perfectly normal throughout her lifetime except when she is on “the pill” to be classified as having a primary hyperlipoproteinemia? If a patient is hyperlipoproteinemic only when ingesting alcohol should he be regarded as having primary hyperlipoproteinemia? Whether the mechanism is known or not, if the response is clearly related to an environmental influence it is secondary. It may be the case that the response to diet or drugs may be influenced by genetic predisposition, and this deserves further study. Nonetheless, when a specific inciting environmental factor can be identified, even if the mechanism is not known, would it not be more in keeping with established patterns of nomenclature to designate that kind of hyperlipoproteinemia as secondary?

Definition of Normal Limits

A 40-year-old man with a cholesterol level above 300 mg/100 ml or triglyceride above 200 mg/100 ml would probably be accepted by everyone as an example of hyperlipidemia. But what about the 25-year-old man with a cholesterol level of 250 mg/100 ml? Definition of the upper limit of normal is quite arbitrary. While the distribution curve for plasma lipid levels in the general population is skewed somewhat to the right there is no clear bimodal distribution. Shall we consider “abnormal” any value more than 1 standard deviation above the mean for age- and sex-matched controls? More than 2 standard deviations above the mean? If risk of coronary heart disease correlates with cholesterol level down to say 220 mg/100 ml then shouldn’t any higher value be considered abnormal? And if risk is still lower in a population like the Japanese with levels far below ours shouldn’t “normal” be replaced by “ideal,” i.e., as low a level as possible as long as achieving it is not associated with any ill effects? These questions have not yet been resolved satisfactorily, and the whole issue is understandably left open in the WHO Memorandum. Until it is resolved, the establishment of cutoff points remains arbitrary and a matter of local option. That being the case, the initial screening for hyperlipoproteinemia can probably be limited to measurement of total cholesterol and total triglyceride levels, further study being done only if one or both of these exceeds the limits elected. A few patients may have “normal” total cholesterol levels yet have a relative increase in β-lipoprotein cholesterol (offset by a relatively low level of α- or pre-β-lipoprotein cholesterol) but this should be uncommon and the elevation not marked.

Primary Hyperlipoproteinemia

If all of the ground rules are observed and if all of the known causes for secondary hyperlipoproteinemia are explored and ruled out, one is left with a diagnosis of primary hyperlipoproteinemia. The lipoprotein pattern, total cholesterol, total triglyceride, and certain additional clinical features will allow a pigeonholing into one of six categories (type II has now been subdivided into IIa and IIb). Do the patients in each pigeonhole then constitute a homogeneous population with regard to genetic basis and pathogenetic mechanism? Certainly this is not established and no such claim is made. Indeed, the authors of the memorandum are careful to point out at the outset that to achieve useful classification, one must go beyond lipoprotein patterns and consider etiology, and that any classification used today is necessarily an open-ended and incomplete one. The classification is at this point strictly descriptive. With the report of the clinical pathologist in hand one should say no more than that “this patient presents with a type II pattern.” Having fully evaluated the patient
and having ruled out all of the possible bases for secondary hyperlipoproteinemia one can say that the patient has "primary type II hyperlipoproteinemia." To say that the patient has "type II disease" may imply more than is justified.

As further research is done it may indeed develop that each category of primary hyperlipoproteinemia embraces a population with a common genetic basis. As discussed above, however, it may develop that several different (possibly related) genotypes can underlie the same phenotype or vice versa. Only further studies on mechanisms regulating lipoprotein concentrations can resolve this issue. Since a given disease entity may give rise at various times to any one of three or four different types of secondary hyperlipoproteinemia, it would not be surprising to find that a given genotype might likewise express itself in the form of different patterns under different environmental circumstances or as the result of interaction with other elements in the genetic constitution. Already there is evidence that both the type IV pattern and the type V pattern can occur within the same sibship or in the same patient at different times. Nor would it be surprising to find that the same phenotype with regard to lipoprotein pattern might arise as the expression of quite different genotypes. After all, the physiologic processes that interact to determine the steady-state concentration of lipoproteins must be manifold; mutations affecting a number of them, individually or in combination, may be capable of yielding the same end result in terms of steady-state lipoprotein concentration and pattern. Some patients with the type IV pattern are reported to have a defect primarily in rate of removal of lipoprotein triglycerides from the plasma9,10 while others are reported to be synthesizing and secreting at an abnormally high rate.11 Even in the case of familial type I disease, the possibility of genetic heterogeneity is not entirely ruled out. For example, low lipoprotein lipase activity could be on the basis of a specific mutation affecting the genome responsible for enzyme production or, in other cases, the low activity might relate to defects in the release of enzyme from cells or in the synthesis of or process of linkage of cofactor (heparin?) to enzyme. As long as we remain clearly aware of the empirical nature of a classification little harm is done by using a label that may embrace more than one entity. Indeed, we have little choice in the matter. Our concern must be that we do not become complacent and that efforts to delineate mechanism(s) continue actively.

Having stated these qualifications let me say that I believe this classification is useful and that its usefulness has already been proved. First, by basing itself on simple methods—inspection of plasma, measurement of total cholesterol and triglyceride, and a relatively simple lipoprotein electrophoresis—it brings a more meaningful way of looking at hyperlipidemia within the reach of every clinical laboratory and every physician. That hyperlipidemia must ultimately be understood and dealt with in terms of hyperlipoproteinemia has been apparent for some time, beginning with the work of Gofman and his associates.12 The present classification does not call for use of the analytical ultracentrifuge. The preparative ultracentrifuge is needed only for definitive diagnosis of type III hyperlipoproteinemia and for delineation of borderline examples of other types. However, type III is a relatively rare condition and from a practical point of view one is less concerned about borderline hyperlipoproteinemias. Thus, generally available methods will suffice in most cases. Second, the classification has provided a manageable vocabulary. *Essential familial hypercholesterolemia* is a 37-letter, 17-syllable tongue twister; *familial type IIa* may not have quite the same ring of authority but it is much handier. "Familial hyperchylomiconemaa" or the eponymic "Bürger-Grütz syndrome" are just as well jetisoned in favor of "type I." Third, no matter how it may be subsequently revised and expanded, it is already playing a useful catalytic role in clinical research. Finally, and most important, it serves to focus attention on differences in prognosis and indicated treatment in different cases. The number of patients studied in this regard is still small, and conclusions must remain tentative. Lipoprotein analyses...
were not included in some of the early epidemiologic studies and intervention trials but certainly differences were noted depending on whether only cholesterol level was elevated (type II) or only triglyceride level was elevated (type IV). Thus, clofibrate was found to be less effective in lowering cholesterol levels than in lowering triglyceride levels. Recent studies show that indeed clofibrate is not fully effective therapy in type II patients but that cholestyramine (and diet) is.\textsuperscript{15, 16}

Considerable controversy has raged about the question of whether hypercholesterolemia or hypertriglyceridemia was the better index of risk with regard to coronary heart disease. Earlier attempts to refine prediction of risk based on lipoprotein patterns determined by analytical ultracentrifugation yielded conflicting results. Data are just beginning to accumulate on the risk associated with different types of hyperlipoproteinemia as defined by the classification under consideration.\textsuperscript{16} We shall await the results of further studies of this kind with great interest. Much remains to be learned and almost certainly our ways of defining and interpreting hyperlipoproteinemia will change. For now the classification (and the point of view from which it springs) recommends itself to us as a simple and useful context for dealing more meaningfully with one of the major risk factors in coronary artery disease.

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_Circulation, Volume XLV, February 1972_
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Circulation. 1972;45:247-251
doi: 10.1161/01.CIR.45.2.247

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