Problems in Family Practice

The Hyperlipoproteinemias

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Much of the laboratory assessment of the hyperlipoproteinemias can be accomplished by simple office procedures. A specific high density lipoprotein known as HDL has created much recent interest as a negative risk factor. However, a critical evaluation of widespread HDL determination is warranted since there is very little of proven clinical value available for HDL modification. Before instituting specific treatment for a hyperlipoproteinemia, the clinician must make his/her own assessment of the effect this treatment may have in the possible prevention and regression of atherosclerosis. There is incomplete evidence that both prevention and regression are possible, but proof is far from established. An appropriate and nutritious diet to lower cholesterol will certainly do no harm and should always be instituted. The ultimate issue then becomes the long range benefit and potential side effects of drug or surgical therapy. As of this time, it appears that enough benefit has been documented for the clinician to proceed cautiously with drug therapy in selected patients.

Any consideration of cholesterol and its relationship to atherosclerosis necessitates an understanding of the role this blood lipid plays as a major atherosclerosis risk factor. Major risk factor for atherosclerosis means that the association has clear-cut statistical significance. From large population epidemiologic studies, three major atherosclerosis risk factors have been established: elevated serum cholesterol, cigarette smoking, and hypertension. Some studies place diabetes mellitus as a fourth major risk factor. The clinical end point of these risk factors is the development of atherosclerosis, by whatever mechanism, such that blood flow in a specific artery is sufficiently compromised to cause tissue damage. Atherosclerosis is the major medical problem of highly developed societies in the western world and elevated serum cholesterol is a major contributing factor. The critical issue, however, is whether or not reduction of this cholesterol by diet or drugs is of benefit. Much evidence suggests that it is, but it is not rigidly established.

Background

Lipoprotein Terminology

Certain definitions need to be understood before assessing an elevated serum cholesterol and

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planning its management. Lipoproteins are blood particles which consist of fat (lipid)—protein associations to assure blood fat solubility and thereby the ability of blood to transport fat. Therefore, a hyperlipoproteinemia is a clinical entity in which one or more lipoproteins are elevated. The major lipoproteins are as follows: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). These are present in serum obtained from a patient after a 14-hour fast during which only water ad lib and essential medications are ingested. Therefore, a fourth major lipoprotein, chylomicrons, should be absent unless there is a specific abnormality in metabolism of this lipoprotein. The hyperlipoproteinemias are best considered as clinical phenotypes. This means that a specific hyperlipoproteinemia only describes a set of clinical and laboratory observations. Nothing regarding underlying mechanisms is implied. Therefore, the genetics involved may be monogenic, polygenic, or sporadic, and different biochemical mechanisms may be involved, all resulting in the same ultimate hyperlipoproteinemia phenotype. As long as these principles are understood, the so-called lipoprotein Typing system is quite useful and accurate as a means of clinical communication and as a guide to treatment. There is currently a group of investigators who want to tear down the Typing system as meaningless and claim that only descriptive terminology such as "familial hypercholesterolemia" is acceptable. This is unnecessary as long as the lipoprotein disease Types are accepted as phenotypes, or a language, and nothing more.

High Density Lipoproteins (HDL)

HDL have assumed new importance in atherosclerotic cardiovascular disease and it is essential for the practicing clinician to understand why. Epidemiologic studies have established a significant statistical association between elevated HDL-cholesterol levels and protection from atherosclerosis.[1] In other words, HDL appear to be a negative risk factor or protective factor against atherosclerosis. Possible mechanisms include, first, the role of HDL in carrying cholesterol back from peripheral tissues, including arterial intima, to the liver for metabolism, and, secondly, competition with LDL for the same arterial intimal cell receptor to prevent entry of LDL-cholesterol into atherosclerotic plaques. Various numerical risk profiles for HDL-cholesterol have been published but the major principle to be noted is that atherosclerosis risk decreases as HDL-cholesterol increases. Indiscriminant determination of only HDL-cholesterol, without determination of VLDL-cholesterol and LDL-cholesterol, does not appear justified since alteration of HDL cannot yet be seen as a practical clinical therapeutic goal. No diet or drug is clearly established to have therapeutic benefit although this may become significant as newer drugs are developed. For now, the clinician is limited to minimal information that regular exercise elevates HDL-cholesterol as does abstinence from cigarette smoking. Many laboratories report LDL-cholesterol determined indirectly from assay of the HDL-cholesterol. The usual mass laboratory HDL-cholesterol determination is made on the supernatant of serum after precipitation of VLDL and LDL with heparin-manganese. The formula is:

$$\text{LDL-cholesterol} = \text{Total triglycerides} - (\text{Triglycerides}/5 + \text{HDL-cholesterol}).$$

This is obviously indirect methodology and much less accurate than direct ultracentrifuge methodology.

Lipoprotein Phenotypes

There are six lipoprotein phenotypes as follows: Type I, Type IIa, Type IIb, Type III, Type IV, and Type V disease. In Type I, only chylomicrons are elevated. In Type IIa, only LDL are elevated, whereas in Type IIb, LDL and VLDL are both elevated. All hyperlipoproteinemias involve only abnormally high levels of normal lipoproteins except for Type III; in this case, an abnormal lipoprotein, which is a chylomicron remnant, is elevated. In Type IV, only VLDL are elevated, and in Type V, both VLDL and chylomicrons are elevated.

