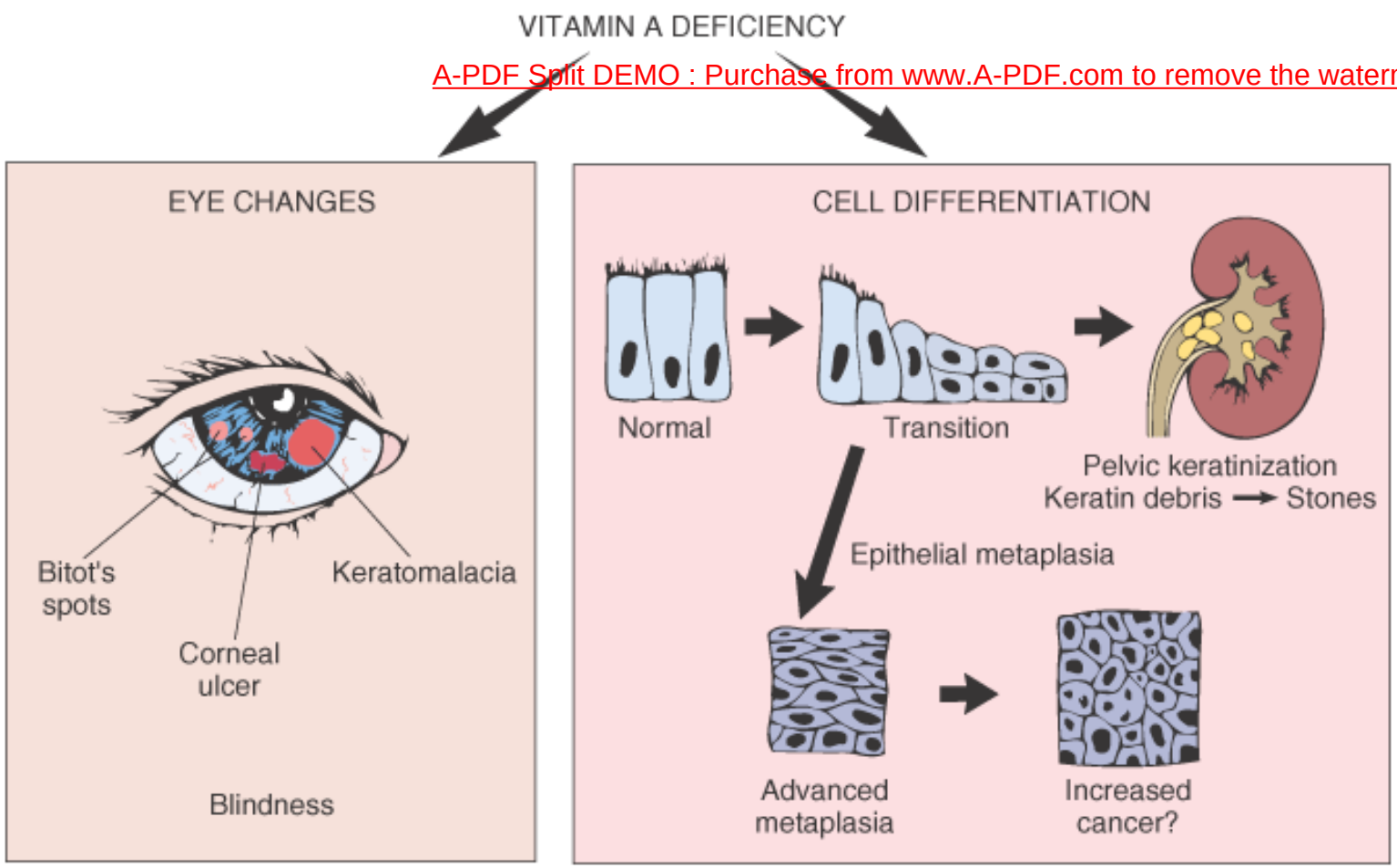
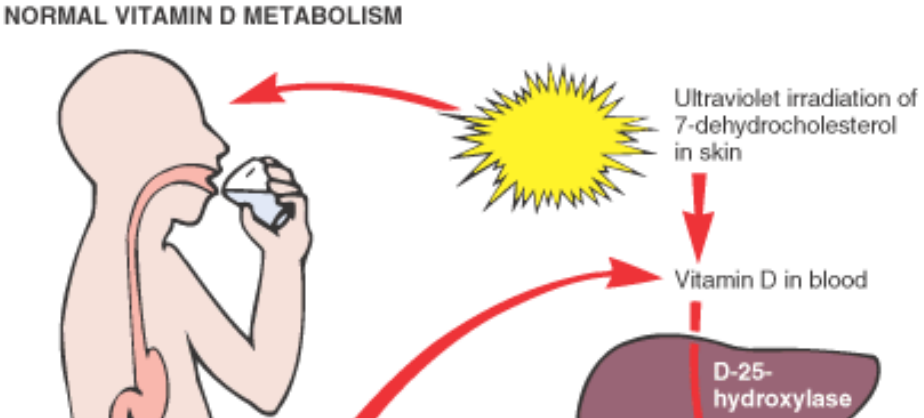
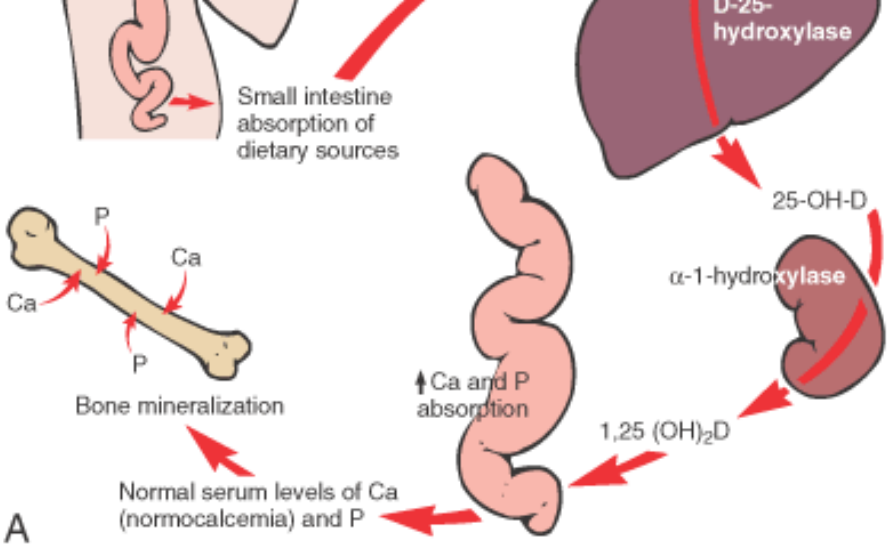


Figure 9-24 *A,* Schema of normal vitamin D metabolism. *B,* Vitamin D deficiency. There is inadequate substrate for the renal hydroxylase (1), yielding a deficiency of $1,25(OH)_2$ D (2), and deficient absorption of calcium and phosphorus from the gut (3), with consequent depressed serum levels of both (4). The hypocalcemia activates the parathyroid glands (5), causing mobilization of calcium and phosphorus from bone (6a). Simultaneously, the parathyroid hormone (PTH) induces wasting of phosphate in the urine (6b) and calcium retention. Consequently, the serum levels of calcium are normal or nearly normal, but the phosphate is low; hence, mineralization is impaired (7).





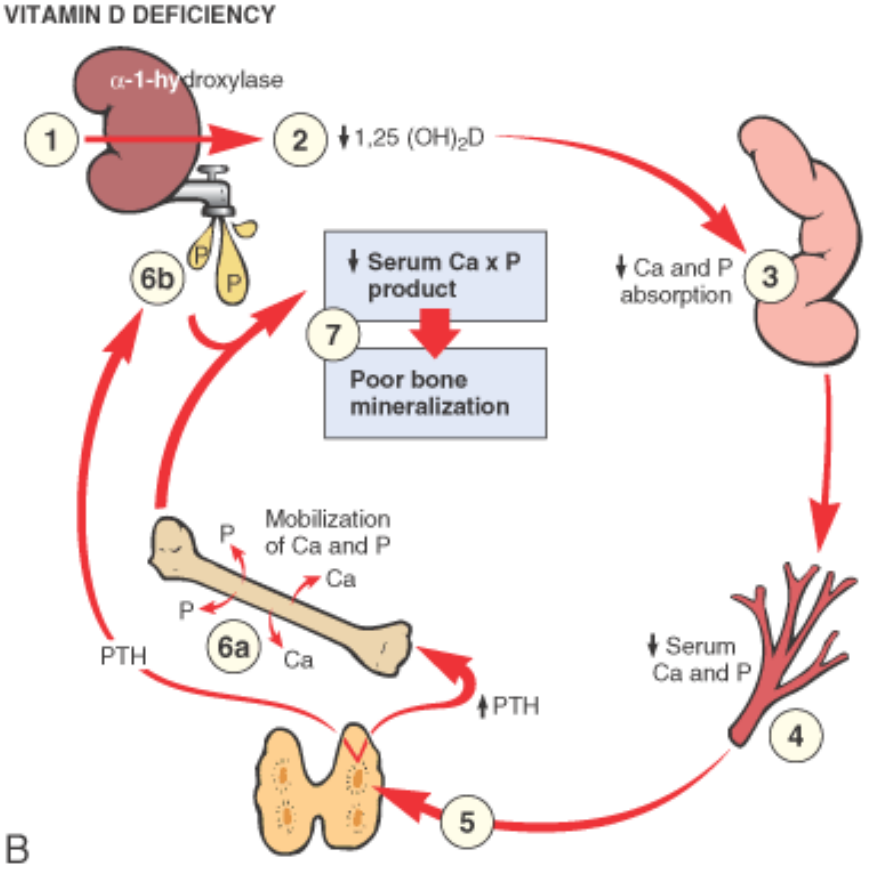


TABLE 9-23 -- Predisposing Conditions for Rickets or Osteomalacia

Inadequate Synthesis or Dietary Deficiency of Vitamin D
Inadequate exposure to sunlight
Limited dietary intake of fortified foods
Poor maternal nutrition
Dark skin pigmentation
Decreased Absorption of Fat-Soluble Vitamin D
Cholestatic liver disease
Pancreatic insufficiency
Biliary tract obstruction
Celiac sprue
Extensive small-bowel disease
Derangements in Vitamin D Metabolism
Increased degradation of vitamin D and 25(OH)D
••Induction of cytochrome P-450 enzymes (phenytoin, phenobarbital, rifampin)
Impaired synthesis of 25(OH)D
••Diffuse liver disease
Decreased synthesis of $1,25(OH)_2$ D
••Advanced renal disease
••Inherited deficiency of renal α_1 -hydroxylase (vitamin D-dependent rickets type I)
End-Organ Resistance to $1,25(OH)_2$ D
Inherited absence of or defective receptors for acute metabolite of vitamin D (vitamin D-dependent rickets type II)
Phosphate Depletion
Poor absorption of phosphate due to chronic use of antacids—binding by aluminum hydroxide
Excess renal tubule excretion of phosphate (X-linked hypophosphatemic rickets)

Figure 9-25 *A,* Detail of a rachitic costochondral junction. The palisade of cartilage is lost. Some of the trabeculae are old, well-formed bone, but the paler ones consist of uncalcified osteoid. *B,* For comparison, normal costochondral function from a young child demonstrates the orderly transition from cartilage to new bone formation.

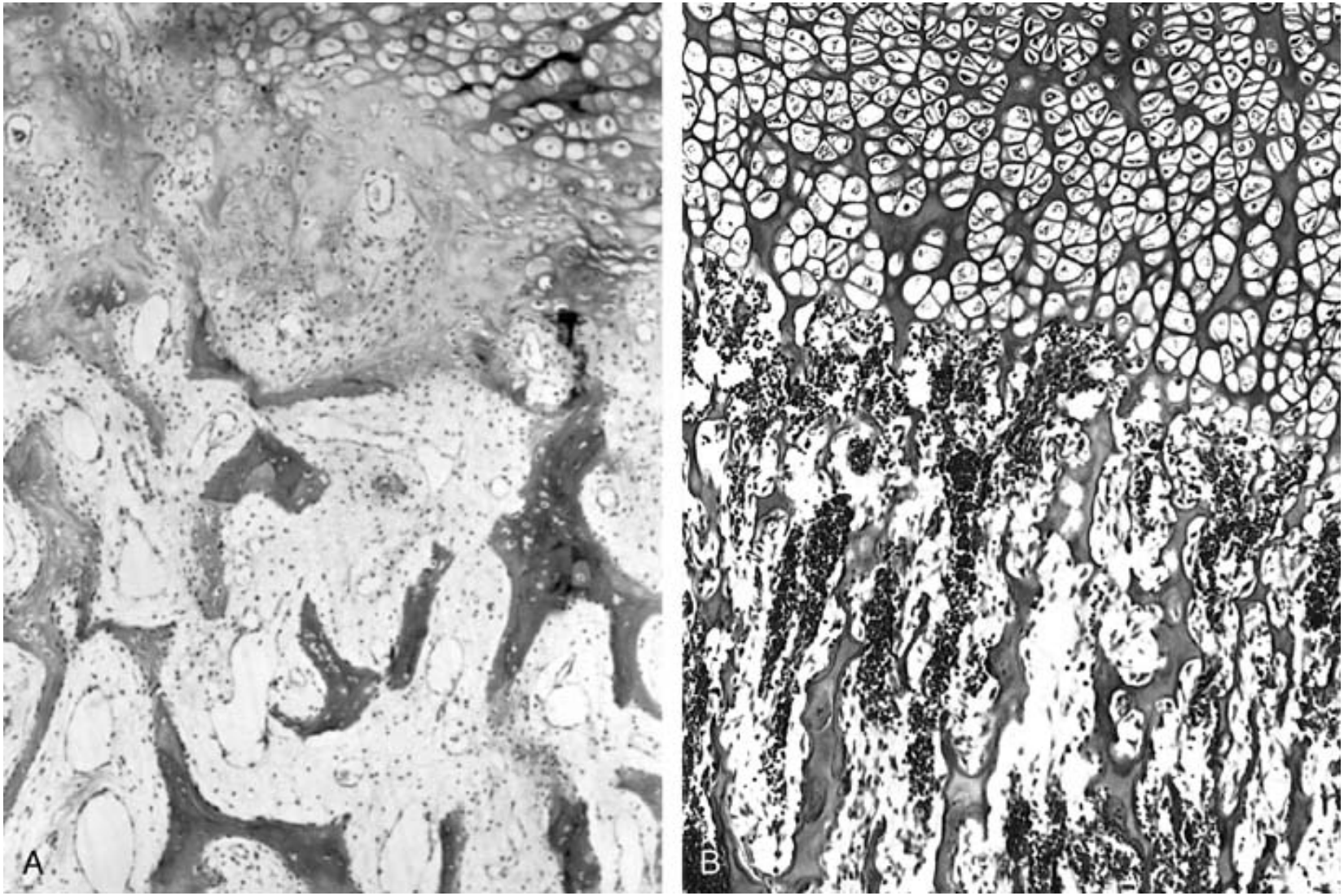


Figure 9-26 Rickets. The bowing of legs in a toddler due to the formation of poorly mineralized bones is evident.

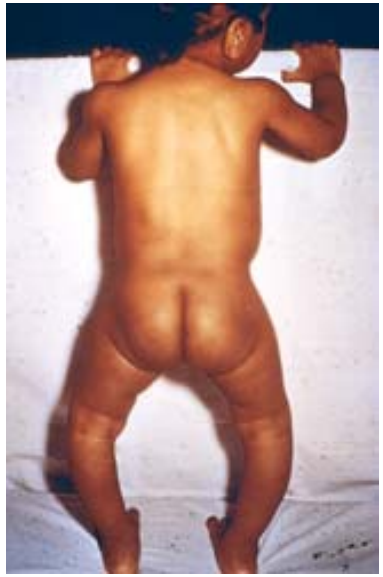


Figure 9-27 *A,* The flabby, four-chambered, dilated heart of wet beriberi. *B,* The peripheral neuropathy with myelin degeneration leading to footdrop, wristdrop, and sensory changes in dry beriberi. *C,* Hemorrhages into the mamillary bodies in the Wernicke-Korsakoff syndrome.

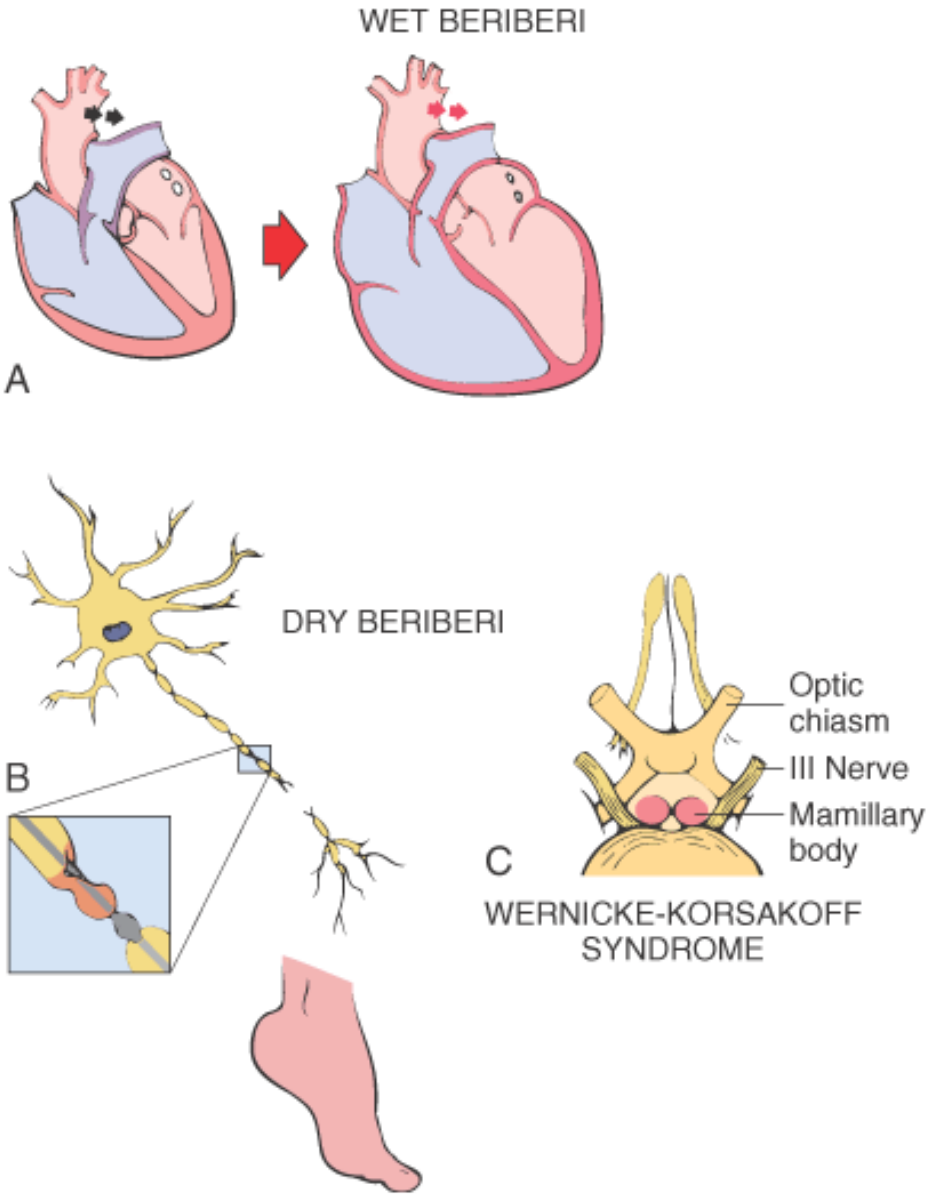


Figure 9-28 The sharply demarcated, characteristic scaling dermatitis of pellagra.

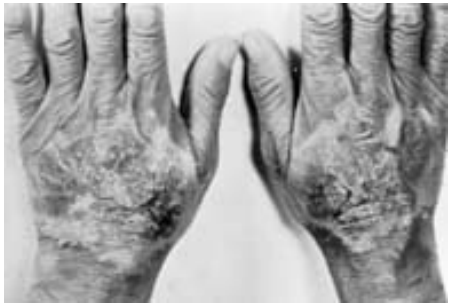
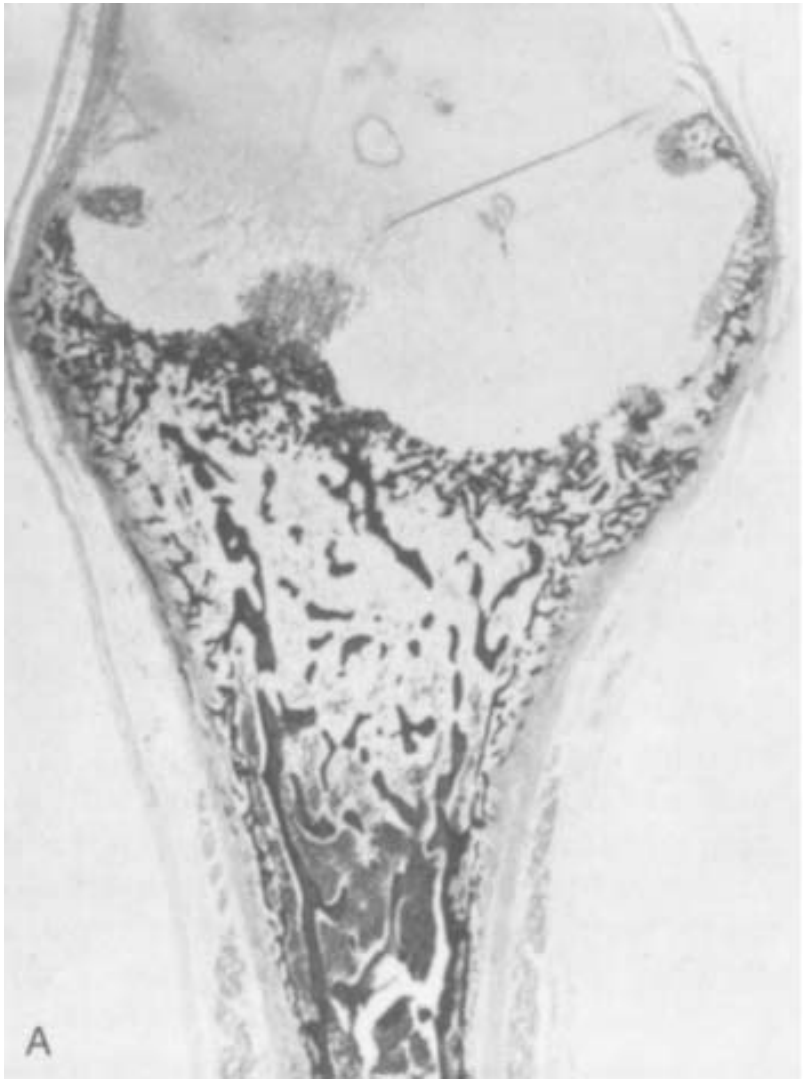


Figure 9-29 *A,* Longitudinal section of a scorbutic costochondral junction with widening of the epiphyseal cartilage and projection of masses of cartilage into the adjacent bone. *B,* Detail of a scorbutic costochondral junction. The orderly palisade is totally destroyed. There is dense mineralization of the spicules but no evidence of newly formed osteoid.



