**Chapter 3. Epidemiology of Coronary Heart Disease**

TEST BANK

True/False Questions

1. Coronary heart disease causes more than 9 million deaths annually.

1. CHD is nearly always a consequence of longstanding atherosclerosis and the development of atheromatous plaques that occlude the coronary arteries.
2. Annual disability adjusted life years (DALY) due to ischemic heart disease are 2 to 3-fold higher in Russia, India, North Africa, and the Middle East than in the USA, Canada, Western Europe, and Japan.
3. Atherosclerosis progresses in sequential stages of endothelial dysfunction over a period of several *months*.
4. In the *Seven Countries Study*, populations consuming a *Mediterranean diet* had the lowest rates of CHD.
5. Results of the *Framingham Heart Study* confirmed the multifactorial nature of CHD.
6. The international MONICA Project has documented a disturbing increasing trend in obesity worldwide.
7. The five major risk factors for CHD are cigarette smoking, hypertension, elevated cholesterol, type 2 diabetes mellitus, and inflammation.
8. Most studies suggest that serum cholesterol level is a better predictor of impending CHD than C-reactive protein.
9. Multiple CHD risk factors rarely cluster in the same individual.

Answers to True/False Questions

1. T
2. T
3. T
4. F
5. T
6. T
7. T
8. T
9. F
10. F

Multiple Choice Questions

1. Name the famous German pathologist who first postulated that atherosclerosis was due to the deposition of lipid-laden plaques in the lining of arteries.
   1. Nikolai Anitschkow
   2. Rudolph Virchow
   3. Louis Pasteur
   4. Edward Jenner
2. The “response to injury” hypothesis states that atherosclerosis is primarily a consequence of:

a. inflammation.

b. high cholesterol.

c. hypertension.

d. smoking.

1. The “dual hypothesis” of atherogenesis primarily involves what two processes?
   1. Smoking & Hypertension
   2. Hypercholesterolemia & Inflammation
   3. Hypercholesterolemia & Smoking
   4. Inflammation & Smoking
2. What cells are the progenitors of foam cells in atherogenesis?
   1. Leukocytes
   2. Lymphocytes
   3. Macrophages
   4. Endothelial cells
3. Which of the following statements are true?
   1. Results of the *Framingham Study* first demonstrated that high cholesterol increases the risk of CHD.
   2. Results of the *Seven Countries Study* first demonstrated that high cholesterol increases the risk of CHD.
   3. Results of the *Framingham Study* demonstrated significant cardioprotection from consuming a “*Mediterranean diet.*”
   4. Results of the *Seven Countries Study* demonstrated significant cardioprotection from consuming a “*Mediterranean diet.*”
   5. Both a and c are true.
   6. Both b and d are true.
4. Which of the following are risk factors for CHD?
   1. High LDL cholesterol
   2. Low LDL cholesterol
   3. Low HDL cholesterol
   4. High HDL cholesterol
   5. Both a and c are true.
   6. Both b and c are true.
5. Which of the following cholesterol levels characterizes an individual at high risk for developing CHD?
   1. Total cholesterol of 240 mg per dl or higher
   2. LDL cholesterol of 140 mg per dl or higher
   3. HDL cholesterol less than 60 mg per dl
   4. All of the above are correct.
6. High blood pressure increases the risk of CHD by 2 to 3-fold in men and women of all ages. Based upon new guidelines established by the American Heart Association, what are the current threshold levels of blood pressure for high CHD risk?
   1. Systolic Blood Pressure of 140 mm Hg or higher
   2. Diastolic Blood Pressure of 90 mm Hg or higher
   3. Systolic Blood Pressure above 130 mm Hg and Diastolic Blood Pressure above 85 mm Hg
   4. Only a and b are correct.
7. Which of the following statements are true?
   1. Chronic tobacco smoking heightens the CHD mortality by 2 to 3-fold.
   2. Chronic exposure to environmental tobacco smoke heightens the relative risk of CHD by about 25%.
   3. Smoking cessation produces an approximate 50% reduction in CHD risk within two years.
   4. All of the above statements are correct.
8. Which of the following blood levels *do not* increase CHD risk?
   1. Elevated Homocysteine
   2. Elevated APO A1
   3. Elevated APO B
   4. Elevated C Reactive Protein
   5. Elevated Glucose

