Table VI.2–2. Summary of Bile Acid Sequestrants

Available drugs	Cholestyramine, colestipol, colesevelam	
Lipid/lipoprotein effects	LDL cholesterol	- ↓ 15–30%
	HDL cholesterol	- ↑ 3–5%
	Triglycerides	- no effect or increase
Major use	To lower LDL cholesterol	
Contraindications		
▫ **Absolute**	Familial dysbetalipoproteinemia Triglycerides >400 mg/dL	
▫ **Relative**	Triglycerides >200 mg/dL	
Efficacy	Clinical trial evidence of CHD risk reduction	
Safety	Clinical trial evidence of lack of systemic toxicity; GI side effects common	
Major side/adverse effects	Upper and lower gastrointestinal complaints common Decrease absorption of other drugs	
Usual daily dose	Cholestyramine	- 4–16g
	Colestipol	- 5–20g
	Colesevelam	- 2.6–3.8g
Maximum daily dose	Cholestyramine	- 24g
	Colestipol	- 30g
	Colesevelam	- 4.4g
Available preparations	Cholestyramine	- 9g packets (4g drug) - 378g bulk
	Cholestyramine "light"	- 5g packets (4g drug) - 210g bulk
	Colestipol	- 5g packets (5g drug) - 450g bulk - 1g tablets
	Colesevelam	- 625 mg tablets

moderate dose of a sequestrant to a statin can further lower LDL cholesterol by 12–16 percent.[839-841] Thus, sequestrants are useful in combined drug therapy with statins. Further, sequestrants combined with plant stanol esters apparently enhance LDL lowering.[842,843] Thus, sequestrants in combination with TLC, including other dietary options for lowering LDL cholesterol (plant stanols/sterols and viscous fiber), should enable many persons to achieve their LDL-cholesterol goal without the need for an agent that is systemically absorbed.

Since sequestrants tend to raise serum triglycerides, they are contraindicated as monotherapy in persons with high triglycerides (>400 mg/dL) and in familial dysbetalipoproteinemia.[844] They generally should be used as monotherapy only in persons with triglyceride levels of <200 mg/dL. Bile acid sequestrants are not contradicted in patients with type 2 diabetes.[845]

Sequestrant therapy can produce a variety of gastrointestinal symptoms, including constipation, abdominal pain, bloating, fullness, nausea, and flatulence.[12] These symptoms often can be lessened by moderate doses of standard sequestrants or use of colesevelam. Sequestrants are not absorbed from the intestine, but can decrease the absorption of a number of drugs that are administered concomitantly. The general recommendation is that other drugs should be taken either an hour before or 4 hours after administration of the sequestrant. Colesevelam, which apparently does not decrease absorption of co-administered drugs, need not be administered separately from other drugs.

Evidence statements: Bile acid sequestrants produce moderate reductions in LDL cholesterol (A1). Sequestrant therapy reduces risk for CHD (A1). They are additive in LDL-cholesterol lowering in combination with other cholesterol-lowering drugs (C1). They lack systemic toxicity (A1).

Recommendation: Bile acid sequestrants should be considered as LDL-lowering therapy for persons with moderate elevations in LDL cholesterol, for younger persons with elevated LDL cholesterol, for women with elevated LDL cholesterol who are considering pregnancy, for persons needing only modest reductions in LDL cholesterol to achieve target goals, and for combination therapy with statins in persons with very high LDL-cholesterol levels.

3) Nicotinic acid

This drug is summarized in Table VI.2–3. Nicotinic acid or niacin favorably affects all lipids and lipoproteins when given in pharmacological doses. Nicotinamide, which is sometimes confused with niacin or nicotinic acid, has only vitamin functions and does not affect lipid and lipoprotein levels. Nicotinic acid lowers serum total and LDL-cholesterol and triglyceride levels and also raises HDL-cholesterol levels. Smaller doses often increase HDL-cholesterol levels, but doses of 2–3 g/day are generally required to produce LDL-cholesterol reductions of 15 percent or greater.[87,147,846-849] Nicotinic acid can also lower Lp(a) up to 30 percent with high doses.[283] Whether Lp(a) lowering by nicotinic acid therapy reduces risk for CHD is not known. Nicotinic acid was shown to reduce the risk of recurrent myocardial infarction in the Coronary Drug Project,[141] and total mortality was decreased in a 15-year followup of the persons who had originally received nicotinic acid.[444] Decreased

Table VI.2–3. Summary of Nicotinic Acid

Available drugs	Crystalline nicotinic acid Sustained-release (or timed-release) nicotinic acid Extended-release nicotinic acid (Niaspan®)
Lipid/lipoprotein effects	LDL cholesterol - ↓ 5–25% HDL cholesterol - ↑ 15–35% Triglycerides - ↓ 20–50%
Major use	Useful in most lipid and lipoprotein abnormalities
Contraindications	
▫ **Absolute**	Chronic liver disease, severe gout
▫ **Relative**	Hyperuricemia; high doses in type 2 diabetes
Efficacy	Clinical trial evidence of CHD risk reduction
Safety	Serious long-term side effects rare for crystalline form; serious hepatotoxicity may be more common with sustained-release form
Major side/adverse effects	Flushing, hyperglycemia, hyperuricemia or gout, upper gastrointestinal distress, hepatotoxicity, especially for sustained-release form
Usual daily dose	Crystalline nicotinic acid - 1.5–3g Sustained-release nicotinic acid - 1–2g Extended-release nicotinic acid (Niaspan®) - 1–2g
Maximum daily dose	Crystalline nicotinic acid - 4.5g Sustained-release nicotinic acid - 2g Extended-release nicotinic acid (Niaspan®) - 2g
Available preparations	Many OTC preparations by various manufacturers for both crystalline and sustained-release nicotinic acid. The extended-release preparation (Niaspan®) is a prescription drug.

rates of atherosclerotic progression were also observed in three quantitative angiographic trials: FATS,[158] HATS,[159] and CLAS[157]. In all of these trials, nicotinic acid was combined with other LDL-lowering drugs and effects were compared to placebo.

Many crystalline preparations of nicotinic acid are available without a prescription and are inexpensive. Some preparations and a new formulation, Niaspan®, are available by prescription. Niaspan® is a proprietary extended-release formulation of nicotinic acid; its use is associated with less flushing than occurs with usual crystalline preparations.