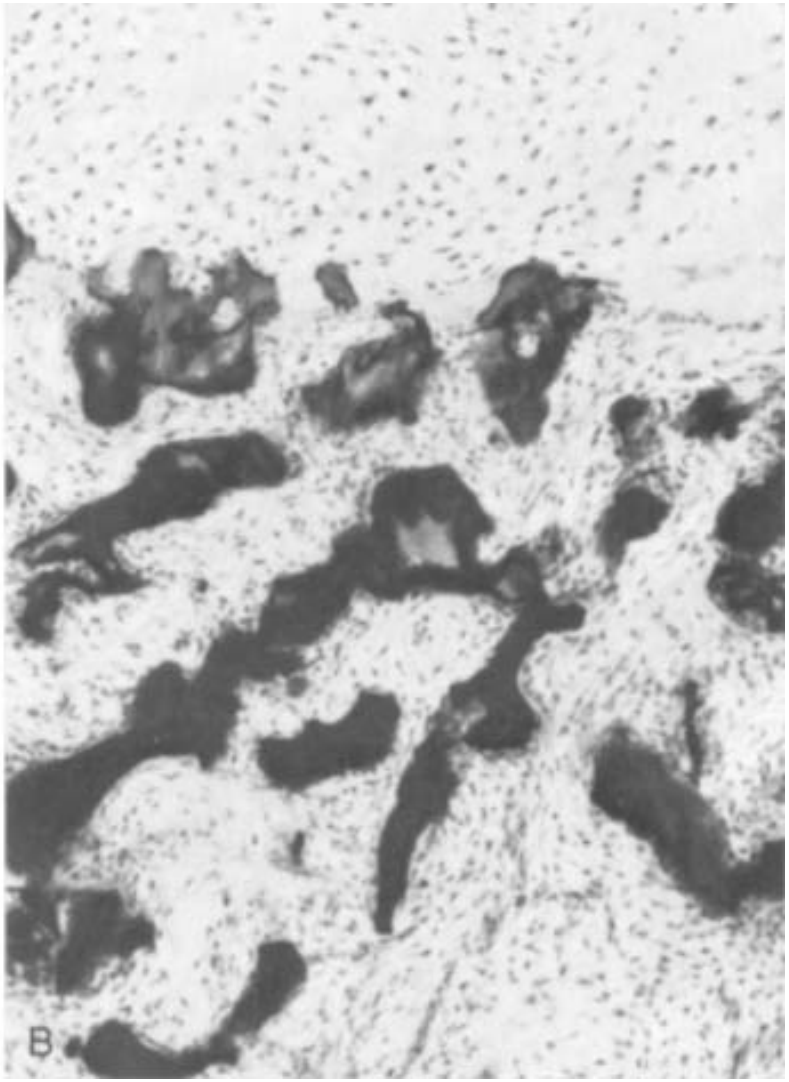


Figure 9-30 The major consequences of vitamin C deficiency.

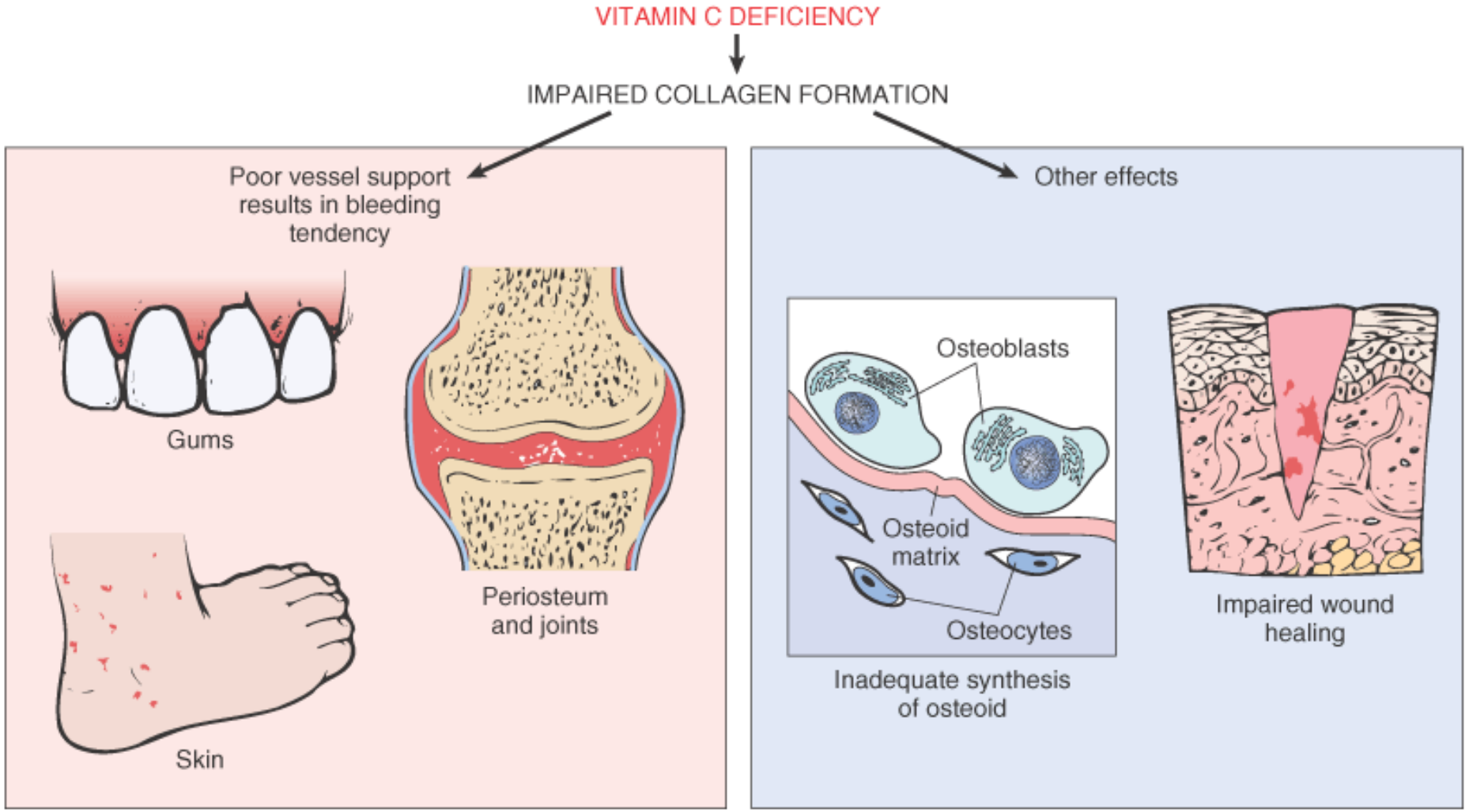


TABLE 9-24 -- Functions of Trace Metals and Deficiency Syndromes

Nutrient	Functions	Deficiency Syndromes
Iron	Essential component of hemoglobin as well as a number of iron-containing metalloenzymes	Hypochromic microcytic anemia
Zinc	Component of enzymes, principally oxidases	Acrodermatitis enteropathica, growth retardation, infertility
Iodine	Component of thyroid hormone	Goiter and hypothyroidism
Selenium	Component of glutathione peroxidase	Myopathy, rarely cardiomyopathy
Copper	Component of cytochrome *c* oxidase, dopamine β-hydroxylase, tyrosinase, lysyl oxidase, and unknown enzyme involved in cross-linking keratin	Muscle weakness, neurologic defects, hypopigmentation, abnormal collagen cross-linking

Manganese	Component of metalloenzymes, including oxidoreductases, hydrolases, and lipases	No well-defined deficiency syndrome
Fluoride	Mechanism unknown	Dental caries

Figure 9-31 Zinc deficiency with hemorrhagic dermatitis around the mouth and eyes.

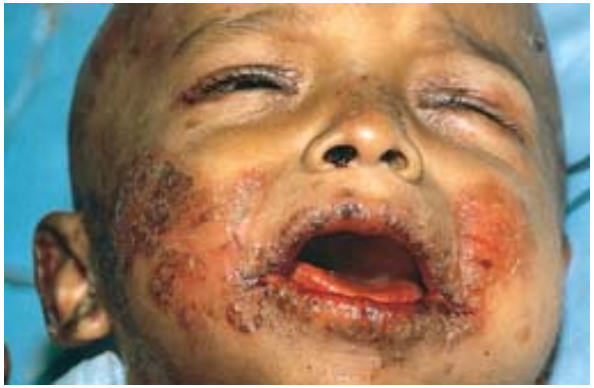


TABLE 9-25 -- Body Mass Index Associated Disease Risk

Obesity Class		**BMI (kg/m^2)**	**Risk**
Underweight		<18.5	Increased
Normal		18.5–24.9	Normal
Overweight		25.0–29.9	Increased
Obesity	I	30.0–34.9	High
	II	35.0–39.9	Very high
Extreme Obesity	III	≥40.0	Extremely high

Data from National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults —The evidence report. Obes Res 6 (suppl 2):515, 1998.

These three components are described next.[80] Not shown in Figure 9-32 is that energy expenditure occurs through a variety of hormonal (e.g., thyrotropin-releasing hormone) and autonomic intermediaries.

Among the afferent signals, insulin and leptin exert long-term control over the energy cycle by activating catabolic circuits and inhibiting anabolic pathways, as discussed in greater detail below. By contrast, ghrelin is predominately a short-term mediator. Produced in the stomach, ghrelin levels rise sharply before every meal and fall promptly when the stomach is "filled." In fact, it is thought that the success of gastric bypass surgery in massively obese individuals may relate more to the associated suppression of ghrelin levels than to an anatomic reduction in stomach capacity.

Whereas both insulin and leptin influence the energy cycle, available data suggest that leptin has a more important role than insulin in the central nervous system control of energy homeostasis.[81] [81A] Hence, our discussion will be focused on leptin, recognizing that leptin and insulin share some of their actions.

It is now established that adipocytes communicate with the hypothalamic centers that control appetite and energy expenditure by secreting leptin, a member of the cytokine family. When there is an abundance of stored energy in the form of adipose tissue, the resultant high levels of leptin cross the blood-brain barrier, binding to leptin receptors. Leptin receptor signaling has two effects: it inhibits anabolic circuits that normally promote food intake and inhibit energy expenditure, and, through a distinct set of neurons, leptin triggers catabolic circuits (Fig. 9-32). *The net effect of leptin, therefore, is to reduce food intake and promote energy expenditure.* Hence, over a period of time, energy stores (adipocytes) are reduced, and weight is lost. This in turn reduces the circulating levels of leptin, and a new equilibrium is reached. This cycle is reversed when adipose tissue is lost and leptin levels are reduced below a threshold. Equilibrium is again reached, since with low leptin levels, the anabolic circuits are relieved of inhibition and catabolic circuits are not activated, resulting in net gain of weight.

The molecular basis of leptin action is extremely complex and not yet fully unraveled. For the most part, leptin exerts its function through a series of integrated neural pathways referred to as the *leptin-melanocortin circuit*, described in Box 9-1 and illustrated in Figure 9-33 . The understanding of this circuitry is important since obesity is a serious public health problem, and development of antiobesity drugs will depend on a full understanding of these pathways.

Obesity, particularly *central obesity, increases the risk for a number of conditions*,[79] including diabetes, hypertension, osteoarthritis, pancreatitis, and many others, listed in Table 9-26 . Only some of these complications are discussed here. The mechanisms underlying these associations are complex and likely to be interrelated. Obesity, for instance, is associated with *insulin resistance* and hyperinsulinemia, important features of non-insulin-dependent, or type II, diabetes, and weight loss is associated with improvement. It has been speculated that excess insulin, in turn, may play a role in the retention of sodium, expansion of blood volume, production of

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Figure 9-32 A simplified schema of the circuitry that regulates energy balance. When sufficient energy is stored in adipose tissue and the individual is well fed, afferent adiposity signals (insulin, leptin, ghrelin) are delivered to the central neuronal processing units, in the hypothalamus. Here the adiposity signals inhibit anabolic circuits and activate catabolic circuits. The effector arms of these central circuits then impact on energy balance by inhibiting food intake and promoting energy expenditure. This in turn reduces the energy stores and the adiposity signals are obtunded. Conversely, when energy stores are low, the available anabolic circuits take over at the expense of catabolic circuits to generate energy stores in the form of adipose tissue, thus generating an equilibrium.

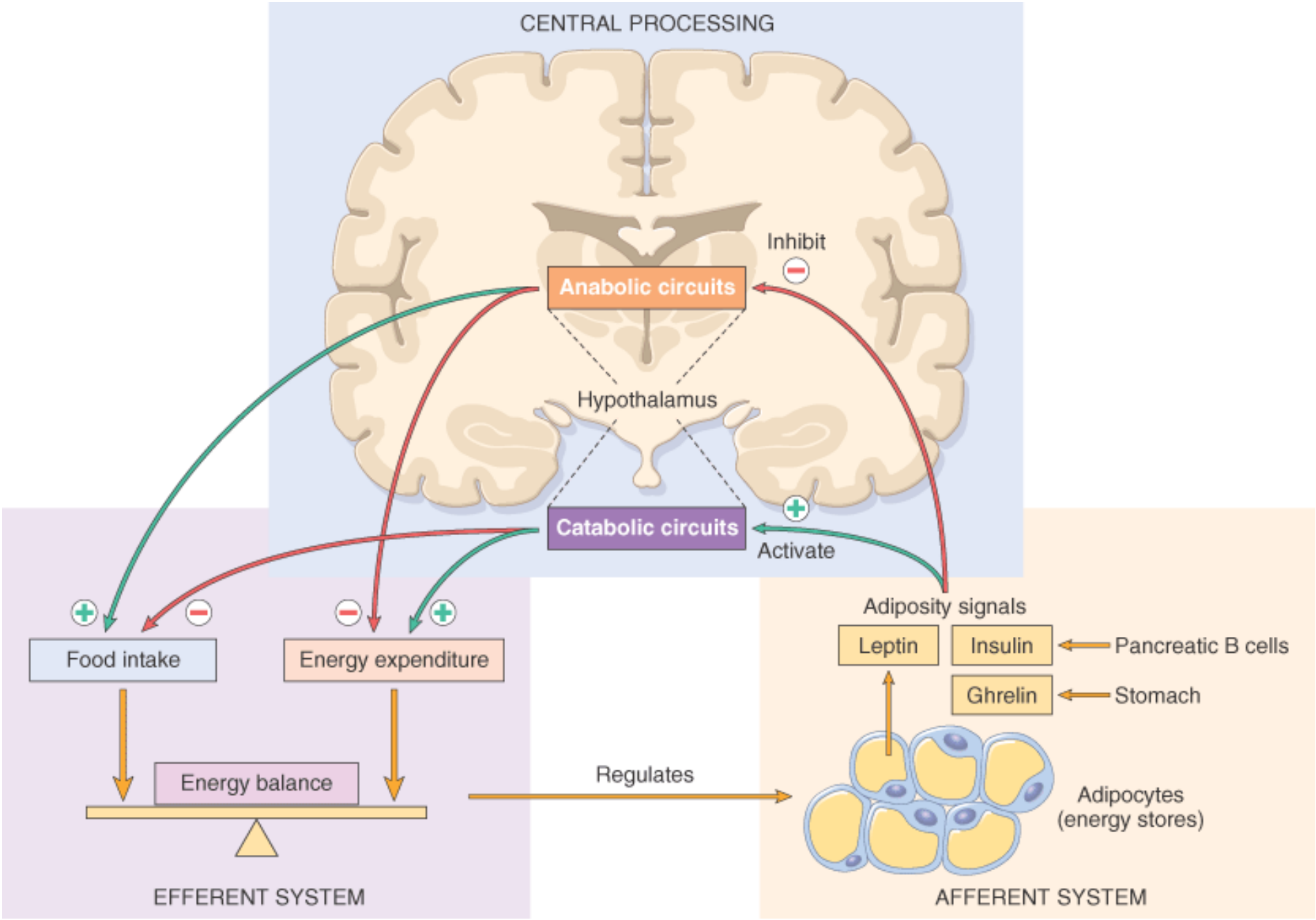
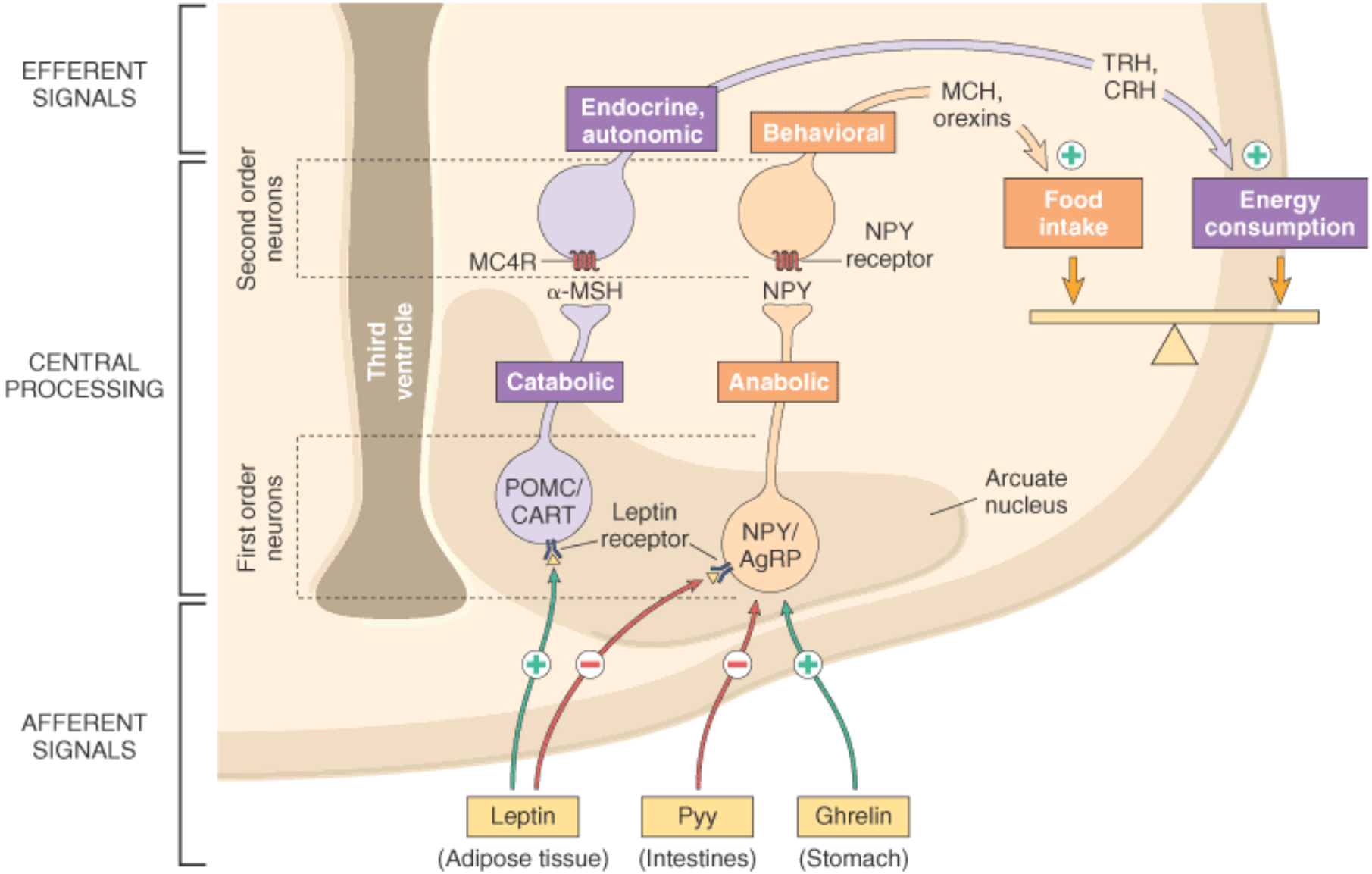


Figure 9-33 The neurohumoral circuits in the hypothalamus that regulate energy balance. Details are in the text.


EFFERENT SIGNALS
CENTRAL PROCESSING
AFFERENT SIGNALS
Second order neurons
First order neurons
Third ventricle
Endocrine, autonomic
Behavioral
TRH, CRH
MCH, orexins
Food intake
Energy consumption
MC4R
α-MSH
NPY receptor
NPY
Catabolic
Anabolic
POMC/ CART
Leptin receptor
NPY/ AgRP
Arcuate nucleus
Leptin
(Adipose tissue)
Pyy
(Intestines)
Ghrelin
(Stomach)

Box 9-1. Genetics of Obesity

Obesity is a disorder with a multifactorial etiology. Only rarely does it result from single gene disorders. Evidence supporting an important role for genes in weight control includes familial clustering of obesity and higher concordance of body mass index (BMI) among monozygotic twins (74%) versus dizygotic twins (32%) living in the same environment. Although monogenic forms of obesity in humans are rare, studies of these genetic forms of obesity and their murine counterparts have significantly advanced our understanding of the molecular basis of obesity. Some of these are discussed below.

In recent years many "obesity" genes have been identified. As might be expected, they encode the molecular components of the neuroendocrine system that regulates energy balance. Leptin, the key player in energy homeostasis, is the product of the *OB* gene. Its role as an antiobesity factor is buttressed by the observation that mice homozygous for mutations in the leptin gene (*OB/OB*) do not secrete leptin, are massively obese, and are "cured" by the administration of exogenous leptin. Mice with mutations in the leptin receptor (*db/db*) are also obese, but, unlike the case with *ob/ob* mice, their obesity cannot be ameliorated by the administration of leptin. In these mice, obesity occurs because the leptin-mediated afferent signals impinging on the hypothalamus fail to regulate appetite and energy expenditure.