The major groupings of the hyperlipoproteinemias can be made as follows: Types IIa, IIb, III, IV, and V (when related to diabetes) are atherogenic lipoprotein phenotypes. Types I and V (when familial) have no clear-cut relation to

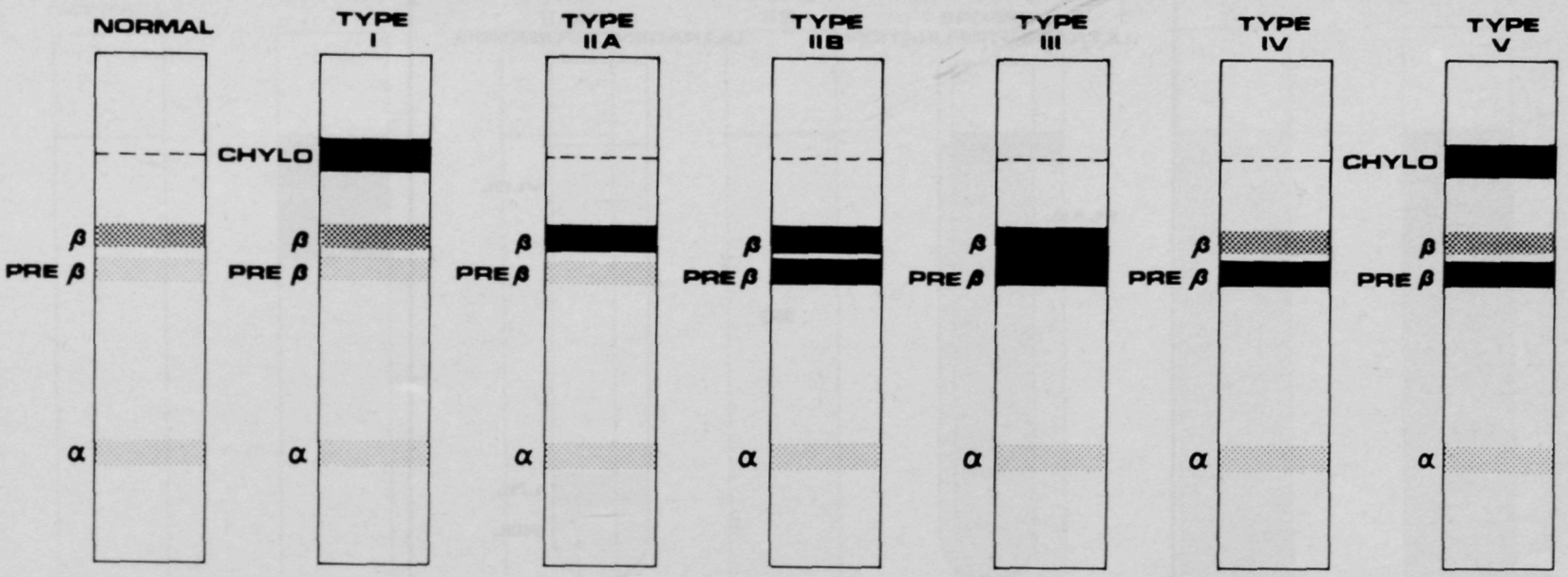

Figure 1. The normal lipoprotein electrophoresis pattern and the patterns of each lipoprotein phenotype are shown schematically. When compared to the normal pattern, the electrophoretic band increases associated with each phenotype are easily seen. In Type III disease, the "Broad Beta" band is present but in actual laboratory methodology it is too indefinite to make the specific diagnosis

atherosclerosis and have clinical syndromes which may respond rapidly to specific treatment, unlike atherosclerosis.

Electrophoresis

Electrophoresis is of no value in assessment of the hyperlipoproteinemias unless used in conjunction with the ultracentrifuge to confirm the abnormal floating beta band present on the top of serum ultracentrifuged at its normal density of 1.006 g/ml. Otherwise the methodology of electrophoresis offers no clarification to serum lipid analysis and may create confusion. Because of "trailing" on electrophoresis and general lack of quantitation by lipoprotein band staining, one Type is easily confused with another. The classic error is to diagnose Type III disease from a so-called broad beta band which in practice is easily confused with a Type IV prebeta band with trailing. However, because of continued usage, it is essential to have the following knowledge of lipoprotein electrophoresis as usually performed at pH 8.6 (Figure 1). Chylomicrons remain at the origin. LDL move the slowest and have beta band mobility. VLDL move a little faster as the prebeta band, and HDL move fastest as the alpha band. It should be understood that both ultracentrifugal and electrophoretic separations of lipoproteins are only physical methods and do not define functional properties. It happens, however, that lipoprotein families with functional differences each tend to concentrate in physically defined groupings, but with definite overlap.

