A national effort is underway to detect and treat patients with high serum cholesterol levels (hypercholesterolemia) and to modify lifestyles of all Americans to reduce average cholesterol concentrations. This effort is founded on the recognition that hypercholesterolemia is a major risk factor for coronary heart disease (CHD) and that therapeutic lowering of cholesterol levels will decrease the risk for CHD. The National Cholesterol Education Program (NCEP)\(^1\) is generating widespread interest and concern among Americans about the dangers of high cholesterol levels, and new questions regarding the best approach to this major public-health problem are emerging. Generally, in management of medical conditions, an understanding of pathogenesis underlies rational therapy. Hypercholesterolemia is no exception. Unfortunately, we lack adequate explanations for the “mass hypercholesterolemia” in the US public. Whereas it is widely assumed that dietary excesses are the major cause, growing evidence implicates genetics as an important factor in many individuals.

Available information on causes of hypercholesterolemia is reviewed, and current definitions of what constitutes an elevated serum cholesterol concentration will be examined. Basic physiologic and biochemical processes regulating serum cholesterol levels will be considered and serve as an introduction to a more detailed consideration of the pathogenesis of hypercholesterolemia.

**Definition and Prevalence of Hypercholesterolemia**

Two approaches can be taken to the definition of hypercholesterolemia. Until recently, hypercholesterolemia was defined as a serum total cholesterol (or low density lipoprotein [LDL] cholesterol) level in the upper 5% of the population.\(^2\) Current distributions of total cholesterol levels in the United States are presented in Table 1.\(^3\) Using this approach, the definition is age and sex specific and depends on the distribution of concentrations in the whole US population; in other countries with different distributions, “abnormal” cholesterol levels might be defined differently. Recently, there is a growing recognition that cholesterol levels are correlated with risk for CHD over a broad range of levels. This link is perhaps best illustrated by the correlation between total serum cholesterol and coronary mortality rates in the 6-year follow-up of screenees of the Multiple Risk Factor Intervention Trial (MRFIT) (Figure 1).\(^4\) Such data have convinced many investigators that elevations of cholesterol should be defined according to their link to CHD. For instance, the National Institutes of Health Consensus Development Conference on Cholesterol\(^5\) divided high cholesterol levels into moderately high and high-risk categories to denote their connection to CHD (Table 2). These definitions were age but not sex specific. Interestingly, they focused on total cholesterol and not LDL cholesterol. For whole populations, total cholesterol is highly correlated with LDL cholesterol, but this is not necessarily true for individuals. For example, a high serum high density lipoprotein (HDL) cholesterol can erroneously put a person in a high-risk category for total cholesterol, which is an obvious weakness of the conference approach.

More recently, the adult treatment panel of the NCEP\(^6\) extended and refined the consensus conference report.\(^5\) Serum total cholesterol levels were redefined into three ranges: desirable (<200 mg/dl), borderline high (200–239 mg/dl), and high (>240 mg/dl). But of more importance, the LDL cholesterol level, not total cholesterol, was the primary focus of diagnosis and treatment. An LDL cholesterol concentration of less than 130 mg/dl was called desirable; between 130 and 159 mg/dl, borderline high risk; and more than 160 mg/dl, high risk. Thus, the term “risk” was applied to only LDL cholesterol levels and not to the total cholesterol. Definitions are neither age nor sex specific. According to epidemiologic data,\(^4\) the population risk for CHD at a total cholesterol level of more than 240 mg/dl (or LDL cholesterol level of more than 160 mg/dl) is approximately twice that of a total cholesterol concentration of less than 200 mg/dl (or LDL cholesterol level of less than 130 mg/dl).

Distributions of LDL cholesterol levels for US adults are shown in Table 3.\(^6\) The prevalence of high total cholesterol levels and high-risk LDL cholesterol levels can be estimated from Tables 1 and 3. For the whole population, the prevalence of each is similar.
On the average, about 25% of all men and women more than 20 years old have LDL cholesterol levels of more than 160 mg/dl, but the prevalence varies considerably by age and gender. Between the ages of 25 and 34 years, a high-risk LDL cholesterol is found in 10–12%, whereas in those more than 55 years old, prevalence is 30–40%. The fact that more than 40% of older people have a high-risk LDL cholesterol reveals the potential magnitude of the issue of “cholesterol management” for the US public; such a liberal definition of “abnormality” can be justified not only by the very high prevalence of CHD in the United States but also by increasing evidence that cholesterol levels can be effectively lowered to decrease CHD risk. In the NCEP’s adult treatment panel report, the term “hypercholesterolemia” was avoided; in the present report, this term generally is used synonymously with a high-risk LDL cholesterol level.

Regulation of LDL Cholesterol Concentrations

The basic pathways of formation and catabolism of circulating LDL are depicted in Figure 2. LDL arises through catabolism of triglyceride-rich lipoproteins. The liver secretes triglyceride-rich, very low density lipoproteins (VLDL). The VLDL surface coat contains apolipoprotein (apo) B-100; apo C-I, C-II, and C-III; and apo E. Apo B-100, or simply apo B, is an integral part of newly secreted VLDL. VLDL apo Cs come primarily from HDL, whereas some apo E is secreted with VLDL and some comes from HDL. Newly secreted VLDL immediately begin to undergo modification in the circulation. They acquire apo Cs, some apo E, and cholesterol esters from HDL. In the peripheral circulation, VLDL triglycerides undergo hydrolysis by lipoprotein lipase (LPL), an enzyme located on the surface of capillary endothelial cells and activated by apo C-II. Hydrolysis of most triglycerides transforms VLDL into VLDL remnants. However, a portion of VLDL is taken up directly by the liver before transformation to remnants. Hepatic uptake occurs via binding of VLDL to “LDL receptors,” possibly to other receptors, or to both. The latter may include the putative chylomicron-remnant receptor or the recently described LDL-cholesterol–like protein.7-9 Up to 50% or even more of newly secreted VLDL is cleared by the liver before reaching the remnant stage.10,11 VLDL remnants, like VLDL, have one of two fates: removal directly by the liver or degradation into LDL by lipolytic removal of remaining triglycerides; the latter may be mediated by hepatic triglyceride lipase (HTGL).