Nicotinic acid appears to alter lipid levels by inhibiting lipoprotein synthesis and decreasing the production of VLDL particles by the liver. It inhibits the peripheral mobilization of free fatty acids, reducing hepatic secretion of VLDL.[850,851] It decreases the plasma concentration of triglyceride, VLDL remnants, and IDL;[88,138] and it causes a shift in LDL composition from the small, denser LDL particles to the larger, more buoyant LDL particles.[852] Nicotinic acid also is the most effective lipid-lowering drug for raising HDL levels.[87] The changes in HDL cholesterol and triglyceride concentrations tend to be curvilinear (log-linear); thus, smaller doses of nicotinic acid still produce significant increases in HDL or reductions in triglyceride with fewer side effects. The increases in HDL cholesterol are generally in the range of 15–30 percent,[87] but increases of 40 percent have been noted with very high doses.[846,849,853,854] The sustained-release preparations usually increase HDL cholesterol levels by only 10–15 percent[853,854] with the exception of Niaspan® which retains the HDL-raising potential of the crystalline form. Nicotinic acid typically reduces triglyceride levels by 20 to 35 percent, but reductions of 50 percent have been noted with high doses in hypertriglyceridemic persons.[87,147,846-849] Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.

The degree of LDL-cholesterol lowering by nicotinic acid has varied in different studies. Some studies report little or no change in LDL levels.[87] However, in one carefully controlled study in patients with hypercholesterolemia,[855] reductions in LDL cholesterol of 5 percent, 16 percent, and 23 percent were noted with daily doses of 1.5, 3.0 and 4.5 grams, respectively. Extended-release nicotinic acid (Niaspan®), which is administered as a single bedtime dose, has been shown to reduce LDL cholesterol by 15 percent at 2 g/day.[147,847,853,856] Because many persons cannot tolerate higher doses, nicotinic acid is typically not used primarily to lower LDL levels. Instead, it is generally used in combination with other drugs, especially the statins.[857]

Nicotinic acid therapy can be accompanied by a number of side effects. Flushing of the skin is common with the crystalline form and is intolerable for some persons. However, most persons develop tolerance to the flushing after more prolonged use of the drug. Less severe flushing generally occurs when the drug is taken during or after meals, or if aspirin is administered prior to drug ingestion. A newer preparation, Niaspan®, is reported to cause less flushing than crystalline nicotinic acid. A variety of gastrointestinal symptoms, including nausea, dyspepsia, flatulence, vomiting, diarrhea, and activation of peptic ulcer may occur. Three other major adverse effects include hepatotoxicity, hyperuricemia and gout, and hyperglycemia. The risk of all three is increased with higher doses, especially at doses of 2g or higher. The risk of hepatotoxicity appears to be greater with the sustained-release preparations, although not with Niaspan®. Impending hepatotoxicity should be considered if there is a dramatic reduction in plasma lipids.[858] Nicotinic acid reduces insulin sensitivity, and higher doses (>3 g/day) often worsen hyperglycemia in persons with type 2 diabetes.[859] Recent studies suggest that lower doses do not unduly worsen hyperglycemia.[860,861] Other adverse effects include conjunctivitis, nasal stuffiness, acanthosis nigricans, ichthyosis, and retinal edema (toxic amblyopia).

Nicotinic acid is usually administered in two or three doses a day, with the exception of Niaspan®, which is administered as a single dose at bedtime. Crystalline nicotinic acid is the least expensive drug, and small doses are especially useful for increasing HDL-cholesterol levels or lowering triglycerides. The timed-release (sustained-release) preparations are designed to minimize cutaneous flushing. When switching from crystalline nicotinic acid to a sustained-release preparation, smaller doses should be used to reduce the risk of hepatotoxicity. The dose can then be carefully titrated upward, generally to a level not exceeding 2 g/day. Rare cases of fulminant hepatitis have been reported with sustained-release preparations.[862-864] Considerable

variation exists among different sustained-release preparations, and persons should be advised not to switch from one preparation to another. Niaspan® is an extended-release preparation; however, its more rapid-release than sustained-release preparation appears to reduce the risk of hepatotoxicity. Niaspan® also is associated with less flushing than with crystalline nicotinic acid. Since many nicotinic acid preparations are available without a prescription, persons should be instructed that nicotinic acid is associated with many severe adverse effects and regular monitoring by a health professional is essential.

Although nicotinic acid can be highly efficacious and favorably modify the lipoprotein profile, especially in patients with atherogenic dyslipidemia, its long-term use is limited for many patients by side effects.[865] For this reason, the drug is generally reserved for patients at higher short-term risk, i.e., for those with CHD, CHD risk equivalents, or multiple (2+) risk factors with 10-year risk for CHD of 10–20 percent. Its use for long-term prevention of CHD in persons with 10-year risk <10 percent is not well established, and in such persons, should be used more cautiously. For example, it is not known whether long-term use of nicotinic acid for lower-risk persons with isolated low HDL cholesterol is beneficial.

Evidence statements: Nicotinic acid effectively modifies atherogenic dyslipidemia by reducing TGRLP, raising HDL cholesterol, and transforming small LDL into normal-sized LDL (C1). Among lipid-lowering agents, nicotinic acid is the most effective HDL-raising drug (C1). Nicotinic acid usually causes a moderate reduction in LDL-cholesterol levels (C1), and it is the most effective drug for reducing Lp(a) levels (C1).

Evidence statements: Nicotinic acid therapy is commonly accompanied by a variety of side effects, including flushing and itching of the skin, gastrointestinal distress, glucose intolerance, hepatotoxicity, hyperuricemia, and other rarer side effects (C1). Hepatotoxicity is more common with sustained-release preparations (D1).

Evidence statement: Nicotinic acid therapy produces a moderate reduction in CHD risk, either when used alone or in combination with other lipid-lowering drugs (A2, B2).

Recommendation: Nicotinic acid should be considered as a therapeutic option for higher-risk persons with atherogenic dyslipidemia. It should be considered as a single agent in higher-risk persons with atherogenic dyslipidemia who do not have a substantial increase in LDL-cholesterol levels, and in combination therapy with other cholesterol-lowering drugs in higher-risk persons with atherogenic dyslipidemia combined with elevated LDL-cholesterol levels.

Recommendation: Nicotinic acid should be used with caution in persons with active liver disease, recent peptic ulcer, hyperuricemia and gout, and type 2 diabetes. High doses of nicotinic acid (>3 g/day) generally should be avoided in persons with type 2 diabetes, although lower doses may effectively treat diabetic dyslipidemia without significantly worsening hyperglycemia.

