

Hypertension and Atherosclerosis:

Case Study: A 68-year-old retired Navy Captain was rushed to the emergency room at Bethesda Naval Hospital after collapsing suddenly during a game of golf. On admission, he was unable to speak and the right side of his body was paralyzed. His blood pressure (BP) was 174/128 mm Hg and his left femoral pulse was undetectable. A routine chest X-ray showed cardiomegaly (i.e. cardiac enlargement). Lab. studies showed a serum cholesterol of 257 mg/dL. He gave a 34 pack-year cigarette smoking history but had quit the habit 4 months ago on the advice of his physician. His younger brother had died of a myocardial infarct 7 years previously. The patient's neurologic status steadily deteriorated and he expired 34 hours after admission. Necropsy disclosed: concentric left ventricular hypertrophy; severe atherosclerosis of the distal aorta, left internal carotid, and left common iliac arteries; bilateral atrophic kidneys with granular surfaces; and a massive acute infarct of the left cerebral hemisphere. Additionally, the left internal carotid artery was occluded by a fresh thrombus.

Definition and Prevalence of Hypertension: The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) defines hypertension as either *sustained systolic blood pressure ≥ 140 mm Hg* or *sustained diastolic blood pressure ≥ 90 mm Hg*. Although both the systolic and diastolic blood pressure increase as a function of advancing age in adults, this definition is not dependent on age. The landmark Framingham study of 5,209 initially asymptomatic men and women has shown that ~20% of whites have BP levels $>160/95$ mm Hg and ~50% have BP levels $>140/90$ mm Hg. In females, there is a substantial increase in the prevalence of hypertension over age 50. *The prevalence of hypertension is twice as great in blacks as in whites and blacks have a ~4-fold greater susceptibility to complications of hypertension than do whites!*

Types and Causes of Hypertension: In most instances (~90-95% of cases), the cause is unknown (**essential hypertension**). In the remainder (**secondary hypertension**), the cause is *secondary* to:

- **renal disease** (e.g. polycystic disease, acute glomerulonephritis, chronic renal failure, renal cell carcinoma).
- **adrenocortical hyperfunction** (e.g. hypersecretion of glucocorticoids or mineralocorticoids due to adrenal tumors or congenital hyperplasia).
- **hyperfunction of the adrenal medulla** (e.g. pheochromocytoma)
- **thyroid dysfunction** (e.g. myxedema).
- **pituitary dysfunction** (e.g. acromegaly).
- **cardiovascular disease** (e.g. coarctation of the aorta, polyarteritis nodosa).
- **pregnancy** (e.g. eclampsia).
- **neurologic disease** (e.g. increased intracranial pressure)
- **medications** (e.g. glucocorticoids, cyclosporine A).

Normal Blood Pressure Homeostasis: BP is determined by the interaction of two variables: **cardiac output** and **arteriolar peripheral resistance**. Cardiac output is influenced by blood volume which, in turn, is affected by sodium homeostasis. In contrast, peripheral resistance (i.e. vascular tone) is modulated by neurohormonal mechanisms and reflects the balance between humoral vasoconstrictor stimuli (e.g. increased blood flow, catecholamines, angiotensin II) and vasodilators (e.g. nitric oxide, bradykinin, prostaglandins). The kidneys also regulate BP via the **renin-angiotensin system**: renin (which is produced by the juxtaglomerular apparatus) converts plasma angiotensinogen to angiotensin I which, in turn, is converted by angiotensin converting enzyme (ACE) to angiotensin II → increased peripheral resistance and increased cardiac output (due to stimulation of aldosterone secretion → increased distal tubular reabsorption of sodium → increased blood volume). Renin secretion is partly regulated by blood volume: decreased blood volume → decreased renal perfusion pressure → decreased glomerular filtration rate → stimulates renin secretion.