LDL is the major cholesterol-carrying lipoprotein in serum. Its lipid core consists almost entirely of cholesterol esters. Typically, about 75% of serum LDL is cleared by the liver,12,13 and the remainder is cleared by a variety of extrahepatic tissues. Normally 20–30% of the LDL pool is removed each day via LDL receptors, and another 10% of the pool is taken up by nonreceptor pathways.14 Consequently, by summing these two pathways, it is apparent that the fractional clearance rate (FCR) for circulating LDL normally will range from 0.30 to 0.40 pools per day.

LDL-receptor activity appears to be a key regulator of LDL cholesterol concentrations.15 The structure of LDL receptors and basic steps in their metabolism are depicted in Figure 3. The LDL-receptor gene resides in chromosome 19.16 The total length of DNA spanned by the human LDL-receptor

### Table 1. Serum Total Cholesterol by Gender and Age

<table>
<thead>
<tr>
<th></th>
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<td>10th</td>
<td>25th</td>
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<td>75th</td>
<td>90th</td>
<td>10th</td>
<td>25th</td>
<td>50th</td>
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<tr>
<td>Men</td>
<td>25–34</td>
<td>152</td>
<td>172</td>
<td>194</td>
<td>220</td>
<td>254</td>
<td>166</td>
<td>187</td>
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<tr>
<td>Women</td>
<td>25–34</td>
<td>145</td>
<td>164</td>
<td>188</td>
<td>215</td>
<td>243</td>
<td>158</td>
<td>177</td>
</tr>
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</table>

Values are given in mg/dl.

FIGURE 1. Plot of relation between plasma cholesterol concentration and coronary heart disease (CHD) mortality in Multiple Risk Factor Intervention Trial participants. Data are taken from follow-up of 356,222 men, ages 35–57 years at baseline. Rates represent age-adjusted 6-year death rate per 1,000 men. From Stamler et al.4

### Table 2. Definition of Hypercholesterolemia From National Institutes of Health Consensus Conference on Cholesterol

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Moderate hypercholesterolemia (mg/dl)</th>
<th>Severe hypercholesterolemia (mg/dl)</th>
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<tbody>
<tr>
<td>20–29</td>
<td>&gt; 200</td>
<td>&gt; 220</td>
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<tr>
<td>30–39</td>
<td>&gt; 220</td>
<td>&gt; 240</td>
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<tr>
<td>≥ 40</td>
<td>&gt; 240</td>
<td>&gt; 260</td>
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### Table 3. Serum Low Density Lipoprotein Cholesterol by Gender and Age

<table>
<thead>
<tr>
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<td>10th</td>
<td>25th</td>
<td>50th</td>
<td>75th</td>
<td>90th</td>
<td>10th</td>
<td>25th</td>
</tr>
<tr>
<td>Women</td>
<td>25–34</td>
<td>83</td>
<td>98</td>
<td>116</td>
<td>139</td>
<td>166</td>
<td>90</td>
</tr>
</tbody>
</table>

Values are given in mg/dl.
gene totals approximately 45.5 kb.17 Messenger RNA (mRNA) for the LDL receptor contains approximately 5.3 kb.18,19 The LDL receptor protein has 860 amino acids and can be divided into six domains15,19; a signal sequence at the amino terminus, a ligand-binding region, a domain having homology to epidermal growth factor, a clustered O-linked sugar domain, a transmembrane region, and a cytoplasmic tail at the carboxyterminus of the protein.

The LDL receptor constitutes an integral membrane protein and is synthesized in the rough endoplasmic reticulum where immature sugars are N-linked to asparagine and O-linked to serine and threonine.20,21 The molecular weight of the receptor protein in the ribosome is 120,000; however, after migration to the Golgi apparatus, where carbohydrate chains are added, molecular weight increases to 160,000.22 Mature receptors then pass to the cell surface, after which they migrate to coated pits; here they cluster and bind to lipoproteins containing apo B-100, apo E, or both. The resulting receptor-ligand complex undergoes internalization by endocytosis and, in the endosome, receptor and ligand dissociate; receptors either recycle to the cell surface or directly enter lysosomes for degradation.23 Thus, the number of LDL receptors on the surface of cells depends not only on the number synthesized but also on the rate of recycling. LDL itself undergoes enzymatic degradation within lysosomes.

Basic Mechanisms of Hypercholesterolemia

Three basic abnormalities can cause a high serum LDL cholesterol: defective clearance of LDL, overproduction of LDL, and overloading of LDL particles with cholesterol esters. Regarding clearance, LDL can leave the circulation by two pathways—
receptor- or nonreceptor-mediated pathways; consequently, delayed clearance of LDL by either pathway theoretically could increase LDL levels. Defects in nonreceptor-mediated clearance are possible but have not been identified; in contrast, delayed receptor-mediated uptake of LDL definitely is a cause of hypercholesterolemia. A reduction in rate of receptor-mediated clearance of LDL could result from an abnormality in LDL receptors or defective LDL that binds poorly to receptors. Both types of defects have now been identified.

The second cause of elevated LDL, namely, overproduction of LDL, likewise may have two causes: overproduction of apo B–containing lipoproteins by the liver and decreased uptake of VLDL or VLDL remnants, allowing for increased conversion of VLDL remnants to LDL. There are increasing data to support the existence of both types of defects.

Finally, if LDL becomes abnormally enriched in cholesterol esters, LDL cholesterol concentrations may rise to an elevated range, even when the number of LDL particles in circulation is not increased. These three categories of defects that cause hypercholesterolemia will be considered in some detail in the following discussion.

**Reduced Clearance of LDL**

*Genetic Defects in the LDL-Receptor Protein*

*Classic familial hypercholesterolemia.* The most severe elevations in LDL cholesterol occur with a disorder called familial hypercholesterolemia (FH), which results from a defect in the gene encoding for LDL-receptor protein. Normally, one gene for the LDL receptor is inherited from each parent, and both genes must function normally to maintain desirable levels of serum LDL cholesterol. If one gene is defective, the offspring will have one half the normal number of LDL receptors, and LDL levels are about twice normal. This condition, called heterozygous FH, occurs in about one in 500 people. Much more rarely—about one in 1 million people—defective LDL receptors derive from both parents; the result, homozygous FH, manifests very severe hypercholesterolemia and greatly accelerated atherosclerosis.

