but the absolute number of cardiovascular deaths also fell below 1 million in 1975 and 1976 for the first time since 1963. Moreover, for the first time since the 1930s, life expectancy projections for the U.S. population are now trending upward (fig. 4). These had held fairly steady for several decades after the eradication of typhoid fever and other widespread infectious diseases that once ravaged the country. Then around 1970, and coinciding with observed decreases in cardiovascular disease mortality, there was an abrupt upturn in the projected life expectancy for all citizens. This upturn applies to males and females as well as to minority and majority populations, and it has been dramatic. For example, the life expectancy for black males has increased by more than 3 years since 1973.

But what of the future? What does it portend? Striking, amazing advances through research have been made in the last 30 years. It is clear that there will be many more. There is no cardiovascular disease or problem that is so complicated that it cannot be attacked, understood and ultimately remedied, but at what price? The NHLBI is focusing increased attention on primary prevention as the only truly cost-effective approach. Waiting to repair or palliate may be too late and is actually more costly.

Primary prevention implies educating physicians and the public about risk factors: the cessation of smoking, the treatment of high blood pressure, the need for all Americans to assume responsibility for their own health maintenance behavior. Primary prevention also means increased support for basic research to define the etiology and pathophysiology of two primary processes still incompletely understood — arteriosclerosis and hypertension. It means the expeditious validation and translation of pertinent new findings emerging from such studies. Thus, prevention of cardiovascular disease includes research through the entire spectrum aimed at averting premature cardiovascular disease, since treatment and palliation are so costly, not only in terms of resources and dollars, but also in terms of human suffering.

As we increase our awareness of the basic processes behind arteriosclerosis and hypertension, we should move ever closer to preventing these diseases and their sequelae. The prevention of premature cardiovascular diseases is the prospect for the future.

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Research Related to Underlying Mechanisms in Atherosclerosis

Daniel Steinberg, M.D., Ph.D.

SUMMARY A brief resume of advances in atherosclerosis research over the past 30 years is presented, emphasizing the multidisciplinary origins of those advances. A somewhat more detailed review of progress in the lipoprotein field is presented as an example to illustrate the pace of research related to atherosclerosis. Finally, an attempt is made to identify some of the research areas that promise to yield valuable new insights in the next 30 years.

In recent years there has been a convergence of research advances from several directions, a coupling of concepts from different disciplines. As a result we are able to formulate more specific, more coherent, testable hypotheses about atherogenesis. Some aspects of these hypotheses are strongly supported by experimental evidence. These hypotheses are not necessarily mutually exclusive; there is reason to believe that there is more than one cause of atherosclerosis, and there may not be a "final common path." Atherosclerosis is, in fact, a disease of multiple interactive etiologies, and prevention may well require intervention along different lines.

Advances Over the Past 30 Years

Documentation of Risk Factors

The documentation by epidemiologists of the risk factors in atherosclerosis has been a landmark of the past 30 years. These risk factors have been discussed in detail (table 1). There has been important interaction between the epidemiologic approach and the approaches at the basic level. For example, the well-documented epidemiologic finding that women, during their reproductive years, enjoy a relatively protected status has stimulated research on the effects of estrogenic hormones on lipoprotein metabolism and more recently on the local metabolism of arterial tissue. The more rapid progression of lesions and the excess coronary heart disease mortality in cigarette
smokers is a challenge to the experimentalist (carbon monoxide? nicotine? other?), but a decisive answer remains to be heard. The finding that high-density lipoprotein (HDL) is a negative risk factor has greatly stimulated research on HDL metabolism.4,6

The Roles of Endothelial Injury and Platelets

The role of local endothelial injury in atherosclerosis has long been recognized, and our understanding of it has increased remarkably (table 2). We now know many factors that can potentially contribute to endothelial damage.7,8 Platelet adherence and aggregation at the artery wall may be pivotal, associated with release of factors that influence further aggregation or that modify arterial metabolism. The complex and elegant prostaglandin story has unfolded rapidly in recent years.8 A new prostaglandin derivative, thromboxane A2, formed by the platelet from a cycloperoxide of arachidonic acid (PGG2), is a powerful stimulant to platelet aggregation as well as a potent vasoconstrictor. However, the same cycloperoxide can be converted by another pathway in endothelial cells to prostacyclin (PGI2), which inhibits platelet aggregation and favors vasodilation.9 These findings suggest why thrombi form at denuded sites but not over intact endothelium. Already we can see the potential for intervening pharmacologically to affect atherogenesis and thrombosis through this system and others involved in platelet aggregation.10

Plasma lipoproteins penetrate into the artery wall, probably even through an intact endothelium. When the endothelial barrier is breached, the underlying cells are suddenly exposed to lipoprotein concentrations some tenfold higher. It has been proposed that hyperlipoproteinemia may itself damage endothelial cells and favor platelet aggregation. If so, we can easily link the “lipid infiltration hypothesis” and the “endothelial injury–platelet aggregation hypothesis.”