Pathogenesis of Essential Hypertension: Current evidence suggests that essential hypertension is a multifactorial disorder in which *environmental factors* (e.g. stress, high dietary salt intake, obesity, physical inactivity, obesity, high alcohol intake) may play a role in genetically susceptible individuals. Studies of

monozygotic and dizygotic twins and of familial aggregation of hypertension have suggested that heredity plays a role in hypertension. Furthermore, certain single nucleotide polymorphisms (SNPs) such as those for renin, β_2 -adrenergic receptor (which regulates vascular tone), α -adducin (a cytoskeletal protein that modulates the Na^+/K^+ pump), and aldosterone synthase genes may contribute to the development of hypertension. However, there is no single gene that determines susceptibility to this disease and **it is highly probable that hypertension represents a complex, multifactorial polygenic disease.**

The role of renin in essential hypertension has not been elucidated fully. Thus, ~20% of patients (especially black hypertensives) have suppressed renin levels whereas ~15% of patients have elevated renin levels. Several mechanisms have been postulated to induce essential hypertension:

- A primary defect in sodium homeostasis → reduction of renal sodium excretion compared with normal individuals → increased fluid volume and peripheral vasoconstriction → elevated BP. Notably, abnormalities of membrane sodium transport have been found in ~35-50% of patients with essential hypertension.
- An abnormal response by the vasculature to circulating pressor substances (e.g. catecholamines) → vasoconstriction → increased peripheral resistance.
- ? a defect in vascular smooth muscle growth and structure → increased peripheral resistance.

Malignant Hypertension: ~5% of hypertensives manifest a rapidly rising BP (often $\geq 160/120$ mm) which, if untreated, is usually fatal within 1-2 years. This condition is referred to as *malignant* or *accelerated hypertension*. Although it can occur *de novo*, it usually develops in patients with preexistent *benign hypertension*. It is characterized clinically by rapidly progressive vascular compromise → visual disturbances (i.e. **hypertensive retinopathy**) due to retinal hemorrhages and exudates and papilledema, cardiac decompensation (i.e. congestive cardiac failure), renal failure, and cerebral abnormalities (e.g. headache, seizures, paralysis and coma). The effects of accelerated hypertension on the brain are known as **hypertensive encephalopathy**.

Pathology of Hypertension: Chronic hypertension induces changes in the smaller muscular arteries and arterioles that are collectively referred to as **arteriosclerosis**. The muscular arteries demonstrate increased layers of intimal elastin (referred to as *reduplication of the internal elastic lamina*). Histologically, there are two types of small blood vessel disease:

- **Hyaline arteriosclerosis**. This comprises homogeneous, pink hyaline thickening of the arteriolar walls in association with narrowing of the lumina. This is especially prominent in the kidney → diffuse impairment of renal blood supply → loss of nephrons → small, atrophic, granular, contracted kidneys. The kidney changes are referred to as **benign nephrosclerosis**. Although characteristic of hypertension, benign nephrosclerosis also can occur in aged individuals as well as in diabetic patients.
- **Hyperplastic arteriosclerosis**. This is seen especially in association with accelerated hypertension and is characterized by concentric, onion skin-like, laminated arteriolar wall thickening with progressive narrowing of the lumina due to smooth muscle cell proliferation and reduplication of the endothelial basement membrane. Also prominent are fibrinoid deposits in association with acute necrosis of the vascular wall (a phenomenon known as **necrotizing arteriolitis**).

Complications of Hypertension: If untreated hypertension can affect multiple organ systems:

- **Heart.** The sustained pressure load on the left side of the heart induces **left ventricular (LV) hypertrophy**. Initially, this comprises symmetric, concentric LV hypertrophy with a small ventricular lumen. With progression of disease → LV dilatation with thinning of the LV wall → congestive cardiac failure.
- **Blood vessels.** Hypertension is a major risk factor for **atherosclerosis** → coronary artery ischemia → **myocardial infarction (MI)**. Hypertension also can precipitate **aortic dissection**.
- **Kidneys.** Renal arteriosclerotic lesions → decreased glomerular filtration rate → **renal failure**. It should be noted that **kidney disease can cause secondary hypertension but primary or**

- **secondary hypertension can lead to renal failure.**
- **Brain.** Atherosclerosis of the carotid system → thrombus formation → **stroke** (i.e. **cerebral infarct**). Hypertension also can induce the development of **Charcot-Bouchard cerebral microaneurysms** → **intracerebral hemorrhage**.
- **Retina.** **Hypertensive retinopathy** can cause blindness.