Parameters of LDL–apo B metabolism in patients with both heterozygous and homozygous FH are illustrated from studies carried out in our institution (Table 4). Compared with normolipidemic, middle-aged men, concentrations of LDL apo B were increased in both forms of FH but were much higher in homozygous FH. FCRs for LDL apo B were markedly reduced in FH homozygotes and distinctly reduced in FH heterozygotes. Moreover, relatively high input (production rates) for LDL apo B characterize both forms of FH. Figure 4 gives our interpretation of these data. A reduced tissue uptake of LDL certainly raises LDL concentrations, but in addition, a decrease in direct removal of VLDL and VLDL remnants by hepatic LDL receptors results in greater conversion of VLDL to LDL, further raising LDL levels. Although the “overproduction” of LDL apo B was originally believed to signify overproduction of apo B–containing lipoproteins, the high input rate for LDL apo B in FH more likely occurs from decreased hepatic removal of VLDL and VLDL remnants, allowing for more of the latter to be converted to LDL.

**Table 4. Lipoprotein Kinetics in Familial Hypercholesterolemia**

<table>
<thead>
<tr>
<th>Group</th>
<th>LDL cholesterol n (mg/dl)</th>
<th>LDL apo B Conc (mg/dl) pools/day</th>
<th>FCR (mg/kg·day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterozygous FH (middle-aged)*</td>
<td>22</td>
<td>281±15</td>
<td>168±9</td>
</tr>
<tr>
<td>Homozygous FH (&lt;20 yr)†</td>
<td>10</td>
<td>675±63</td>
<td>409±42</td>
</tr>
<tr>
<td>Middle-aged men (normal)‡</td>
<td>14</td>
<td>143±9</td>
<td>101±5</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. Conc, concentrations; FCR, fractional catabolic rate; input, input rate, used synonymously with production rate; FH, familial hypercholesterolemia.

*Patients were 17 men and 5 women; mean age, 44±9 (±SEM) years.

†Patients were 2 males and 8 females; mean age, 8±1 (±SEM) years.

‡Subjects were 14 men and 0 women; mean age, 56±2 (±SEM) years.

The fundamental abnormalities that occur in the LDL-receptor protein have been uncovered by the detailed studies of Brown and Goldstein and their associates. It was assumed early that a single genetic defect underlies the clinical syndrome of FH; subsequently, however, a host of abnormalities causing hypercholesterolemia have been identified. Four different classes of mutations have been described to date: they occur in families having a variety of ethnic origins and are summarized in Figure 5. Mutations vary from large insertions and deletions to single-base changes that introduce missense or nonsense codons, and they can occur over the entire width of the gene. In class I mutations, no LDL-receptor protein can be detected. So far, six different mutations have been identified in this class; they

![Figure 4](https://exampleserver.com/figure4.png)
are domains which is normal theolemia. CHD). Conceivably, however, the five domains of the mature LDL-receptor protein (see Figure 3) are the exons that encode them (shown below the gene). Sites of mutations are indicated, and a key for the symbols is given in the box. Reproduced with permission from Russell et al.30

include 6 to more than 10 kb deletions spanning the promoter and exon 1, and 4–5 kb deletions in the regions of exons 13–15. For class II mutations, transport of the LDL receptor to the surface of the cell is delayed; three examples include a 3–base pair deletion in exon 4,30,36 a nonsense mutation in exon 14,37 and a missense mutation in exon 11.30 A similar defect in receptor transport has been found in the Watanabe heritable hyperlipidemic (WHHL) rabbit, which is an animal model for human FH; the mutation in this rabbit consists of a 12–base pair deletion in exon 4.36 In class III mutations, defective receptors fail to bind to LDL particles. Two such mutations show deletions in exons 7 and 8\(^*\) and in exon 5,39 whereas another has a 14 kb duplication in exons 2–8.40 Finally, five different mutations produce defective internalization (class IV); these mainly reside in exons 16–18, which encode for the membrane-spanning region of the receptor molecule.41–44

Milder forms of familial hypercholesterolemia. Most of the defects described above produce classic heterozygous FH (i.e., a syndrome characterized by severe hypercholesterolemia, tendon xanthomas, and premature CHD). Conceivably, however, some patients could possess defects in the LDL-receptor protein and still not manifest severe hypercholesterolemia. Indeed, parents of children with homozygous FH sometimes present with only moderate hypercholesterolemia (LDL cholesterol, 160–220 mg/dl).45,46

These parents are obligate FH heterozygotes and must have abnormal genes for LDL receptors. Hobbs et al.47 recently described a family in which several obligate FH heterozygotes showed relatively low LDL cholesterol levels. They postulated that nonhypercholesterolemic heterozygotes carried an “LDL-lowering gene” that offset their defect in LDL receptors.

Several compensating mechanisms can be visualized that could prevent development of severe hypercholesterolemia in FH heterozygotes; a few of these can be considered. First, the one normal LDL-receptor gene might be stimulated to supranormal activity and, thus, override the defective receptor. LDL-receptor activity undoubtedly varies considerably from one person to another; in some, it must be inherently high. Second, the defect in the abnormal receptor might be relatively mild such that its binding to LDL is reduced but not obliterated. For example, a point mutation in the LDL receptor could modify its configuration and produce this effect. Moreover, if the defective receptor were to recognize apo E, but not apo B, hepatic removal of VLDL and VLDL remnants should be normal even though LDL clearance is reduced; because input of LDL would not be increased, only moderate hypercholesterolemia should develop. Third, another possibility is a reduced synthesis of apo B-containing lipoproteins, because of either an abnormal apo B protein48,49 or a defective regulation of apo B synthesis.50 Fourth, the
hepatic secretion rate of VLDL apo B could be normal, but the rate of direct removal of VLDL could be abnormally high, leaving less VLDL for conversion to LDL. For example, if there is a unique remnant receptor, which is different from the LDL receptor, its activity might be high and thereby enhance direct removal of VLDL; this effect could partially offset a decrease in LDL-receptor activity. Finally, changes in the composition of VLDL could promote VLDL binding to existing receptors and thereby reduce amounts of VLDL converted to LDL. Future studies may reveal that many people indeed do have defects in the LDL-receptor protein that induce hypercholesterolemia, but because of mitigating factors such as those listed above, the degree of LDL elevation is not severe.