From in vivo studies we are learning how the damaged endothelium repairs itself. Studies of endothelial cells in culture promise to teach us still more about the growth and metabolism of these all-important cells. They form a fragile barrier between the artery wall and the torrent of blood that pours by containing a number of unfriendly elements, including platelets and lipoproteins.

Characterization of Smooth Muscle Cells in Lesions and Their Role

The fact that atherosclerotic lesions are proliferative lesions has not always been fully considered. The pathologists have taught us that the major cellular element involved is probably the smooth muscle cell (table 3). We can grow it in culture and study how it reacts to lipoproteins, to anoxia, to hormones, etc. Platelets appear to contain (and release) a very potent factor that is mitogenic for smooth muscle cells. The possibility that viruses or other mutagenic agents may help trigger proliferation is also under investigation.

Demonstration that Intervention is Feasible

Thirty years ago there were still many who considered atherosclerosis inevitable. That nihilism is now obsolete (table 4). First, regression of atherosclerosis has been clearly demonstrated in animals, most importantly in nonhuman primates.12 Second, prevention in man has been shown with regard to at least one risk factor—cigarette smoking. The risk in smokers who quit returns in a few years to a level not significantly higher than that in matched nonsmokers.13

The question of whether correction of hyperlipidemia reduces risk is controversial. The weight of experimental and epidemiologic evidence is at least as good as—or actually better than—the evidence that correcting hyperglycemia reduces risk of chronic diabetic complications. Three studies present evidence to suggest that low-cholesterol, low-saturated fat diets

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**Table 1. Epidemiologic Documentation of Major Risk Factors**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipoproteinemia</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Obesity</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Age</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Sex</td>
<td>Risk factor for coronary heart disease</td>
</tr>
<tr>
<td>Low HDL level</td>
<td>Risk factor for coronary heart disease</td>
</tr>
</tbody>
</table>

---

**Table 2. Extension of the Endothelial Injury Hypothesis**

| Endothelial damage (hemodynamic factors, metabolites, hormones, toxins, viruses) |
| Platelet aggregation, release of proliferative factors |
| Prostaglandin formation and release (thromboxane-prostacyclin; aspirin) |
| Penetration of plasma lipoproteins |
| Endothelial cell repair (cell culture studies) |

---

**Table 3. Definition of the Role of Smooth Muscle Cells**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microanatomic studies</td>
<td>Lipoprotein uptake and catabolism</td>
</tr>
<tr>
<td>Cell culture studies</td>
<td>Growth factors</td>
</tr>
</tbody>
</table>

---

**Table 4. Demonstration That Intervention is Feasible**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression of lesions in animal models</td>
<td>Conclusive</td>
</tr>
<tr>
<td>Reduction of risk in former cigarette smokers</td>
<td>Conclusive</td>
</tr>
<tr>
<td>Reduction of risk with reduction of plasma lipoprotein levels</td>
<td>Probable but not conclusive</td>
</tr>
<tr>
<td>Reduction of coronary death rate</td>
<td>Conclusive, but for reasons still uncertain (coronary heart disease death rate down by 19–35% since 1968)</td>
</tr>
</tbody>
</table>
both lower plasma cholesterol levels and reduce the incidence of atherosclerotic complications.\textsuperscript{14-16} The number of subjects studied was less than optimal and none of the studies was free of flaws in experimental design or problems in interpretation. Nevertheless, the positive results recorded must not be ignored. Thus, the “lipid hypothesis” is not without support from direct experimental testing in clinical trials.