The Ultracentrifuge

A basic understanding of ultracentrifuge terminology and principles is of value in studying the lipoprotein phenotypes (Figure 2). Normal serum has a solvent density of 1.006 g/ml. With ultracentrifugation, VLDL float at this density and LDL and HDL sink. At density 1.063 g/ml, LDL floats, and at density 1.210 g/ml, HDL, the lipoprotein with the greatest mass, floats. Following separations, these lipoproteins are analyzed by their cholesterol content. Previously, lipoprotein analysis by ultracentrifugation has been laborious, time-consuming, and impractical for a clinical laboratory not supported by research funds. The usual ultracentrifugation run takes almost 24 hours at 40,000 RPM. Recently, however, the Beckman Instruments Co., Palo Alto, California, has developed an automated table-top lipoprotein ultracentrifuge analysis system consisting of an extremely high speed air driven ultracentrifuge that runs at 100,000 RPM and develops 200,000 times the force of gravity. In addition, the system has a separate lipoprotein fractionator and a cholesterol analyzer. Lipoprotein analysis can be completed in two to three hours and expressed as VLDL-cholesterol, LDL-cholesterol, and HDL-cholesterol. Analysis time and cost have been brought to a practical level. Use of the ultracentrifuge is essential to diagnose

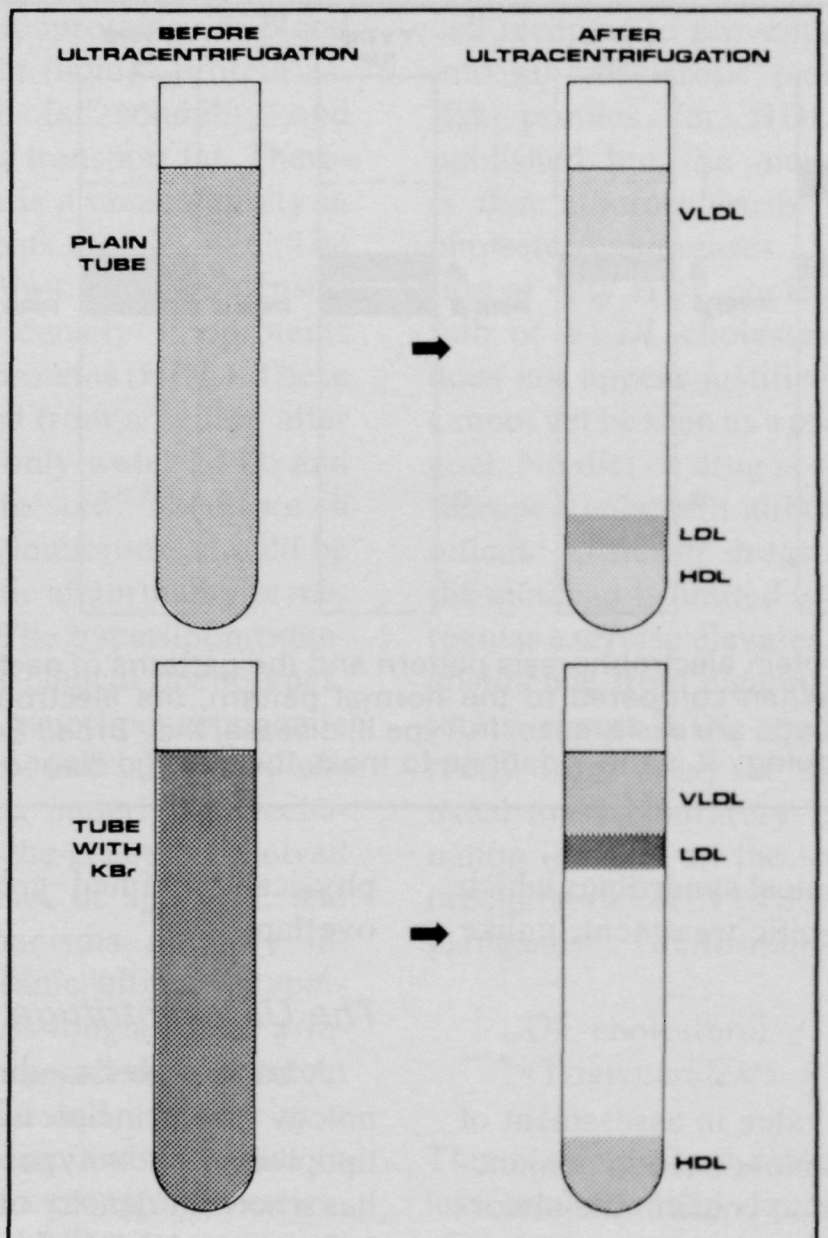

Figure 2. Ultracentrifuge methodology is shown schematically. In the top tube with unaltered density of 1.006 g/ml, only very low density lipoproteins (VLDL) float to the top after ultracentrifugation. In the bottom tube, KBr is added to raise the density to 1.063 g/ml and both VLDL and low density lipoproteins (LDL) float, leaving high density lipoproteins (HDL) on the bottom

precisely Types IIb, III, and IV. The reason for this is that serum lipid chemistry levels of both cholesterol and triglycerides are elevated and it is only possible to guess between Type IIb and Type IV by the more equally elevated lipid levels observed in Type IIb and the more markedly elevated triglyceride levels in Type IV. Therefore, elevation of both VLDL and LDL points to Type IIb and elevation of VLDL alone to Type IV. Type III is a more special case since the abnormal chylomicron and/or VLDL remnant which is elevated must initially be floated by ultracentrifugation and then confirmed by electrophoresis, lipid staining of the small remnant throughout the infranatant, or excess cholesterol richness of the top fraction.

