Medical Progress

The Hyperlipoproteinemias

A Simplified Classification and Approach to Therapy

ROBERT ZELIS, M.D., DEAN T. MASON, M.D., AND JAMES F. SPANN, JR., M.D., *Davis*

■ *It is now clear that the various hyperlipidemias represent a heterogenous group of disorders, each having various clinical and laboratory characteristics, prognosis and treatment. The three disorders commonly associated with premature atherosclerotic vascular disease are Type II (hyperbetalipoproteinemia), Type III ("broad beta" or "floating beta" disease) and Type IV (hyperprebetalipoproteinemia or, endogenous hypertriglyceridemia).*

The diagnosis of each of these three disorders can be suggested by the fasting serum cholesterol level and the appearance of the fasting serum after it has remained overnight in a refrigerator. Type II disease is characterized by a clear serum and a pronounced to moderate hypercholesterolemia. It is treated by reducing dietary cholesterol and saturated fats, increasing dietary polyunsaturated fats, and cholestyrmine. Type IV disease is characterized by a turbid serum indicating hypertriglyceridemia and a normal or only slightly elevated serum cholesterol level. It is treated with weight reduction, a low carbohydrate diet and clofibrate. Type III disease is characterized by both a turbid serum and increased cholesterol levels. It is treated with weight reduction, a low cholesterol diet and clofibrate.

With the treatment of all disorders the lipid values should improve; however, with the treatment of Type III disorder both triglyceride and cholesterol levels return to normal, xanthoma resorb and there is an improvement in the peripheral blood flow, indicating that there has been amelioration of the atherosclerotic process.

ALTHOUGH IT HAS been long recognized that the level of serum cholesterol is a good indicator of the risk of developing premature coronary vascular disease,[1,2] this determination alone does not provide the physician with enough information for the rational approach to the therapy of the patient with hyperlipidemia. Over the past decade, many investigators have contributed significantly to our understanding of this heterogeneous group of disorders.[3,4,5,6] The classification system of Fredrickson, Levy and Lees based on the mobility of the various lipoprotein fractions provides us with the simplest approach to the understanding, diagnosis and treatment of the hyperlipoproteinemias.[3,4]

It is not the purpose of this paper to provide a complete review of this complicated field. Rather, on the basis of what has been learned about the typing system from lipoprotein electrophoresis and ultracentrifugation techniques, we would like to present a simple office approach to the diagnosis (Table 1) and management (Table 2) of these problems for practicing physicians.

It has been suggested that two pieces of information will provide the physician with an initial approach to the classification of the type of lipoprotein abnormality with which an individual patient may be afflicted.[4] These are the serum cholesterol after a 14-hour fast and the appearance of this serum after it has remained in the refrigerator overnight.

Types I and V

The appearance of the serum after standing overnight in a refrigerator will be either clear, turbid or creamy. If there is a definite cream layer which has separated from a turbid layer below, this indicates the presence of chylomicrons. Following a 14-hour fast, the only patients with hyperchylomicronemia are those with Type I or Type V hyperlipoproteinemia. Both of these disorders are characterized by a decreased tolerance to dietary fat which is not cleared from the blood.

Type I disease is rare, appears during childhood, associated with recurrent attacks of abdominal pain, and is caused by a deficiency in one or more lipoprotein lipase. It is not associated with premature vascular disease and is treated by severe dietary fat restrictions.

On the other hand, Type V disease is characterized by endogenous as well as exogenous hypertriglyceridemia and usually is secondary to other disorders, namely, pancreatitis, diabetic acidosis, alcoholism, nephrosis and hypothyroidism. The familial nature of the primary form of this disease is not clear since the Type IV disorder will often occur in these families as well.

Both Type V and Type I disease are associated with attacks of severe abdominal pain, which usually respond well to marked restriction of the dietary fat intake. Treatment of Type V disease further consists of weight reduction and controlling the primary disorder when one is present. The association of coronary artery disease with Type V hyperlipoproteinemia is unclear.

Type II

We would now like to turn to Types II, III and IV hyperlipoproteinemia with which the association of premature coronary artery disease is quite clear. A recent study of patients with angiographically proved coronary artery disease demonstrated that 80 percent under the age of 50 years had Type II or Type IV disease, with about half of the patients in each group.[7] Although Type III disease is much less common, it is important to recognize it, since it is associated with generalized vascular disease and is exquisitely sensitive to treatment.

The determination of the Type II hyperlipoproteinemia abnormality in an office practice is quite simple (Table 1). The basic defect in this disorder is hyperbetalipoproteinemia probably secondary to decreased betalipoprotein catabolism,[8] resulting in elevation of serum cholesterol above 280 mg per 100 ml, usually without an associated rise in serum triglycerides. Therefore, the overnight serum of these patients is clear. Although tendinous and tuberous xanthoma are sometimes seen, in most patients with Type II disease the diagnosis will be missed if one depends upon finding xanthoma. When primary Type II disease is suspected, it is important to rule out the secondary forms. Hyperbetalipoproteinemia can be produced by excess dietary intake of cholesterol rich foods, hypothyroidism, myeloma, macroglobulinemia, liver disease and nephrosis.