4) Fibric acid derivatives (fibrates): gemfibrozil, fenofibrate, clofibrate

These drugs are summarized in Table VI.2–4. There are three fibrates—gemfibrozil, fenofibrate, and clofibrate—currently available in the United States. Other fibrate preparations, including bezafibrate and ciprofibrate, are available outside the United States. The fibrates are primarily used for lowering triglycerides because the LDL-cholesterol-lowering effects of gemfibrozil and clofibrate are generally in the range of 10 percent or less in persons with primary hypercholesterolemia. Only slight changes in LDL cholesterol are noted in persons with combined hyperlipidemia, and LDL-cholesterol levels generally rise on fibrate therapy in persons with hypertriglyceridemia.[866,867] Fenofibrate frequently reduces LDL-cholesterol levels by 15 to 20 percent when triglycerides are not elevated; other fibrates not available in the United States are also more effective in lowering LDL cholesterol.[868-870] Therapy with clofibrate and gemfibrozil reduced risk of fatal and non-fatal myocardial infarction in two large primary prevention trials,[139,149] and gemfibrozil therapy reduced CHD death and non-fatal myocardial infarction and stroke in a recently reported secondary prevention trial.[48] However, this beneficial effect on cardiovascular outcomes has not been observed in all large fibrate trials.[141,153]

Table VI.2–4. Summary of Fibric-Acid Derivatives

Available drugs	Gemfibrozil, fenofibrate, clofibrate	
Lipid/lipoprotein effects	LDL cholesterol	- ↓ 5–20% (in nonhypertriglyceridemic persons); may be increased in hypertriglyceridemic persons
	HDL cholesterol	- ↑ 10–35% (more in severe hypertriglyceridemia)
	Triglycerides	- ↓ 20–50%
Major uses	Hypertriglyceridemia, atherogenic dyslipidemia	
Contraindications	Severe hepatic or renal insufficiency	
Efficacy	Clinical trials indicate a moderate reduction in CHD risk	
Safety	Serious side effects seemingly do not occur in the long term, although early studies suggested an increase in non-CHD mortality	
Major side/adverse effects	Dyspepsia, various upper gastrointestinal complaints, cholesterol gallstones, myopathy	
Usual daily dose	Gemfibrozil	- 600 mg bid
	Fenofibrate	- 200 mg daily
	Clofibrate	- 1000 mg bid
Maximum daily dose	Gemfibrozil	- 1200 mg
	Fenofibrate	- 200 mg
	Clofibrate	- 2000 mg
Available preparations	Gemfibrozil	- 600 mg tablets
	Fenofibrate	- 67 and 200 mg tablets
	Clofibrate	- 500 mg capsules

There has been some concern about the short-term safety of the fibrates. Although nonfatal myocardial infarction fell by 25 percent in the WHO Clofibrate Study, a primary prevention study, total mortality was significantly higher in the clofibrate group, due to an increase in non-CHD deaths.[149] The use of clofibrate in general medical practice decreased markedly after this study. The Helsinki Heart Study, a primary prevention trial employing gemfibrozil, demonstrated a 37 percent reduction in fatal and non-fatal myocardial infarctions and no change in total mortality during the course of the study.[139] After 8.5–10 years of followup, non-cardiac death and all cause mortality were numerically higher in the group that had received gemfibrozil during the study.[412] However, this increase was *not* statistically significant. Moreover, after 10 years of followup, no difference in cancer rates was observed between those who had received gemfibrozil or placebo. In the Veterans Administration HDL Intervention Trial (VA-HIT),[48] a secondary prevention trial, gemfibrozil therapy reduced risk for CHD death and nonfatal myocardial infarction by 22 percent; stroke rates also were reduced by gemfibrozil therapy. In this study, there was no suggestion of an increased risk of non-CHD mortality. Neither was there an increase in non-CHD mortality from fibrate therapy in the recently reported Bezafibrate Infarction Prevention (BIP) study.[153] Furthermore, worldwide clinical experience with various fibrates is vast. No evidence of specific toxicity that enhances non-CHD mortality has emerged. This experience, taken in the light of all the clinical trials, provides little support for the concern that fibrates carry significant short-term toxicity that precludes their use for appropriately selected persons.

The mechanism of action of the fibrates is complex and there may be some variation among the drugs in this class. Recent research shows fibrates to be agonists for the nuclear transcription factor *peroxisome proliferator-activated receptor-alpha (PPAR-alpha).*[871] Through this mechanism, fibrates downregulate the apolipoprotein C-III gene and upregulate genes for apolipoprotein A-I, fatty acid transport protein, fatty acid oxidation, and possibly lipoprotein lipase.[872] Its effects on

lipoprotein lipase and apolipoprotein C-III (an inhibitor of lipoprotein lipase) enhance the catabolism of TGRLP, whereas increased fatty acid oxidation reduces formation of VLDL triglycerides. These effects account for serum triglyceride lowering, which is the major action of fibrates. Serum triglyceride lowering combined with increased synthesis of apolipoprotein A-I and A-II tend to raise HDL-cholesterol levels.[873] Triglyceride lowering also transforms small, dense LDL into normal-sized LDL.[874] The effect of PPAR activity on other atherogenic mechanisms is now being evaluated.[875,876]

The fibrates typically reduce triglyceride by 25–50 percent; the greater reductions generally occur in severely hypertriglyceridemic individuals.[867] Fibrates usually raise HDL cholesterol by 10–15 percent, but greater increases can occur in persons with very high triglyceride levels and very low HDL-cholesterol levels. Thus fibrates, like nicotinic acid, primarily target atherogenic dyslipidemia. In addition, the ability of fibrates to lower triglycerides has led to their wide usage in persons having very high triglyceride levels and chylomicronemia.[867] The purpose of fibrate therapy in such persons is to reduce the risk for acute pancreatitis. Their value for this purpose is well recognized. Finally, fibrates are highly effective for reducing beta-VLDL concentrations in persons with dysbetalipoproteinemia.[877]

Whether fibrate modification of atherogenic dyslipidemia reduces risk for CHD is an important issue. Results of clinical trials with fibrates are summarized in Tables II.3–3 and II.3–4. The major primary prevention trials were the WHO clofibrate trial and the Helsinki Heart Study gemfibrozil trial.[139,149] In both trials, CHD incidence was significantly reduced by fibrate therapy. Early secondary prevention trials with clofibrate therapy gave suggestive evidence of CHD risk reduction. In another secondary prevention trial, the Coronary Drug Project, clofibrate therapy failed to significantly reduce risk for CHD.[141] Likewise, in the BIP trial, bezafibrate therapy did not significantly reduce recurrent major coronary events in persons with established CHD.[153] In contrast, gemfibrozil therapy in the VA-HIT[48] trial showed wide benefit by significantly reducing CHD events and strokes in persons with established CHD (Table II.3–4 and Table II.8–3b). Thus, taken as a whole, clinical trials of fibrate therapy strongly suggest a reduction in CHD incidence, although results are less robust than with statin therapy. Further, a reduction in total mortality, which would have required a greater reduction in CHD mortality than observed, has not been demonstrated with fibrate therapy (see Table II.9–1). This failure does not rule out a benefit of fibrate therapy but certainly suggests less efficacy than with statin therapy.