Diagnostic Considerations

Simple Office Procedures

Much information can be obtained by determination of serum cholesterol and serum triglycer-

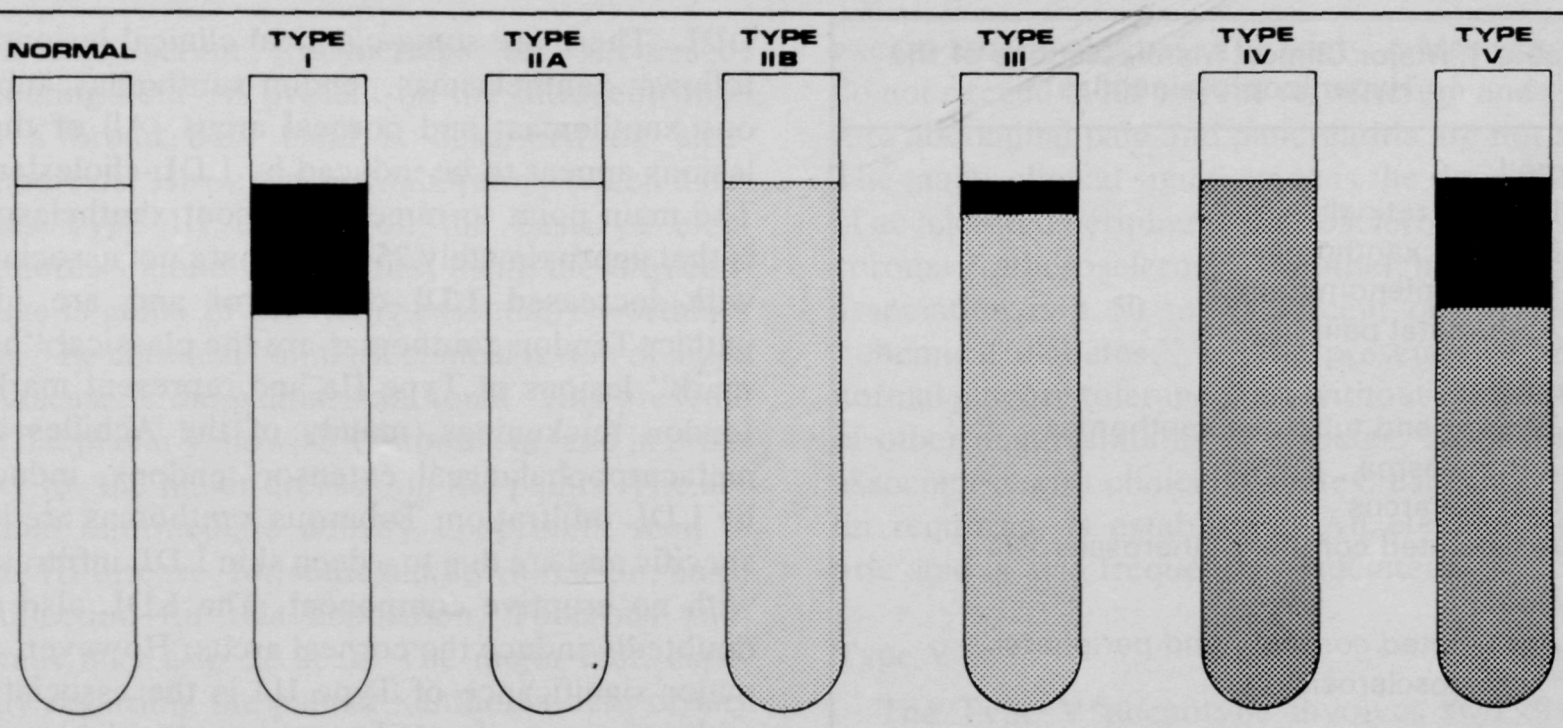

Figure 3. The serum patterns associated with each lipoprotein phenotype are shown schematically in comparison to clear normal serum. These serum patterns are observed after serum from patients fasting 14 hours are allowed to stand overnight in a refrigerator at just above freezing temperature

ides and observation of 14-hour fasting serum allowed to stand overnight in a refrigerator (Figure 3). These procedures alone are sufficient for precise diagnosis of Types I, IIa, and V. In Type I, the triglycerides are markedly elevated and the cholesterol is normal; in the standing serum there is a dense top white cream layer of accumulated and coalesced chylomicrons with clear serum beneath and the diagnosis of Type I phenotype is complete. In Type IIa, cholesterol is markedly elevated while triglycerides remain normal; the standing serum is completely clear since the elevated LDL do not have sufficient dimension to diffract light but remain dispersed. In Type V, both chylomicrons and VLDL are elevated. Therefore, serum triglycerides are markedly elevated and cholesterol is elevated due to the VLDL increase since this lipoprotein contains cholesterol equal in concentration to approximately 20 percent of the triglycerides. The standing serum has a dense top chylomicron layer and diffuse turbidity beneath from the VLDL which diffract light but remain in stable dispersion.

Lipoprotein Phenotypes

The six primary clinical hyperlipoproteinemias each need to be considered separately. The focus will be on the classical clinical manifestations (Table 1) and specific laboratory definition.