Perhaps the best example of regression of atherogenesis in man is the child with homozygous familial hypercholesterolemia on whom Starzl and coworkers performed a portacaval shunt.\textsuperscript{17} Plasma cholesterol levels fell from over 800 to below 400. During the following year, skin xanthomata regressed almost completely and angina disappeared. The pressure drop across the aortic valve fell from 56 mm Hg to 10 mm Hg. Coronary angiography preoperatively showed extensive diffuse narrowing in the major vessels and the circumflex artery was not even visualized. A year later all three large vessels were visualized and there remained only three discrete areas of focal narrowing. Unfortunately, this child died suddenly, presumably an arrhythmic death.\textsuperscript{18}

The death rate from coronary heart disease is decreasing nationwide,\textsuperscript{18} which suggests that atherosclerosis and its clinical sequelae are not inevitable.

**Advances in Lipoprotein Structure and Metabolism**

Until the late 1940s we dealt with total plasma lipid levels (cholesterol, triglycerides, phospholipids), but had little or no insight into the nature of the vehicles involved in transporting these water-insoluble substances.

**Structure**

The status in 1948 is summarized in table 5A. Splitting had not progressed beyond $\alpha$ and $\beta$. Apoproteins had not been studied at all, and virtually nothing was known about lipoprotein metabolism except for the existence of a still rather mysterious “lipemia-clearing factor.”

The status in 1978 (table 5B) is rather different.\textsuperscript{20-22} The splitting process has proceeded apace, leading to this already formidable and still growing list of lipoprotein subfractions, normal and pathologic. The apoprotein moieties have been intensively studied, five of them have been totally sequenced and some of the special structural features have been defined that allow them to interact intimately with lipids. Several apoproteins have been shown to have important functional roles in lipoprotein metabolism rather than, or in addition to, their structural role. For example, apo C-II activates lipoprotein lipase. The physiologic importance of this activator function is best illustrated by a family with hyperlipoproteinemia and a selective deficiency in apo C-II.\textsuperscript{23} Apoprotein A-I also has a functional role, that of activating lecithin-cholesterol acyltransferase. The exact role of apoprotein E is unknown, but it is already evident that it must be important in lipoprotein secretion and cholesterol transport.

**Table 5. Comparison of the Status of Lipoprotein Research: 1948 vs 1978**

<table>
<thead>
<tr>
<th>Classes</th>
<th>Apoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>No data</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Biosynthesis, interconversions, degradation</td>
</tr>
</tbody>
</table>

**B. The plasma lipoproteins: 1978**

<table>
<thead>
<tr>
<th>Classes</th>
<th>Apoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL</td>
<td>apo A-I (sequenced)</td>
</tr>
<tr>
<td>IDL</td>
<td>apo A-II (sequenced)</td>
</tr>
<tr>
<td>LDL</td>
<td>apo B</td>
</tr>
<tr>
<td>HDL$_1$</td>
<td>apo C-I (sequenced)</td>
</tr>
<tr>
<td>HDL$_2$</td>
<td>apo C-II (sequenced)</td>
</tr>
<tr>
<td>HDL$_3$</td>
<td>apo C-III$_a$</td>
</tr>
<tr>
<td>HDL$_4$</td>
<td>apo C-III$_d$</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>apo D (“thin-line” protein)</td>
</tr>
<tr>
<td>Lp X</td>
<td>apo E-I</td>
</tr>
<tr>
<td>apo E-II (arginine-rich)</td>
<td></td>
</tr>
</tbody>
</table>

Biosynthesis, interconversions, degradation

VLDL and HDL secreted by liver and intestine
VLDL $\rightarrow$ IDL (“remnants”) $\rightarrow$ LDL $\rightarrow$ HDL
Free fatty acid transport; fatty acid transport cycle
Lipoprotein lipase
Hepatic lipase
Lecithin-cholesterol acyltransferase
Activator function of apoproteins (C-II, A-I, E, others)
Peripheral degradation of LDL
High-affinity receptor mechanism (apo B, apo E)

Abbreviations: VLDL = very low density lipoproteins; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein.
The liver synthesizes and secretes primarily very low density lipoproteins (VLDL) and HDL (fig. 1). The production of lipoproteins by the intestine is possibly important as well. The triglycerides of chylomicrons and VLDL are removed in the capillary beds by lipoprotein lipase that is tightly bound to endothelial cells. It has been suggested that degradation products formed during clearing may contribute to atherogenesis, although this hypothesis remains tentative. VLDL degradation yields an intermediate-density lipoprotein (IDL) or “remnant.” This fraction accumulates in patients with familial dysbetalipoproteinemia (type III hyperlipoproteinemia) and it appears to be highly atherogenic. The final product of VLDL degradation is LDL, the major carrier of cholesterol in the plasma and the lipoprotein most closely linked to atherogenesis. Recent studies show that not all of the LDL in plasma need be derived from LDL. Under some circumstances, notably in familial hypercholesterolemia, a large fraction of plasma LDL is secreted as such directly into the plasma compartment. Moreover, not all of the apoprotein B in VLDL reaches LDL; particularly in patients with hyperlipoproteinemia a significant fraction of VLDL apo B leaves the plasma without going through LDL. These very recent developments introduce important new concepts and suggest new approaches to research on the mechanisms underlying the various clinical forms of hyperlipoproteinemia.