Several studies have employed fibrates in combination with LDL-lowering drugs in persons with combined hyperlipidemia (elevated LDL + atherogenic dyslipidemia). Combination therapy improves the overall lipoprotein profile compared to either fibrates or LDL-lowering drugs alone. This finding has led to a movement for considering use of fibrates in combination with statins in high-risk individuals whose triglyceride levels are still elevated. In some persons, this combination may better achieve the secondary target for non-HDL cholesterol than will statins alone. Nonetheless, to date no clinical trials have been published that compare statins vs. statins + fibrates on CHD outcomes.

The fibrates are generally well-tolerated in most persons. Gastrointestinal complaints are the most common complaints. All drugs in this class appear to increase the lithogenicity of bile, increasing the likelihood of cholesterol gallstones.[878] A portion of the excess deaths reported in the WHO Clofibrate Study was related to gallstone disease.[879] The fibrates bind strongly to serum albumin and so may displace other drugs that bind with albumin. For example, fibrates displace warfarin from its albumin-binding sites, thereby increasing the latter's anticoagulant effect. Fibrates are excreted primarily by the kidney; consequently, elevated serum levels occur in persons with renal failure and risk for myopathy is greatly increased. The combination of a fibrate with a statin also increases the risk for myopathy, which can lead to rhabdomyolysis.[823,880] None of these well-established side effects can account for the increased total mortality observed in the WHO clofibrate study.[881,882] The increase in non-CHD deaths remains unexplained. An increase in non-CHD mortality has not been confirmed by subsequent trials with fibrate therapy.

Evidence statements: Fibrates are effective for modifying atherogenic dyslipidemia, and particularly for lowering serum triglycerides (C1). They produce moderate elevations of HDL cholesterol (C1). Fibrates also are effective for treatment of dysbetalipoproteinemia (elevated beta-VLDL) (C1). They also can produce some lowering of LDL, the degree of which may vary among different fibrate preparations (C1). Fibrates also can be combined with LDL-lowering drugs in treatment of combined hyperlipidemia to improve the lipoprotein profile, although there is no clinical-trial evidence of efficacy for CHD risk reduction with combined drug therapy (C1, D1).

Evidence statements: Fibrate therapy moderately reduces risk for CHD (A2, B1). It may also reduce risk for stroke in secondary prevention (A2).

Evidence statements: Evidence for an increase in total mortality due to an increased non-CHD mortality, observed in the first large primary prevention trial with clofibrate, has not been substantiated in subsequent primary or secondary prevention trials with other fibrates (gemfibrozil or bezafibrate) (A2, B1). Nonetheless, fibrates have the potential to produce some side effects. Fibrate therapy alone carries an increased risk for cholesterol gallstones (A2), and the combination of fibrate and statin imparts an increased risk for myopathy (B2).

Recommendations: Fibrates can be recommended for persons with very high triglycerides to reduce risk for acute pancreatitis. They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-VLDL). Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL cholesterol and atherogenic dyslipidemia. They also should be considered in combination with statin therapy in persons who have elevated LDL cholesterol and atherogenic dyslipidemia.

c. Other drugs

Probucol is no longer available in the United States and in most other countries. This drug has powerful antioxidant properties, which is theoretically beneficial. In one angiographic trial, probucol therapy failed to retard femoral atherogenesis; neither was a reduction in CHD risk observed. There is some current interest in reports that probucol reduced the restenosis rates following angioplasty.[883,884]

d. n-3 (omega) fatty acids

n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum triglycerides by reducing hepatic secretion of triglyceride-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3–12 g/day have been used depending on tolerance and severity of hypertriglyceridemia.

Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD (see Section V.3.c). Although this usage falls outside the realm of "cholesterol management," the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. The n-3 fatty acids can be derived from either foods (n-3 rich vegetable oils or fatty fish) or from fish-oil supplements. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

e. Hormone replacement therapy (HRT)

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature.[885-887] Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either

Table VI.2–5. Major Characteristics and Outcomes of HERS Trial

Patient Characteristics	Study Design	Clinical Outcomes (E+P vs. Placebo)	Side Effects
2,763 postmenopausal women	Randomized, double-blind	CHD events 172 vs. 176	Thromboembolic events (E+P ≥ placebo)
Age <80 years (mean age 67 years)	Placebo vs. 0.625 mg of conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate (E+P)	CHD death 71 vs. 58	Gallbladder disease (E+P ≥ placebo)
History of CHD	Duration: 4.1 years	Non-fatal MI 116 vs. 129	
Absent hysterectomy			
BMI >27 kg/m2			
45% on lipid-lowering drugs at entry			

estrogen alone, or in combination with progestin, reduces risk for CHD in primary and secondary prevention. However, benefit of estrogen replacement was not confirmed in a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS).[493] A subsequent angiographic study also revealed no apparent benefit from HRT.[888] The major features of the HERS trial are shown in Table VI.2–5.

As shown in the table, estrogen/progestin replacement produced no overall benefit for the entire duration of the trial. Moreover, both CHD death and non-fatal myocardial infarction were increased, especially during the first year. Estrogen/progestin (E+P) replacement increased risk for thromboembolic events and caused more gallbladder disease.[493,889] Thus, E+P produced no overall benefit for the entire study and increased risk for CHD events, thromboembolic events, and gallbladder disease in the early phase of the trial. There was a suggestion, however, that E+P reduced non-fatal myocardial infarction in the latter years of the trial. A 3-year followup study is currently in progress. The overall interpretation of the trial by the investigators was that HRT should not be initiated in postmenopausal women with CHD for the purpose of reducing risk of CHD, but if women had already been on HRT for a period of time, they could continue, with the expectation that there may be some later benefit. The mechanism for the early increase in CHD events and increased thromboembolic events has not been clearly defined, but it appears that E+P administration was associated with a prothrombotic tendency.