Type I

Type I hyperlipoproteinemia is quite rare and therefore of little interest to the usual clinical practice. However, it is still important to the overall context of the hyperlipoproteinemias. The genetics appear to involve a recessive gene. There is a specific enzyme system deficiency or abnormality and this involves the lipoprotein lipase (LPL) system. LPL appears to consist of multiple enzymes and one or more are abnormal or deficient in Type I disease. LPL is the critical control point in metabolism of ingested triglycerides which enter the blood as chylomicrons via intestinal lymph. Without normally functioning LPL, chylomicrons accumulate in the blood serum. Measurement of serum lipids shows extremely high triglyceride levels with normal serum cholesterol since chylomicrons are triglyceride rich but contain very little cholesterol. The blood has a cream of tomato soup appearance and, therefore, lipemia retinalis is one of the major clinical manifestations. This is merely the "creamy" blood showing through the translucent retinal arteries and veins. Eruptive xanthomas are a major clinical manifestation and these consist of chylomicron triglyceride infiltrations into subepidermal areas of

Table 1. Major Clinical Manifestations of the Hyperlipoproteinemias

Type I
- Lipemia retinalis
- Eruptive xanthomas
- Hepatosplenomegaly
- Abdominal pain

Type IIa
- *Tendon* and tuberous xanthomas
- Xanthelasma
- Corneal arcus
- Accelerated coronary atherosclerosis

Type IIb
- Accelerated coronary and peripheral atherosclerosis

Type III
- *Palmar* and tuberous xanthomas
- Acclerated peripheral atherosclerosis

Type IV
- Accelerated peripheral atherosclerosis

Type V
- Lipemia retinalis
- Eruptive xanthomas
- Hepatosplenomegaly
- Abdominal pain

the skin with associated xanthomatous elevations and inflammation. Hepatosplenomegaly is present due to chylomicron uptake in the reticuloendothelial cells of these organs and thereby distention of the liver and splenic capsules is a factor in abdominal pain. However, induction of severe pancreatitis by the lipid accumulation is a major clinical manifestation and can lead to serious and even fatal hemorrhagic pancreatitis.

Type IIa

Type IIa hyperlipoproteinemia results mainly from an autosomal dominant gene with a population frequency of approximately 1 per 500. There can also be polygenic or sporadic forms. There is a marked elevation of serum LDL due to increased synthesis of LDL. As a result, serum cholesterol is elevated since LDL are rich in this lipid but serum triglycerides are normal due to the low content in LDL. There are some classical clinical lesions as follows: xanthelasmas, tendon xanthomas, tuberous xanthomas, and corneal arcus. All of these lesions appear to be induced by LDL-cholesterol. The main point to remember about xanthelasmas is that approximately 25 percent are not associated with increased LDL-cholesterol and are idiopathic. Tendon xanthomas are the classical "hallmark" lesions of Type IIa and represent marked tendon thickenings, mainly of the Achilles and metacarpophalangeal extensor tendons, induced by LDL infiltration. Tuberous xanthomas are less specific and are due to a deep skin LDL infiltration with no eruptive component. The LDL also undoubtedly induce the corneal arcus. However, the major significance of Type IIa is the association with severe accelerated coronary atherosclerosis. This can reach the extreme of a homozygous autosomal dominant female with a serum cholesterol of 1,000 mg/100 ml, dying of a myocardial infarction at ten years of age.

Type IIb

Type IIb is one of the two most common clinical hyperlipoproteinemias. Genetically, it appears to be monogenic, polygenic, or sporadic. Both serum cholesterol and serum triglycerides are elevated due to the variable elevations of both LDL and VLDL. There are no classical skin or other specific lesions. The major clinical significance is the association with accelerated atherosclerosis, both coronary and peripheral. The term peripheral atherosclerosis refers to the occurrence of atherosclerotic plaques at any arterial site other than the coronary arteries.

Type III

Type III disease is considered relatively rare but with the availability of appropriate ultracentrifuge methodology and the performance of large screening studies, it appears that the disease occurs more frequently than just a rare case. Multiple genetic patterns are probably involved. Type III is the only hyperlipoproteinemia with an abnormal lipoprotein consisting of an abnormal composition of normal B and C peptides. This apparently results from formation of a remnant of chylomicron and/or VLDL metabolism due to a deficiency somewhere in the LPL enzyme system. This remnant is frequently referred to as intermediate density lipoprotein. Both serum choles-

terol and serum triglycerides are increased. "Floating beta" is present on the ultracentrifuge and a broad beta band is described on electrophoresis. However, any laboratory which diagnoses Type III disease on the basis of electrophoresis alone without first using the ultracentrifuge is guilty of providing essentially worthless data. The classical hallmark clinical lesion of Type III disease is the palmar xanthoma. This presents as a flat planar yellowish xanthoma in, and in proximity to, the major creases on the palms. The abnormal intermediate density lipoprotein seen in Type III disease, for some unknown reason, has a predilection for this deposition. Tuberous xanthomas may also be seen. The major fact, especially regarding the palmar xanthoma here or any other xanthoma in any other phenotype, is that despite the designation as a hallmark lesion, such xanthomas are found only in severe cases of the specific phenotype. If the clinician makes the Type diagnosis only when a specific xanthoma is found, the diagnosis will be missed most of the time. The major clinical significance of Type III disease is the development of accelerated atherosclerosis, especially peripheral.