Once it is suspected that Type II hyperlipoproteinemia is primary, it is most important to screen

From the Cardiopulmonary Section, Departments of Medicine and Physiology, University of California, Davis, School of Medicine.

Assistant Professor of Medicine and Assistant Professor of Physiology (Zelis); Professor of Medicine and Professor of Physiology (Mason); Associate Professor of Medicine and Associate Professor of Physiology (Spann).

Submitted February 5, 1970.

Reprint requests to: Cardiopulmonary Section, Department of Medicine, University of California, Davis, School of Medicine, Davis, Ca. 95616 (Dr. Zelis).

TABLE 1.—*Hyperlipoproteinemia—Diagnosis*

	II	III	IV
Cholesterol*	↑↑	↑↑	Nl (↑)
Serum	Clear	Turbid	Turbid
Triglycerides	Nl (↑)	↑	↑↑
Electrophoresis	↑ Beta	Broad Beta	↑ Pre-Beta
Ultracentrifugation			
<1.006	No Beta	Beta (TG/C<2:1)	Pre-Beta (TG/C>2:1)
>1.006	↑ Beta	Nl Beta	Nl Beta
CHO Induction	0	+	+
Xanthoma	O (Tendinous)	Palmar	O (Eruptive)

*Note: All determinations of serum cholesterol and triglyceride are performed on blood drawn after a 14-16-hour fast, and the serum examined after being chilled 24 hours. Types I and V are distinguished by the presence of a cream layer on top of the chilled fasting serum, indicating the presence of chylomicrons.

Nl = normal, TG/C = triglyceride to cholesterol ratio, CHO = carbohydrate.

TABLE 2.—*Hyperlipoproteinemia—Treatment*

	II	III	IV
Weight	..	↓	↓
Diet	Balanced Cholesterol<300 mg ↑ u/s fat	Same as II	Low CHO ↑ u/s fat
Drugs	Cholestyramine (Questran, Cuemid) 16-32 gm/day	Clofibrate (Atromid-S) 2 gm/day	(± Clofibrate)
Family screening	Adults—*children mandatory*	Adults	Adults

u/s = unsaturated to saturated fat ratio, CHO = carbohydrate.

other family members since there is a high probability that relatives will be affected by this autosomal dominant disease. Indeed, the demonstration of a serum cholesterol greater than 90 mg per 100 ml or a beta-cholesterol greater than 45 mg per 100 ml in cord blood will make the diagnosis in a newborn. After one year of age, the determination in a child of serum cholesterol greater than 260 mg per 100 ml or beta-cholesterol greater than 220 mg per 100 ml provides the diagnosis. The demonstration of this disorder in children gives a more helpful prognosis since they are often easier to treat by dietary alterations than are adults. Treatment of adults is difficult since the hyperlipidemia often responds poorly to dietary alterations and drugs (Table 2). Weight reduction is usually ineffective in reducing the level of serum cholesterol. Generally, a diet low in cholesterol (less than 300 mg per day), low in saturated fat and high in unsaturated fat will produce a 20 to 25 percent reduction in the serum cholesterol. The American Heart Association diet is suitable for this, provided egg yolks are completely excluded.

The drug of choice for this disorder is cholestyramine in doses from 16 to 32 grams per day. It is poorly tolerated by many patients, who complain of symptoms of nausea and constipation. But if it is tolerated, an additional reduction in serum cholesterol can always be expected from it. The drug will frequently lower serum cholesterol to the normal range. Less effective forms of therapy are beta-sitosterol, nicotinic acid and D-thyroxine. Nicotinic acid often causes flushing in clinically useful doses and D-thyroxine often causes an exacerbation of angina pectoris in susceptible patients secondary to its metabolic effects. Clofibrate has been reported to provide only a slight reduction in serum cholesterol, averaging about 9 percent.[9]

Type IV

Type IV hyperlipoproteinemia is probably a heterogeneous group of disorders about which there is no universal accord.[3,5,6] Quite simply, this disease can be thought of as resulting from excess triglyceride production by the liver from dietary carbohydrates or under utilization of triglycerides by peripheral tissue. It is recognized by the finding of a turbid serum, which indicates hypertriglyceridemia, and a relatively normal or only slightly elevated serum cholesterol (Table 1).