Estrogen therapy favorably influences lipid and lipoprotein levels, but this did not translate into a reduction in CHD risk in the HERS trial. In postmenopausal women, orally administered estrogen preparations (0.625 mg of conjugated estrogen or 2 mg of micronized estradiol) reduce LDL-cholesterol levels by 10–15 percent and increase HDL-cholesterol levels up to 15 percent.[890-892] Co-administration of progestin may decrease the HDL-cholesterol-raising effect of estrogen. In the HERS trial, the mean difference between E+P minus placebo was an 11 percent decrease in LDL cholesterol, a 10 percent increase in HDL cholesterol and an 8 percent increase in triglycerides.

There is no definitive explanation for why the epidemiologic/observational studies provided markedly different results from the HERS trial. The HERS trial clearly demonstrates the need for controlled clinical trials. Some investigators postulate that if lower doses of estrogen, different progestins, younger age group, estrogen only, or women without CHD had been employed, the results may have been different. The NHLBI Women's Health Initiative is utilizing the same hormonal preparation in a wide range of ages in an estrogen-only and in an estrogen/progestin group in women without CHD.[683] This trial may answer some of the questions, but the results will probably not be available before 2003. There is also a possibility of an increased risk of breast cancer with prolonged HRT.[893-897]

Evidence statements: Hormone replacement therapy in postmenopausal women does not reduce risk for major CHD events or coronary deaths in secondary prevention (A2). Moreover, hormone replacement therapy carries an increased risk for thromboembolism and gallbladder disease (A2).

Recommendation: Hormonal replacement therapy cannot be recommended for the express purpose of preventing CHD. Instead, control of risk factors should be the primary approach to reducing CHD risk in women. There may be other valid reasons for hormonal replacement therapy, such as for management of perimenopausal and postmenopausal symptoms or for treatment or prevention of osteoporosis.

1) Selective estrogen receptor modulators (SERM)—Raloxifene

A number of SERMs are under development. Raloxifene imparts benefits similar to those of HRT on bone density in postmenopausal women. Raloxifene also has an LDL-cholesterol-lowering effect similar to that of estrogen, but the HDL-raising effect appears to be less.[898] Clinical trials to evaluate its effect on CHD risk are underway. Again, until controlled clinical trials are available that demonstrate a reduction in CHD risk, this class of drugs should not be considered for the purpose of CHD prevention. SERMs also increase the risk of thromboembolic events.

f. Miscellaneous drugs and therapeutic approaches

1) Investigational drugs

Many new cholesterol-lowering drugs with a wide range of mechanistic actions are currently in various phases of development. It is still too early to predict which drugs will be approved by the FDA and what their long-term toxicities may be. They will also have the near-term disadvantage of lacking clinical trials documenting a reduction in CHD clinical events.

2) Other approaches

With the advent of statins, effective control of LDL-cholesterol levels can now be achieved in the majority of persons with either monotherapy or drug combinations. Persons with severe forms of hypercholesterolemia or other hyperlipidemias who cannot be adequately controlled should be referred to a center specializing in lipid disorders. LDL apheresis is now available for persons with very high LDL levels, but the procedure is costly and time-consuming. The FDA recently approved two commercial techniques for this purpose: (1) a heparin-induced extracorporeal lipoprotein precipitation, and (2) a dextran sulfate cellulose adsorbent for removal of lipoproteins.

3. Selection of drugs for elevated LDL cholesterol

Reduction in serum concentrations of LDL cholesterol is the primary approach to lowering the risk of CHD in both primary and secondary prevention. In persons whose triglycerides are elevated along with LDL cholesterol, it may also be desirable to lower triglycerides and increase HDL-cholesterol concentrations. Several factors influence the selection of initial drug therapy in individual persons. These include the lipoprotein profile and magnitude of change needed to attain goals of therapy, concurrent drug therapies that may increase the risk of side effects with specific drugs, and the presence of other medical disorders that may influence drug metabolism or be adversely influenced by a specific hypolipidemic drug.

Statins are the most effective class of drugs for reducing LDL-cholesterol concentrations: they are well tolerated, easy to administer, and they are usually the first drugs used. Five statins (lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin) are approved for clinical use in the United States.* Available statins differ somewhat in the degree of LDL-cholesterol lowering that can be achieved per mg dose. In addition, the metabolic clearance of these drugs also vary. Simvastatin and lovastatin undergo metabolic inactivation by the 3A4 isozyme of cytochrome P-450 (CYP 3A4); atorvastatin is also a substrate for CYP 3Y4, though some of its metabolites remain active; and fluvastatin is metabolized by CYP 2C9. Pravastatin appears not to be metabolized by the P-450 system. These differences can have implications for drug-drug interactions, particularly where the concern is myopathy related to elevated systemic levels of the statin. Statins vary in the dose required to produce a given degree of LDL lowering. Whether different doses that

* Cerivastatin was withdrawn from the market by the manufacturer in August, 2001.

produce the same degree of LDL lowering differ in side effect profiles is unknown because of a lack of direct comparison studies. For all statins, the incidence of side effects increases with higher doses. The degree of LDL lowering that is required to achieve target goals and the percent of LDL lowering that is seen with the usual starting dose and maximum dose of the statins are illustrated in Table VI.3–1. In general, for every doubling of the dose of a statin, LDL levels fall by approximately 6 percent.

The dose of statin required to achieve target goals can be extrapolated from Table VI.3–1. However, the response of an individual may vary considerably and cannot be predicted. The LDL response may be influenced by a number of factors, including diet and drug compliance, the genetic cause of hypercholesterolemia, gender and hormonal status, apo E phenotype, and differences in drug absorption and metabolism. There is a tendency in current clinical practice to initiate therapy with the usual starting dose, but the dose often is not titrated upwards to achieve target goals. Persons requiring large LDL reductions will never achieve target goals with the starting dose of some statins. Since the absolute incidence rates of side effects are not much greater at higher doses of currently available preparations, persons requiring major LDL-cholesterol lowering should be started on doses (or their equivalents) used in most clinical trials. Doses can then be increased as needed to achieve the recommended LDL goal. Alternatively, a second LDL-lowering drug (e.g., bile acid sequestrant or nicotinic acid) can be added to standard doses of statin.