**Down-Regulation of LDL-Receptor Synthesis**

The activity of LDL receptors is regulated not only by the structure of the LDL-receptor gene but also by controlling factors outside the gene itself. The immediate regulation of LDL-receptor synthesis resides in the promoter region of the gene. Available data suggest that the promoter is controlled in a typical way (i.e., by a series of activator and inhibitory proteins). Thus, interaction between activator proteins and the promoter region initiates transcription, whereas inhibitor proteins reduce receptor synthesis. The latter proteins apparently respond to an oxygenated derivative of cholesterol, the exact nature of which has not been determined. In any case, amounts of oxysterol available to the nucleus of the cell ultimately determine rates of LDL-receptor synthesis. The availability of active oxysterol apparently depends on amounts of cholesterol in the cell; in essence, when cellular content of cholesterol increases, synthesis of LDL receptors declines. The critical pool of cholesterol that generates the suppressive oxysterol may not be the total cellular content of cholesterol but rather a smaller, "metabolically active" pool of cholesterol. If such a pool exists, its site and size are unknown; nonetheless, its activity almost certainly is under the influence of overall cholesterol metabolism. This explains why diet- or drug-induced changes in whole-body metabolism of cholesterol affect rates of LDL-receptor synthesis.

Metabolic down-regulation of LDL-receptor synthesis could be a common cause of moderate hypercholesterolemia. By reducing the synthesis of LDL receptors, such an abnormality should delay the clearance of LDL from plasma. LDL turnover studies conducted in our laboratory suggest that this mechanism pertains to many patients with elevated LDL (Table 5). For example, in a group of hypercholesterolemic patients who had no clinical evidence of heterozygous FH, FCRs for LDL apo B were low; moreover, input rates for LDL in these patients were not increased as they were in FH patients. Two mechanisms could account for delayed removal of LDL in these patients: they had either a moderately reduced activity of LDL receptors or a defective LDL that binds poorly to LDL receptors. To distinguish between these two mechanisms, we performed a study in which LDL isolated from the hypercholesterolemic patients was labeled with radioiodine and reinjected simultaneously with a normal person’s LDL that had been labeled with another isotope of iodine. We assumed that if retarded clearance of LDL occurred because of a reduced activity of LDL receptors, both forms of labeled LDL (autologous and homologous) should decay at identical rates. In 10 of 15 hypercholesterolemic patients tested, identical decay curves for the two tracers, in fact, were observed. Figure 6 shows four typical examples. Both tracers revealed similar rates of decay, indicating that hypercholesterolemic patients had normal LDL particles; because decay rates were relatively slow, they must have had a reduced activity of LDL receptors. Assuming that most of these patients did not have mild heterozygous FH, down-regulation of LDL-receptor synthesis is the most likely explanation for the delayed clearance of LDL and elevated LDL cholesterol. Results in the few remaining patients, who had a different response, will be discussed below.

The synthesis of LDL receptors in the 10 patients could have been suppressed in four ways. First, abnormalities of the promoter region of the gene might have been defective, making it overly sensitive to down-regulation. Second, catabolism of mRNA for LDL-receptors could be enhanced. Third, intranuclear events involving oxysterols, activator or inhibitor proteins, or their interactions could have interfered with normal transcription. And fourth, the size of the "active" pool of cholesterol, which is the source of regulatory sterol, may have been increased. These possible mechanisms can be considered in the context of factors known to influence LDL cholesterol levels.

**Abnormalities in cholesterol metabolism.** The "metabolically active" pool of cholesterol in liver cells apparently depends on processes that regulate total intracellular cholesterol. These are absorption, syn-

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**Table 5. Lipoprotein Kinetics in Primary Moderate Hypercholesterolemia (Predominant Reduced LDL Clearance)**

<table>
<thead>
<tr>
<th>Group</th>
<th>LDL cholesterol (mg/dl)</th>
<th>LDL apo B Conc (mg/dl)</th>
<th>FCR (mg/dl) (poools/day)</th>
<th>Input (mg/kg-day)</th>
</tr>
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<tbody>
<tr>
<td>Primary moderate hypercholesterolemia (middle-aged)*</td>
<td>11</td>
<td>197±7</td>
<td>129±3</td>
<td>0.24±0.01</td>
</tr>
<tr>
<td>Middle-aged men (normal)†</td>
<td>14</td>
<td>143±9</td>
<td>101±5</td>
<td>0.30±0.01</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. Conc, concentrations; FCR, fractional catabolic rate; input, input rate, used synonymously with production rate.

*Patients were 11 men and 0 women; mean age, 59±9 (±SEM) years.
†Subjects were 14 men and 0 women; mean age, 56±2 (±SEM) years.
thesis, and catabolism of cholesterol, the latter including formation of bile acids and secretion of cholesterol into bile. Abnormalities in several parameters of cholesterol metabolism could cause hypercholesterolemia by increasing the hepatic pool of cholesterol. For example, Kesäniemi, Miettinen, and Ehnholm$^{58-60}$ reported that many patients with moderate hypercholesterolemia have abnormally high rates of absorption of dietary cholesterol. Further, McNamara et al$^{61}$ identified patients who fail to adjust to high cholesterol diets with the expected down-regulation of cholesterol synthesis; such patients tend to raise their serum cholesterol in response to high cholesterol intakes. Finally, Miettinen et al$^{62}$ reported that some hypercholesterolemic patients have relatively low rates of conversion of cholesterol into bile acids, which also could raise intracellular cholesterol. The precise reasons for these abnormalities have not been elucidated, but all should increase the "active" pool of cholesterol in the liver and thereby down-regulate LDL-receptor synthesis.