Type IV

Type IV disease is the other of the two most common hyperlipoproteinemias (along with Type IIb). The genetics probably involve monogenic, polygenic, and sporadic forms. The only increased lipoprotein is VLDL and thereby, serum triglycerides are markedly increased and serum cholesterol is moderately increased in an approximate ratio of: triglycerides increase to cholesterol increase $\cong$ 5:1. On electrophoresis, the VLDL show up as a prebeta band. The elevated serum VLDL level probably represents the end product of two different mechanisms: excess VLDL synthesis or overproduction and decreased VLDL breakdown probably due to some LPL enzyme system deficiency. Various investigators in the field have argued hotly for one mechanism or the other. The actual situation appears to be that the Type IV phenotype has at least two clear-cut underlying mechanisms. In either case, carbohydrate, especially in the form of simple 6 and 12 carbon sugars (the major component of all "good" sweets), promotes triglyceride production. Clinically, there are no associated xanthomas or other specific lesions except atherosclerosis. The triglycerides generally do not exceed 2,000 mg/100 ml of serum and therefore abdominal pain and pancreatitis are not seen. The major clinical significance is the development of accelerated peripheral atherosclerosis and some coronary atherosclerosis. Another major clinical association is a 50 to 90 percent occurrence of "chemical diabetes," ie, the presence of an abnormal glucose tolerance test without the presence of other manifestations of diabetes. No increased association with clinical diabetes, especially insulin requiring, is established. An elevated serum uric acid is also frequently associated.

Type V

The Type V phenotype involves two distinct subtypes, best defined on a biochemical basis. First, there is the rare familial subtype associated with a partial (and probably involving multiple constituent enzymes) LPL enzyme system deficiency with no clearly established genetics other than a familial relationship. The most common subtype is associated with the insulin requiring diabetic. Insulin is an essential in vivo co-factor for the LPL enzyme system. On occasion, this co-factor effect is insufficient due to an inadequately low insulin dose or due to an undefined decrease in insulin co-factor effect in the presence of otherwise good diabetes control. One aspect of this is the diabetic who clinically does not need insulin for control of carbohydrate metabolism but in whom insulin is found essential to manage his Type V phenotype. A small dose of just 5 to 15 units of NPH insulin may control the lipid problem. Serum triglycerides are markedly increased and serum cholesterol is moderately increased. Both chylomicrons and VLDL are increased, in both cases probably due to various defects at points throughout the LPL enzyme system. Because of the VLDL increase, there is moderate cholesterol elevation as in the Type IV phenotype. Observation of standing serum shows both a dense top creamy chylomicron layer and diffuse turbidity from VLDL underneath. Electrophoresis shows both a chylomicron band at the origin and a dense prebata band just beyond a normal beta band. Because of the very high triglyceride elevations due to the accumulated chylomicrons, with triglyceride levels up to 10,000 mg/100 ml of serum, the clinical manifestations are exactly the same as in Type I disease: lipemia retinalis, erup-

tive xanthomas, hepatosplenomegaly, pancreatitis, and abdominal pain.

Prevention of Atherosclerosis

One of the major issues in the management of the hyperlipoproteinemia phenotypes is whether or not treatment is of any value in the prevention of atherosclerosis. The major issue actually appears to be cholesterol reduction since cholesterol is a major atherosclerotic plaque constituent and mainly gets there from the serum, whereas there are essentially no triglycerides in a plaque. However, triglyceride reduction is essential in effecting maximum cholesterol reduction due to the presence of cholesterol in VLDL. Clearly the issue is not settled, but there have been definite data that suggest but do not prove atherosclerosis prevention by cholesterol lowering. Three dietary studies stand out in this regard. At the Los Angeles Veterans Administration Hospital, dietary modification resulted in a 12 percent decrease in cholesterol as compared to the control group.[2] The study reported a significant decrease in overall atherosclerosis mortality but the results did not hold for each key subgroup such as myocardial infarction deaths. The New York City anticoronary club compared dietary groups and for the group with cholesterol reduction, there was a significant decrease in new coronary events.[3] Two different Finnish mental hospitals have been studied with a cholesterol lowering diet used at one and then the other hospital.[4] This study reported a significant decrease in myocardial infarction mortality in men but not in women. A few drug studies have looked at prevention of atherosclerosis by cholesterol lowering. The Coronary Drug Project[5] was a secondary prevention study in that all of the participants had had a previous myocardial infarction. There were multiple problems with the study and insufficient cholesterol lowering. For example, only a six percent cholesterol reduction was obtained with clofibrate and associated was a very slight decrease in total myocardial infarction mortality but a slight increase in nonfatal events. With nicotinic acid, a ten percent cholesterol reduction was obtained and, in association, there was a statistically significant decrease only in nonfatal myocardial infarctions. The bottom line is that prevention studies have suggested statistically significant protection from atherosclerosis in various limited clinical subgroups but none has proven across-the-board statistically significant atherosclerosis prevention.