Although leptin receptors are expressed at several sites in the brain, those most critical for regulation of the leptin-melanocortin circuit are expressed in the arcuate nucleus of the hypothalamus. There are two major types of neurons in this locale that bear leptin receptors: one set (*oraxogenic*) produces appetite-stimulating neurotransmitters called neuropeptide Y (NPY) and agouti-related peptide (AgRP). These are appropriately called NPY/AgRP neurons (see Fig. 9-33). As can be surmised from the discussion in the text, leptin reduces the expression of NPY and AgRP. The other set of leptin-sensitive neurons, the so-called POMC/CART neurons, transcribe two *anorexigenic* neuropeptides—α-melanocyte-stimulating hormone (α-MSH) and cocaine and amphetamine-related transcript (CART). Both of these peptides are products of proopiomelanocortin (POMC). When the POMC/CART neurons are activated by leptin signals, they exert catabolic effects mainly through the secretion of α-MSH. As indicated in Figure 9-33 , the NPY/AgRP and POMC/CART neurons are referred to as first-order neurons of the leptin-melanocortin circuit, since they are the initial targets of leptin action. The neurotransmitters produced by them (NPY, AgRP, and α-MSH) then interact through their own specific receptors with second-order neurons that trigger the efferent systems with peripheral actions. The effects of these neurotransmitters are described next.

In the anabolic pathway, the first-order NPY/AgRP neurons make monosynaptic connections to second-order neurons, which express oraxogenic peptides melanin-concentrating hormone (MCH) and oraxins A and B. As illustrated in Figure 9-33 , NPY released from first-order neurons binds to its receptor on second-order neurons and thus transmits feeding signals. Such signals are attenuated when leptin is in excess and are activated by low levels of leptin. AgRP, like NPY, exerts anabolic effects but by a somewhat distinct mechanism.

α-MSH produced by the POMC/CART neurons exerts its catabolic effects by binding to a set of second-order neurons (in the paraventricular nucleus) that express the melanocortin 4 receptor (MC4R). Catabolic output from the MC4R neurons is relayed to the periphery via the endocrine and autonomic systems. This reduces feeding and increases energy expenditure. The energy-consuming actions of MC4R neurons are mediated in part by the release of thyrotropin-releasing hormone (TRH), which activates the thyroxine axis through the anterior pituitary; TRH not only increases thermogenesis via secretion of thyroxine, but it is also an appetite suppressant. Corticotropin-releasing hormone (CRH) is another product of MC4R neurons. It induces anorexia and also activates the sympathetic nervous system. A subset of MC4R neurons projects to sympathetic motor output areas. Fibers from these areas innervate brown adipose tissue, rich in β_3 -adrenergic receptors. When these receptors are stimulated, they cause fatty acid hydrolysis and also uncouple energy production from storage. Thus, the fats are literally burned, and energy so produced is dissipated as heat.

It is noteworthy that each of the six single gene defects that give rise to human obesity involves proteins in the leptin-melanocortin pathway. Four of these are autosomal recessive and affect the leptin receptor, POMC, and PC1. (The last mentioned is a prohormone convertase that cleaves POMC). In all these cases, there is profound hyperphagia and childhood-onset massive obesity. While these four forms of genetic obesity are quite rare, those caused by mutations in the melanocortin receptor, MC4R, are by comparison quite common. In a recent study, 5% to 8% of a cohort of 500 obese individuals had functionally important mutations in the MC4R gene.[83] In these patients, despite abundant fat stores and leptin, energy consumption cannot be stimulated. The sixth monogenic form of human obesity results from mutation in a transcription factor (SIM1) that is essential for the formation of second-order leptin neurons.

Despite the remarkable advances in our understanding of genetic control of pathways that regulate energy balance, the genetic basis of the most common forms of human obesity

remains mysterious. As a multifactorial disorder, one might expect mutations or polymorphisms in several genes of small effect that give rise to obesity in concert with environmental factors. It is interesting to note that blood leptin levels are elevated in most humans with obesity. Clearly, the high levels of leptin are unable to down-regulate the anabolic pathways or activate the catabolic pathways. The basis of such leptin resistance is unclear but it may be contributed to by a decrease in the ability of leptin to cross the blood-brain barrier, possibly due to defective transport across endothelial cells. The fact that in some obese individuals leptin levels in the cerebrospinal fluid are lower than in the plasma supports this hypothesis.

TABLE 9-26 -- Medical Complications Associated with Obesity

Gastrointestinal	Gallstones, pancreatitis, abdominal hernia, NAFLD (steatosis, steatohepatitis, and cirrhosis), and possibly GERD
Endocrine/metabolic	Metabolic syndrome, insulin resistance, impaired glucose tolerance, type II diabetes mellitus, dyslipidemia, polycystic ovary syndrome
Cardiovascular	Hypertension, coronary artery disease, congestive heart failure, arrhythmias, pulmonary hypertension, ischemic stroke, venous stasis, deep vein thrombosis, pulmonary embolus
Respiratory	Abnormal pulmonary function, obstructive sleep apnea, obesity hypoventilation syndrome
Musculoskeletal	Osteoarthritis, gout, low back pain
Gynecologic	Abnormal menses, infertility
Genitourinary	Urinary stress incontinence
Ophthalmologic	Cataracts
Neurologic	Idiopathic intracranial hypertension (pseudotumor cerebri)
Cancer	Esophagus, colon, gallbladder, prostate, breast, uterus, cervix, kidney
Postoperative events	Atelectasis, pneumonia, deep vein thrombosis, pulmonary embolus

Data from Klein S, Wadden T, Sugerman HJ: AGA technical review on obesity. Gastroenterol 123:882, 2002. NAFLD, non-alcoholic fatty liver disease; GERD, gastroesophageal reflux disease.

excess norepinephrine, and smooth muscle proliferation that are the hallmarks of hypertension. Regardless of whether these pathogenic mechanisms are actually operative, *the risk of developing hypertension among previously normotensive persons increases proportionately with weight*. Obesity is also associated with a somewhat distinctive metabolic syndrome, the so-called *syndrome X*, which is characterized by abdominal obesity, insulin resistance, hypertriglyceridemia, low serum HDL, hypertension, and increased risk for coronary artery disease.[82]

Obese persons are likely to have hypertriglyceridemia and a low HDL cholesterol value, and these factors may increase the risk of *coronary artery disease*. The association between obesity and heart disease is not straightforward, and the linkage may be related to the associated diabetes and hypertension rather than to weight. Nevertheless, the American Heart Association has recently added obesity to its list of major risk factors.[79]

Nonalcoholic steatohepatitis occurs in adolescents and adults who are obese and have type II diabetes. Fatty change accompanied by liver cell injury and inflammation may progress to fibrosis or regress following weight loss.

Cholelithiasis (gallstones) is six times more common in obese than in lean subjects. The mechanism is mainly an increase in total body cholesterol, increased cholesterol turnover, and augmented biliary excretion of cholesterol in the bile, which in turn predisposes to the formation of cholesterol-rich gallstones (Chapter 18).

Hypoventilation syndrome is a constellation of respiratory abnormalities in very obese persons. It has been called the *pickwickian syndrome,* after the fat lad who was constantly falling asleep in Charles Dickens' *Pickwick Papers*. Hypersomnolence, both at night and during the day, is characteristic and is often associated with apneic pauses during sleep, polycythemia, and eventual right-sided heart failure.

Marked adiposity predisposes to the development of degenerative joint disease (*osteoarthritis*). This form of arthritis, which typically appears in older persons, is attributed in large part to the cumulative effects of wear and tear on joints. It is reasonable to assume that the greater the body burden of fat, the greater the trauma to joints with passage of time.

Obesity increases the risk of *ischemic stroke* in both men and women. Abdominal obesity is associated with increased risk of *venous thrombosis*.

Somewhat controversial is the association between obesity and cancer. A recent large prospective study has revealed an association between increasing BMI and mortality from many forms of cancer, including cancers of the esophagus, colon, rectum, liver, and non-Hodgkin lymphoma.[84] The basis of this association is difficult to discern. With hormone-dependent cancers, such as those arising in the endometrium, the blame can be placed on hormonal imbalance since obesity is known to raise estrogen levels, but for others we remain in the dark.

DIET AND SYSTEMIC DISEASES

The problems of undernutrition and overnutrition, as well as specific nutrient deficiencies, have been discussed; however, the composition of the diet, even in the absence of any of these problems, may make a significant contribution to the causation and progression of a number of diseases. A few examples suffice here.

Currently one of the most important and controversial issues is the contribution of diet to atherogenesis. The central question is, Can dietary modification prevent or retard the development of atherosclerosis (most importantly, coronary artery disease)? The average adult in the United States consumes an inordinate amount of fat and cholesterol daily, with a ratio of saturated fatty acids to polyunsaturated fatty acids of about 3:1. Vegetable oils (e.g., corn and safflower oils) and fish oils contain polyunsaturated fatty acids and are good sources of cholesterol-lowering lipids. Fish oil fatty acids belonging to the omega-3, or n-3, family have more double bonds than do the omega-6, or n-6, fatty acids found in vegetable oils. A recent meta-analysis of 11 studies with over 16,000 patients revealed that a diet enriched in omega-3 fatty acids (vs. placebo) significantly reduced the incidence of fatal myocardial infarction and sudden cardiac death.[85]

There are other examples of the effect of diet on disease:

- Hypertension is beneficially affected by restricting sodium intake.
- Dietary fiber, or roughage, resulting in increased fecal bulk, has a preventive effect against diverticulosis of the colon.
- People who consume diets that contain abundant fresh fruits and vegetables with limited intake of meats and processed foods have a lower risk of myocardial infarction. One mechanism that may explain these epidemiologic observations is the association of hyperhomocysteinemia with increased intake of meats and decreased intake of vitamin B_6 , vitamin B_{12} , and folate. Excess levels of homocysteine are hypothesized to contribute to atherosclerosis (Chapter 11).
- Calorie restriction has been convincingly demonstrated to increase life span in experimental animals. The basis of this striking observation is not entirely clear (Chapter 1).

• Even lowly garlic has been touted to protect against heart disease (and also, alas, kisses), although research has yet to prove the effect on heart disease unequivocally.

CHEMOPREVENTION OF CANCER

Epidemiologic studies have provided evidence that populations who consume large quantities of fruits and vegetables in their diets have a lower risk of cancer. It is hypothesized that carotenoids that are converted to vitamin A in the liver and intestine may be important in the primary chemoprevention of cancer. [86] The following mechanisms are proposed for the anticarcinogenic effects of carotenoids and retinoids:

- Retinoic acid promotes differentiation of mucus-secreting epithelial tissues. Supplementation of the diet with beta-carotene and retinol is hypothesized to reverse squamous metaplasia and preneoplastic lesions in the respiratory tract of cigarette smokers and workers exposed to asbestos.
- Fruits and vegetables provide antioxidants such as betacarotene, vitamins C and E, and selenium that prevent oxidative damage to DNA.
- Vitamin A can enhance immune responses; other retinoids may modulate inflammatory reactions that are potential sources of reactive oxygen and nitrogen intermediates.

Notwithstanding such theoretical considerations, clinical studies on the role of vitamin A supplementation and cancer risk have failed to provide clear answers. Clinical trials using beta-carotene and retinyl palmitate as primary preventive agents against lung cancer were terminated because the participants showed an excess of lung cancers and increased mortality. On the other hand, 13-*cis*-retinoic acid was effective in prevention of secondary squamous cell carcinomas of the head and neck region. These apparently conflicting results are not easily explained; however, there are multiple chemical forms of retinoids that alter gene expression, cell proliferation, differentiation, and apoptosis by binding to six different nuclear receptors. Some retinoids are associated with significant toxicity, including dry skin, conjunctivitis, and hypertriglyceridemia. Until the biochemical and molecular mechanisms of action of individual retinoids and other antioxidants are understood, it is unwise to recommend dietary supplements for the primary chemoprevention of cancer. However, a diet rich in fruits, vegetables, and unprocessed grains that is low in fat and animal protein has been associated with a decreased risk of cardiovascular disease and some types of cancer.[84]

High animal fat intake combined with low fiber intake has been implicated in the causation of colon cancer. The most convincing explanation for these associations is as follows: high fat intake increases the level of bile acids in the gut, which in turn modifies intestinal flora, favoring the growth of microaerophilic bacteria. The bile acids or bile acid metabolites produced by these bacteria might serve as carcinogens or promoters. The protective effect of a high-fiber diet might relate to (1) increased stool bulk and decreased transit time, which decrease the exposure of mucosa to putative offenders, and (2) the capacity of certain fibers to bind carcinogens and thereby protect the mucosa.

Attempts to document these theories in clinical and experimental studies have, on the whole, led to contradictory results.

Thus, we must conclude that, despite many tantalizing trends and proclamations by "diet gurus," to date there is no definite proof that diet can cause or protect against cancer. Nonetheless, concern persists that carcinogens lurk in things as pleasurable as a juicy steak and rich ice cream.

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Chapter 10 - Diseases of Infancy and Childhood *

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Children are not merely little adults, and the diseases they get are not merely variants of adult diseases. Many childhood conditions are unique to, or at least take distinctive forms in, this stage of life and so are discussed separately in this chapter. Diseases originating in the perinatal period are important in that they account for significant morbidity and mortality. As would be expected, the chances for survival of live-born infants improve with each passing week. This differential represents, at least in part, a triumph of improved medical care. Better prenatal care, more effective methods of monitoring the condition of the fetus, and judicious resort to cesarean section before term when there is evidence of fetal distress all contribute to bringing into this "mortal coil" live-born infants who in past years might have been stillborn. These infants represent an increased number of *high-risk* infants. Nonetheless, the infant mortality rate in the United States has shown a decline from a level of 20.0 deaths per 1000 live births in 1970 to about 6.9 deaths in 2000.[1] Although the death rate has continued

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* The contributions of Dr. Deborah Scofield to this chapter in earlier editions are gratefully acknowledged.

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to decline for all infants, American blacks continue to have an infant mortality rate more than twice (13.9 deaths per 1000 live births) that of American whites (6.0 deaths). Worldwide, the infant mortality rates vary widely, from as low as 3 deaths per 1,000 live births in Sweden, to as high as 82 deaths in the Indian subcontinent.

Each stage of development of the infant and child is prey to a somewhat different group of disorders. The data available permit a survey of four time spans: (1) the neonatal period (the first 4 weeks of life), (2) infancy (the first year of life), (3) age 1 to 4 years, and (4) age 5 to 14 years.

The major causes of death in infancy and childhood are cited in Table 10-1 . Congenital anomalies, disorders relating to short gestation (prematurity) and low birth weight, and sudden infant death syndrome (SIDS) represent the leading causes of death in the first 12 months of life. Once the infant survives the first year of life, the outlook brightens measurably. In the next two age groups—1 to 4 years and 5 to 14 years—injuries resulting from accidents have become the leading cause of death (see Table 10-1). Among the natural diseases, in order of importance, congenital anomalies and malignant neoplasms assume major significance. It would appear then that, in a sense, life is an obstacle course. For the great majority, the obstacles are surmounted or, even better, bypassed. We now take a closer look at the specific conditions encountered during the various stages of infant and child development.

Congenital Anomalies

Congenital anomalies are morphologic defects that are present at birth, but some, such as cardiac defects and renal anomalies, may not become clinically apparent until years later. The term *congenital* does not imply or exclude a genetic basis for the birth defect. It is estimated that about 3% of newborns have a *major anomaly*, defined as an anomaly having either cosmetic or functional significance. As indicated in Table 10-1 , they are the most common cause of mortality in the first year of life and contribute significantly to morbidity and mortality throughout the early years of life. In a real sense, anomalies found in live-born infants represent the less serious developmental failures in embryogenesis that are compatible with live birth. Perhaps 20% of fertilized ova are so anomalous that they are blighted from the outset. Others may be compatible with early fetal development, only to lead to spontaneous abortion. Less severe anomalies allow more prolonged intrauterine survival, with some disorders terminating in still-birth and those still less significant permitting live birth despite the handicaps imposed.

DEFINITIONS

Before proceeding, we define some of the terms used for various kinds of errors in morphogenesis—*malformations, disruptions, deformations, sequences*, and *syndromes*.

• *Malformations* represent primary errors of morphogenesis, in other words there is an *intrinsically abnormal developmental process* (Fig. 10-1). They are usually multifactorial rather than the result of a single gene or chromosomal defect. Malformations may present in several patterns. Some, such as congenital heart defects and anencephaly (absence of brain), involve single body systems, whereas in other cases multiple malformations involving many organs may coexist.

• *Disruptions* result from secondary destruction of an organ or body region that was previously normal in development; thus, in contrast to malformations, disruptions arise from an *extrinsic disturbance in morphogenesis. Amniotic*

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bands, denoting rupture of amnion with resultant formation of "bands"that encircle, compress, or attach to parts of the developing fetus, are the classic example of a disruption (Fig. 10-2). A variety of environmental agents may cause disruptions (see below). Understandably, disruptions are not heritable and hence are not associated with risk of recurrence in subsequent pregnancies.

• *Deformations*, like disruptions, also represent an *extrinsic disturbance of development* rather than an intrinsic error of morphogenesis. Deformations are common problems, affecting approximately 2% of newborn infants to varying degrees. Fundamental to the pathogenesis of deformations is localized or generalized compression of the growing fetus by *abnormal biomechanical forces*, leading eventually to a variety of structural abnormalities. The most common underlying factor responsible for deformations is *uterine constraint*. Between the 35th and 38th weeks of gestation, rapid increase in the size of the fetus outpaces the growth of the uterus, and the relative amount of amniotic fluid (which normally acts as a cushion) also decreases. Thus, even the normal fetus is subjected to some form of uterine constraint. Several factors increase the likelihood of excessive compression of the fetus resulting in deformations. *Maternal factors* include first pregnancy, small uterus, malformed (bicornuate) uterus, and leiomyomas. *Fetal or placental factors* include oligohydramnios, multiple fetuses, and abnormal fetal presentation. An example of a deformation is clubfeet, often a component of Potter sequence, described later.

• A *sequence* is a pattern of cascade anomalies. Approximately half the time, congenital anomalies occur singly; in the remaining cases, multiple congenital anomalies are recognized. In some instances, the constellation of anomalies may be explained by a single, localized aberration in organogenesis (malformation, disruption, or deformation) leading to secondary effects in other organs. A good example of a sequence is the *oligohydramnios* (or *Potter*) *sequence* (Fig. 10-3). Oligohydramnios (decreased amniotic fluid) may be caused by a variety of unrelated maternal, placental, or fetal abnormalities. Chronic leakage of amniotic fluid because of rupture of the amnion, uteroplacental

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insufficiency resulting from maternal hypertension or severe toxemia, and renal agenesis in the fetus (as fetal urine is a major constituent of amniotic fluid) are all causes of oligohydramnios. The fetal compression associated with significant oligohydramnios, in turn, results in a classic phenotype in the newborn infant, including flattened facies and positional abnormalities of the hands and feet (Fig. 10-4). The hips may be dislocated. Growth of the chest wall and the contained lungs is also compromised so that the lungs are frequently hypoplastic, occasionally to the degree that they are the cause of fetal demise. Nodules in the amnion *(amnion nodosum)*are frequently present.

• A *syndrome* is a constellation of congenital anomalies, believed to be pathologically related, that, in contrast to a sequence, *cannot* be explained on the basis of a single, localized, initiating defect. Syndromes are most often caused by a single etiologic agent, such as a viral infection or specific chromosomal abnormality, which simultaneously affects several tissues.

TABLE 10-1 -- Cause of Death Related with Age

Causes *	**Rate** †
Under 1 Year: All Causes	**727.4**
Congenital malformations, deformations, and chromosomal anomalies	
Disorders related to short gestation and low birth weight	
Sudden infant death syndrome (SIDS)	
Newborn affected by maternal complications of pregnancy	

Newborn affected by complications of placenta, cord, and membranes	
Respiratory distress of newborn	
Accidents (unintentional injuries)	
Bacterial sepsis of newborn	
Intrauterine hypoxia and birth asphyxia	
Diseases of the circulatory system	
1–4 Years: All Causes	**32.6**
Accidents and adverse effects	
Congenital malformations, deformations, and chromosomal abnormalities	
Malignant neoplasms	
Homicide and legal intervention	
Diseases of the heart ‡	
Influenza and pneumonia	
5–14 Years: All Causes	**18.5**
Accidents and adverse effects	
Malignant neoplasms	
Homicide and legal intervention	
Congenital malformations, deformations, and chromosomal abnormalities	
Suicide	
Diseases of the heart	
15–24 Years: All Causes	**80.7**
Accidents and adverse effects	
Homicide	
Suicide	
Malignant neoplasms	
Diseases of the heart	

*Causes are listed in decreasing order of frequency. All causes and rates are preliminary 2000 statistics. *(Minino AM, Smith BL. Deaths: Preliminary data for 2000. National Vital Statistics Report, 49:12, 2001).*

†Rates are expressed per 100,000 population.

‡Excludes congenital heart disease.