**Increased sensitivity to dietary saturated fatty acids.**

One dietary factor known to raise the plasma LDL level is a high intake of saturated fatty acids. Mechanisms whereby saturated fatty acids increase LDL cholesterol concentrations are not fully understood, but available data suggest that they act primarily to reduce receptor-mediated clearance of LDL.$^{63,64}$ Although saturated fatty acids could interfere with receptor function by decreasing membrane fluidity,$^{65}$ a more likely mechanism is down-regulation of receptor synthesis. Indeed, Fox et al$^{66}$ showed that high intakes of saturated fatty acids reduce mRNA for LDL receptors in baboon liver. If the latter mechanism holds true for humans, saturated acids may expand the "active" pool of cholesterol, a mechanism that unfortunately would be subtle and difficult to detect experimentally.

An important question is whether some individuals are uniquely sensitive to saturated fatty acids and, thus, show a hypercholesterolemic response beyond that of most other people. In a recent report,$^{67}$ we claimed that some people indeed are overly sensitive to dietary saturated fatty acids; our data are shown in Figure 7. Levels of total cholesterol and LDL cholesterol are shown for a series of patients who received diets high in monounsaturated fatty acids and high in saturated fatty acids. Some individuals showed marked increases in cholesterol levels when saturated fatty acids were exchanged for monounsaturates, whereas in others, rises were less steep. Thus, some patients appeared to be high-responders, whereas others were low-responders. High-responders generally had higher levels of cholesterol on the high-monounsaturated diet than did low-responders. Whether high-responders possess an inherited defect to account for their excessive

**FIGURE 6. Plots of plasma decay curves of radiolabeled autologous LDL ( △ ) and homologous LDL (■) for four patients with primary moderate hypercholesterolemia. All patients had relatively slow decay rates for autologous LDL, but because homologous LDL decayed at the same rate, it can be assumed that their LDL particles were not abnormal. Reproduced with permission from Vega and Grundy.$^{57}$**
saturated fatty acids has not been determined, but this is a strong possibility.

Decline in estrogen levels in postmenopausal women. LDL levels are known to be sensitive to hormonal factors. One such hormone is estrogen. In laboratory animals, estrogens given at relatively high doses stimulate the synthesis of LDL receptors.68 Moreover, in postmenopausal women, LDL cholesterol levels usually are lower than those in men (Table 3); however, after the menopause, LDL concentrations in women rise considerably and even exceed those in men. In fact, postmenopausal women as a group manifest higher LDL levels than any other segment of the population.3,69 This high prevalence of hypercholesterolemia in older women probably relates more to loss of estrogen than to increasing obesity because high LDL levels are common in both obese and nonobese postmenopausal women.70 The precise connection between estrogens and LDL-receptor activity in women remains to be determined, but perhaps a high intranuclear concentration of estrogens acts on the promoter region of the LDL-receptor gene to enhance transcription; if so, loss of estrogen after the menopause should reduce LDL-receptor synthesis.

Hypothyroidism (and reduced metabolic rate). Another hormone affecting LDL concentrations is thyroxine. High levels of thyroxine apparently stimulate synthesis of LDL receptors.71 It is well known that hyperthyroidism causes hypercholesterolemia, whereas hypothyroidism raises LDL levels. Whether ineffective action of thyroid hormone commonly contributes to moderate hypercholesterolemia is not known. Some researchers72,73 have speculated that the rise of LDL cholesterol levels that occurs with aging results in part from a decrease in activity of LDL-receptors; if so, this change could be secondary to a decline in resting metabolic rate, possibly related to a decline in tissue sensitivity to thyroid hormone. This mechanism could explain in part why moderate hypercholesterolemia is relatively uncommon in early adulthood but usually develops in middle age (Tables 1 and 3).

Mental stress. Another phenomenon that may have a hormonal basis is the rise of serum cholesterol levels that occurs with mental stress. This response has been found repeatedly in people undergoing periods of mental stress74–77 and might be due to increased secretion of adrenal corticosteroids or catecholamines. Such a response to mental or “environmental” stress may help to explain the common observation that LDL cholesterol levels almost always decline when patients enter the metabolic ward where day-to-day stresses are reduced. A decline in LDL levels often occurs on metabolic wards even when patients are fed “cholesterol-raising” diets.78,79 Because LDL cholesterol levels so commonly fall in this setting, it is not unreasonable to postulate that many cases of hypercholesterolemia in outpatients depend on the stresses of modern society. These stresses could contribute to the “mass hypercholesterolemia” found in many industrialized societies.

Defective Apo B-100

A reduced rate of clearance for serum LDL might result from an LDL particle that binds poorly to LDL receptors. To test for this abnormality, we conducted studies57 on turnover rates of autologous and homologous LDL in hypercholesterolemic patients, as described above. Five of our 15 patients showed a normal rate of decay in radioactivity for normal homologous LDL, but autologous LDL disappeared more slowly. Results in four of these patients are shown in Figure 8. Having reduced affinity for LDL receptors, the five patients most likely possessed an abnormal LDL. This possibility was examined further in collaboration with investigators at the Gladstone Foundation, University of California, San Francisco. By testing LDL from several of our hypercholesterolemic patients for binding to LDL receptors in cultured skin fibroblasts, Innerarity et al80 found that one sample had reduced binding to LDL receptors. Further study of this patient’s relatives uncovered decreased binding of LDL to receptors in three generations of hypercholesterolemic relatives. It must be noted that apo B-100 in an individual potentially consists of two forms, one derived from each parent. Thus, most individuals having defective apo B-100 presumably are heterozygotes (i.e., only one of two forms of apo B is abnormal). Binding studies80 suggested that about 30% of LDL particles present in serum of affected patients were normal-binding LDL, whereas about 70% bound poorly. Enrichment of poorly binding LDL in serum could be
predicted because most normal-binding LDL would have been preferentially removed by tissues, leaving behind poor-binding LDL.