Answers to Multiple Choice Questions

1. b
2. a
3. c
4. c
5. f
6. e
7. d
8. c
9. d
10. b

Essay Questions

1. Define *coronary heart disease* (*ischemic heart disease*) and characterize its association with atherogenesis.

Answer: *Ischemic Heart Disease/Coronary Heart Disease* refers to a deficiency of blood supply to the heart muscle leading to deprivation of oxygen essential for the proper functioning of the myocardium and related heart tissues and structures. About 98% of the time, ischemic heart disease results from atherosclerosis (atherogenesis), a long-term process leading to the development of lipid-laden plaques within blood vessels of the heart and other organs. Such atherosclerotic plaques can cause stenosis (narrowing) and obstruction of the coronary arteries, and they can also rupture resulting in thrombotic or embolic occlusion of coronary blood vessels. A thrombus refers to the formation of a stationary clot upon rupture of an atherosclerotic plaque within a blood vessel while an embolus refers to a clot that breaks away from its original site of plaque rupture and travels downstream in the blood and occludes a smaller caliber blood vessel.

1. Define and discuss the two theories of atherogenesis.

Answer: Atherosclerosis (atherogenesis) refers to the development of atheromas in the arterial walls of humans and other mammals. Atheromas consist of focal deposits of plaque material that develop just beneath the intima (the endothelial lining) of arteries. These fibrofatty plaques have a lipid core of cholesterol and cholesterol derivatives covered by a fibrous cap of smooth muscle.

Two theories of atherosclerosis have been the subject of longstanding debate among cardiovascular researchers: the “*lipid hypothesis,*” which involves deposition of lipids and cholesterol beneath the endothelial lining of arteries, and the “*response to injury hypothesis,*” which involves sequential recursive inflammation. Nearly 150 years ago, the famous German pathologist Rudolph Virchow postulated that the accumulation of lipids in arteriolar walls causes atherosclerosis and also suggested that the disease process involved *inflammation* stimulated by the abnormal sub-intimal presence of lipids.

The “*dual hypothesis*” is a combination of these two theories in the following sequence of pathogenesis: (1) hypercholesterolemia (in particular, high LDL cholesterol) induces adhesion of leukocytes to the arterial endothelium, (2) circulating monocytes and lymphocytes penetrate into the subendothelial space, (3) oxidized LDL cholesterol accumulates beneath the endothelium, (4) macrophages are attracted to the developing lesion and become engorged with oxidized LDL cholesterol to form “*foam cells,*” (5) the sustained presence of oxidized LDL cholesterol and its derivative forms stimulate a vicious cycle of recursive inflammation involving infiltration by macrophages and other immune cells, (6) focal areas of cell necrosis ensue, and (7) smooth muscle cells grow over the lesion producing a fibrous cap.

1. Discuss current international patterns of CHD mortality and morbidity.

Answer: Of the 18 million deaths caused by cardiovascular disease annually, more than 9 million (approximately 50%) are attributable to ischemic/coronary heart disease. This condition is nearly always a consequence of longstanding atherosclerosis and the development of atheromatous plaques that occlude the coronary arteries. Ischemic heart disease often culminates in myocardial infarction and sudden cardiac death. The global pattern of disability-adjusted years of life (DALY) lost to ischemic heart disease reflects the highest disease burdens in many developing nations of the world including Russia, India, North Africa, and the Middle East. By comparison, lower DALY values are observed in developed nations such as the USA, Canada, Western Europe, Japan, and Australia/New Zealand where improvements in the healthcare system have produced declines in the mortality and morbidity from ischemic heart disease.

1. Discuss key findings of the three major prospective studies of CHD: the *Seven Countries Study*, the *Framingham Study,* and *MONICA*.

Answer: The *Seven Countries Study* conducted by Ancel Keys and colleagues examined the effects of diet in an international prospective cohort of 12,763 men, aged 40 to 59 years, in sixteen population samples from seven different countries (Italy, Greece, former Yugoslavia, the Netherlands, Finland, United States, and Japan). The study was the first to demonstrate that serum cholesterol is a biomarker of impending coronary heart disease and that the risk increases with intake of saturated fats and decreases with intake of monounsaturated fatty acids (primarily from olive oil). Risk increases were also associated with elevated blood pressure (hypertension), cigarette smoking, sedentary lifestyle, and obesity.

Since 1948, investigators at Harvard University have been following generations of the residents of Framingham, Massachusetts, to better understand the determinants of heart disease. The initial cohort consisted of 5,209 randomly selected members of the adult population of Framingham, 30 to 62 years of age, who were enrolled for study in 1948. The ongoing study now includes a second generation of 5,124 men and women (offspring of the original cohort), a third generation of 4,095 men and women, and a new spouse cohort that is currently enrolling subjects. While there have been many research milestones, perhaps the most important finding from the Framingham Study is that coronary heart disease is multifactorial involving both independent effects as well as synergistic interactions of a number of major risk factors including cigarette smoking, hypercholesterolemia, type 2 diabetes mellitus, hypertension, sedentary lifestyle, obesity, dietary factors, and genetic factors.