We know now that the protein moiety of LDL is predominantly degraded in peripheral tissues, not in the liver as we formerly believed. Degradation of the protein, which occurs intracellularly, leaves the cholesterol without its carrier. Since the peripheral cells cannot degrade cholesterol (steroidogenic endocrine glands excepted) it would just accumulate progressively were there no mechanism for transporting it back to the liver. About 2 g of cholesterol is associated with the amount of LDL protein degraded daily — a sizeable burden — and presumably the artery wall bears its share of this burden. One of the unsolved problems under active investigation is the nature of this “reverse cholesterol transport” process (fig. 2). A favored hypothesis is that HDL may be the carrier and that lecithin-cholesterol acyltransferase plays an essential role. This might account in part for the negative correlation between HDL levels and coronary heart disease risk. An additional mechanism proposed to explain the protective effect of HDL is that it inhibits cellular uptake of LDL. Thus, HDL may both decrease the rate of entrance of cholesterol into cells via LDL and increase the rate of cholesterol release from cells.

Certainly one of the most important advances in recent years has been the elucidation of LDL-cell interaction, building on the rapid developments in cell biology (fig. 3). Peripheral cells bind LDL to high-affinity membrane receptors that are concentrated in specialized areas on the membrane (“coated pits”). The LDL molecules are internalized in endocytotic vesicles, which then fuse with primary lysosomes. There the several components of the LDL are degraded. The protein is broken down to free amino acids, which leave the cell rapidly. The cholesterol ester is hydrolyzed and the free cholesterol released then exerts several important regulatory functions. First, it suppresses endogenous cholesterol synthesis. Second, it stimulates cholesterol esterification so that any excess cholesterol is temporarily stored in ester form. Finally, it suppresses the synthesis of new LDL receptors, thus allowing the cell to regulate its own supply of cholesterol. The most compelling evidence supporting this scheme has come from studies of cells from patients with familial hypercholesterolemia, cells that lack the high-affinity receptor. This deficiency presumably accounts for the patients’ grossly elevated LDL levels. The linkage between their deficiency in

[Diagram of lipoprotein metabolism]

**Figure 1.** Schematic representation of pathways involved in lipoprotein synthesis and degradation. Newly secreted VLDL is acted on by lipoprotein lipase bound to the capillary endothelium, the triglyceride breakdown products being taken up in peripheral tissues. Most of the apoproteins other than apo B (and some of the phospholipid and cholesterol) are lost in the process, resulting in a much smaller, triglyceride-poor lipoprotein of intermediate density (IDL), which is finally converted to low-density lipoprotein (LDL). This is in fairly rapid equilibrium, with a large pool of LDL in the liver. Most LDL apo B, however, is degraded extracellularly. As discussed in the text, some LDL is directly secreted by the liver, especially in patients with familial hypercholesterolemia. Nascent HDL is secreted in the form of disc — essentially bilayers of phospholipid — rich in apo E. The steady-state HDL results from the action of lecithin-cholesterol acyltransferase (LCAT) on the disc and the exchange of apoproteins with other lipoprotein fractions. The site of HDL degradation is uncertain but some evidence indicates that HDL apoproteins may also be degraded peripherally.

Metabolism**20-22, 24-28

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Figure 2. Schematic representation of "reverse cholesterol transport," i.e., transport of cholesterol from peripheral tissue back to the liver. See text for discussion. HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein; C = free cholesterol; CE = cholesterol ester; PL = phospholipid; TG = triglyceride; FA = fatty acid; aGP = α-glycerophosphate; TCA = trichloroacetic acid.

Figure 3. Schematic representation of current concepts of the cellular metabolism of low-density lipoprotein (LDL). See text for discussion. TCA = trichloroacetic acid.

receptors and their accelerated atherogenesis is still unclear. Paradoxically, the total daily turnover in these patients is elevated — twice normal. Is this due to functioning low-affinity receptors? Is it attributable to cell types that have a different cell membrane system? Is the atherogenesis due to direct LDL damage to arterial endothelium so that arterial smooth muscle cells bear an exceptional burden? To what extent does extracellular deposition of lipoprotein lipids contribute? Much remains to be learned, but now at least we have well-defined paradigms within which to work.