Regression of Atherosclerosis

Atherosclerosis regression by cholesterol reduction is another major concept that is the dream of all practicing clinicians who care for patients with cardiovascular disease. The concept is not new. During World War II, patients with severe wasting disease from concentration camps were compared to persons with similar genetic and environmental background (a tragic way to have such information become available). Those patients with marked wasting disease had a much lower incidence of atherosclerosis.[6] The data are, of course, indirect, but both groups most probably started with the same baseline levels of serum cholesterol and long-term atherosclerotic plaques and therefore atherosclerosis regression by cholesterol reduction is suggested. Regression of atherosclerosis in Type III disease has been reported by indirect methodology. Of all the hyperlipoproteinemia phenotypes, cholesterol reduction is most responsive in Type III disease, both to diet and a specific drug, clofibrate. Zelis et al[7] reported marked improvement in plethysmographically measured peripheral arm circulation after cholesterol reduction in a series of diet and clofibrate treated Type III patients. Blankenhorn et al[8] have performed the most comprehensive prospective study of atherosclerosis regression. They have developed a way to quantitate femoral angiographic images by digital computer. In several patients with femoral artery peripheral atherosclerosis associated with hyperlipoproteinemia, cholesterol reduction by diet and drugs has resulted in regression of atherosclerosis as shown by sequential digitized femoral angiograms. Buchwald has studied several Type IIa phenotype patients before and after 40 to 50 percent cholesterol reduction achieved by surgical bypass of the distal 200 cm of the ileum.[9] In a few sequential coronary and peripheral arteriograms there have been definite plaque size reductions. Other studies in the literature consist of various case reports, such as a Type IIa patient with regression of renal artery atherosclerosis documented by sequential angiograms and associated cure of hypertension, both following cholestyramine reduction of choles-

terol.[10] As with atherosclerosis prevention, the bottom line in atherosclerosis regression is that it has and can be achieved in selected clinical cases but there is not, thus far, a statistically significant proven relationship to cholesterol reduction.

Treatment of Hyperlipoproteinemia

If the clinician accepts cholesterol reduction in patients as worthwhile, then the following describes a rational therapeutic approach (Table 2). The cornerstone of medical management is always diet, and an appropriate diet for each hyperlipoprotein phenotype should be selected. Some investigators have claimed that dietary content directed at a specific phenotype is of no definite value and that only overall calorie restriction is of value. This claim is not well founded and caloric restriction as well as selection of foods of specific carbohydrate and fat content is the management of choice. One question asked by many clinicians is what cholesterol level they should hope to achieve in their patients. The so-called normal serum cholesterol reported by various clinical laboratories frequently ranges from 150-300 mg/100 ml and this is extremely misleading. What it represents is the range of mean serum cholesterol ± two standard deviations or 97 percent of the population. This may be acceptable for an enzyme assay with a large error in determination but not for serum cholesterol which has a margin of error from two to five percent. Therefore, the best so-called normal serum cholesterol to strive for is a value less than 200 mg/100 ml. Data from the Framingham study[11] suggest this as appropriate since, as serum cholesterol rises above 200 mg/100 ml, there is a linear increase in the occurrence of clinical cardiovascular episodes. However, even this level may be too high and thereby reflect the increased atherosclerosis in the developed countries of the western world, since specific world populations with almost no coronary atherosclerosis have serum cholesterol levels less than 150 mg/100 ml. One final treatment concept before discussing specific management is the use of more than one hypolipidemic drug. This appears to be of value, just as in hypertension, to maximize the therapeutic effect and minimize the drug related side effects. This has worked well, in the author's experience, with marked additional cholesterol reduction.

Table 2. Treatment of the Hyperlipoproteinemias

Type I
- Low triglyceride diet
- Medium chain fatty acid triglycerides
- No drug

Type IIa
- Low cholesterol polyunsaturated fat diet
- Cholestyramine or colestipol are drugs of choice
- Dextrothyroxine
- Nicotinic acid
- Probucol

Type IIb
- Low cholesterol polyunsaturated fat diet
- Some carbohydrate restriction
- Cholestyramine or colestipol are drugs of choice
- Dextrothyroxine
- Nicotinic acid
- Probucol

Type III
- Low cholesterol polyunsaturated fat diet
- Decrease carbohydrate intake
- Clofibrate

Type IV
- Low carbohydrate diet
- Reduced alcohol intake
- Clofibrate
- Nicotinic acid

Type V
- Low triglycerides, low carbohydrate diet
- Insulin when even mild diabetes associated
- Nicotinic acid

Type I and Type V

A specific hyperlipoproteinemia treatment group to consider is the group with clinical manifestations which may respond rapidly to treatment and may represent a medical emergency. This includes Type I and Type V disease in which the skin lesions, pancreatitis, and acute abdominal pain may be resolved rapidly by triglyceride reduction. For Type I disease, the only dietary treatment is marked restriction of oral triglyceride intake. There is no drug therapy of any benefit and the only other modification to be made is the use of oral medium chain fatty acid triglycerides (fatty

acids with ten carbons or less). These provide calories without promoting triglyceride and chylomicron synthesis by the intestine since the medium chain fatty acids go directly via portal venous blood to be metabolized by the liver. For Type V disease, dietary carbohydrate must be restricted in addition to triglyceride restriction due to the VLDL elevation associated with the increased chylomicrons. Nicotinic acid may be of some value, and insulin in the Type V subtype associated with diabetes mellitus is essential.

The other specific hyperlipoproteinemia treatment group is management of those phenotypes associated with atherosclerosis. Specific dietary and drug therapeutic approaches to achieve cholesterol and triglyceride reduction are outlined below. Most dieticians will provide a specific phenotypic diet to the patient.