The apo B-100 molecule is a large apolipoprotein having a molecular weight of 550 kDa and consisting of 4,536 amino acids. A high degree of polymorphism apparently exists in the apo B-100 structure, but it is uncertain how much this variability in primary structure affects apoprotein function. Previously, some researchers were of the opinion that a single amino-acid mutation in apo B-100 could not significantly affect binding of LDL to receptors. The suggestion was made that apo B molecule probably has multiple sites of binding to LDL receptors. However, a monoclonal antibody, MB-47, inhibits binding of LDL to LDL receptors; seemingly, MB-47 interacts with the apo B-100 molecule in the boundary region between the T-2 and T-3 segments of apo B, and consequently, there may be a single receptor-binding region of the apo B molecule. This observation further raised the possibility that the mutation in familial defective apo B-100 resides in the region bound by MB-47. Indeed, Weisgraber et al. noted that MB-47 binds abnormally to the defective apo B-100; instead of binding less than normal to LDL as might be expected, MB-47 actually had enhanced binding to LDL when the latter contained defective apo B-100. Although this enhanced reaction cannot be readily explained, it does suggest that a defect in apo B-100 exists in the region of apo B that binds to MB-47.

The possibility that familial defective apo B-100 contains a defect in the receptor-binding domain led Soria et al. to search for the specific defect by molecular biological techniques. A thorough sequence analysis of the two alleles from a patient with defective apo B-100 revealed a mutation in the codon for amino acid 3,500, causing substitution of glutamine for arginine. This same mutation was found in several affected relatives of the two families with this disorder. Soria et al. suggested the mutation in the codon for amino acid 3,500 (CGG→CAG) is a CG mutational “hot spot” that may give rise to familial defective apo B-100 fairly commonly.

This mutation at amino acid 3,500, which causes hypercholesterolemia, now has been noted in several families; however, it probably is not the only defect in the primary structure of apo B that can cause increased LDL levels. In our previous study, several patients had hypercholesterolemia on the basis of delayed removal of autologous LDL, yet they did not manifest the 3,500 mutation. On the basis of our limited data, it appeared that up to one third of patients with moderate hypercholesterolemia, who

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**Figure 8.** Plots of plasma decay curves of radiolabeled autologous LDL (△) and homologous LDL (□) for four patients with primary moderate hypercholesterolemia. In all patients, decay rates for autologous LDL were relatively slow, whereas those for homologous LDL were normal. This suggests that the hypercholesterolemia in the patients was due to a defective LDL that did not bind normally to LDL receptors. Reproduced with permission from Vega and Grundy.
had a reduced clearance rate for LDL, had some variant of defective apo B-100.\textsuperscript{57} More investigations will be required to determine the nature and frequency of these defects.

**Cholesterol Ester Enrichment of LDL Particles**

Another factor that can affect the LDL cholesterol concentration is the amount of cholesterol ester carried in each LDL particle. If the cholesterol ester content of lipoprotein particles is increased, the LDL cholesterol level will rise. There appear to be three sources of LDL cholesterol ester. VLDL remnants contain cholesterol esters; these are carried into LDL by the catabolism of remnants. Further enrichment of LDL can occur by direct transfer of cholesterol esters from HDL via a specific transfer protein,\textsuperscript{87} and esterification of unesterified cholesterol on the surface of the LDL particle by lecithin cholesterol acyl transferase (LCAT) provides a small quantity of LDL cholesterol ester.\textsuperscript{88} When lipoproteins first enter the density range of LDL, they double as not “saturated” with cholesterol esters. Indeed, much of the so-called “heterogeneity” of LDL appears to be related to variable quantities of cholesterol ester in the nonpolar core of LDL particles. Amounts of cholesterol ester in LDL particles seemingly can vary by as much as 40%, as reflected by ratios of LDL cholesterol to apo B that can range between 1.0 and 1.8.\textsuperscript{57,89} Therefore, factors that affect this ratio can be considered.

**Delayed clearance of LDL.** One influence on the ratio of LDL cholesterol to apo B is the residence time of circulating LDL. When LDL disappears rapidly from the blood stream, it does not circulate long enough to become enriched in cholesterol esters. Patients with hypertriglyceridemia, for example, often have a rapid clearance of LDL that may account for their cholesterol-poor LDL particles. Hypertriglyceridemic patients, nonetheless, usually have normal or elevated levels of LDL apo B, showing that LDL particle concentrations are not reduced, even when LDL-cholesterol levels are low. On the other hand, when clearance rates for serum LDL are low, ratios of LDL cholesterol to apo B become relatively high. For example, a high ratio occurs in patients with heterozygous FH,\textsuperscript{27} primary moderate hypercholesterolemia,\textsuperscript{56} and familial defective apo B-100;\textsuperscript{57} in all three disorders, removal rates for LDL are reduced. Prolonged circulation of LDL seemingly allows for accumulation of cholesterol esters and raises LDL cholesterol levels above those expected from the LDL apo B levels alone.

**Apo E-4.** Apo E occurs in three different forms: E-2, E-3, and E-4.\textsuperscript{90,91} One gene for each isoform is inherited from each parent; thus, every person has two isoforms. The most common allele is E-3, the next common is E-4, and the least common is E-2.\textsuperscript{92,93} When E-4 is present, LDL cholesterol levels tend to be somewhat raised; in the presence of E-2, levels are relatively low.\textsuperscript{59,94,95} The reason for this difference may relate to relative affinities of different isoforms for LDL receptors. E-2 has the lowest affinity, E-3 is intermediate, and E-4 apparently has the highest affinity for LDL receptors.\textsuperscript{96} Therefore, VLDL containing E-4 should be cleared via LDL receptors more readily than VLDL having other isoforms of apo E, especially E-2. The increased direct uptake of VLDL could lead to increased delivery of cholesterol to the liver and, hence, to down-regulation of LDL receptors; this would raise LDL cholesterol concentrations.\textsuperscript{97} Perhaps more likely, if E-4 promotes direct removal of VLDL by LDL receptors, then VLDL should compete more effectively than LDL for receptor uptake; this, too, should delay clearance of LDL. The slowing of LDL clearance would enrich LDL particles with cholesterol esters; if so, LDL cholesterol levels would be increased out of proportion to the rise in LDL–apo B concentrations. Evidence also has been presented for an alternate hypothesis, namely, increased absorption of cholesterol in the presence of E-4 and down-regulation of hepatic LDL receptors by exogenous cholesterol.\textsuperscript{59}