Treatment of Hypertension: A variety of agents are used for treating hypertension including diuretics, α -adrenergic and β -adrenergic receptor blockers, vasodilators, ACE inhibitors, angiotensin receptor antagonists, and calcium channel antagonists.

Atherosclerosis: The term **atherosclerosis** implies a disease of elastic (e.g. aorta, carotids, iliac) and muscular (e.g. coronary, popliteal) arteries that results in *the progressive accumulation of smooth muscle cells (SMC), lipids, and extracellular matrix constituents within the intima*. The continued growth of the lesions eventually encroaches on other layers of the arterial wall and narrows the lumen of the vessel.

Complications of Atherosclerosis: These include:

- **Luminal occlusion** by atheromatous plaques or by **thrombi** that form over plaques → impaired blood flow.
- **Ulceration** → release of thrombogenic substances → **thrombosis**.
- **Dystrophic calcification**.
- **Hemorrhage** into a plaque.
- **Plaque rupture** → *embolization* of atheromatous material.
- **Aneurysm** formation. Localized abnormal dilatation of the aorta (or other major arteries) results from destruction, weakening and thinning of the media secondary to atherosclerotic plaque formation in the overlying intima.

Clinical Sequelae of Atherosclerosis:

- **Ischemic Heart Disease (IHD) → MI.** Ischemia causes decreased tissue oxygenation due to impaired tissue perfusion. IHD afflicts > 11 million people in the US and is the most common, serious, life-threatening illness in this country. It causes more deaths and disability and incurs greater economic costs than any other illness in the developed world.
- **Stroke.** This occurs when *acute ischemia* is confined to a localized area of the brain → **cerebral infarct**.
- **Ischemic encephalopathy.** This happens when there is global ischemia to the brain as a consequence of *chronic poor blood flow*.
- **Gangrene of the extremities** (also known as **peripheral vascular disease**). This occurs when a major limb artery (e.g. femoral, popliteal, tibial) is occluded.
- **Abdominal aortic aneurysm.** These are frequently noted below the origin of the renal arteries and in the iliac vessels. Catastrophic rupture can prove fatal.

Epidemiology and Risk Factors for Atherosclerosis: This disease is much more common in the US and parts of Western Europe than in Central and South America, Japan, and Africa. While geography may play a role, other risk factors such as age, gender, lifestyle, diet, and personal habits are clearly also important risk factors:

- **Age.** Clinically detectable sequelae of atherosclerosis usually do not become manifest before middle age. The incidence of IHD and MI increases 5-fold between the ages of 40 and 60. The incidence of stroke and peripheral vascular disease also increases progressively beyond the age of 60.
- **Gender.** In general, men are more susceptible to the clinical sequelae of atherosclerosis than are women and the onset of these effects occurs earlier in men. Although women are, to a large extent, “protected” against the complications of this disease during the childbearing years (? because of high circulating estrogen levels), the incidence of MI rises rapidly after the menopause and approximates that of males by age 70. Premenopausal women have higher HDL (i.e. so-