Type IIa

Type IIa disease responds best to a low cholesterol, polyunsaturated fat diet. Cholestyramine to a dose of 24 gm per day and colestipol to a dose of 30 gm per day are drugs of choice. These drugs can give a 30 to 40 percent cholesterol reduction and appear to be quite safe since they never enter the blood stream but work by binding bile acids in the intestine which causes cholesterol reduction as increased amounts of the lipid are converted to bile acids. The major problem with these drugs is their inconvenience as an insoluble powder to be mixed in liquid, their excessive expense, their relatively unpleasant taste to many patients, and their association with a high incidence of gastrointestinal bloating and constipation. Nicotinic acid in a dose up to 3 gm per day is of value. It is best taken postprandially to ameliorate the frequent flushing, and sustained release preparations also appear to help in this regard. Probucol is a relatively new drug for Type IIa disease, and in its recommended dose of 500 mg twice a day, it results in few side effects and appears to be quite effective. Both nicotinic acid and probucol appear to inhibit cholesterol synthesis. If there is no evidence of clinical coronary atherosclerosis, dextrothyroxine appears to be a well-tolerated and effective drug which can be taken once a day in a dosage of up to 8 mg per day after building up gradually to that dose. Dextrothyroxine appears to function by accelerating cholesterol catabolism.

The surgical management of Type IIa disease must still be considered basically investigational but it is important to be aware of the possibilities. The best known and best established surgical procedure for cholesterol reduction is the ileal bypass.[9] The distal 200 cm of ileum contain the major bile acid reabsorption sites. Exclusion of the distal ileum from the main intestinal flow results in marked bile acid loss in the feces. As a result, much endogenous cholesterol is utilized in bile acid synthesis and the serum cholesterol drops 40 to 50 percent. Formation of a surgical portacaval shunt can also result in a 40 to 50 percent cholesterol reduction.[12] This shunt probably works by excluding intestinal hormones from the liver where they are essential for cholesterol biosynthesis. Formation of a portacaval shunt is a major procedure with significant risk and is strictly investigational. The ileal bypass involves no more than the risk of a basic laparotomy. Nevertheless, it represents a major therapeutic step and is basically investigational although this author will consider it for extreme serum cholesterol elevations over 400 mg/100 ml in young patients. It must not be confused with the total small bowel bypass for morbid obesity which is a high-risk procedure.

Type IIb

Type IIb disease also responds best to a low cholesterol, polyunsaturated fat diet with additional carbohydrate restriction. Cholestyramine and colestipol are the drugs of choice. Nicotinic acid may work especially well synergistically with cholestyramine or colestipol.[13] Probucol and dextrothyroxine are also of value.

Type III

Type III disease responds best to the same diet as Type IIb. The response of Type III disease to diet is the best of any hyperlipoproteinemia phenotype. The clear-cut drug of choice for Type III disease is clofibrate and its effectiveness in reducing cholesterol in this phenotype is striking. It probably works by inhibition at some point in cholesterol and triglyceride synthesis, but LPL system activation has also been described.[14] Despite some increased deaths from conditions related to the liver and the biliary and intestinal systems associated with clofibrate in a recent large study, its benefit as the specific drug for marked cho-

lesterol reduction would appear to outweigh any such possible contraindication.[15] The appropriate guideline for the use of clofibrate is to continue to employ the drug if it has a significant cholesterol lowering effect in a specific phenotype but to avoid it if its cholesterol reducing effect is minimal.

Type IV

Type IV phenotype responds best to dietary carbohydrate restriction, and triglyceride and associated cholesterol reduction can be quite striking. Reduced alcohol intake is also of major benefit. Clofibrate and nicotinic acid appear to be the most effective drugs.

Contraindicated Drugs

Some specific comments on drug therapy in the hyperlipoproteinemias appear indicated. Heparin has no place in the treatment of any hyperlipoproteinemia. It is an essential co-factor of the LPL enzyme system and intravenous injection releases active LPL into the serum so that it can be analyzed in a research laboratory to document the enzyme deficiency in Type I and V phenotypes. However, there is no enzyme for heparin to activate in vivo in these phenotypes, and therefore the firm statement is made that heparin has no value in the treatment of any hyperlipoproteinemia.

The practicing clinician should be completely aware of the status of chelation therapy with ethylene diamine tetraacetic acid (EDTA). This has been advanced by some individuals as a means to resolve atherosclerotic plaques because of chelation of calcium by EDTA. First, most obstructing plaques do not need to have advanced to the stage of widespread calcification; secondly, in such an advanced plaque, there are no vaso vasorum or effective diffusion from the arterial lumen so that EDTA will never reach its intended calcium chelation site anyway. EDTA is a potentially dangerous drug. Individual patients have spent thousands of dollars for a series of intravenous EDTA infusions which are dangerous and of no proven and confirmed therapeutic benefit. There does not appear to be any place for EDTA in the treatment of atherosclerosis or any hyperlipoproteinemia.

Conclusion

The major issue for clinicians is whether or not cholesterol reduction benefits their patients, since the role of this lipid in atherosclerosis is established. A cholesterol lowering diet will do no harm and may reduce atherosclerosis. The major decision comes with the use of a hypolipidemic drug. As of this time, it appears that enough benefit has been documented to proceed cautiously with drug therapy in selected patients.

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