Figure 10-1 Malformations. Human malformations can range in severity from the incidental to the lethal. *Polydactyly* (one or more extra digits) and *syndactyly* (fusion of digits), both of which are illustrated in *A*, have little functional consequence when they occur in isolation. Similarly, *cleft lip (B)*, with or without associated *cleft palate*, is compatible with life when it occurs as an isolated anomaly; in the present case, however, this child had an underlying *malformation syndrome* (trisomy 13) and expired because of severe cardiac defects. The stillbirth illustrated in *C* represents a severe and essentially lethal malformation, where the midface structures are fused or ill-formed; in almost all cases, this degree of external dysmorphogenesis is associated with severe internal anomalies such as maldevelopment of the brain and cardiac defects. *(Pictures A and C courtesy of Dr. Reade Quinton, and B courtesy of Dr. Beverly Rogers, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)*

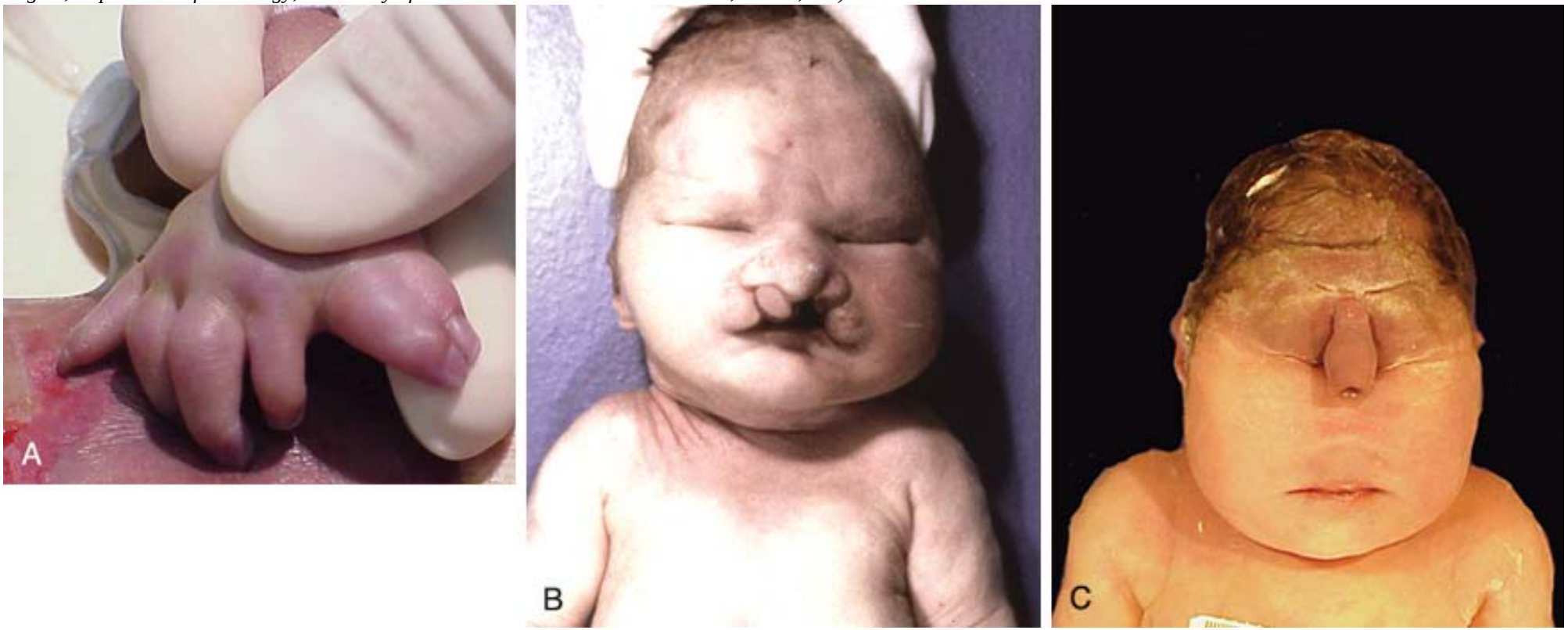

Figure 10-2 Disruption. Disruptions occur in a normally developing organ because of an extrinsic abnormality that interferes with normal morphogenesis. *Amniotic bands* are a frequent cause of disruptions. In the illustrated example, note the placenta at the right of the diagram and the band of amnion extending from the top portion of the amniotic sac to encircle the leg of the fetus. *(Courtesy of Dr. Theonia Boyd, Children's Hospital of Boston, MA.)*

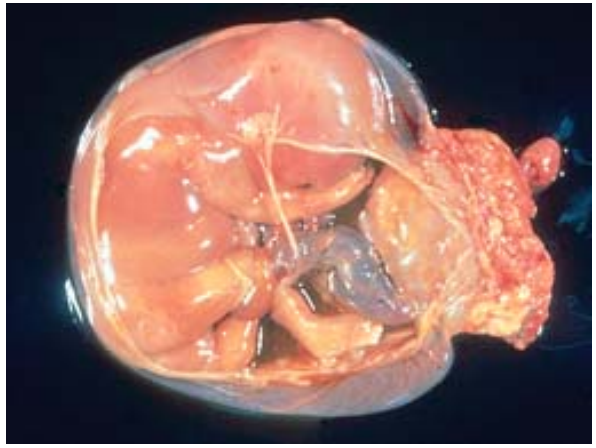

Figure 10-3 Schematic diagram of the pathogenesis of the oligohydramnios sequence.

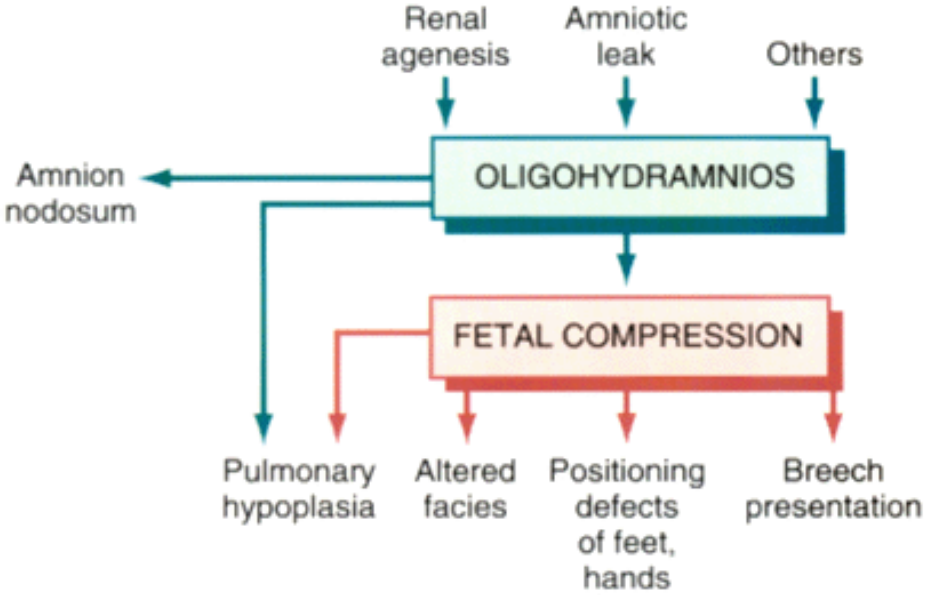

Figure 10-4 Infant with oligohydramnios sequence. Note the flattened facial features and deformed right foot (talipes equinovarus).

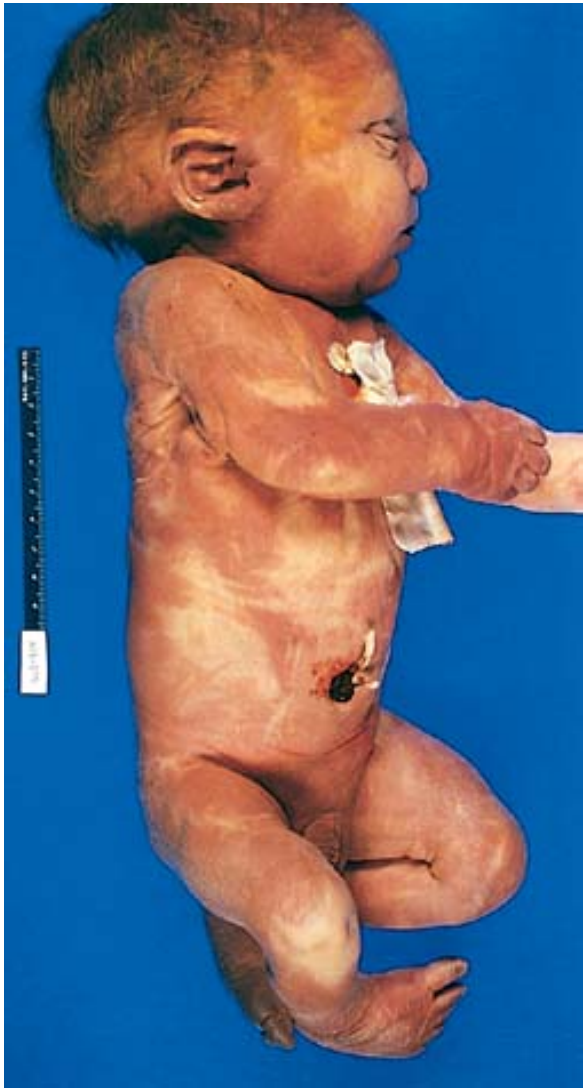

TABLE 10-2 -- Causes of Congenital Anomalies in Humans

Cause	Frequency (%)
Genetic	
Chromosomal aberrations	10–15
Mendelian inheritance	•2–10
Environmental	
Maternal/placental infections	•2–3
••Rubella	

••Toxoplasmosis	
••Syphilis	
••Cytomegalovirus	
••Human immunodeficiency virus (HIV)	
Maternal disease states	•6–8
••Diabetes	
••Phenylketonuria	
••Endocrinopathies	
Drugs and chemicals	•1
••Alcohol	
••Folic acid antagonists	
••Androgens	
••Phenytoin	
••Thalidomide	
••Warfarin	
••13-*cis*-retinoic acid	
••Others	
Irradiations	•1
Multifactorial (Multiple Genes ? Environment)	**20–25**
Unknown	**40–60**
Adapted from Stevenson RE, et al (eds): Human Malformations and Related Anomalies. New York, Oxford University Press, 1993, p. 115.	

Single gene mutations of large effect may underlie major congenital anomalies, which, as expected, follow mendelian patterns of inheritance.[2] Of these, approximately 90% are inherited in an autosomal dominant or recessive pattern, while the remainder segregates in an X-linked pattern. Not surprisingly, many of the mutations that give rise to birth defects involve abrogation of function of genes involved in normal organogenesis and development. For example, holoprosencephaly is the most common developmental defect of the forebrain and midface in humans (see Chapter 28); mutations of *sonic hedgehog*, a gene involved in developmental patterning (see below), have been reported in a subset of patients with holoprosencephaly.[3] Similarly, mutations of a downstream target of sonic hedgehog signaling, *GLI3*, have been reported in patients with anomalies of digits, either conjoined digits *(syndactyly)* or supernumerary digits *(polydactyly)*.

Environmental Causes

Environmental influences, such as viral infections, drugs, and irradiation, to which the mother was exposed during pregnancy may cause fetal malformations (the appellation of "malformation" is loosely used in this context, since technically, these anomalies represent *disruptions*).

Viruses.

Many viruses have been implicated in causing malformations, including the agents responsible for rubella, cytomegalic inclusion disease, herpes simplex, varicella-zoster infection, influenza, mumps, human immunodeficiency virus (HIV), and enterovirus infections. Among these, the rubella virus and cytomegalovirus are the most extensively investigated. With all viruses, the gestational age at which the infection occurs in the mother is critically important. *The at-risk period for rubella infection extends from shortly before conception to the 16th week of gestation*, the hazard being greater in the first 8 weeks than in the second 8 weeks.[4] The incidence of malformations is reduced from 50% to 20% to 7% if infection occurs in the first, second, or third month of gestation. The fetal defects are varied, but the major tetrad comprises cataracts, heart defects (persistent ductus arteriosus, pulmonary artery hypoplasia or stenosis, ventricular septal defect, tetralogy of Fallot), deafness, and mental retardation, referred to as *rubella embryopathy*.

Intrauterine infection with cytomegalovirus, mostly asymptomatic, is the most common fetal viral infection. This viral disease is considered in detail in Chapter 8 ; *the highest at-risk period is the second trimester of pregnancy*. Because organogenesis is largely completed by the end of the first trimester, congenital malformations occur less frequently than in rubella; nevertheless, the effects of virus-induced injury on the formed organs are often severe. Involvement of the central nervous system is a major feature, and the most prominent clinical changes are mental retardation, microcephaly, deafness, and hepatosplenomegaly.

Drugs and Other Chemicals.

A variety of drugs and chemicals have been suspected to be teratogenic, but perhaps less than 1% of congenital malformations are caused by these agents. The list includes thalidomide, folate antagonists, androgenic hormones, alcohol, anticonvulsants, warfarin (oral anticoagulant), and 13-*cis*-retinoic acid used in the treatment of severe acne.[5] For example, *thalidomide*, once used as a tranquilizer in Europe, caused an extremely high frequency (50% to 80%) of limb abnormalities in exposed fetuses.[6] *Alcohol*, perhaps the most widely used agent today, is a teratogen. Affected infants show growth retardation, microcephaly, atrial septal defect, short palpebral fissures, maxillary hypoplasia, and several other minor anomalies. These together are labeled the *fetal alcohol syndrome*.[7] While cigarette smoke-derived nicotine has not been convincingly demonstrated to be a teratogen, there is a high incidence of spontaneous abortions, premature labor, and placental abnormalities in pregnant smokers; babies born to smoking mothers often have a low birth weight and may be prone to sudden infant death syndrome (see later). *In light of these findings, it is best to avoid nicotine exposure altogether during pregnancy.*

Radiation.

In addition to being mutagenic and carcinogenic, radiation is teratogenic. Exposure to heavy doses of radiation during the period of organogenesis leads to malformations, such as microcephaly, blindness, skull defects, spina bifida, and other deformities. Such exposure occurred in the past when radiation was used to treat cervical cancer.

Maternal Diabetes.

Among maternal conditions listed in Table 10-2 , diabetes mellitus is a common entity, and despite advances in antenatal obstetric monitoring and glucose

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control, the incidence of major malformations in infants of diabetic mothers stands between 6% and 10% in most series. Maternal hyperglycemia-induced fetal hyperinsulinemia results in increased body fat, muscle mass, and organomegaly *(fetal macrosomia)*; cardiac anomalies, neural tube defects, and other central nervous system malformations are some of the major anomalies seen in *diabetic embryopathy*.[8]

Multifactorial Causes

The genetic and environmental factors just discussed account for no more than half of human congenital anomalies. The causes of the vast majority of birth defects, including some relatively common disorders such as cleft lip and cleft palate, remain unknown. In these anomalies, it would appear that inheritance of a certain number of mutant genes and their interaction with the environment is required before the disorder is expressed. In the case of congenital dislocation of the hip, for example, depth of the acetabular socket and laxity of the ligaments are believed to be genetically determined, whereas a significant environmental factor is believed to be frank breech position in utero, with hips flexed and knees extended. The importance of environmental contribution to multifactorial inheritance is underscored by a dramatic reduction in the incidence of neural tube defects by periconceptional intake of folic acid in the diet.[9] [10] The approximate frequency of some common congenital anomalies in the United States is presented in Table 10-3 . Both temporal and regional variability are common in the reporting of many malformations. For example, between 1979 and 1989, there was a mean annual percent decrease in the incidence of anencephaly of 6.4 and a mean annual increase in the incidence of atrial septal defect of 22.0.[11]

PATHOGENESIS OF CONGENITAL ANOMALIES

The pathogenesis of congenital anomalies is complex and still poorly understood, but certain general principles of

TABLE 10-3 -- Approximate Frequency of the More Common Congenital Malformations in the United States

Malformation	Frequency per 10,000 Total Births
Clubfoot without central nervous system anomalies	25.7
Patent ductus arteriosus	16.9
Ventricular septal defect	10.9
Cleft lip with or without cleft palate	•9.1
Spina bifida without anencephalus	•5.5
Congenital hydrocephalus without anencephalus	•4.8
Anencephalus	•3.9
Reduction deformity (musculoskeletal)	•3.5
Rectal and intestinal atresia	•3.4

Adapted from James LM: Maps of birth defects occurrence in the U.S., birth defects monitoring program (BDMP)/CPHA, 1970–1987. Teratology 48:551, 1993.

developmental pathology are relevant regardless of the etiologic agent.

The timing of the prenatal teratogenic insult has an important impact on the occurrence and the type of anomaly produced (Fig. 10-5). The intrauterine development of humans can be divided into two phases: (1) the embryonic period occupying the first 9 weeks of pregnancy and (2) the fetal period terminating at birth.

In the *early embryonic period* (first 3 weeks after fertilization), an injurious agent damages either enough cells to cause death and abortion or only a few cells, presumably allowing the embryo to recover without developing defects. *Between the third and the ninth weeks, the embryo is extremely susceptible to teratogenesis,* and the peak sensitivity during this period occurs between the fourth and the fifth weeks. During this period, organs are being crafted out of the germ cell layers. The *fetal period* that follows organogenesis is marked chiefly by the further growth and maturation of the organs, with greatly reduced susceptibility to teratogenic agents. Instead the fetus is susceptible to growth retardation or injury to already formed

organs. It is therefore possible for a given agent to produce different anomalies if exposure occurs at different times of gestation.

Teratogens and genetic defects may act at several steps involved in normal morphogenesis. These include the following: [12]

- Proper *cell migration* to predetermined locations that influence the development of other structures
- *Cell proliferation*, which determines the size and form of embryonic organs
- *Cellular interactions* among tissues derived from different structures (e.g., ectoderm, mesoderm), which affect the differentiation of one or both of these tissues
- *Cell-matrix associations*, which affect growth and differentiation
- *Programmed cell death (apoptosis)*, which, as we have seen, allows orderly organization of tissues and organs during embryogenesis (Chapter 1)
- *Hormonal influences* and *mechanical forces*, which affect morphogenesis at many levels.

The complex interplay between environmental teratogens and intrinsic genetic defects is underscored by the fact that features of dysmorphogenesis caused by environmental insults can be recapitulated by certain genetic defects. This is exemplified in the relationship between the teratogen, retinoic acid (see below and Fig. 10-6), and two growth factors—transforming growth factor (TGF) and fibroblast growth factor (FGF)—both involved in morphogenesis. As discussed later, retinoic acid can induce defects in palatal development *(cleft lip and cleft palate)*, possibly by impacting on multiple targets associated with secondary palatal development. In experimental models of retinoic acid teratogenesis, abnormal expression of TGF and FGF has been reported in the developing palate.[13] [14] Not unexpectedly, therefore, rare single gene mutations in one or more of these growth factors or their receptors may also cause palatal abnormalities. There is an association, for example, between rare mutations of the *TGF-α* gene and nonsyndromic cleft lip or cleft palate in humans;[15] in addition, loss of function of the epidermal growth factor receptor, which acts as a receptor for TGF-α, can result in abnormal palatogenesis.[16] Disruption of TGF-β3 in mice also results in cleft palate.[17]

Figure 10-5 Critical periods of development for various organ systems and the resultant malformations. *(Modified and redrawn from Moore KL: The Developing Human, 5th ed. Philadelphia, WB Saunders, 1993, p. 156.)*

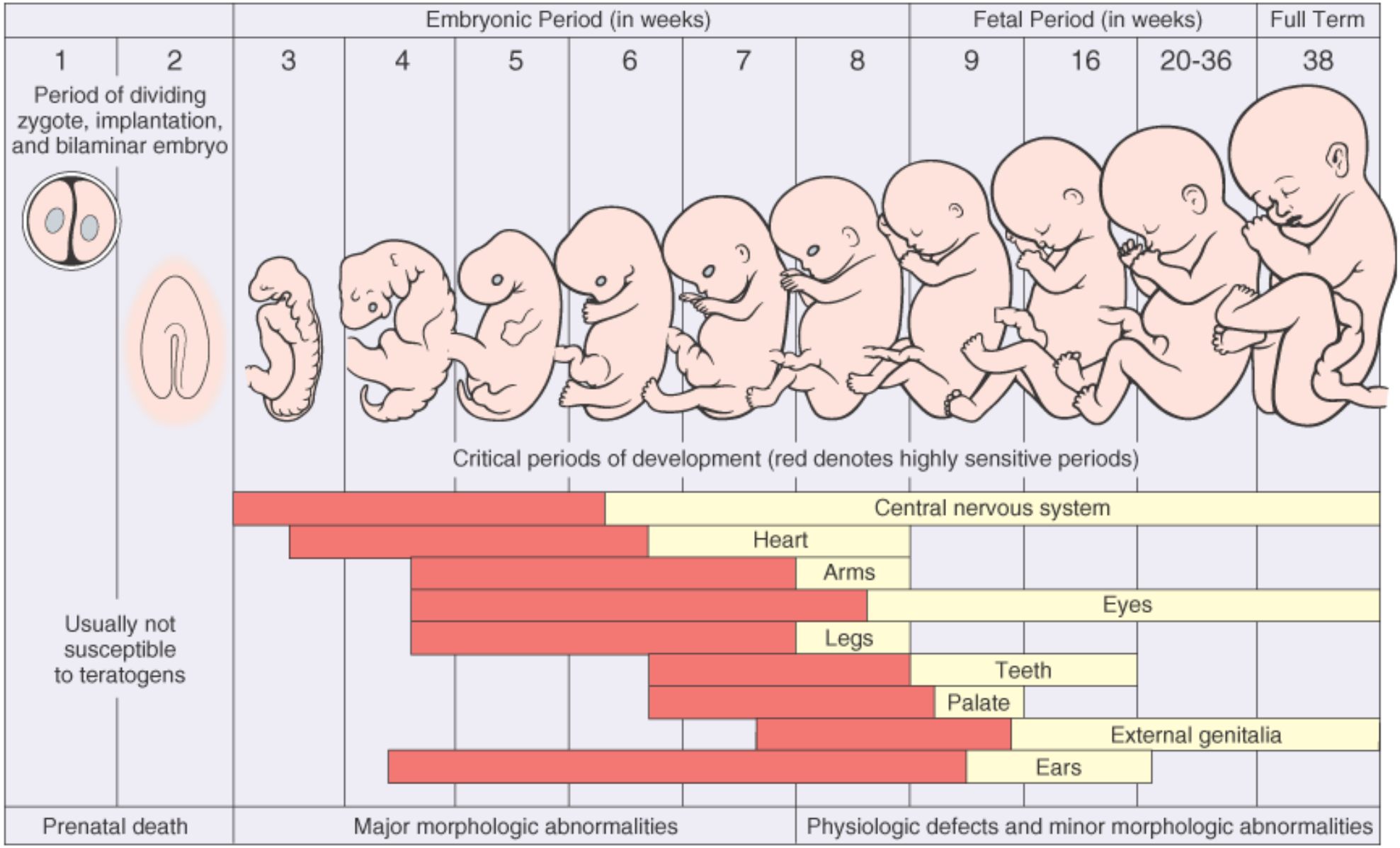


Figure 10-6 Schematic representation of the postulated role of retinoic acid in normal development, the general features of its deficiency (vitamin A deficiency) *(left)* and retinoic acid embryopathy *(right)*. *1*, Retinol in the maternal circulation is bound by retinol-binding protein (RBP), which is synthesized by the placenta and enters the fetal circulation. *2*, Once in fetal cells, retinol is bound by cytoplasmic retinol-binding protein (CRBP), which *(3)* regulates the conversion to retinoic acid and metabolites. The retinoic acid either remains in the cytoplasm (bound to cytoplasmic/cellular retinoic acid-binding protein *[CRABP])* or *(4)* enters the nucleus, where it is bound to nuclear retinoic acid receptors *(RAR, RXR)*. The retinoic acid-receptor complex acts as a transcriptional regulator of various patterning genes (e.g., *HOX*) that have the appropriate retinoic acid response element *(RARE)*. Expression of the binding proteins and receptors in various tissues and at various times during embryogenesis may be a mechanism of selectively modulating the action of retinoic acid. This differential expression may also explain the pattern of abnormalities seen in vitamin A deficiency and retinoic acid embryopathy.