**Increased LDL Production**

Another potential cause for elevated LDL cholesterol concentrations is an enhanced input of LDL. This mechanism signifies an increased conversion of VLDL (or VLDL remnants) to LDL, and it does not necessarily denote oversynthesis of apo B–containing lipoproteins by the liver. Previous isotope-kinetic studies revealed that an increased influx of LDL apo B frequently is accompanied by a high flux rate for VLDL apo B; to earlier investigators,\textsuperscript{98–104} a high input rate for VLDL apo B suggested hepatic over-synthesis of apo B. Other explanations, however, are possible, as shown in Figure 9. First, as discussed before, enhanced conversion of VLDL to LDL can result from a reduced activity of LDL receptors (Figure 9A); when less VLDL is removed directly by the liver because of low receptor activity, more VLDL is converted to LDL. Second, the liver could synthesize and secrete an excess of VLDL apo B into plasma (Figure 9B); if this occurs, the catabolic cascade should be flooded with lipoproteins and, consequently, more VLDL will be transformed to

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure9.png}
\caption{Schematic of mechanisms for increased production (input) of LDL. These include (A) decreased activity of LDL receptors, (B) increased hepatic secretion of apo B–containing lipoproteins, (C) decreased uptake of newly secreted VLDL, and (D) decreased uptake of VLDL remnants.}
\end{figure}
LDL. Third, direct removal of VLDL by the liver could be reduced because of factors other than a deficiency of LDL receptors (Figure 9C); again, more VLDL particles would be converted to LDL. Fourth, direct removal of VLDL remnants could be reduced, even though LDL-receptor activity is normal (Figure 9D); this, too, should enhance conversion of VLDL to LDL. Finally, a combination of these mechanisms could exist in a single individual. Each of these potential mechanisms can be considered briefly.

**Reduced LDL-Receptor Activity**

Enhanced conversion of VLDL to LDL is marked particularly in patients with homozygous FH; studies from this institution\(^{22,105,106}\) and others\(^{28,107}\) have shown that input rates for LDL in FH heterozygotes are twofold to threefold that of normal. This pattern was interpreted first to mean an increased hepatic secretion of apo B-containing lipoproteins,\(^{25}\) but when it was shown more recently that LDL receptors can remove VLDL and VLDL remnants, a high secretion rate for VLDL was not required to explain the high input of LDL. This concept was clarified by work in the WHHL rabbit, an animal model that resembles human homozygous FH because it has a marked deficiency of LDL receptors. Likewise, isostopic studies in WHHL rabbits showed a high input rate for LDL,\(^{108}\) but oversynthesis of apo B-containing lipoproteins seemingly does not occur in these animals\(^{29}\); instead, more VLDL is converted to LDL. Patients with heterozygous FH, as those with homozygous FH, have a high input of LDL;\(^{25}\) this, too, can be explained by decreased clearance of VLDL and VLDL remnants (Figures 4 and 9B).

In humans, use of tracers for simultaneous study of VLDL and LDL metabolism suggest that a large fraction of the excessive input of LDL in FH heterozygotes occurs via “direct” input of LDL.\(^{109}\) In other words, lipoproteins enter the LDL fraction without passing through the circulating pool of VLDL. Some researchers believe that the liver directly synthesizes LDL, but another explanation of “direct synthesis” of LDL is a rapid conversion of a subfraction of VLDL to LDL.\(^{110}\) Newly secreted (nascent) VLDL seemingly can have fates other than being transformed into the usual VLDL found in circulation. Some nascent VLDL probably are cleared from circulation rapidly, whereas another portion may be rapidly converted to LDL. Currently available isostopic techniques cannot accurately trace all of the fates of newly secreted lipoproteins, and the apparent “direct synthesis” of LDL may represent rapid degradation of nascent VLDL to LDL. Another possibility is that the liver secretes small VLDL- or LDL-sized particles that are rapidly transformed into LDL.\(^{109}\)

**Increased Hepatic Secretion of Apo B-Containing Lipoproteins**

**Nephrotic syndrome.** The hypercholesterolemia of the nephrotic syndrome almost certainly results from enhanced hepatic secretion of apo B-containing lipoproteins (Figure 9B).\(^{111-116}\) Loss of albumin or other proteins in the urine apparently stimulates synthesis of proteins in the liver; one such protein is apo B. The liver of nephrotic animals definitely produces an excess of lipoproteins.\(^{112,116}\) The most striking plasma lipid abnormality in patients with the nephrotic syndrome is an elevated LDL cholesterol.\(^{114,115}\) Oversecretion of all apo B-containing lipoproteins might be expected to elevate VLDL levels as well, but early in the course of the disease, lipolysis of VLDL triglycerides occurs rapidly, and only LDL accumulates excessively in plasma. In nephrotic animals, hepatic oversynthesis of cholesterol also occurs,\(^{116}\) and part of the severe hypercholesterolemia of nephrosis might be explained by a concomitant downregulation of LDL-receptor synthesis. Even so, the latter cannot explain most of nephrotic hypercholesterolemia, which instead is due to enhanced hepatic secretion of apo B-containing lipoproteins.

**Obesity.** The relation between obesity and hypercholesterolemia is complex. Many individuals with elevated levels of LDL cholesterol are overweight, and weight reduction in these individuals can cause a fall in LDL cholesterol concentrations. In contrast, other obese individuals are not hypercholesterolemic; some even have abnormally low levels of LDL. Metabolic studies in humans\(^{117-119}\) strongly suggest that obesity enhances production of apo B-containing lipoproteins (Figure 9B). In many epidemiologic surveys, obesity appears to be a contributing factor to higher cholesterol levels, and overweight may partly account for the rise of LDL cholesterol levels with aging; indeed, a review of available data suggests that obesity may account for as much as one half the increase in cholesterol levels that occurs in high-risk compared with low-risk populations.\(^{120-122}\) When high caloric intakes are accompanied by increased intakes of saturated fatty acids and cholesterol, the hypercholesterolemic response will be accentuated.\(^{123}\) Thus, for the whole population, the overproduction of lipoproteins tends to raise LDL-cholesterol levels, although this response does not necessarily occur in all individuals.