Table VI.3–1. Achieving Target LDL-Cholesterol (LDL-C) Goals (mg/dL)

Baseline LDL-C	130	160	190	220
	(Percent Reduction to Achieve Target Goals)			
Target LDL-C <100	23	38	47	55
Target LDL-C <130	—	19	32	41
Target LDL-C <160	—	—	16	27

Average Percent Reduction in LDL Cholesterol With Usual Starting Dose and Maximal Statin Dose*

		Starting Dose	Maximum Dose
Lovastatin	20, 80 mg	24%	40%†
Pravastatin	20, 80 mg	24%	34%†
Simvastatin	20, 80 mg	35%	46%
Fluvastatin	20, 80 mg	18%	31%
Atorvastatin	10, 80 mg	37%	57%

* Maximum dose currently approved by the FDA.
† Administered in divided doses.

The bile acid sequestrants are the second most effective class of drugs for lowering LDL-cholesterol levels. They are particularly useful in combination with statins to achieve major reductions in LDL-cholesterol levels. They can either be added to a statin when maximal doses of statin have not achieved target goals, or they can be added to lower doses of statin if there are concerns about the tolerability and side effects of higher doses. Cholestyramine (8–16 g/day) or colestipol (10–20 g/day) usually produce 10–20 percent reductions in LDL cholesterol when administered as monotherapy, and colesevelam lowers LDL cholesterol by 12–18 percent. Similar reductions in LDL cholesterol are noted when the sequestrants are added to low doses of statins, but the additional LDL-cholesterol lowering is less when added to statins given at higher doses. For purposes of drug safety, bile acid sequestrants can be considered as monotherapy in younger persons, women considering pregnancy, and when only modest LDL lowering is needed.

The LDL-cholesterol-lowering effects of nicotinic acid are usually modest and can be quite variable. Reductions in LDL of 5–23 percent have been noted with doses of 1.5–4.5g of crystalline nicotinic acid and 10–20 percent at 2.0–3.0g of Niaspan®.[147,856,899,900] Nicotinic acid should be considered if additional LDL-cholesterol lowering is required after statin administration, especially in persons who do not tolerate sequestrants or who prefer to take medication in tablet form. Nicotinic acid is also considered if, in addition to LDL-cholesterol lowering, increases in HDL cholesterol and decreases in triglycerides and Lp(a) are needed.

The fibrates usually do not significantly enhance LDL-cholesterol lowering when added to a statin. However, if a patient is not at LDL target level and has not tolerated a bile acid sequestrant or nicotinic acid, addition of fenofibrate may enhance LDL lowering in some patients;[901] it may also be useful if the patient has concomitant atherogenic dyslipidemia.[902]

The use of drugs for treatment of other forms of dyslipidemia (severe hypercholesterolemias, isolated low HDL, hypertriglyceridemias, diabetic dyslipidemia, and other secondary forms of hyperlipidemia) are considered in Section VII.

a. Practical advice on combined drug therapy

Some persons will require combined drug therapy to reach ATP III treatment goals. Combination therapy may be needed to provide additional reduction of LDL cholesterol, to achieve the goal for non-HDL cholesterol, to treat severe hypertriglyceridemia, and if it seems advisable, to raise HDL-cholesterol levels. Although it seems desirable to improve the overall lipoprotein profile with combined drug therapy, major randomized controlled trials have not been carried out to test for efficacy and safety in large numbers of persons. Nonetheless, several smaller trials and angiographic trials have provided evidence of positive benefit from combined drug therapy.

1) Statin—bile acid sequestrant combination

In the majority of persons who are treated with a statin, the LDL-cholesterol goal can be reached. However, in persons with severe polygenic or familial hypercholesterolemia, a statin alone may not be enough. In these cases, combination therapy with a bile acid sequestrant or nicotinic acid added to the statin, or a sequestrant-nicotinic acid combination, should be considered for additional LDL-cholesterol lowering. Of these, the statin-sequestrant combination may be the most effective, reducing LDL cholesterol by as much as 70 percent. The alternative combinations are generally less effective.

Following are practical considerations when utilizing statins and sequestrants in combination.

- The dose of the sequestrant in the statin-sequestrant combination can be low or moderate. Higher doses do not appear to add signficiantly to LDL-cholesterol-lowering efficacy.[903-905]
- Since the statin-sequestrant combination may more effectively lower LDL than a maximum dose of statin, consideration should be given to use of a combination approach early in the course of treating persons with very high LDL-cholesterol levels.[841,905]
- The LDL-cholesterol lowering achieved with the statin-sequestrant combination appears to have a ceiling beyond which there is little if any additional LDL lowering even if the statin or sequestrant doses are further increased. In these cases, consideration can be given to adding a third agent, such as nicotinic acid. Bile acid sequestrants will reduce the bioavailability, but not the LDL-lowering action, of the statin when administered together. Thus, the drugs may be given together. However, it is probably best to give the statin at night (bedtime) and the sequestrant with each meal. It is not necessary to separate the time of administration of colesevelam and statins.
- If the statin-sequestrant combination is not successful in achieving the LDL-cholesterol goal, addition of nicotinic acid to the combination can be considered.[467] Studies have shown that the use of Niaspan® provides equivalent effect on lipid parameters and is better tolerated than immediate release of nicotinic acid.[863]

2) Statin—fibrate combination therapy

The combination of statins and fibrates has proven to be highly effective for improvement of the lipoprotein profile in patients with combined hyperlipidemia.[902,906-908] It also may be useful for patients with elevated LDL cholesterol and atherogenic dyslipidemia. A statin + fibrate can reduce both LDL cholesterol and VLDL cholesterol (i.e., non-HDL cholesterol) in patients with elevated triglycerides. Since the primary aim of cholesterol management is LDL reduction, statin therapy usually will be introduced before fibrates. In some patients with high triglycerides, both LDL and non-HDL goals can be attained with higher doses of statins. However, an alternative approach is to use a statin + fibrate. To date no clinical trials have been carried out in patients with hypertriglyceridemia to document the relative value of these two approaches.

The major concern about this combination is the potential for occurrence of myopathy. In the past, this combination was widely thought to be "contraindicated" because of the potential danger of myopathy. More recently, statin-fibrate combination therapy has been used with apparent safety in the majority of persons. It should be noted that the specific combination of cerivastatin and gemfibrozil caused

more clinical myopathy than is noted with other statin drugs. This is one factor that led to the voluntary withdrawl of cerivastatin from the market. Several key points must be kept in mind when using statin-fibrate combination therapy.