The *MONICA Project* (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) was initiated during the 1980s by the World Health Organization in order to monitor the diverse international trends in mortality from cardiovascular disease and changes in major CVD risk factors in selected populations. Results suggest that the age-adjusted mortality from coronary heart disease is decreasing due to reduced rates of hypertension, cigarette smoking, and hypercholesterolemia. Nevertheless, the data reflect a disturbing upward trend in the overall prevalence of obesity in recent decades.

1. Document known risk factors for CHD and chemopreventive agents.

Answer: Major risk factors for ischemic heart disease include cigarette smoking, hypertension, elevated cholesterol, type 2 diabetes mellitus, and elevated C-reactive protein (which appears to be a valid measure of vascular inflammation).

In addition to the epidemiologic investigations that initially established elevated blood cholesterol (*hypercholesterolemia*) as a risk factor for coronary heart disease, the results of many large clinical trials have provided definitive evidence that reducing cholesterol either by non-pharmacologic methods or by pharmaceutical medications (*statins*) leads to a significant reduction in the risk.

It is well known that elevated blood pressure (*hypertension*) increases the risk of developing ischemic/coronary heart disease.

*Cigarette smoking* is not only the dominant cause of lung cancer, chronic bronchitis, and emphysema, but addiction to the smoking habit is also one of the major causes of ischemic/coronary heart disease.

Coronary heart disease often follows the diagnosis of *type 2 diabetes*, particularly in individuals with uncontrolled *hyperglycemia* and *hyperinsulinemia*.

Multiple prospective studies have demonstrated that small elevations in blood levels of the acute reactive inflammatory biomarker, *C-reactive protein* (CRP) accurately predict increasing risk of coronary heart disease.

Elevated homocysteine in the blood (*hyperhomocysteinemia*) has recently emerged as a potentially modifiable independent risk factor for atherosclerosis and atherothrombosis involving the coronary and peripheral circulation.

Blood levels of specific types of apolipoproteins and lipoproteins influence the risk of developing coronary heart disease. Increased risk is associated with a high level of Apo B and low level of Apo A. The INTERHEART Study found that the *ApoB100/ApoA1 ratio* was the strongest risk factor for acute myocardial infarction among all those measured.

Many other molecular factors are undoubtedly involved in determining the ultimate disposition of patients suffering from ischemic heart disease.

Vasoconstrictive factors such as angiotensin II, endothelin, and prostaglandin E2 are balanced by vasodilatory factors such as nitric oxide, serotonin and prostacyclin. Platelet activation, aggregation, and clotting are modulated by adenosine diphosphate (ADP), serotonin, and thromboxane A2.

1. Discuss the relative predictive values of serum cholesterol and C Reactive Protein.

Answer: Serum cholesterol has consistently proven to be a valid independent biomarker of impending ischemic heart disease. Multiple prospective studies have recently demonstrated that small elevations in blood levels of the acute reactive inflammatory biomarker, C-reactive protein (CRP), accurately predict increasing risk of coronary heart disease. Some studies suggest that C-reactive protein may be a better independent predictor of impending cardiovascular disease than serum cholesterol.

1. Discuss molecular mechanisms by which type 2 diabetes increases the risk of CHD development.

Answer: Coronary heart disease often follows the diagnosis of type 2 diabetes, particularly in individuals with uncontrolled hyperglycemia and hyperinsulinemia. In patients with long term hyperglycemia, non-enzymatic reactions between sugars and proteins form advanced glysolated end products (AGE) that may accumulate in the walls of blood vessels and heighten the process of atherogenesis. Hyperinsulinemia *per se* might increase the risk by altering fat metabolism resulting in hyperlipidemia.

1. What strategies would you propose for the primary prevention of CHD?

Answer: Ischemic/Coronary Heart Disease is influenced by multiple interactive factors including tobacco addiction, hypertension, dyslipidemia, insulin resistance,glucose intolerance, vascular inflammation, physical inactivity, and obesity. These individual factors rarely occur in isolation, and the degree of hazard depends on the number of risk factors present in a given individual. Fortunately, most of these risk factors are modifiable through lifestyle choices, e.g., abstinence from tobacco use, regular aerobic physical exercise, weight control, and consumption of a *heart healthy* diet.