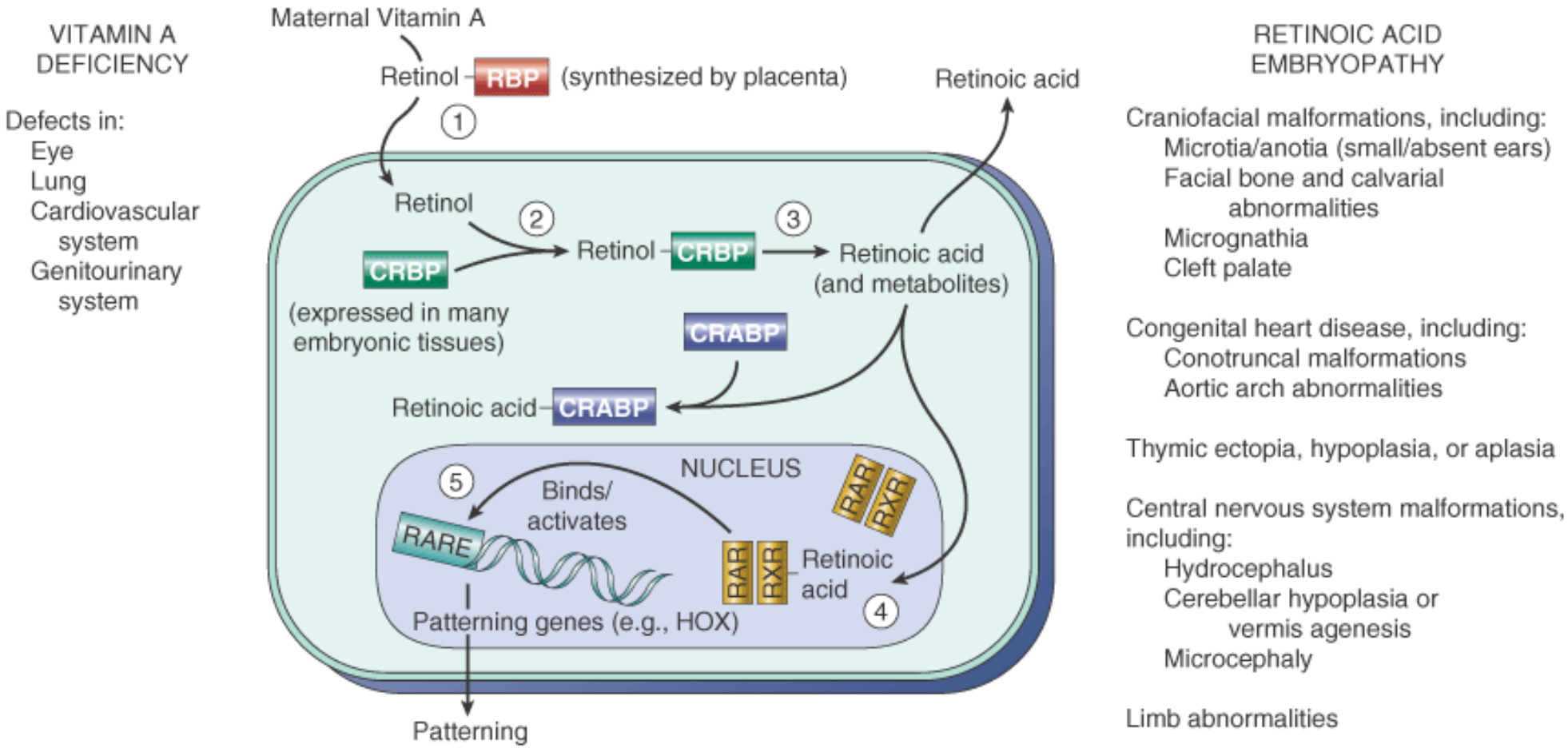


Figure 10-7 Diagrammatic representation of constitutional chromosomal mosaicism. *A*, Generalized. *B*, Confined to the placenta. *C*, Confined to the embryo. *(Modified and redrawn from Kalousek DK: Confined placental mosaicism and intrauterine development. Pediatr Pathol 10:69, 1990.)*

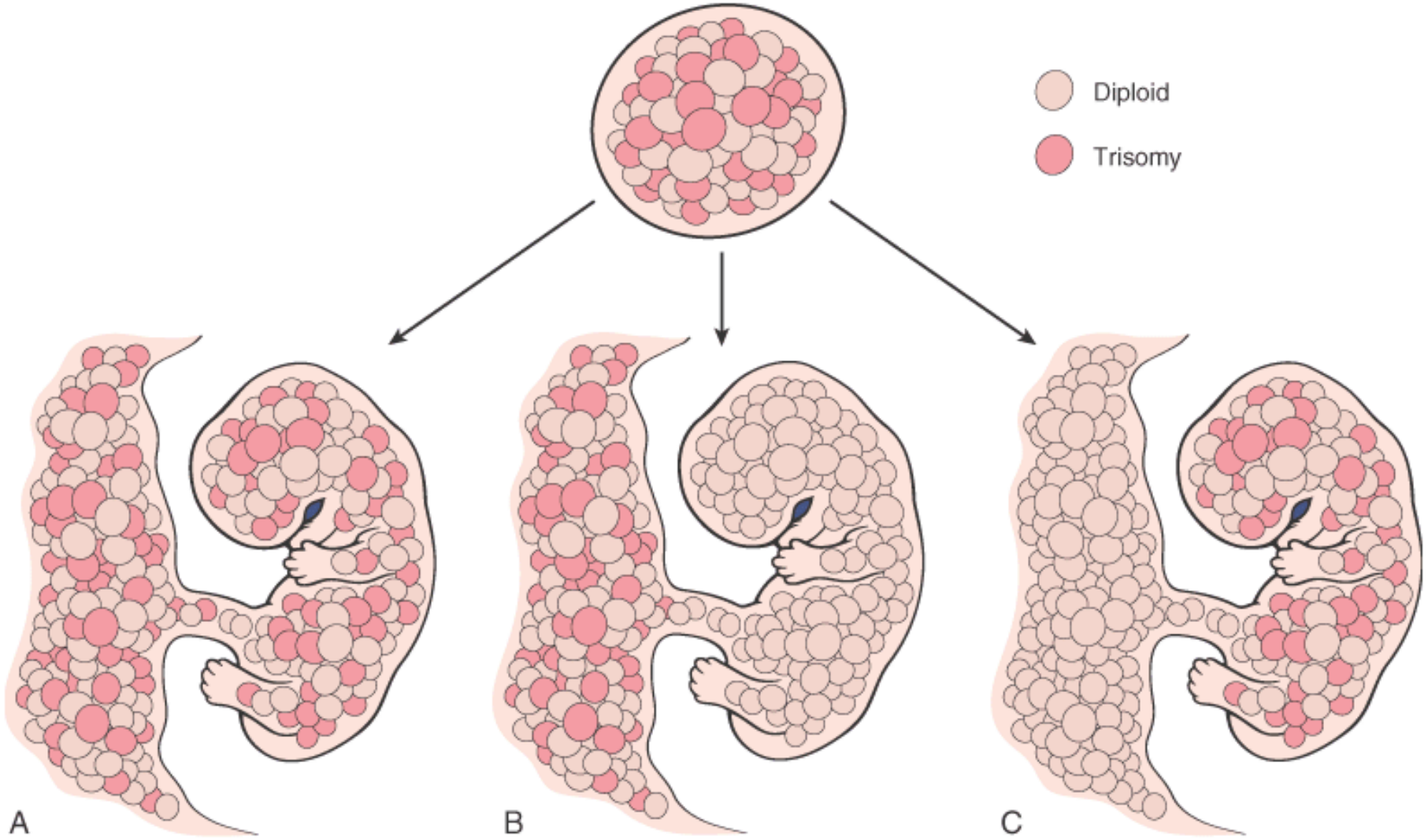
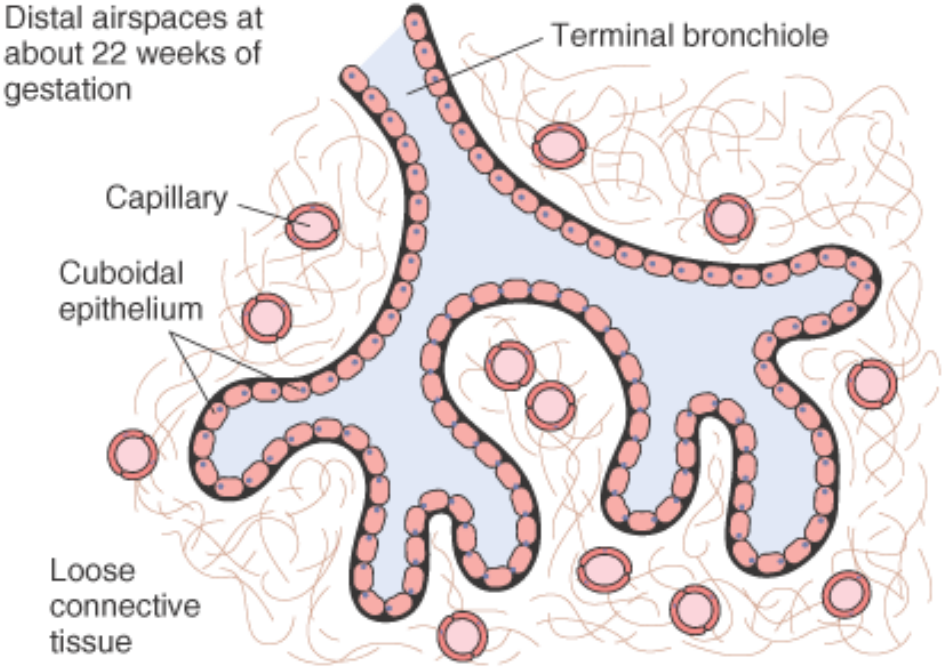


Figure 10-8 Schematic diagrams of fetal lung maturation.



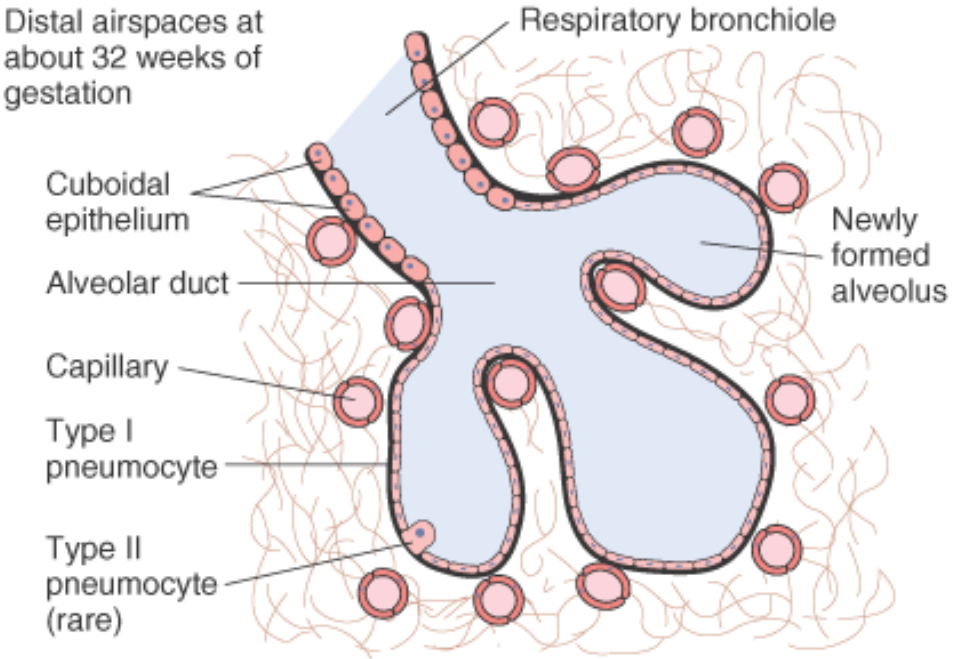


TABLE 10-4 -- Evaluation of the Newborn Infant *

Sign	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

Data from Apgar V: A proposal for a new method of evaluation of the newborn infant. Anesth Analg 32:260, 1953.

*Sixty seconds after the complete birth of the infant (disregarding removal of the cord and placenta), the five objective signs are evaluated and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition.

risk for birth injury, in particular those involving the skeletal system and peripheral nerves. We briefly discuss only injuries involving the head because they are the most ominous.

Intracranial hemorrhages are the most common important birth injury. These hemorrhages are generally related to excessive molding of the head or sudden pressure changes in its shape as it is subjected to the pressure of forceps or sudden precipitate expulsion. Prolonged labor, hypoxia, hemorrhagic disorders, or intracranial vascular anomalies are important predispositions. The hemorrhage may arise from tears in the dura or from rupture of vessels that traverse the brain. The substance of the brain may be torn or bruised, leading to intraventricular hemorrhages or bleeding into the brain substance. The consequences of intracranial hemorrhages are mentioned later under germinal matrix hemorrhage.

Caput succedaneum and *cephalhematoma* are so common, even in normal uncomplicated births, that they hardly merit the designation *birth injury*. The first refers to progressive accumulation of interstitial fluid in the soft tissues of the scalp, giving rise to a usually circular area of edema, congestion, and swelling at the site where the head begins to enter the lower uterine canal. Hemorrhage may occur into the scalp, producing a cephalhematoma. Both forms of injury are of little clinical significance and are important only insofar as they must be differentiated from skull fractures with attendant hemorrhage and edema. In approximately 25% of cephalhematomas, there is an underlying skull fracture. Such skull fractures may occur in cases of precipitate delivery, inappropriate use of forceps, or prolonged labor with disproportion between the size of the fetal head and birth canal.

Perinatal Infections

Infections of the embryo, fetus, and neonate are manifested in a variety of ways and are mentioned as etiologic factors in numerous other sections within this chapter. Here we discuss only the general routes and timing of infections. In general, fetal and perinatal infections are acquired via one of two primary routes—*transcervically* (also referred to as *ascending*) or *transplacentally (hematologic)*. Occasionally, infections occur by a combination of the two routes in that an ascending microorganism infects the endometrium and then the fetal bloodstream via the chorionic villi.

TRANSCERVICAL (ASCENDING) INFECTIONS

Most bacterial and a few viral (e.g., herpes simplex II) infections are acquired by the cervicovaginal route. Such infections may be acquired in utero or around the time of birth. In general,

the fetus acquires the infection either by inhaling infected amniotic fluid into the lungs shortly before birth or by passing through an infected birth canal during delivery. As previously stated, preterm birth is often an unfortunate consequence and may be related either to damage and rupture of the amniotic sac as a direct consequence of the inflammation or to the induction of labor associated with a release of prostaglandins by the infiltrating neutrophils. Chorioamnionitis of the placental membranes and funisitis are usually demonstrable, although the presence or absence and severity of chorioamnionitis do not necessarily correlate with the severity of the fetal infection. In the fetus infected via inhalation of amniotic fluid, pneumonia, sepsis, and meningitis are the most common sequelae.

TRANSPLACENTAL (HEMATOLOGIC) INFECTIONS

Most parasitic (e.g., toxoplasma, malaria) and viral infections and a few bacterial infections (i.e., *Listeria, Treponema*) gain access to the fetal bloodstream transplacentally via the chorionic villi. This hematogenous transmission may occur at any time during gestation or occasionally, as may be the case with hepatitis B and HIV, at the time of delivery via maternal-to-fetal transfusion. The clinical manifestations of these infections are highly variable, depending largely on the gestational timing and microorganism involved.

Some infections, such as those with *parvovirus B19* (which causes *fifth disease* in the mother), may induce spontaneous abortion, stillbirth, hydrops fetalis, and congenital anemia.[40] While the virus can bind to different cell types, replication occurs only in erythroid cells, and diagnostic viral cytopathic effect can be recognized in late erythroid progenitor cells of infected infants (Fig. 10-9).

The *TORCH group of infections* (see above) are grouped together because they may evoke similar clinical and pathologic manifestations, including *fever*, *encephalitis*, *chorioretinitis*, *hepatosplenomegaly*, *pneumonitis*, *myocarditis*, *hemolytic anemia*, *and vesicular or hemorrhagic skin lesions*. Such infections occurring early in gestation may also cause chronic sequelae in the child, including growth and mental retardation, cataracts, congenital cardiac anomalies, and bone defects.

ONSET OF SEPSIS

Perinatal infections can also be grouped clinically by whether they tend to result in *early-onset* (within the first 7 days of life) versus *late-onset* sepsis (from 7 days to 3 months). Most cases of early-onset sepsis are acquired at or shortly before birth and tend to result in clinical signs and symptoms of pneumonia, sepsis, and occasionally meningitis within 4 or 5 days of life. Group B streptococcus is the most common

Figure 10-9 Bone marrow from an infant infected with parvovirus B19. The arrows point to two erythroid precursors with large homogeneous intranuclear inclusions and a surrounding peripheral rim of residual chromatin.

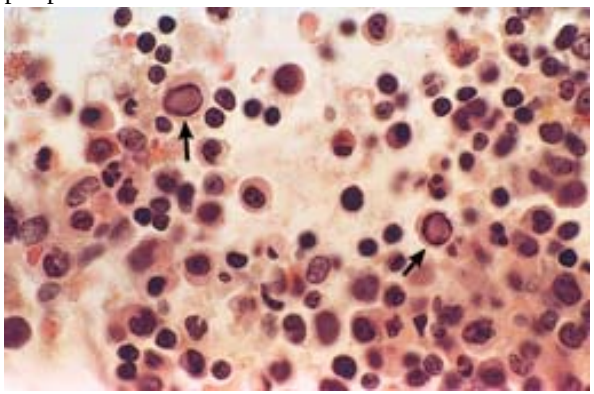


Figure 10-10 Schematic outline of the pathophysiology of the respiratory distress syndrome (see text).

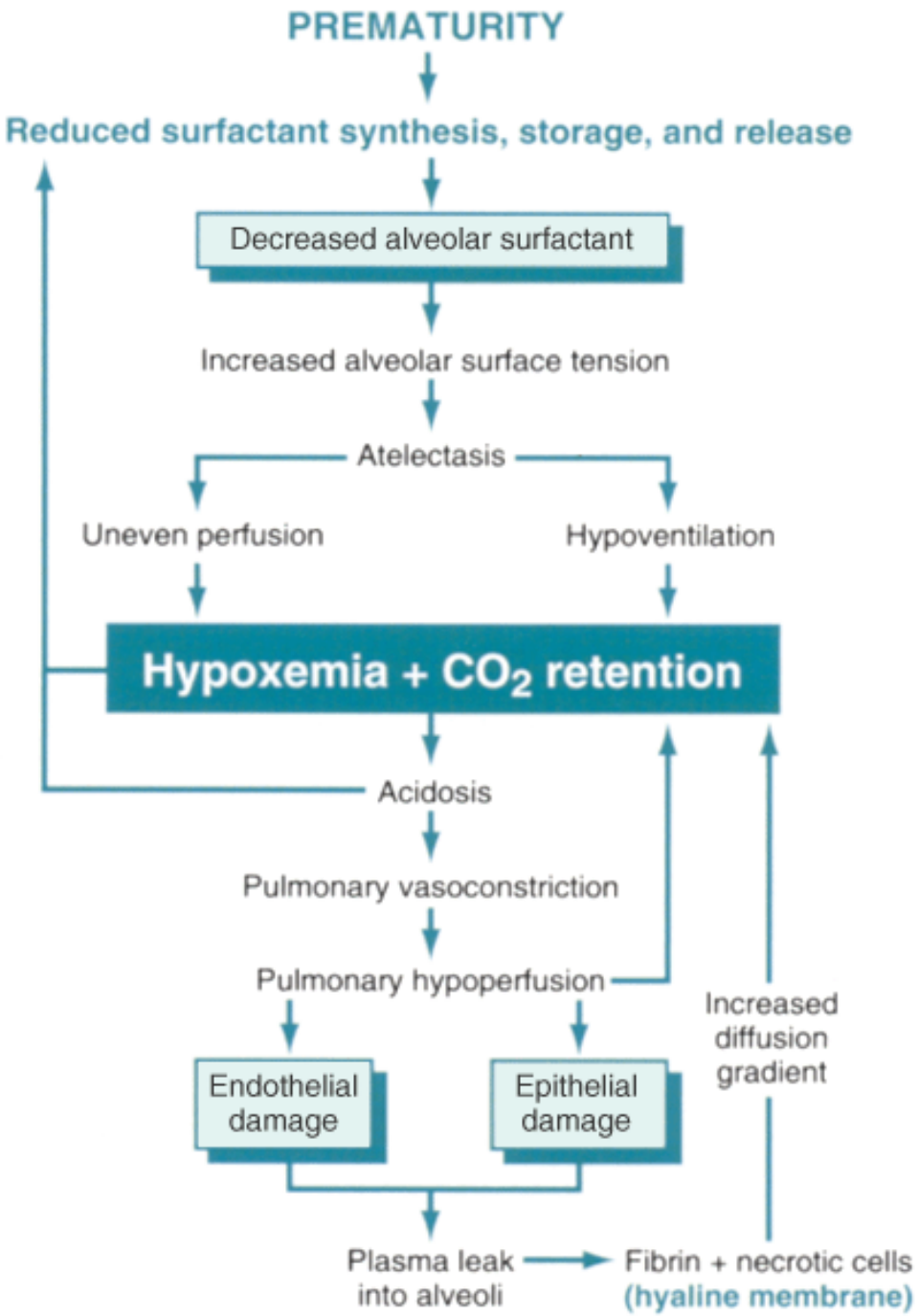


Figure 10-11 Hyaline membrane disease. There is alternating atelectasis and dilation of the alveoli. Note the eosinophilic thick hyaline membranes lining the dilated alveoli.