- Ensure that the patient has normal renal function.
- Ensure that there are no potential drug interactions that could increase the systemic blood levels of either the statin or fibrate.
- Limit the initial dose of the statin to a starting or intermediate dose when combining it with a fibrate. The dose of statin can then be increased cautiously.
- Teach the patient to recognize and report symptoms of muscle soreness, tenderness, and pain.
- Obtain a creatine kinase (CK) blood level prior to beginning combination therapy to document the patient's baseline level. Repeat this measurement if the patient reports muscle symptoms suggestive of myopathy.
- If the patient experiences muscle soreness, tenderness, or pain, with or without CK elevations, rule out common causes such as exercise or strenuous work. Advise moderation in activity for persons who experience this finding during combination therapy.
- Discontinue combination therapy if a CK greater than ten times the upper limit of normal (ULN) is encountered in a patient with muscle soreness, tenderness, or pain. Wait for symptoms to vanish and CK levels to return to normal before reinitiating therapy with either drug and use a lower dose of the drug(s).

If the patient experiences muscle soreness, tenderness, or pain with either no CK elevation or a moderate elevation (i.e., between three and ten times the upper limit of normal), monitor the patient's symptoms and CK levels until symptoms resolve and the CK returns to normal or until the clinical situation worsens to the point described above, mandating discontinuation of therapy. Following are summary comments reflecting current experience with these issues.

- Although not consistent in the literature, the general terminology used to describe muscle toxicity with these agents includes *myalgia* to reflect muscle symptoms without CK elevations, *myositis* for increased CK levels without muscle symptoms, and *myopathy* for muscle symptoms with CK elevations. Severe myopathy *(rhabdomyolysis)* may subsequently occur. Technically, all of these terms fall under the category of *myopathy*.
- Statin therapy appears to carry a small but definite risk of myopathy when used alone. According to several large databases, the incidence of myopathy is reported to be 0.08 percent with lovastatin and simvastatin.[816,820,909] Elevations of CK greater than ten times the ULN have been reported in 0.09 percent of persons treated with pravastatin. All currently marketed statins appear to have a similar potential for causing this adverse effect.
- Fibrate treatment alone appears to be associated with some risk of muscle toxicity, although probably less than that of statins.
- Of the nearly 600 persons who have participated in controlled clinical trials of a statin and fibrate combination, 1 percent have experienced a CK greater than three times ULN without muscle symptoms and 1 percent have been withdrawn from therapy because of muscle pain.[814,902,910-915] None of these events were considered serious. No cases of rhabdomyolysis or myoglobinuria have been encountered in these clinical trials. The experience in these trials is predominantly with lovastatin and gemfibrozil. Other statin-fibrate combinations may well give similar results. A prior report from FDA surveillance of a 30 percent incidence of myopathy associated with a statin-fibrate combination and a 5 percent incidence of myopathy associated with a statin-nicotinic acid combination appears to be a gross overestimate of the problem.[823]

3) Statin—nicotinic acid combination therapy

This combination is attractive because of the favorable effects of nicotinic acid on atherogenic dyslipidemia. Combining the powerful LDL-lowering action of statins with the triglyceride-lowering and HDL-raising actions of nicotinic acid offers the potential to correct most forms of complex dyslipidemias. The relative inexpensiveness of nicotinic acid also makes for an attractive combination. Several small-scale clinical trials speak to the efficacy of this combination for

modifying an abnormal lipoprotein pattern and even for favorably affecting coronary outcomes.[158] The disadvantages of the combination lie mainly in the side effect profile of nicotinic acid. There is little evidence that the combination is synergistic in producing side effects. Whether the statin-nicotinic acid combination increases the risk for myopathy is uncertain. Some investigators have found that combining relatively small doses of nicotinic acid with a statin produces an improvement in the lipoprotein profile comparable to that obtained with a statin-fibrate combination, and probably with a lower risk for myopathy.[916] This potential advantage, however, may be offset by the inability of some persons to tolerate the side effects of nicotinic acid.

4) Fibrate—nicotinic acid combination therapy

This combination has not been studied extensively, but it is attractive for atherogenic dyslipidemia. In the Stockholm Ischaemic Heart Disease study, a fibrate (clofibrate) + nicotinic acid significantly reduced CHD events in persons with established CHD.[152] Otherwise, it is largely untried.

4. Initiation, monitoring and followup of drug treatment

a. Initiation of LDL-lowering drug therapy

Consideration should be given to starting statin therapy for LDL reduction simultaneously with TLC in persons with CHD or a CHD equivalent who have LDL ≥130 mg/dL (see previous discussion on drug options when LDL-cholesterol levels are in the range of 100–129 mg/dL). Initiation of drug therapy seems especially advisable when the patient is hospitalized for an acute coronary event or intervention. When therapy is begun in this setting, persons have demonstrated a very high adherence rate, presumably because of the associated importance of the treatment in preventing recurring events. Early initiation of statin therapy also takes advantage of effects of LDL lowering on endothelial function and plaque stabilization.

Consideration may also be given to starting statin therapy simultaneously with TLC in primary prevention persons who have marked hypercholesterolemia, where it is clear that diet alone will not reduce the patient's LDL cholesterol to goal.

In all other persons, a period of lifestyle modification should precede initiation of drug therapy. This period should be long enough for persons to integrate TLC into their routine and for the effects of this intervention to be manifest. Generally, no more than 3 months is required.

b. Baseline measurements

Prior to initiating drug therapy, baseline lipid and lipoprotein measurements that will be used to follow the drug's efficacy and safety should be documented. Except for acute hospitalization, the initial lipoprotein profile upon which treatment decisions are based should be the average of two measurements done one to four weeks apart while the patient is consistently following a low-fat diet. Baseline measurements also include liver function tests (i.e., ALT or AST), CK and appropriate medical history. Table VI.4–1 lists selected baseline and followup measures for other lipid-modifying drug therapy.

c. Interval of follow up

With good adherence, maximum LDL lowering, as well as lowering of triglyceride and raising of HDL cholesterol, is achieved within 6 weeks of initiating drug therapy. Thus, the first followup visit should occur 6–8 weeks after initiating drug therapy. In the case of nicotinic acid, where doses must be titrated by the patient to a therapeutic level, the first followup visit should occur 6–8 weeks after the patient has reached the initial targeted dose, generally 1,000–1,500 mg daily. If the dose is increased, monitoring should be continued at 6–8 weeks until the final dose is determined.