**Primary increased secretion of apo B-containing lipoproteins.** Several researchers\(^{96-103,124}\) suggest that the clinical syndrome familial combined hyperlipidemia represents an example of primary hepatic oversecretion of apo B. Families with this disorder clinically resemble those with nephrotic dyslipidemia (i.e., they have hypercholesterolemia, hypertriglyceridemia, or both).\(^{125-127}\) Because nephrotic hyperlipidemia apparently results from oversecretion of apo B-containing lipoproteins, the same defect logically could underlie familial combined hyperlipidemia. In support, many patients with familial combined hyperlipidemia manifest high flux rates for VLDL apo B and LDL apo B; when LDL cholesterol levels are high, the elevation derives from increased input of LDL apo B, not from reduced FCRs for LDL apo B.\(^{102}\) Certainly isotope kinetic data for VLDL apo B metabolism are consistent with increased hepatic
secretion of VLDL apo B (Figure 9B); still, no direct evidence confirms that the liver can synthesize or secrete excess VLDL apo B in response to a specific inherited defect. For instance, there are no data to indicate the presence of increased amounts of mRNA for apo B in liver of patients with familial combined hyperlipidemia. Moreover, a careful examination of isotope kinetic data reveals other possible reasons for increased flux for VLDL apo B and LDL apo B in this condition, as discussed below.

**Decreased in Direct Removal of VLDL**

Several studies\textsuperscript{10,11} reveal that a significant fraction of newly secreted VLDL is removed directly from the circulation; if the direct removal pathway were to be decreased, more VLDL could be transformed into VLDL remnants and, hence, to LDL (Figure 9C). Because isotope kinetic studies of VLDL apo B reflect flux of VLDL remnants more than flux of nascent VLDL, a reduction in direct uptake of nascent VLDL would be manifest in these studies by an apparent increased input of VLDL apo B; this response, in turn, could be mistakenly interpreted as an enhanced hepatic secretion of apo B–containing lipoproteins. Of interest, LDL–apo B kinetics should distinguish between these two mechanisms for enhanced LDL input (i.e., increased secretion of VLDL and decreased direct removal of VLDL). More specifically, a high secretion of VLDL should raise both direct removal of VLDL and conversion of VLDL to LDL; if so, FCRs for LDL should be relatively low because excess quantities of VLDL would occupy many available LDL receptors. On the other hand, if direct uptake of VLDL is reduced even in the presence of normal secretion rates for VLDL, more VLDL will be converted to LDL; as a result, fewer LDL receptors will be occupied by VLDL, and FCRs for LDL should be relatively high. Because LDL are relatively poor ligands for LDL receptors compared with VLDL and VLDL remnants and because of decreased VLDL uptake, an increased input of LDL could raise LDL–apo B concentrations. Our isotope kinetic studies in a series of patients with primary hypercholesterolemia have identified several individuals who have increased input rates for LDL apo B (Table 6). In general, these patients had high FCRs for LDL. Therefore, they were more likely to have a decrease in direct removal of VLDL (Figure 9C) than an increased input of apo B–containing lipoproteins (Figure 9B).

The mechanisms whereby direct removal of VLDL might be decreased are unclear. Some patients may have a mild deficiency of lipoprotein lipase. Such a defect might not be severe enough to cause significant hypertriglyceridemia, but it still could be sufficient to retard direct removal of VLDL particles; if so, more VLDL would be diverted to VLDL remnants and then LDL. Indeed, Babirak et al\textsuperscript{128} recently reported that patients who are heterozygous for familial lipoprotein lipase deficiency often have increases in LDL cholesterol, LDL apo B, or both, yet they do not have hypertriglyceridemia. This observation could be explained by the mechanism shown in Figure 9C. Whatever the underlying reason, a decrease in direct removal of VLDL probably can contribute to elevated LDL levels.

**Decreased Direct Removal of VLDL Remnants**

Finally, enhanced conversion of VLDL to LDL could follow decreased direct removal of VLDL remnants (Figure 9D). The LDL–apo B kinetics of these hypercholesterolemic patients shown in Table 6 could be explained by this mechanism as well as by that of Figure 9C. However, when VLDL-remnant uptake is decreased, concentrations of VLDL remnants typically rise more than LDL.\textsuperscript{129,130} This usually occurs in patients with E-2/E-2 or E-3/E-2 isofrom patterns of apo E. The presence of these isoforms can impart a factitious elevation of LDL; since the usual estimation of LDL cholesterol level in clinical laboratories includes IDL with LDL, an increase in IDL, which occurs commonly with E-2/E-2 or E-2/E-3 genotypes, causes overestimation of LDL cholesterol. In this case, elevated cholesterol results from high IDL, not LDL.

**Combined Defects in Lipoprotein Metabolism**

A final possibility is that enhanced input of LDL and, thus, high LDL cholesterol levels may be due to combined defects in lipoprotein metabolism. In other words, a patient could possess more than one of the abnormalities shown in Figure 9. For example, if an individual had a high secretion of apo B–containing lipoproteins due to obesity (Figure 9B), a reduced activity of LDL receptors (Figure 9A), and a mildly decreased activity of lipoprotein lipase (Figure 9C), the likely result would be a striking rise in LDL cholesterol. Because of the high frequency of hypercholesterolemia in the population, it is likely that multiple abnormalities in VLDL and LDL metabolism occur frequently in single individuals.
Summary

This review indicates the complexity of the pathogenesis of hypercholesterolemia. Although dietary factors undoubtedly contribute to high LDL cholesterol levels in our society, the potential for genetic abnormalities in transport of plasma cholesterol is enormous. A multiplicity of processes affect each point of regulation, for example, synthesis and secretion of lipoproteins, apolipoprotein function, and clearance of LDL from the circulation. All of these modifying factors are under genetic control, and inherited defects in any of them may raise LDL cholesterol concentrations. In this regard, many people may have inherited enhanced sensitivity to dietary saturated fatty acids and cholesterol or to high caloric intake that combines with genetic defects to produce hypercholesterolemia. An understanding of the relative contributions of dietary, genetic, and secondary factors in the causation of hypercholesterolemia is critical for the development of a rational strategy for management of the “mass hypercholesterolemia” occurring in the US public.

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