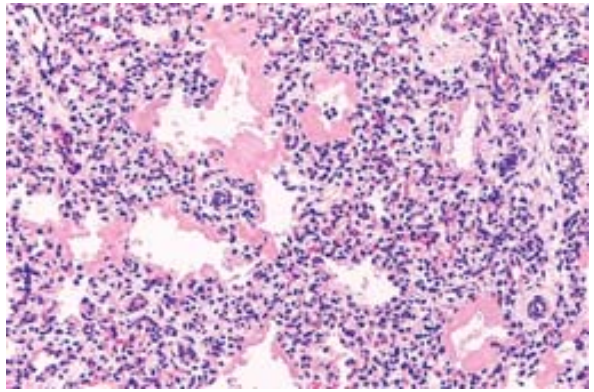


Figure 10-12 Necrotizing enterocolitis. *A,* Postmortem examination in a severe case of NEC shows the entire small bowel is markedly distended with a perilously thin wall (usually this implies impending perforation). *B,* The congested portion of the ileum corresponds to areas of hemorrhagic infarction and transmural necrosis microscopically. Submucosal gas bubbles *(pneumatosis intestinalis)* can be seen in several areas *(arrows).*

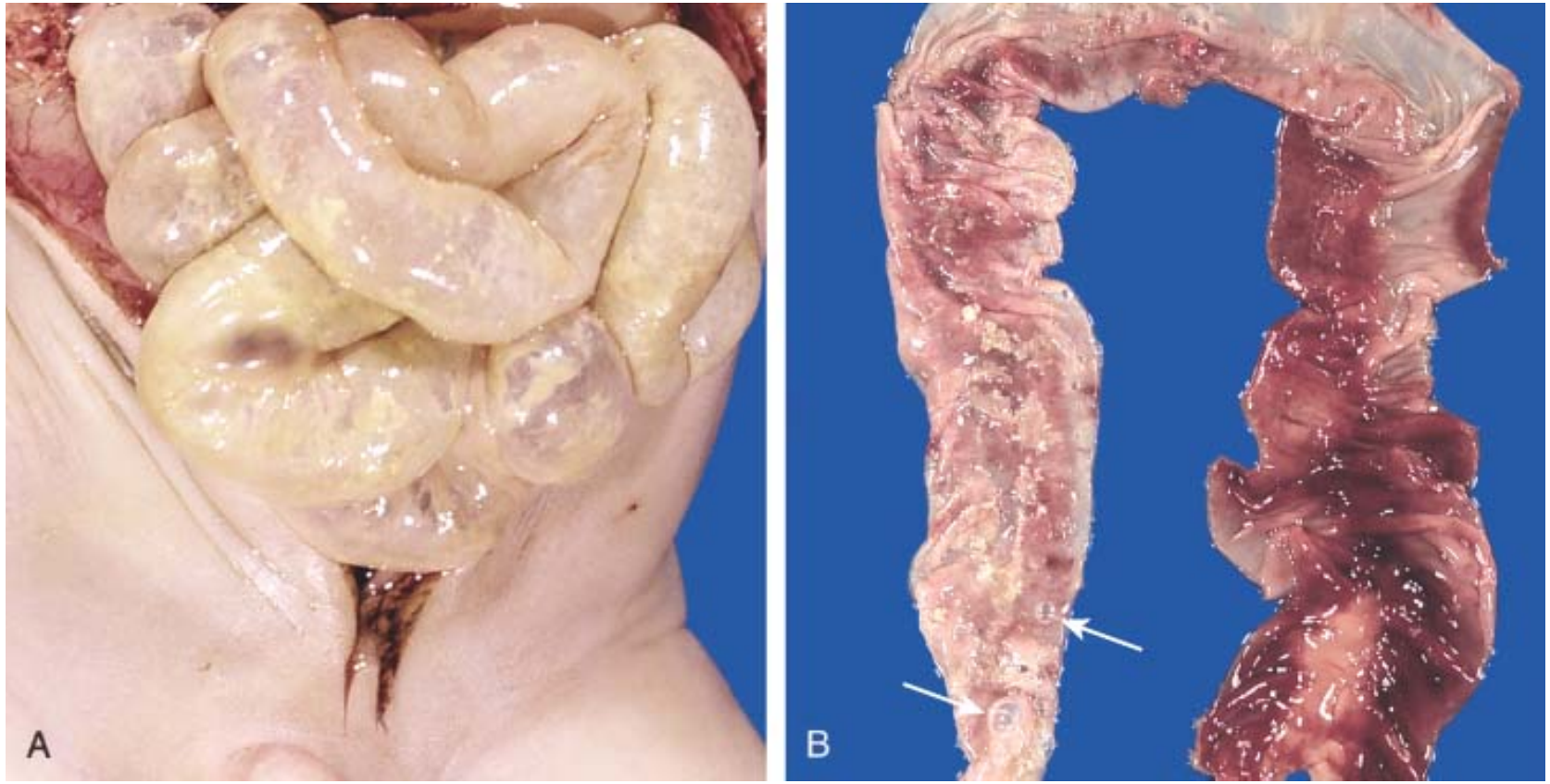


Figure 10-13 Hydrops fetalis. There is generalized accumulation of fluid in the fetus. In *B,* fluid accumulation is particularly prominent in the soft tissues of the neck, and this condition has been termed *cystic hygroma*. Cystic hygromas are characteristically seen, but not limited to, constitutional chromosomal anomalies such as 45,X0 karyotypes. *(Courtesy of Dr. Beverly Rogers, Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX.)*

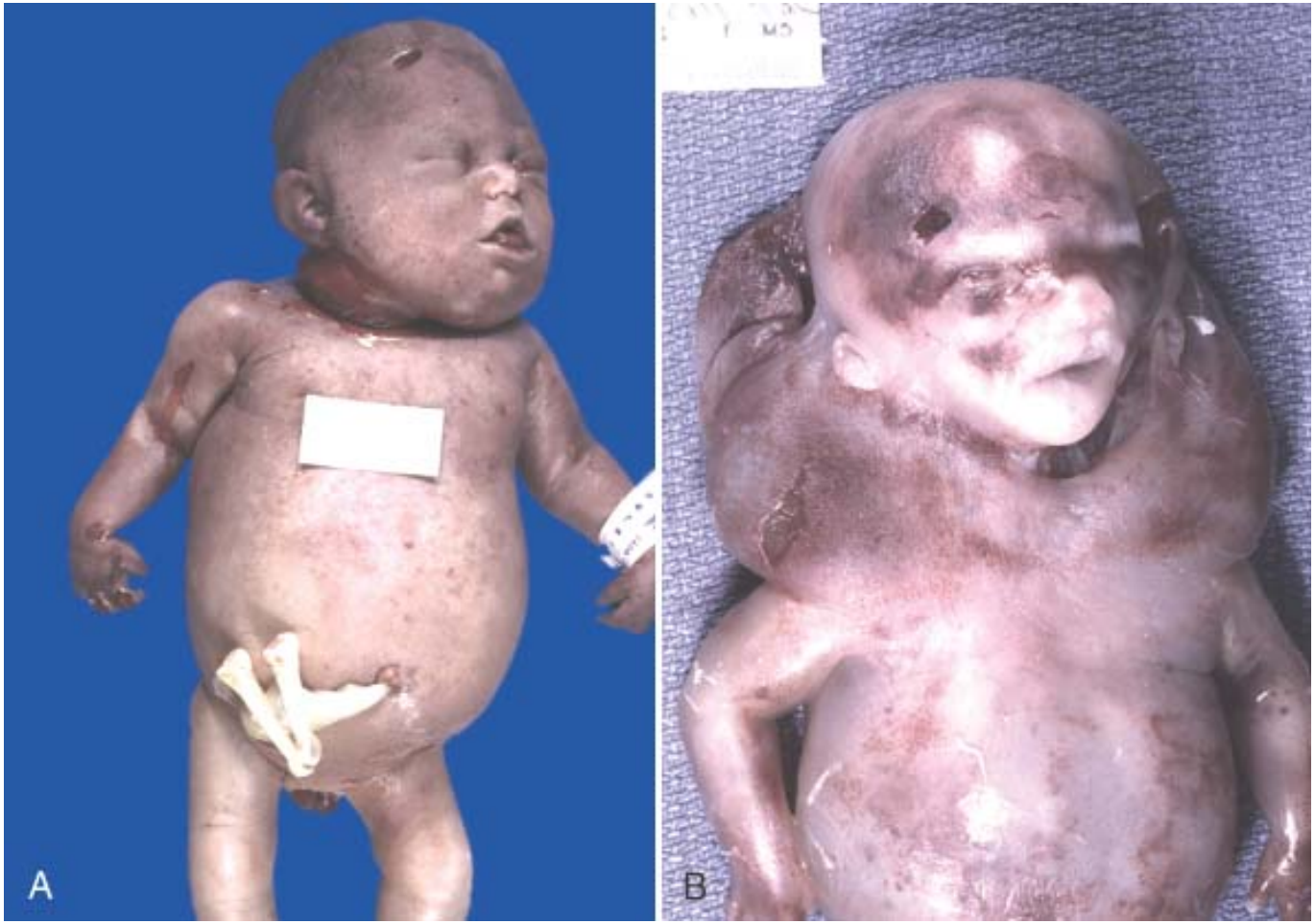


TABLE 10-5 -- Selected Causes of Hydrops Fetalis (in decreasing order of frequency)

Cardiovascular
Malformations
Tachyarrhythmia
High-output failure
Chromosomal
Turner syndrome
Trisomy 21, trisomy 18
Thoracic Causes
Cystic adenomatoid malformation

Diaphragmatic hernia
Fetal Anemia
Homozygous alpha-thalassemia
Parvovirus B19
Immune hydrops (Rh and ABO)
Twin Gestation
Twin-to-twin transfusion
Infection (excluding parvovirus)
Cytomegalovirus
Syphilis
Toxoplasmosis
Major Malformations
Tumors
Metabolic disorders
Note: The cause of fetal hydrops may be undetermined ("idiopathic") in up to 20% of cases. *Data from Machin GA: Hydrops, cystic hygroma, hydrothorax, pericardial effusions, and fetal ascites, In Gilbert-Barness E (ed): Potter's Pathology of Fetus and Infant. St. Louis, Mosby-Year Book, 1997.*

IMMUNE HYDROPS

Immune hydrops is defined as a hemolytic disease in the newborn caused by blood-group incompatibility between mother and child. When the fetus inherits red cell antigenic determinants from the father that are foreign to the mother, a maternal immune reaction may occur, leading to hemolytic disease in the infant. Any of the numerous red cell antigenic systems may theoretically be involved, but the major antigens known to induce clinically significant immunologic disease are the ABO and certain of the Rh antigens. The incidence of immune hydrops in urban populations has declined remarkably, owing largely to the current methods of preventing Rh immunization in at-risk mothers. Successful prophylaxis of this disorder has resulted directly from an understanding of its pathogenesis.

Etiology and Pathogenesis.

The underlying basis of immune hydrops is the immunization of the mother by blood group antigens on fetal red cells and the free passage of antibodies from the mother through the placenta to the fetus (Fig. 10-14). Fetal red cells may reach the maternal circulation during the last trimester of pregnancy, when the cytotrophoblast is no longer present as a barrier, or during childbirth itself. The mother thus becomes sensitized to the foreign antigen.

Of the numerous antigens included in the Rh system, only the D antigen is the major cause of Rh incompatibility. Several

Figure 10-14 Pathogenesis of immune hydrops fetalis (see text).

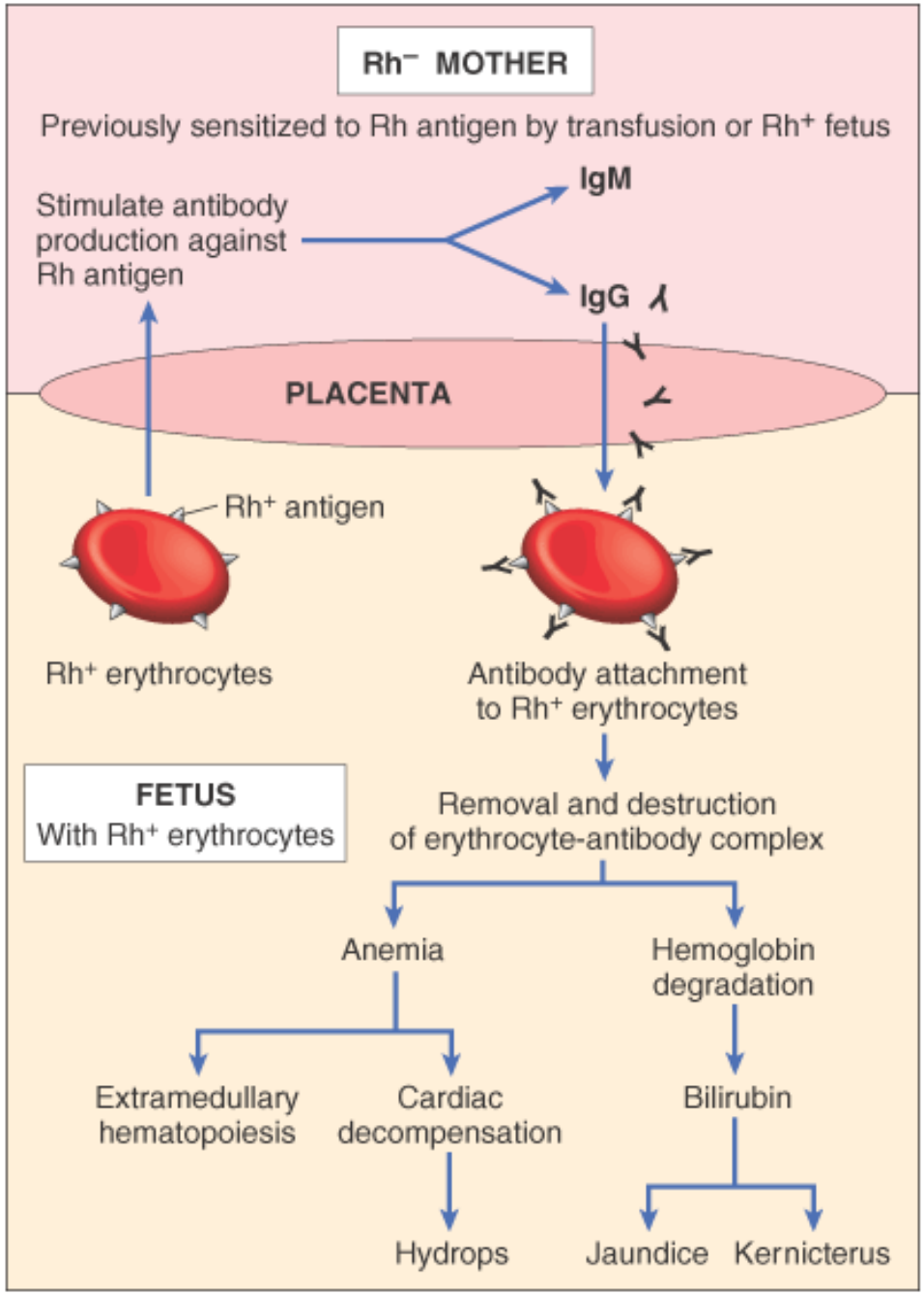


Figure 10-15 Numerous islands of extramedullary hematopoiesis (small blue cells) are scattered among mature hepatocytes in this infant with nonimmune hydrops fetalis.

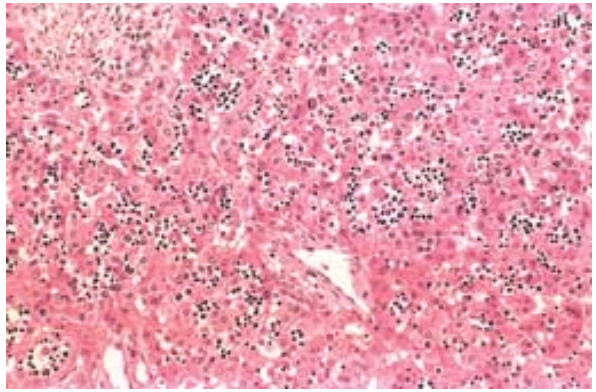


Figure 10-16 Kernicterus. Severe hyperbilirubinemia in the neonatal period, for example, secondary to immune hemolysis, results in deposition of bilirubin pigment in the brain parenchyma. This occurs because the blood-brain barrier is less well developed in the neonatal period than it is in adulthood. Infants who survive develop long-term neurologic sequelae.

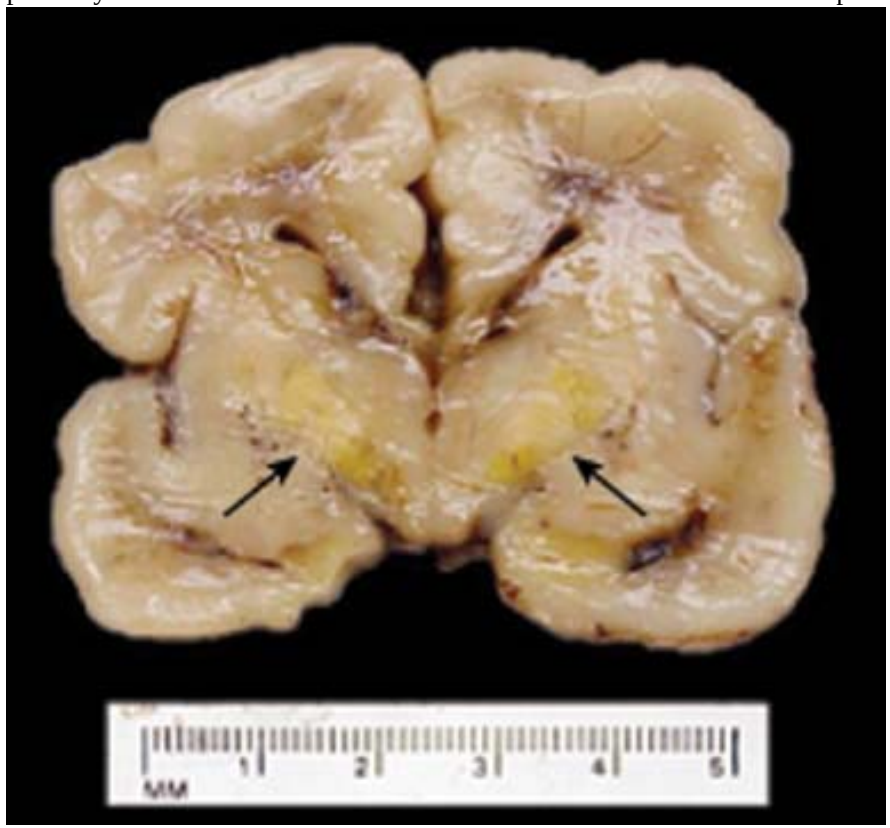


TABLE 10-6 -- Abnormalities Suggesting Inborn Errors of Metabolism

General
Dysmorphic features

Deafness
Self-mutilation
Abnormal hair
Abnormal body or urine odor ("sweaty feet"; "mousy or musty"; "maple syrup")
Hepatosplenomegaly; cardiomegaly
Hydrops
Neurologic
Hypotonia or hypertonia
Coma
Persistent lethargy
Seizures
Gastrointestinal
Poor feeding
Recurrent vomiting
Jaundice
Eyes
Cataract
Cherry red macula
Dislocated lens
Glaucoma
Muscle, Joints
Myopathy
Abnormal mobility
Adapted from Barness LA and Gilbert-Barness E: Metabolic diseases, In Gilbert-Barness E (ed): Potter's Pathology of Fetus and Infant. St. Louis, Mosby-Year Book, 1997.

Homozygotes with this autosomal recessive disorder classically have a severe deficiency of phenylalanine hydroxylase, leading to hyperphenylalaninemia and its pathologic consequences. Affected infants are normal at birth but within a few weeks develop a rising plasma phenylalanine level, which in some way impairs brain development. Usually by 6 months of life *severe mental retardation* becomes evident; fewer than 4% of untreated PKU children have intelligence quotient values greater than 50 or 60. About one third of these children are never able to walk, and two thirds cannot talk. *Seizures*, other neurologic abnormalities, *decreased pigmentation of hair* and skin, and eczema often accompany the mental retardation in untreated children. Hyperphenylalaninemia and the resultant mental retardation can be avoided by restriction of phenylalanine intake early in life. Hence, a number of screening procedures are routinely used for detection of PKU in the immediate postnatal period.

Many clinically normal female PKU patients who are treated with dietary control early in life reach childbearing age. Most of them discontinue dietary treatment and have marked hyperphenylalaninemia. Between 75% and 90% of children born to such women are mentally retarded and

---

microcephalic, and 15% have congenital heart disease, even though the infants themselves are heterozygotes. This syndrome, termed *maternal PKU*, results from the teratogenic effects of phenylalanine or its metabolites that cross the placenta and affect specific fetal organs during development.[62] The presence and severity of the fetal anomalies directly correlate with the maternal phenylalanine level, so *it is imperative that maternal dietary restriction of phenylalanine is initiated before conception and continues throughout the pregnancy*.

The biochemical abnormality in PKU is an inability to convert phenylalanine into tyrosine. In normal children, less than 50% of the dietary intake of phenylalanine is necessary for protein synthesis. The rest is irreversibly converted to tyrosine by a complex *hepatic phenylalanine hydroxylase system* (Fig. 10-17), which, in addition to the enzyme *phenylalanine hydroxylase*, has two other components: the cofactor *tetrahydrobiopterin (BH_4)* and the enzyme *dihydropteridine reductase*, which regenerates BH_4 . Although neonatal hyperphenylalaninemia can be caused by deficiencies in any of these components, 98% to 99% of cases are attributable to abnormalities in phenylalanine hydroxylase. With a block in phenylalanine metabolism owing to lack of phenylalanine hydroxylase, minor shunt pathways come into play, yielding phenylpyruvic acid, phenyllactic acid, phenylacetic acid, and *o*-hydroxyphenylacetic acid, which are excreted in large amounts in the urine in PKU. Some of these abnormal metabolites are excreted in the sweat, and phenylacetic acid in particular imparts a strong *musty* or *mousy odor* to affected infants. It is believed that excess phenylalanine or its metabolites contribute to the brain damage in PKU.

At the molecular level, several mutant alleles of the phenylalanine hydroxylase gene have been identified. Each mutation induces a particular alteration in the enzyme resulting in a corresponding quantitative effect on residual enzyme activity ranging from complete absence to 50% of normal values. The degree of hyperphenylalaninemia and clinical phenotype is inversely related to the amount of residual enzyme activity. Infants with mutations resulting in a lack of phenylalanine hydroxylase activity present with the classic features of PKU, while those with up to 6% residual activity present with milder disease. Moreover, some mutations result in only modest elevations of phenylalanine levels, and the affected children have no neurologic damage. This latter condition, referred to as *benign hyperphenylalaninemia*, or *mild PKU*, is important to recognize because the individuals may well test *positive* in screening tests but do not develop the stigmata of classic PKU.[63] Measurement of serum phenylalanine levels differentiates benign hyperphenylalaninemia and classic PKU.

Although dietary restriction of phenylalanine is relatively successful in reducing or preventing the mental retardation associated with PKU, there are problems with long-term compliance (resulting in a decline in mental or behavioral status)

Figure 10-17 The phenylalanine hydroxylase system.

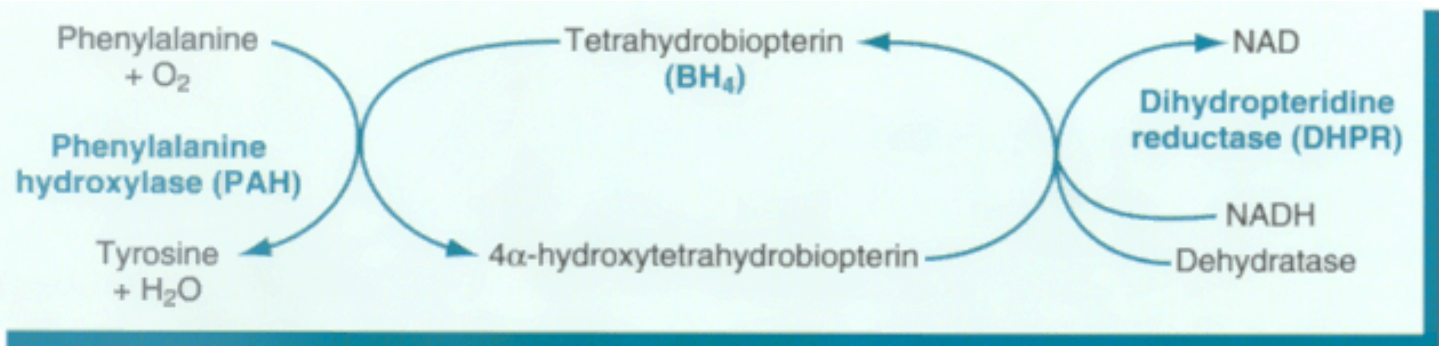


Figure 10-18 Pathways of galactose metabolism.