If the initial dose of the drug must be increased or another drug added in an effort to reach the treatment goal(s), the patient should be seen in another 6–8 weeks for followup evaluation of the new drug regimen. This process should be repeated until the patient has reached his/her treatment goal(s).

Once the patient has achieved the treatment goal(s), followup intervals may be reduced to every 4–6 months. The primary focus of these visits is encouragement of long-term adherence with therapy. Lipoprotein profiles should be assessed at least annually, and preferably at each clinic visit to promote compliance.

Table VI.4–1. Monitoring Parameters and Followup Schedule

Drug	Monitoring Parameters	Followup Schedule
Bile Acid Sequestrants	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea	Evaluate symptoms initially, and at each followup visit. Also check time of administration with other drugs.
Nicotinic Acid	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash	Evaluate symptoms initially, and at each followup visit.
	Peptic ulcer	Evaluate symptoms initially, then as needed.
	Fasting blood sugar (FBS) Uric acid	Obtain an FBS and uric acid initially, 6–8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia.
	ALT and AST	Obtain an ALT/AST initially, 6–8 weeks after reaching a daily dose of 1,500 mg, 6–8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated.
Statins	Muscle soreness, tenderness or pain	Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each followup visit. Obtain a CK when persons have muscle soreness, tenderness, or pain.
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated.
Fibrates	Abdominal pain, dyspepsia, headache, drowsiness	Evaluate symptoms initially, and at each followup visit.
	Cholelithiasis	Evaluate history and symptoms initially, and then as needed.

d. Followup treatment decisions

Followup visits are used to enhance adherence and to determine whether persons have achieved their treatment goal(s). If they have not, changes in the drug regimen should be made to attempt to reach these goals. In most cases, LDL goals can be achieved by titrating doses of the statin or bile acid sequestrant upward to the maximum recommended dose. This may be done systematically one step at a time. For example, the dose of a statin may be doubled at each visit to achieve an additional 6–7 percent LDL lowering with each dose titration. However, when the difference between the patient's on-treatment LDL cholesterol and his/her goal is great, consideration may be given to making larger changes in the drug dose. Alternatively, another LDL-lowering drug may be added (e.g., adding a bile acid sequestrant to a statin), as described above. If the decision is made to replace a less efficacious statin with a more efficacious one to achieve the LDL goal, one statin may be discontinued and the new statin started the next day. A dose titration scheme for commonly used lipid-modifying drugs is presented in Table VI.3–1.

If a patient has high triglycerides (≥200 mg/dL) the non-HDL-cholesterol goal should be addressed. If the patient was earlier treated with a statin to achieve the LDL goal, increasing its dose beyond that used to reach the LDL goal may assist in reaching the non-HDL-cholesterol goal. In many instances, however, reaching the non-HDL-cholesterol goal will require the addition of a triglyceride-lowering drug such as nicotinic acid or a fibrate to the LDL-lowering drug. Clinical experience suggests that if nicotinic acid is selected, the immediate release and polygel sustained-release dosage form (Niaspan®) should be titrated to 1,000–1,500 mg daily by the patient before a followup assessment visit is scheduled. If needed, immediate release nicotinic acid may be further titrated to 3,000 mg daily. If a fibrate is selected, dose titrations are not needed as the initial dose is also the maximum dose. Followup visits for these assessments may also be scheduled 6–8 weeks apart.

ATTACHMENT 1 (Part 7)

(ATP-III)

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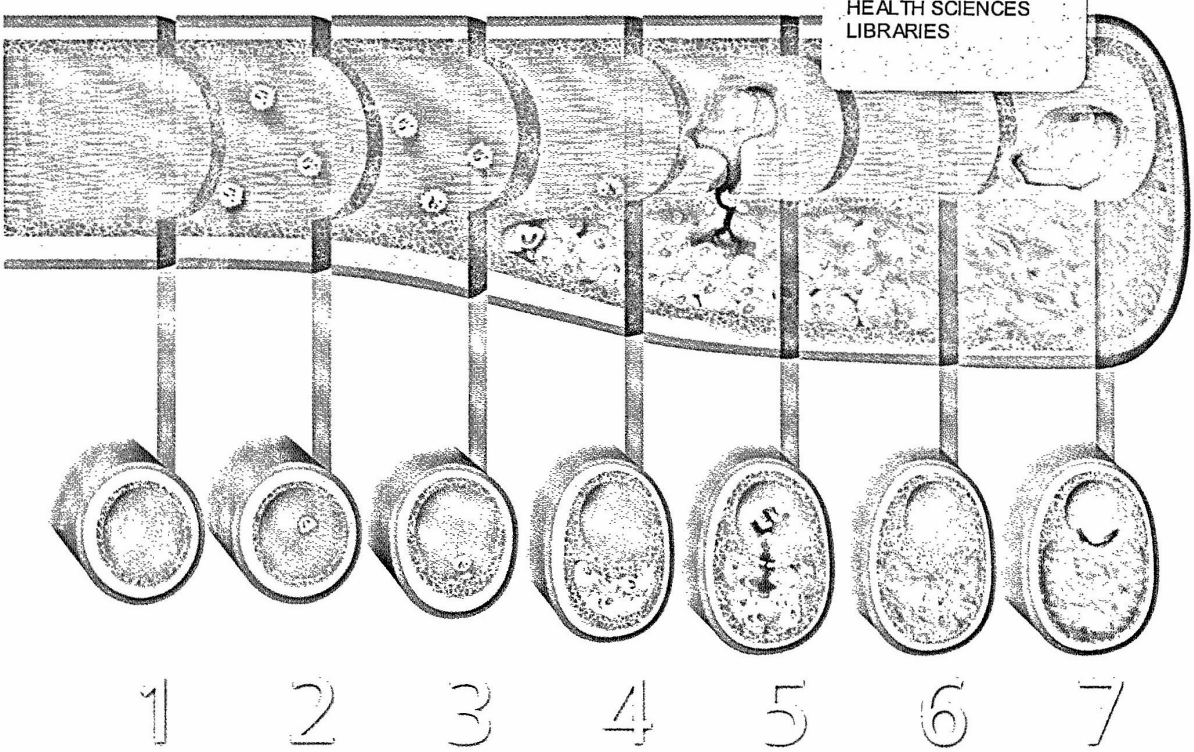

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