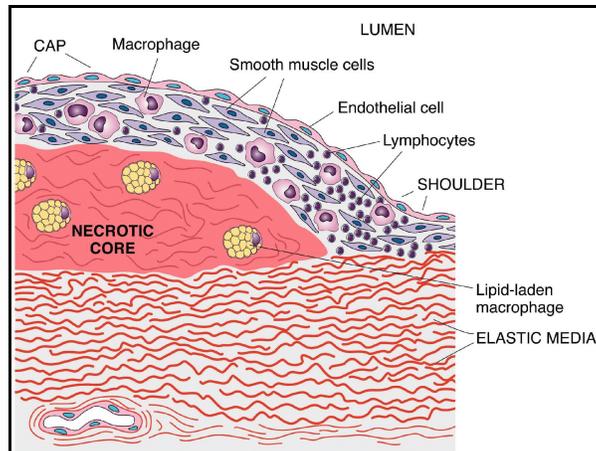
- called “good cholesterol”) levels than men whereas HDL levels decline after the menopause.
- **Genetics.** It is well-recognized that the prevalence of IHD and stroke is far greater in some families than in the comparably aged general population. This *familial predisposition* is believed to be polygenic in nature → familial clustering of multiple risk factors (e.g. diabetes mellitus, hypertension, and hereditary hyperlipidemia syndromes).
- **Cigarette smoking.** The incidence of MI and of abdominal aortic aneurysms is markedly increased in smokers. Thus, smoking ≥ 1 pack of cigarettes/day over several years can increase the risk of IHD by as much as 3-fold.
- **Hypertension.** Elevated systolic and/or diastolic BP predisposes to the development of IHD and stroke. Conversely, lowering the BP can reduce the incidence of MI and stroke.
- **Diabetes mellitus.** Both male and female diabetics have an increased risk of stroke and have double the risk of developing MI compared with non-diabetics. Diabetics also have ~100-fold increased risk of developing gangrene of the extremities compared with the general population. Diabetics have an abnormal plasma lipoprotein profile associated with insulin resistance, known as **diabetic dyslipidemia**. It is characterized by hypercholesterolemia, abnormally dense LDL (i.e. so-called “bad cholesterol”) particles, and low HDL levels.
- **Homocysteinemia.** Epidemiologic studies have shown a correlation between elevated serum homocysteine levels and increasing risk of stroke, IHD, and peripheral vascular disease. Also, **homocystinuria** patients (who have a rare, inherited inborn error of homocysteine metabolism associated with homocysteinemia) have an increased risk of multiple vascular occlusions.
- **Hyperlipidemia.** Patients with **homozygous familial hypercholesterolemia** and/or **familial hypertriglyceridemia** have a significantly increased risk of developing IHD. Furthermore, high circulating levels of lipoprotein (a) [Lp(a)] are associated with increased risks of IHD and atherosclerosis of the larger cerebral vessels. Lp(a) is a modified form of LDL that inhibits fibrinolysis and promotes smooth muscle proliferation. **There has been considerable debate and controversy over the years regarding the role of different blood lipid components in promoting atherogenesis and, consequently, the importance of diet and cholesterol-lowering drugs in preventing IHD and stroke in the general population!** Serum cholesterol levels ≥ 240 mg/dL are known to significantly increase the risk of IHD. High dietary intake of cholesterol and saturated animal fats (e.g. in cream, butter and egg yolks) → elevated blood cholesterol level.
- **Infection and inflammation.** There is evidence that several infectious agents possibly may be implicated in the pathogenesis of atherosclerosis. *Chlamydia pneumoniae*, cytomegalovirus, and *Herpes simplex* virus have been detected in atherosclerotic plaques. However, seroepidemiologic evidence for such associations remains inconclusive. Although these agents might not cause atherosclerosis, they (and the ensuing host immune response) might potentiate atherogenesis by inducing inflammation. **Notably, serological markers of inflammation correlate with risk of IHD.** Elevated levels of C-reactive protein can prospectively predict the risk of MI.

Multiple risk factors have a multiplicative effect: when 3 risk factors (e.g. smoking, hypertension, and hypercholesterolemia) are present, the risk of MI increases 7-fold.

Pathology of Atherosclerotic Lesions: The hallmark of atherosclerosis is the so-called **atheromatous plaque**. These plaques are focal elevated, pale yellow or white, smooth-surfaced lesions originating within the intima that impinge on the lumen. They vary greatly in size and, because they do not span the full circumference of the artery, they have an eccentric distribution. As the disease progresses, the plaques become more numerous. Although patchy in distribution, they can involve numerous arteries in the body in the following *descending order of frequency and severity*: lower abdominal aorta and iliac arteries > proximal coronary arteries > popliteal arteries > internal carotid arteries > arteries of the circle of Willis. The arteries of the upper extremities and the thoracic aorta are not usually involved.