On lipoprotein electrophoresis patients with this disease characteristically will be found to have particles of pre-beta mobility. Pre-beta particles are a complex of triglyceride with alpha and beta-

lipoproteins. This disease, likewise, may be a secondary manifestation of diabetes mellitus, pancreatitis, alcoholism, nephrotic syndrome, hypothyroidism, progestational hormones, weight gain or emotional stress. Further, since serum triglycerides rise after an acute myocardial infarction concomitant with a fall in serum cholesterol, phenotyping is best deferred for two months until the serum lipids have stabilized.

Unlike Type II disease, when the Type IV disorder is familial, it will be clinically manifest in less than 5 percent of the propositi before 20 years of age. Familial screening for this disorder, therefore, is best limited to relatives beyond the second decade.

One of the difficulties in making the diagnosis of Type IV hyperlipoproteinemia is that the level of serum triglycerides fluctuates widely from day to day. It is, therefore, imperative before this diagnosis is definitely established to have demonstrated a persistent hypertriglyceridemia, above 180 mg per 100 ml, on more than one fasting blood specimen. Likewise, response to treatment can only be definitely ascertained by the demonstration of a sustained reduction in the serum triglycerides. Since patients will show a decided increase in the level of the serum triglycerides with weight gain or with feeding of an isocaloric high carbohydrate diet (7 grams of carbohydrate per kilogram of body weight), treatment of this disorder is quite clear and consists of sharp reduction in total calories to achieve ideal body weight and restriction of the dietary carbohydrate intake. Dietary carbohydrate should be replaced with polyunsaturated fats. For this purpose, a modified diet such as might be prescribed for a patient with adult onset diabetes is usually quite adequate. Indeed, the distinction between the Type IV patient with abnormal glucose tolerance and the patient who has mild diabetes with hyperlipidemia is pragmatically nonessential. Both types of patients should be treated similarly, with weight reduction and carbohydrate restriction. With this therapy there is usually a significant number of patients who respond with a return of the serum triglycerides to near normal levels. For patients resistant to dietary management, clofibrate may be quite useful in a dose of 2 grams per day. Although clofibrate does not seem to prevent the hypertriglyceridemia which occurs with high carbohydrate feeding,[9] it is still effective in patients who are unable to follow an appropriate diet.

Type III

Type III hyperlipoproteinemia is a unique, uncommon, familial, recessive disorder which is characterized by the production of an abnormal betalipoprotein with an unusually high affinity for triglycerides. Because of the high triglyceride content, this betalipoprotein will float on ultracentrifugation. In the preparative ultracentrifuge, the betalipoprotein of the serum will normally gravitate to the bottom of the test tube as the low density lipoprotein fraction. The abnormal betalipoprotein formed in patients with Type III disease, however, floats to the top of the tube and imparts to the very low density lipoprotein fraction an unusually high concentration of cholesterol. This characteristic has caused this disorder to be occasionally referred to as "floating beta disease." On lipoprotein electrophoresis the abnormal betalipoprotein displays a broad band of migration tending to overlap both the normal beta and pre-beta bands and has caused this disease also to be referred to as "broad beta disease."

This disorder cannot be diagnosed with certainty in an office practice, since ultracentrifugation techniques are necessary. However, the finding of an elevated serum cholesterol of 400 to 600 mg per 100 ml and a turbid serum suggests that it may be present (Table 1). An elevated serum triglyceride of roughly equal magnitude to the serum cholesterol increases the suspicion that the patient has this disorder. Clinically, one can be more certain of the diagnosis by the finding of palmar xanthoma which appear as yellow streaks in the palmar creases. This is highly characteristic of this disorder. One often sees tuberoeruptive xanthoma on the extensor surfaces of the extremities as well.

Although Type III hyperlipoproteinemia is uncommon, it is extremely important that patients so affected be recognized since treatment invariably produces dramatic results. Weight reduction and a low cholesterol, balanced diet can be actively combined with clofibrate therapy to reduce the serum cholesterol and triglyceride values to normal. Moreover, the sustained reductions in plasma lipid values often result in resorption of xanthoma and improvement in symptoms of intermittent claudication and angina pectoris.[10]

Although Type III disease is an uncommon disorder, it has provided a useful model to answer an important question which arose soon after the association between elevated serum cholesterol