Our knowledge of the mechanisms of hyperlipoproteinemia has increased enormously since 1948 (table 6). Today we can, in at least five categories of primary hyperlipoproteinemia, identify the protein deficiency involved. Moreover, in many forms of secondary hyperlipoproteinemia we can draw schemes that account for them within the context of our lipoprotein-transport paradigm.

Goals for the Next 30 Years (table 7)

Although dietary intervention does lower lipoprotein levels in most patients and while we do have drugs that are quite effective, our therapeutic success is limited, particularly in patients with familial hypercholesterolemia. How we grade our success depends, of course, on what we believe the appropriate goal should be. If you believe that the appropriate goal is to reach cholesterol levels like those found in a Japanese population (147 mg/dl in men 45–49 years), we get a fairly low grade. What we in the United States call a "normal" cholesterol level is actually a level associated with a very high incidence of fatal myocardial infarction. I see no reason to be self-
TABLE 6.  Comparison of Metabolic Lesions Established: 1948 vs 1978

A.  Metabolic lesions established: 1948
   None

B.  Metabolic lesions established: 1978
   1. Familial hyperchylomicronemia (phenotype I) — lipoprotein lipase deficiency
   2. Familial hypercholesterolemia (phenotype IIa) — LDL receptor deficiency
      Receptor binding deficiency, total
      Receptor binding deficiency, partial
      Internalization deficiency
   3. Familial dysbetalipoproteinemia (phenotype III) — apoprotein E-III deficiency (probable)
   4. Familial hypertriglyceridemia (phenotype IV) — apoprotein C-II deficiency (activator)
   5. Familial lecithin-cholesterol acyltransferase deficiency

We could inhibit cell uptake of lipoproteins, if we could facilitate reverse cholesterol transport — we might slow atherogenesis. Efforts to further clarify the local cellular processes — the initiating mechanisms in particular — must be encouraged.

The development of an effective noninvasive method for the assessment of atherosclerotic lesions in vivo must have high priority. This becomes evident if we ask what we would do if basic research tomorrow yielded exciting evidence implicating some particular factor in atherogenesis? How would we conclusively establish that such a factor was indeed relevant? As things stand now, proof requires a long-term intervention trial involving large numbers of subjects. Such trials are difficult and expensive, so much so that we may never be able to test promising hypotheses. However, if we could follow the progression of lesions in individual patients we might get an answer in a short time with a reasonably small number of subjects. Success here could dramatically change the time scale of future developments in atherosclerosis research.

Most important, we need advances in basic research. Researchers who frankly declared their commitment to study of the atherogenic process 30 years ago were few in number. Thirty years ago, the available research tools were relatively crude and the background of basic science was limited. Since then, our research methods have improved and basic knowledge has grown enormously. Then, it was difficult even to know where to begin and how to define meaningful, focused questions; now we have specific, well-formulated hypotheses and sophisticated methods to test them.

Acknowledgments

The author acknowledges valuable discussions with Dr. Russell Ross, Dr. Gardner McMillan and Dr. Robert I. Levy during the planning of this presentation.

References


TABLE 7.  Some of the Important Goals for the Next 30 Years

1. Development of more effective ways to modify plasma lipoprotein levels (e.g., lower LDL to "Japanese levels"; raise HDL; ? decrease chylomicron and VLDL flux)
2. Development of methods for modifying arterial wall metabolism (e.g., facilitate endothelial repair; inhibit proliferative responses of smooth muscle cells; modify lipoprotein uptake and metabolism—transendothelial movement or cellular uptake; increase rate of cholesterol efflux)
3. Development of noninvasive (or invasive but safe) methods for assessing the status of atherosclerotic lesions in vivo (e.g., ultrasound; arteriography; scanning after injection of appropriate markers)
4. Development of more effective ways to modify behavior (e.g., cigarette smoking, calorie intake, dietary pattern, exercise)
5. Expansion of basic research to make these goals attainable (e.g., biochemistry, cell biology, immunology, bioengineering, physiology, pharmacology, psychology)
isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature 163: 663, 1976
Research related to underlying mechanisms in atherosclerosis.
D Steinberg

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