Histologically, a well-established plaque has two components: a **lipid core** (composed of mainly of

cholesterol and cholesterol esters) covered by a **fibrous cap** - see figure below. The lipid core contains a *necrotic center* comprising a disorganized mass of lipid, cholesterol crystals (which appear as so-called *cholesterol clefts* in tissue sections), fibrin, organized thrombi, plasma proteins, and necrotic debris. A characteristic feature of the lipid core is the presence of large, lipid-laden *foam cells* that are derived from blood monocytes and SMC. The overlying fibrous cap is composed of SMC and dense extracellular matrix. The shoulder of the cap contains macrophages, T-cells (both CD4+ and CD8+), SMC, and proliferating small blood vessels (i.e. *neovascularization*). Plaques continually undergo remodeling characterized by necrosis, degeneration, extracellular matrix synthesis, and *dystrophic calcification*.



Atherosclerotic Plaque: Adapted from Figure 10-11A from Rubin & Farber, 3rd Edition.

Pathogenesis of Atherosclerosis: There are believed to be five possible major contributory factors to the pathogenesis of atherosclerosis:

- **Endothelial injury.** *Chronic, repetitive, non-denuding endothelial injury* is believed to play a critical role in initiating and/or perpetuating atherosclerotic lesions → increased endothelial permeability, increased leukocyte adhesion, and enhanced thrombotic potential. *Hemodynamic effects* (e.g. due to hypertension and altered circulatory flow patterns at artery bifurcations) and *hypercholesterolemia* (→ generation of reactive oxygen species), *homocysteinemia*, and *products of cigarette smoke* may either induce or potentiate endothelial injury.
- **Lipids.** The major lipids in atheromatous plaques are *plasma-derived cholesterol and cholesterol esters*. Hypercholesterolemia and *inherited dyslipidemias* → lipoproteins accumulate in the arterial wall at sites of increased endothelial permeability. Generation of reactive oxygen species by endothelial cells and macrophages in early lesions → modification of lipids to form *oxidized LDL* → ingested by macrophages via their *scavenger receptors* → induction of *foam cells* in atherosclerotic lesions. Oxidized LDL also is chemotactic for circulating monocytes and modulates the secretion of cytokines by macrophages, T-cells, and SMC in the arterial wall.
- **Monocytes/macrophages.** Circulating monocytes adhere to injured endothelium via cognate *adhesion receptors* → migrate into the underlying intima → transform into macrophages → ingest oxidized LDL → transform into foam cells. Monocytes secrete a variety of cytokines (e.g. IL-1 β , MCP-1, TNF- α , TGF- β , TGF- α , FGF, and PDGF) which perpetuate intimal inflammation by promoting endothelial adhesiveness, smooth muscle recruitment (from the media) and proliferation (in the intima), chemotaxis of monocytes and lymphocytes (from the circulation), and stimulation of extracellular matrix production (in the fibrous cap).
- **Smooth muscle cells.** SMC produce extracellular matrix. It is believed that SMC proliferation and extracellular matrix production are responsible for converting early fatty streaks into mature atheromatous plaques.
- **Infection** (see above).

Fatty Streaks: Fatty streaks composed of foam cells are flattened areas in the aortas of infants and children. In adolescents, fatty streaks may develop in the coronaries sites where atheromas develop in adults. It is not known whether these fatty streaks are precursors of atheromatous plaques.

Prevention and Treatment of Atherosclerosis: The risks of atherosclerosis can be significantly lessened by lifestyle modifications such as regular exercise, a low cholesterol diet rich in omega-3 fatty acids, smoking cessation, and treatment of hypertension and diabetes mellitus. Patients with high LDL levels can be treated with HMG-CoA reductase inhibitors (e.g. lovastatin). Calcified plaques in the coronary arteries can be detected at a relatively early stage by electron beam computed tomography (EBCT)/ultrafast CT scan. Advanced atheromatous coronary occlusions may require percutaneous transluminal coronary angioplasty (PTCA), coronary stents, or coronary bypass grafts. Abdominal aortic aneurysms can be repaired by endovascular prosthetic grafts.