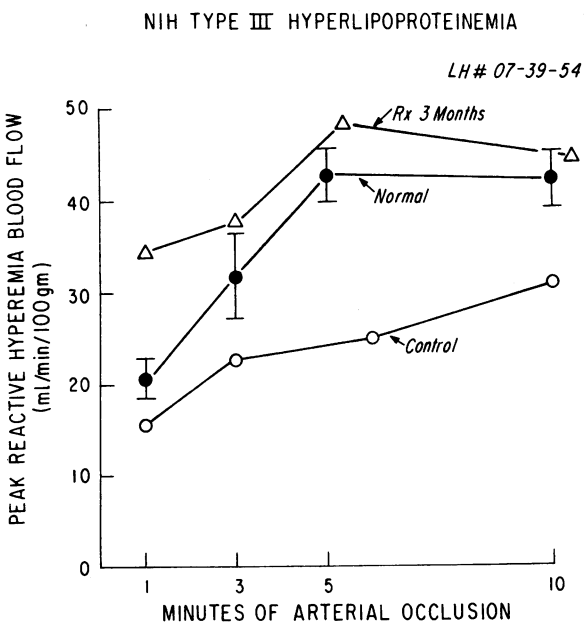

Chart 1.—Peak reactive hyperemia blood flow following release of various durations of arterial occlusion in 23 normal subjects (closed circles) (±SEM) and in a patient with Type III hyperlipoproteinemia before (open circles) and after (open triangles) three months of treatment with diet and clofibrate.

and coronary artery disease was recognized. That question was: Can one affect the course of vascular disease by altering the levels of serum cholesterol? Although population studies have tended to answer this question in the affirmative,[11,12] the results of prospective studies have not been striking and there has been one study which did not show increased longevity with the treatment of hyperlipidemia.[13]

Population studies, of necessity, require that large numbers of subjects be examined for a long period. Controlling all the variables in such an investigation often proves difficult. It would seem that examining the changes which take place in an isolated vascular bed in a single individual during treatment of the hyperlipidemia would provide a more direct answer. Since serial evaluation of the coronary circulation is difficult and since it is difficult to predictably maintain the serum lipids of patients with the more common Type II and Type IV disorders within normal limits for prolonged periods, it was decided to look elsewhere for an answer to this problem.

Specifically, it was noted that patients with Type III hyperlipoproteinemia have peripheral as well as coronary vascular disease. Functional evaluation of the peripheral circulation, unlike that of the coronary circulation, is fairly easily accomplished by means of venous occlusion plethysmography.[14,15] It has been previously noted that the peak reactive hyperemia blood flow seen after release of five to ten minutes of arterial occlusion is a good indicator of the degree to which the peripheral circulation is affected by vascular disease.[15-17]

As can be seen in Chart 1, when the duration of arterial occlusion is prolonged beyond five minutes, there is no further increase in the peak blood flow response on restoration of the circulation. This has been considered the maximal ability of the blood vessels to dilate. It will be noted in the one patient shown with Type III disease before treatment that there was a decided limitation of the dilator capacity of the peripheral blood vessels secondary to peripheral atherosclerosis. However, after three months of therapy with diet and clofibrate which maintained the serum lipids at a normal level, the peak reactive hyperemia blood flow response returned to normal levels. This response to treatment was typical of the six patients studied with Type III disease and peripheral vascular disease. The average increase in peak blood flow was 55 percent in their most severely affected extremity.

Recent anatomic evidence helps to confirm our suggestion that the cholesterol in the atheroma of Type III patients is particularly labile.[18] We would further suggest that in patients with the Type II and Type IV disorders, in which the cholesterol in the lipid-rich plaques appears to be much less labile and for which the treatment is less satisfactory, perhaps with prolonged therapy there may be at least retardation of the progression of the vascular disease as well.

Conclusion

From these observations it can be seen that the examination of the fasting serum cholesterol alone is not sufficient to diagnose and treat the various disorders of lipoprotein metabolism. However, with the simple expedient of examining the fasting serum after it has been allowed to remain in the refrigerator overnight, one can discover patients with lipoprotein abnormalities who would be missed by serum cholesterol determination alone. Furthermore, this procedure provides an initial approach to the classification and rational management of the particular type of disorder with which the patient is affected. It is only with proper classification that these various disorders can be

properly treated. In addition, recent research has suggested that with the proper treatment of these atherogenic disorders there may be not only an arresting of the atherosclerotic process but a reversal of the process as well.

Trade and Generic Names of Drugs

Questran®, Cuemid® ..... cholestyramine
Atromid-S® ..... clofibrate

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CORTICOSTEROID EFFECT ON THE EYE

"Our laboratory assays of corticosteroid effect on the eye are crude and poor and approximate; and yet our own work, and particularly the work of David Brown, would indicate that taking an ordinary drop of dexamethasone (trade named Decadron) and diluting it approximately 1,000 times gives you topically in an experimental graft rejection system about the same kind of corticosteroid effect that you expect in a man taking 35 mg of prednisone daily. So that the effective steroid concentration you get in the cornea from oral corticosteroids seems incredibly less, at least in the system we used, than we get from topical corticosteroids. Or put another way, we can get enormously effective concentrations of corticosteroids in the cornea from topical administration — something you can't get when you consider kidney transplants, heart transplants, and things of that sort."

—Herbert E. Kaufman, M.D., Gainesville, Ga.
Extracted from *Audio-Digest Ophthalmology,* Vol. 6, No. 23, in the Audio-Digest Foundation's subscription series of tape-recorded programs.