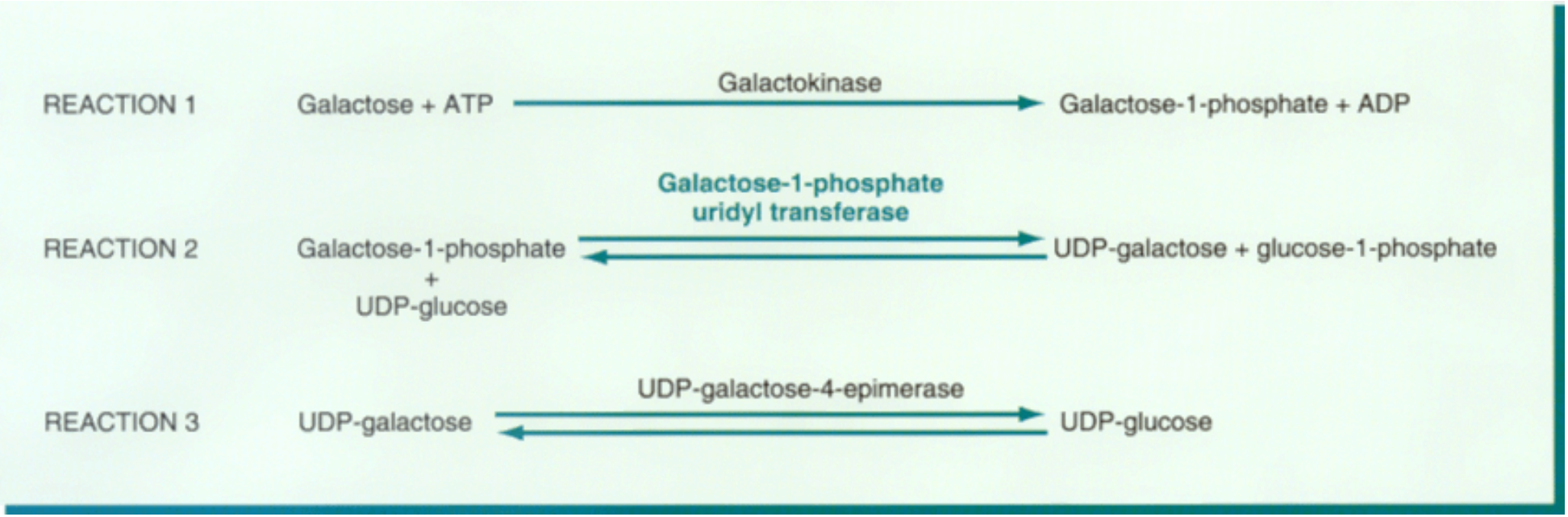


Figure 10-19 Galactosemia. The liver shows extensive fatty change and a delicate fibrosis. *(Courtesy of Dr. Wesley Tyson, The Children's Hospital, Denver, CO.)*

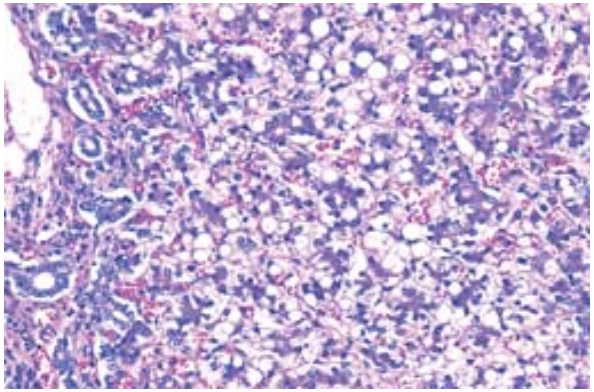


Figure 10-20 *Top*, Normal cystic fibrosis transmembrane conductance regulator (CFTR) structure and activation. CFTR consists of two transmembrane domains, two nucleotide-binding domains (NBD), and a regulatory R domain. Agonists (e.g., acetylcholine) bind to epithelial cells and increase cAMP, which activates protein kinase A, the latter phosphorylating the CFTR at the R domain, resulting in opening of the chloride channel. *Bottom*, CFTR from gene to protein. The most common mutation in the *CFTR* gene results in defective protein folding in the Golgi/ER and degradation of CFTR before it reaches the cell surface. Other mutations affect synthesis of CFTR, nucleotide-binding and R domains, and membrane-spanning domains.

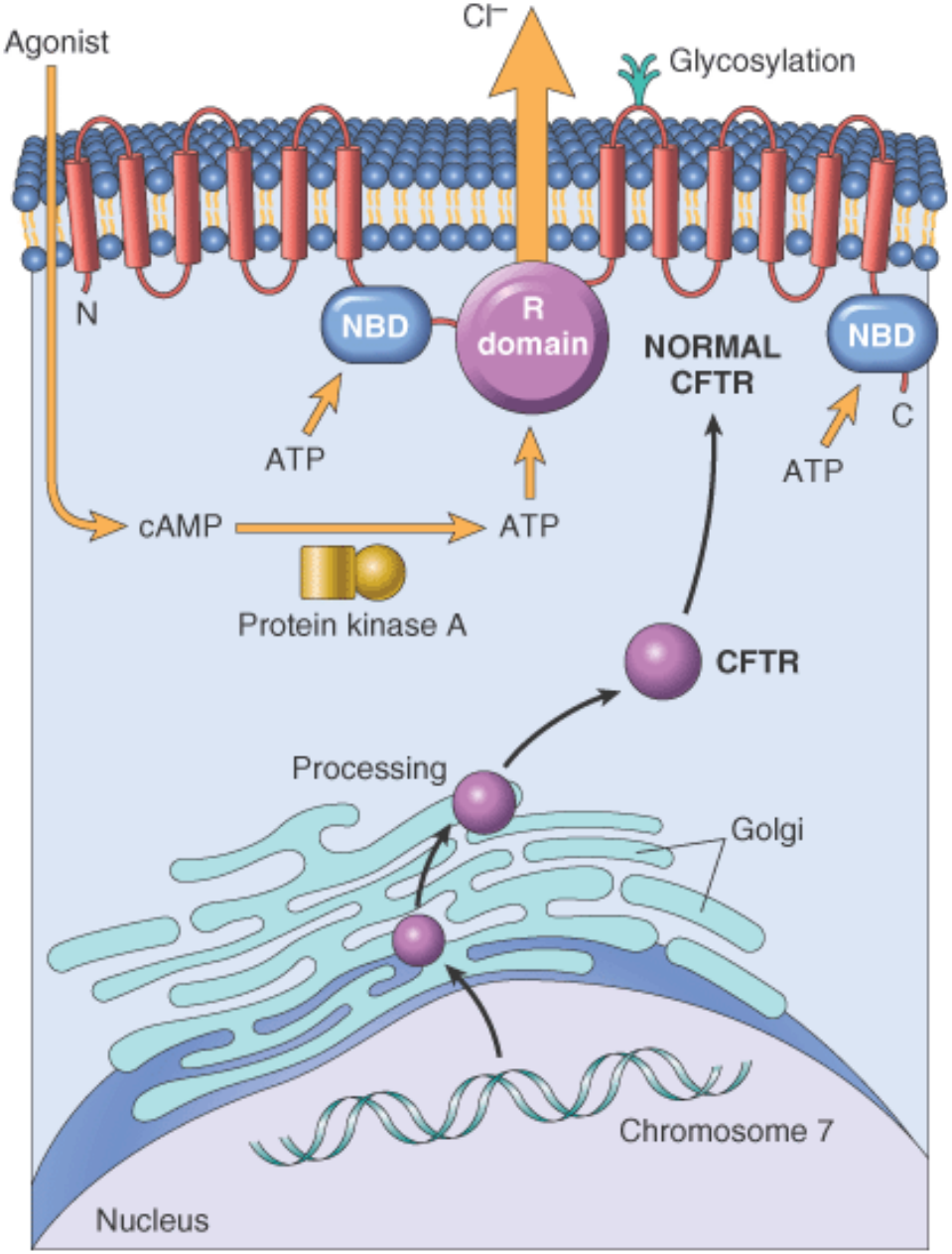


Figure 10-21 Chloride channel defect in the sweat duct *(top)* causes increased chloride and sodium concentration in sweat. In the airway *(bottom)*, cystic fibrosis patients have decreased chloride secretion and increased sodium and water reabsorption leading to dehydration of the mucus layer coating epithelial cells, defective mucociliary action, and mucus plugging of airways. CFTR, Cystic fibrosis transmembrane conductance regulator; EnaC, Epithelial sodium channel.

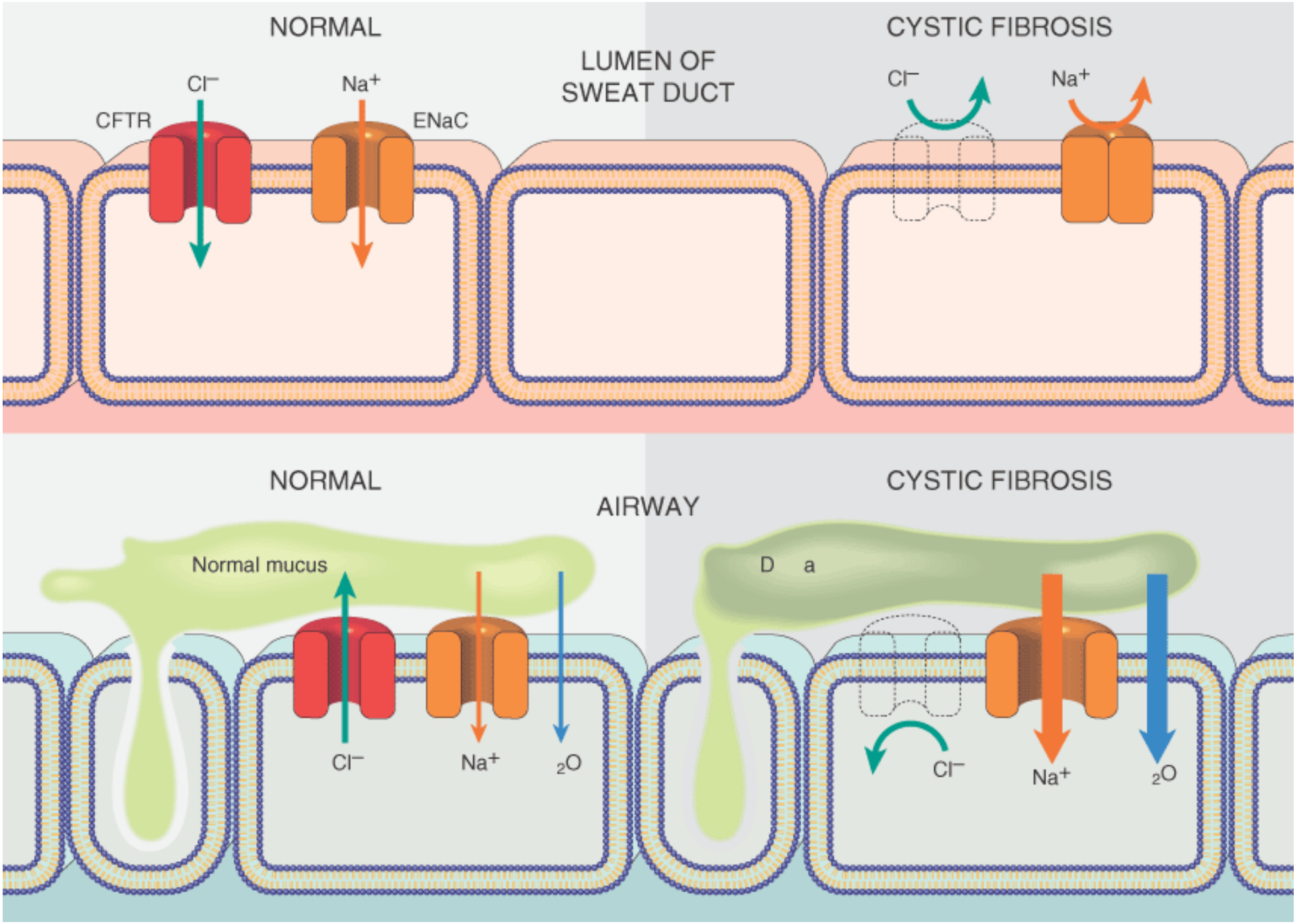


Figure 10-22 The many clinical manifestations of mutations in the cystic fibrosis gene, from most severe to asymptomatic. *(Redrawn from Wallis C: Diagnosing cystic fibrosis: blood, sweat, and tears. Arch Dis Child 76:85, 1997.)*

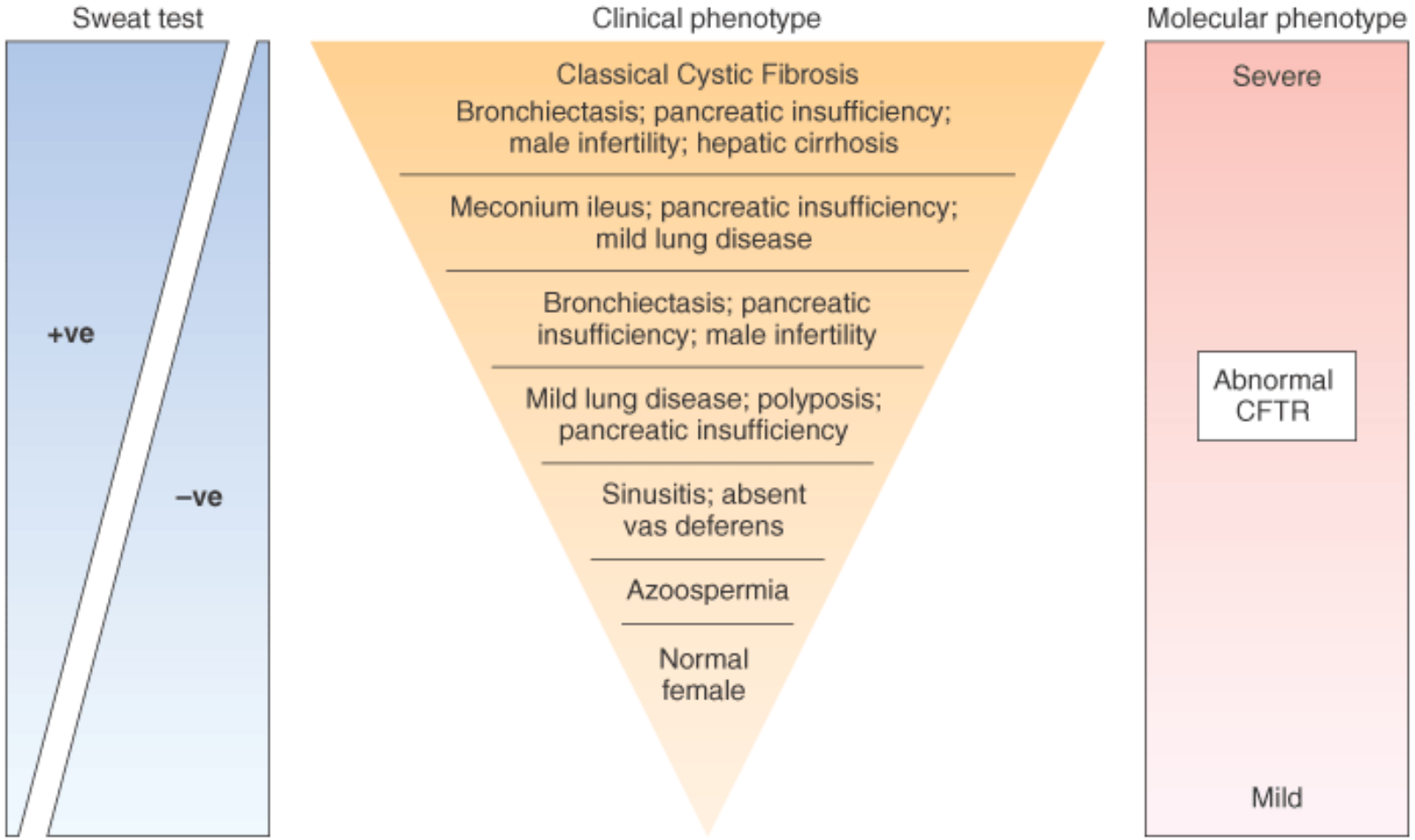


Figure 10-23 Lungs of a patient dying of cystic fibrosis. There is extensive mucus plugging and dilation of the tracheobronchial tree. The pulmonary parenchyma is consolidated by a combination of both secretions and pneumonia—the green color associated with *Pseudomonas* infections. *(Courtesy of Dr. Eduardo Yunis, Children's Hospital of Pittsburgh, Pittsburgh, PA.)*

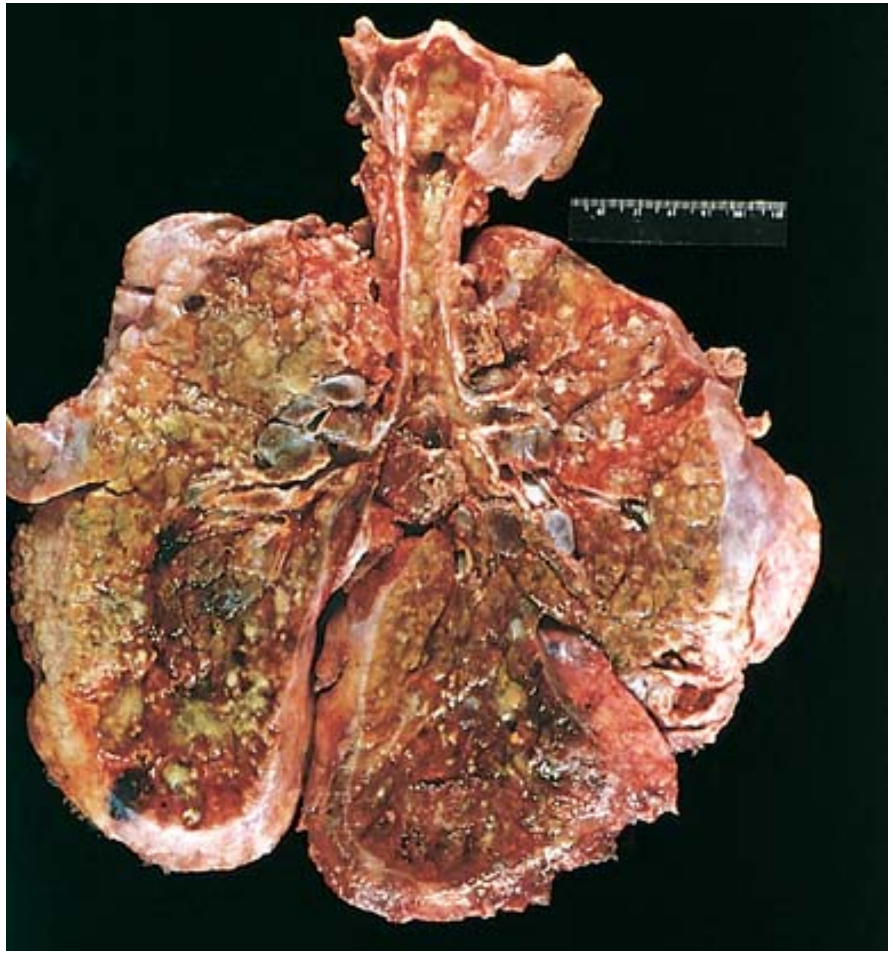


Figure 10-24 Mild to moderate cystic fibrosis changes in the pancreas. The ducts are dilated and plugged with eosinophilic mucin, and the parenchymal glands are atrophic and replaced by fibrous tissue.

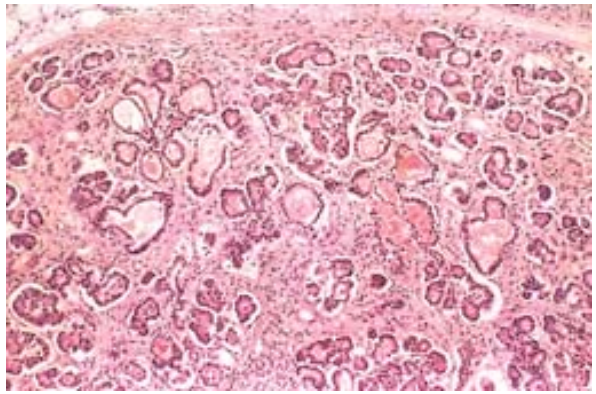


TABLE 10-7 -- Clinical Features and Diagnostic Criteria for Cystic Fibrosis

1. *Chronic sinopulmonary disease manifested by*
•••a. Persistent colonization/infection with typical cystic fibrosis pathogens, including *Staphylococcus aureus*, nontypeable *Hemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*, *Burkholderia cepacia*
•••b. Chronic cough and sputum production
•••c. Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
•••d. Airway obstruction manifested by wheezing and air trapping
•••e. Nasal polyps; radiographic or computed tomographic abnormalities of paranasal sinuses
•••f. Digital clubbing
2. *Gastrointestinal and nutritional abnormalities, including*
•••a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
•••b. Pancreatic: pancreatic insufficiency, recurrent pancreatitis
•••c. Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis, or multilobular cirrhosis
•••d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, complications secondary to fat-soluble vitamin deficiency
3. *Salt-loss syndromes: acute salt depletion, chronic metabolic acidosis*
4. *Male urogenital abnormalities resulting in obstructive azoospermia (congenital bilateral absence of vas deferens)*
Criteria for Diagnosis of Cystic Fibrosis
One or more characteristic phenotypic features,
••OR a history of cystic fibrosis in a sibling,
••OR a positive newborn screening test result
AND
An increased sweat chloride concentration on two or more occasions
••OR identification of two cystic fibrosis mutations,
••OR demonstration of abnormal epithelial nasal ion transport
Adapted with permission from Rosenstein BJ, Cutting GR: The diagnosis of cystic fibrosis: a consensus statement. J Pediatrics 132:589;1998.

from onset at birth to onset years later, and from involvement of one organ system to involvement of many. Approximately 5% to 10% of the cases come to clinical attention at birth or soon after because of an attack of *meconium ileus*. Distal intestinal obstruction can also occur in older individuals, manifesting as recurrent episodes of right lower quadrant pain sometimes associated with a palpable mass in the right iliac fossa.

Exocrine pancreatic insufficiency occurs in the majority (85–90%) of patients with cystic fibrosis and is associated with "severe" *CFTR* mutations on *both* alleles (e.g., *ΔF508/ΔF508*), whereas 10% to 15% of patients with one "severe" and one "mild" *CFTR* mutation *(ΔF508/R117H)* or two "mild" *CFTR* mutations retain enough pancreatic exocrine function so as not to require enzyme supplementation (*pancreas sufficient* phenotype). [80] Pancreatic insufficiency is associated with protein and fat malabsorption and increased fecal loss. Manifestations of malabsorption (e.g., large, foul stools, abdominal distention, and poor weight gain) appear during the first year of life. The faulty fat absorption may induce deficiency of the fat-soluble

vitamins, resulting in manifestations of avitaminosis A, D, or K. Hypoproteinemia may be severe enough to cause generalized edema. Persistent diarrhea may result in rectal prolapse in up to 10% of children with cystic fibrosis. The *pancreas sufficient* phenotype is usually not associated with other gastrointestinal complications, and in general, these individuals demonstrate excellent growth and development. The diagnosis of an underlying *CFTR* mutation in individuals with pancreas sufficient cystic fibrosis is suspected because of abnormal or borderline sweat chloride levels, a positive family history, or because of concomitant infertility in a male patient. "*Idiopathic*" *chronic pancreatitis* occurs in a subset of patients with pancreas sufficient cystic fibrosis and is associated with recurrent abdominal pain with

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life-threatening complications.[85] These patients have other features of cystic fibrosis, such as pulmonary disease. By contrast, "idiopathic" chronic pancreatitis can also occur as an isolated late-onset finding in the absence of other stigmata of cystic fibrosis (Chapter 19); bi-allelic *CFTR* mutations (usually one "mild", one "severe") are demonstrable in the majority of these individuals, qualifying their inclusion as *nonclassic or atypical cystic fibrosis. Endocrine pancreatic insufficiency* (i.e., diabetes) is uncommon in cystic fibrosis, and usually accompanied by substantial destruction of pancreatic parenchyma.

Cardiorespiratory complications, such as persistent lung infections, obstructive pulmonary disease, and *cor pulmonale*, are the single most common cause of death (~80%) in patients in the United States. By age 18, 80% of patients with classic cystic fibrosis harbor *P. aeruginosa*, and 3.5% harbor *Burkholderia cepacia.* [86] With the indiscriminate use of antibiotic prophylaxis against *Staphylococcus*, there has been an unfortunate resurgence of resistant strains of *Pseudomonas* in many patients. Individuals who carry a "severe" *CFTR* mutation on one allele and a "mild" *CFTR* mutation on the other allele may exhibit late-onset mild pulmonary disease, another example of nonclassic or atypical cystic fibrosis.[81] Patients with mild pulmonary disease usually have mild or no pancreatic disease. *Idiopathic bronchiectasis*, a poorly defined entity in adults where no discernible cause for the bronchiectasis can be found, has been linked to *CFTR* mutations in a subset of cases. *Recurrent sinonasal polyps* can occur in up to 25% of patients with cystic fibrosis; hence, children who present with this finding should be tested for abnormalities of sweat chloride.

Significant *liver disease* occurs late in the natural history of cystic fibrosis and used to be foreshadowed by pulmonary and pancreatic involvement; however, with increasing life expectancies, liver disease has also received increasing attention. In fact, after cardiopulmonary and transplantation-related complications, liver disease is the most common cause of death in cystic fibrosis. Most studies suggest that symptomatic or biochemical liver disease in cystic fibrosis has its onset at or around puberty, with a prevalence of approximately 13% to 17%. [87] However, *asymptomatic hepatomegaly* may be present in up to a third of the individuals. Obstruction of the common bile duct may occur due to stones or sludge; it presents with abdominal pain and the acute onset of jaundice. As previously noted, *diffuse biliary cirrhosis* may develop in up to 5% of individuals with cystic fibrosis.

Approximately 95% of males with cystic fibrosis are *infertile*, as a result of obstructive azoospermia. As mentioned earlier, this is most commonly due to bilateral absence of vas deferens (also called CBAVD). CBAVD can occur as a consequence of several conditions, but bi-allelic *CFTR* mutations are the most common cause (present in 50% to 75% of cases).[88] [89]

In most cases, the diagnosis of cystic fibrosis is based on persistently elevated sweat electrolyte concentrations (often the mother makes the diagnosis because her infant tastes salty), characteristic clinical findings (sinopulmonary disease and gastrointestinal manifestations), or a family history. A minority of patients with cystic fibrosis, especially those with at least one "mild" *CFTR* mutation, may have a normal or near-normal sweat test (<60 mM/L). Measurement of nasal transepithelial potential difference in vivo can be a useful adjunct under these circumstances; individuals with cystic fibrosis demonstrate a significantly more negative baseline nasal potential difference than controls. Sequencing the *CFTR* gene is, of course, the "gold standard" for diagnosis of cystic fibrosis. Therefore, in patients with suggestive clinical findings or family history (or both), genetic analysis may be warranted. It is important to inform the molecular laboratory whether the individual has classic cystic fibrosis or conforms to one of the nonclassic or atypical variants (CBAVD, late-onset pulmonary disease, or idiopathic chronic pancreatitis), so the appropriate "mild" *CFTR* mutations are also analyzed. A recent study has demonstrated that a subset of patients with nonclassic or atypical cystic fibrosis may not reveal *CFTR* mutations in one or both alleles.[90] This indicates that other genetic loci (perhaps those that encode proteins interacting with CFTR) may also produce a partial phenotype resembling cystic fibrosis.

Advances in management of cystic fibrosis include both improved control of infections and bilateral lung (or lobar), heart-lung, liver, pancreas, or liver-pancreas transplantation. Children and adolescents undergoing bilateral lung transplantation have overall survival rates around 70%. These improvements in management mean that more patients are now surviving to adulthood; the median life expectancy is close to 30 years and continues to increase. In principle, cystic fibrosis, like other single gene disorders, should be amenable to gene therapy. In vitro, it has been possible to correct the chloride defect in epithelial cells of cystic fibrosis patients by both viral and nonviral vector-based transfer of the *CFTR* gene; even a single copy of the wild-type *CFTR* gene is able to revert the cystic fibrosis phenotype. Clinical trials with gene therapy in humans are still in their early stages but provide a source of hope for millions of cystic fibrosis patients worldwide.

Sudden Infant Death Syndrome (SIDS)

SIDS is a disease of unknown cause. The National Institute of Child Health and Human Development defines SIDS as "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, *including performance of a complete autopsy, examination of the death scene, and review of the clinical history*."[91] An aspect of SIDS that is not stressed in the definition is that the infant usually dies while asleep, hence the pseudonyms of *crib death* or *cot death*.

Epidemiology.

As infantile deaths owing to nutritional problems and microbiologic infections have come under control in countries with higher standards of living, SIDS has assumed greater importance in many countries, including the United States. SIDS is the leading cause of death between age 1 month and 1 year in this country and the third leading cause of death overall in infancy, after congenital anomalies and diseases of prematurity and low birth weight. Due largely to nationwide SIDS awareness campaigns by organizations such as the American Academy of Pediatrics, there has been a significant drop in SIDS-related mortality in the past decade, from over 5000 annual deaths in 1990 to approximately 2600 deaths in 1999. Worldwide, in countries where unexpected infant deaths are diagnosed as SIDS only after postmortem examination, the death rates from SIDS (20 to 100/100,000 live births) are comparable to death rates in the United States (77/100,000 live births).

Approximately 90% of all SIDS deaths occur during the first 6 months of life, most between ages 2 and 4 months. This narrow window of peak susceptibility is a unique characteristic that is independent of other risk factors (to be described) and the geographic locale. Most infants who die of SIDS, die at home, usually during the night after a period of sleep. Only rarely is the catastrophic event observed, but even when seen, it is reported that the apparently healthy infant suddenly turns blue, stops breathing, and becomes limp without emitting a cry or struggling. Most infants have had minor manifestations of an upper respiratory infection preceding the fatal event. The term *apparent life-threatening event (ALTE)* has been applied to those infants who could be resuscitated after such an episode. [92] Infants with ALTE are often siblings of SIDS victims and harbor a range of physiologic abnormalities such as frequent or prolonged apnea, diminished chemoreceptor sensitivity to hypercarbia and hypoxia, and impaired control of heart, respiratory rate, and vagal tone.[92] Some of these infants later succumb to SIDS.

Morphology.

At autopsy, a variety of findings have been reported. They are usually subtle and of uncertain significance and are not present in all cases. **Multiple petechiae** are the most common finding in the typical SIDS autopsy (~80% of cases); these are usually present on the thymus, visceral and parietal pleura, and epicardium. Grossly, the lungs are usually congested, and **vascular engorgement** with or without **pulmonary edema** is demonstrable microscopically in the majority of cases. These changes possibly represent agonal events, since they are found with comparable frequencies in *explained* sudden deaths in infancy. Within the upper respiratory system (larynx and trachea), there may be some histologic evidence of recent infection (correlating with the clinical symptoms), although the changes are not sufficiently severe to account for death and should not detract from the diagnosis of SIDS. The central nervous system demonstrates **astrogliosis** of the brain stem and cerebellum. Sophisticated morphometric studies have revealed quantitative brainstem abnormalities such as **hypoplasia of the arcuate nucleus** or a subtle decrease in brain stem neuronal populations in several cases;[93] [94] these observations are not uniform, however, and not amenable to most "routine" autopsy

procedures. Nonspecific findings include frequent persistence of hepatic **extramedullary hematopoiesis** and **periadrenal brown fat**; it is tempting to speculate that these latter findings relate to chronic hypoxemia, retardation of normal development, and chronic stress. Thus, autopsy usually fails to provide a clear cause of death, and this may well be related to the etiologic heterogeneity of SIDS. The importance of a postmortem examination rests in identifying other causes of sudden unexpected death in infancy, such as unsuspected infection, congenital anomaly, or a genetic disorder (Table 10-8), the presence of any of which would *exclude* a diagnosis of SIDS, and in ruling out the unfortunate possibility of traumatic child abuse.

Pathogenesis.

The circumstances surrounding SIDS have been explored in great detail, and it is generally accepted that

TABLE 10-8 -- Risk Factors and Postmortem Findings Associated with Sudden Infant Death Syndrome

Parental
Young maternal age (age <20 years)
Maternal smoking during pregnancy
Drug abuse in *either* parent, specifically paternal marijuana and maternal opiate, cocaine use
Short intergestational intervals
Late or no prenatal care
Low socioeconomic group
African American and American Indian ethnicity (? socioeconomic factors)
Infant
Brain stem abnormalities, associated defective arousal, and cardiorespiratory control
Prematurity and/or low birth weight
Male sex
Product of a multiple birth
SIDS in a prior sibling
Antecedent respiratory infections
? Gastroesophageal reflux
Environment
Prone sleep position
Sleeping on a soft surface
Hyperthermia
Postnatal passive smoking

Postmortem Abnormalities Detected in Cases of Sudden Unexpected Infant Death *
Infections
• Viral myocarditis
• Bronchopneumonia
Unsuspected congenital anomaly
• Congenital aortic stenosis
• Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA)
Traumatic child abuse
• Intentional suffocation (filicide)
Genetic and metabolic defects
• Long QT syndrome (*SCN5A* and *KCNQ1* mutations)
• Fatty acid oxidation disorders (*MCAD*, *LCHAD*, *SCHAD* mutations)
• Histiocytoid cardiomyopathy (*MTCYB* mutations)
• Abnormal inflammatory responsiveness (partial deletions in *C4a* and *C4b*)

*SIDS is not the only cause of sudden unexpected death in infancy but rather is *a diagnosis of exclusion*. Therefore, performance of an autopsy may often reveal findings that would explain the cause of sudden unexpected death. These cases should *not*, strictly speaking, be labeled as "SIDS." SCN5A, sodium channel, voltage-gated, type V, alpha polypeptide; KCNQ1, potassium voltage-gated channel, KQT-like subfamily, member 1; MCAD, medium-chain acyl coenzyme A dehydrogenase; LCHAD, long-chain 3-hydroxyacyl coenzyme A dehydrogenase; SCHAD, short-chain 3-hydroxyacyl coenzyme A dehydrogenase; MTCYB, mitochondrial cytochrome b; C4, complement component 4.

it is a *multifactorial condition*, with a variable mixture of contributing factors. A "triple risk" model of SIDS has been proposed, which postulates the intersection of three overlapping factors: (1) *a vulnerable infant*, (2) *a critical developmental period in homeostatic control*, and (3) *an exogenous stressor(s)*. [95] According to this model, several factors make the infant vulnerable to sudden death during the critical developmental period (i.e., age 1 month to 1 year). These vulnerability factors may be attributable to the parents or the infant, while the exogenous stressor(s) is attributable to the environment (Table 10-8).

While numerous factors have been proposed to account for a vulnerable infant, *the most compelling hypothesis is that SIDS reflects a delayed development of arousal and cardiorespiratory control*.[96] Regions of the brain stem, particularly the *arcuate nucleus*, located in the ventral medullary surface, play a critical role in the body's "arousal" response to noxious stimuli such as hypercarbia, hypoxia, and thermal stress encountered during sleep. In addition, these areas regulate breathing, heart rate, and body temperature. In certain infants, for yet unexplained reasons, there may be a maldevelopment or delay in maturation of this region, compromising the arousal response to noxious stimuli. This physiologic impairment is compounded by other factors, such as sleeping position or infection (see below). Support of this hypothesis comes from postmortem studies in SIDS victims demonstrating both *quantitative* abnormalities (e.g., arcuate hypoplasia and decrease in neuronal density) as well as *qualitative* abnormalities (e.g., reduced serotonergic and muscarinic receptor binding) in the

brain stem.[93] [97] [98] Whether these changes are primary or merely the manifestation of a more "upstream" deficit remains to be elucidated. Recently, some candidate genes have been identified from experimental animal models, which may provide a genetic basis to abnormal neural regulation in the brainstem. For example, *Krox20*, a homeobox gene, appears to be required for hindbrain segmentation and myelination. Mouse models lacking *Krox20* function exhibit abnormally slow respiratory rhythm and prolonged apnea.[99] Similarly, brain-derived neurotrophic factor (BDNF) is required for normal development of the central respiratory rhythm, including the stabilization of central respiratory output that occurs after birth. Loss of one or both *BDNF* alleles results in an approximately 50% depression of central respiratory frequency compared with wild-type controls, while hypoxic ventilatory drive is deficient or absent.[100] Whether knowledge gleamed from these animal models of central respiratory dysfunction will be applicable to humans remains to be seen.

Epidemiologic studies of infant deaths have found additional risk factors for SIDS (Table 10-8). Infants who are born before term or who are low birth weight are at increased risk, and risk increases with decreasing gestational age or birth weight. Male sex is associated with a slightly greater incidence of SIDS. SIDS in a prior sibling is associated with a fivefold relative risk of recurrence, underscoring the importance of a genetic and/or shared environmental predisposition; *traumatic child abuse needs to be carefully excluded under these circumstances*. Most SIDS babies have an immediate prior history of a mild respiratory tract infection, but no single causative organism has been isolated. These infections may predispose an already vulnerable infant to even greater impairment of cardiorespiratory control and delayed arousal. In this context, laryngeal chemoreceptors have emerged as a putative "missing link" between upper respiratory tract infections, the prone position (see below), and SIDS. When stimulated, these laryngeal chemoreceptors elicit an apneic and bradycardic reflex.[101] Stimulation of the chemoreceptors is augmented by respiratory tract infections, which increase the volume of secretions, and by the prone position, which impairs swallowing and clearing of the airways even in healthy infants. In a previously vulnerable infant with impaired arousal, the apneic and bradycardic reflex may prove fatal.

Maternal smoking during pregnancy has consistently emerged as a risk factor in epidemiologic studies of SIDS, with children exposed to in utero nicotine having more than double the risk of SIDS compared to children born to nonsmokers. [102] Young maternal age, frequent childbirths, and inadequate prenatal care are all risk factors associated with increased incidence of SIDS in the offspring. African Americans and American Indians have significantly higher rates of SIDS deaths than Caucasians. It is not obvious whether these ethnic trends represent the effects of genetic make up or the effects of lower socioeconomic status, which by itself is a risk factor for SIDS.

Among the potential environmental factors, prone sleeping position, sleeping on soft surfaces, and thermal stress are possibly the most important modifiable risk factors for SIDS.[103] The prone position predisposes an infant to one or more recognized noxious stimuli (hypoxia, hypercarbia, and thermal stress) during sleep. In addition, the prone position is also associated with decreased arousal responsiveness compared to the supine position. Results of studies from Europe, Australia, New Zealand, and the United States showed clearly increased risk for SIDS in infants who sleep in a prone position, prompting the American Academy of Pediatrics to recommend placing *healthy infants on their back* when laying them down to sleep. This "Back To Sleep" campaign has resulted in substantial decreases in SIDS-related deaths since its inception in 1994.[104]

It should be noted that SIDS is not the only cause of sudden unexpected deaths in infancy. In fact, SIDS is a diagnosis of exclusion, requiring careful examination of the death scene and a complete postmortem examination. The latter can reveal an unsuspected cause of sudden death in up to 20% or more of "SIDS" babies (Table 10-8). Infections (e.g., viral myocarditis or bronchopneumonia) are the most common causes of sudden "unexpected" death, followed by an unsuspected congenital anomaly. In part due to advancements in molecular diagnostics and knowledge of the human genome, several genetic causes of sudden "unexpected" infant death have emerged. For example, fatty acid oxidation disorders, characterized by defects in mitochondrial fatty acid oxidative enzymes, may be responsible for up to 5% of sudden death in infancy; of these, a *deficiency in medium-chain acyl-coenzyme A dehydrogenase* is the most common.[105] Retrospective analyses of SIDS cases have also revealed mutations of cardiac sodium and potassium channels, which result in a form of cardiac arrhythmia characterized by prolonged QT intervals; these account for no more than 1% of SIDS deaths.[106] Other newly emerging genetic causes of *explained* sudden death are listed in Table 10-8 .

Only 2% of all malignant tumors occur in infancy and childhood; nonetheless, cancer (including leukemia) is a leading cause of death from disease in the United States in children over age 4 and up to age 14. Neoplastic disease accounts for approximately 9% of all deaths in this cohort; only accidents cause significantly more deaths. Benign tumors are even more common than cancers. Most benign tumors are of little concern, but on occasion they cause serious disease by virtue of their location or rapid increase in size.

It is sometimes difficult to segregate, on morphologic grounds, true tumors or neoplasms from tumor-like lesions in the infant and child. In this context, two special categories of tumor-like lesions should be distinguished from true tumors.

The term *heterotopia* (or *choristoma*) is applied to microscopically normal cells or tissues that are present in abnormal locations. Examples of heterotopias include a rest of pancreatic tissue found in the wall of the stomach or small intestine or a small mass of adrenal cells found in the kidney, lungs, ovaries, or elsewhere. The heterotopic rests are usually of little significance, but they can be confused clinically with neoplasms. Rarely, they are sites of origin of true neoplasms, producing the paradox of an adrenal carcinoma arising in the ovary.

The term *hamartoma* refers to an excessive but focal overgrowth of cells and tissues native to the organ in which it occurs. Although the cellular elements are mature and identical to those found in the remainder of the organ, they do not reproduce the normal architecture of the surrounding tissue. Hamartomas can be thought of as the linkage between malformations and neoplasms—the line of demarcation between a hamartoma and a benign neoplasm is frequently tenuous and is variously interpreted. Hemangiomas, lymphangiomas, rhabdomyomas of the heart, adenomas of the liver, and developmental cysts within the kidneys, lungs, or pancreas are interpreted by some as hamartomas and by others as true neoplasms. The frequency of these lesions in infancy and childhood and their clinical behavior give credence to the

Figure 10-25 Congenital capillary hemangioma at birth (*A*) and at age 2 years (*B*) after spontaneous regression. *(Courtesy of Dr. Eduardo Yunis, Children's Hospital of Pittsburgh, Pittsburgh, PA.)*

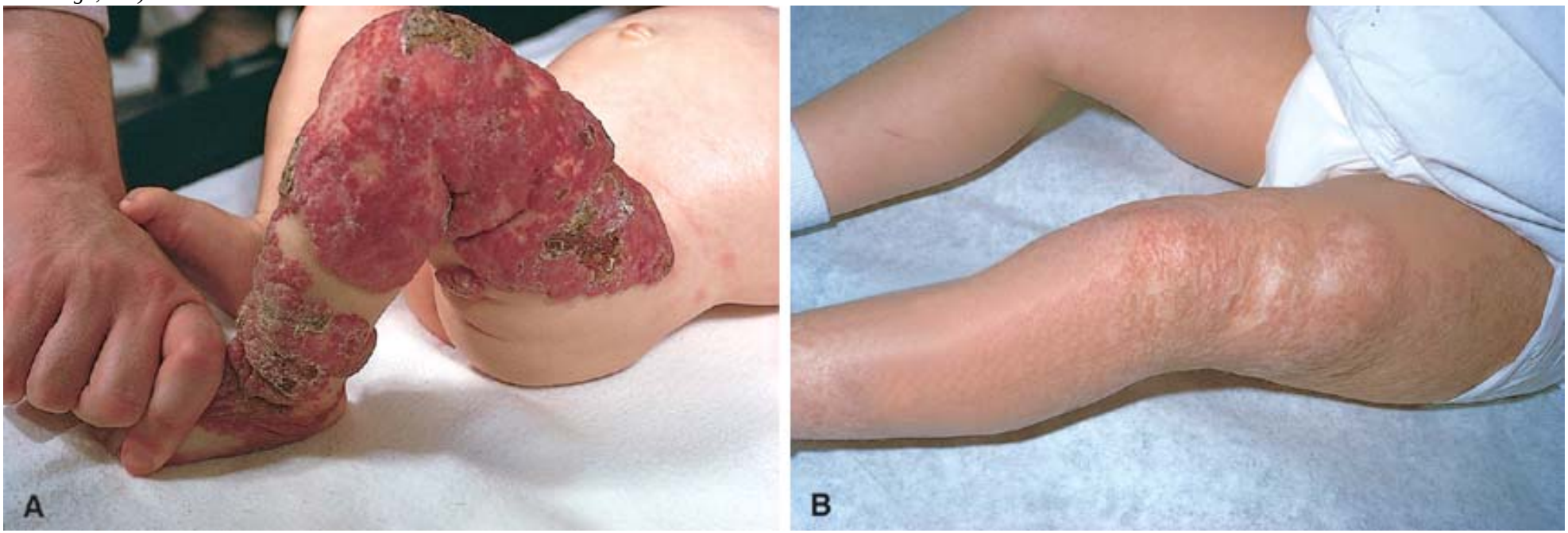


Figure 10-26 Sacrococcygeal teratoma. Note the size of the lesion compared with that of the infant.

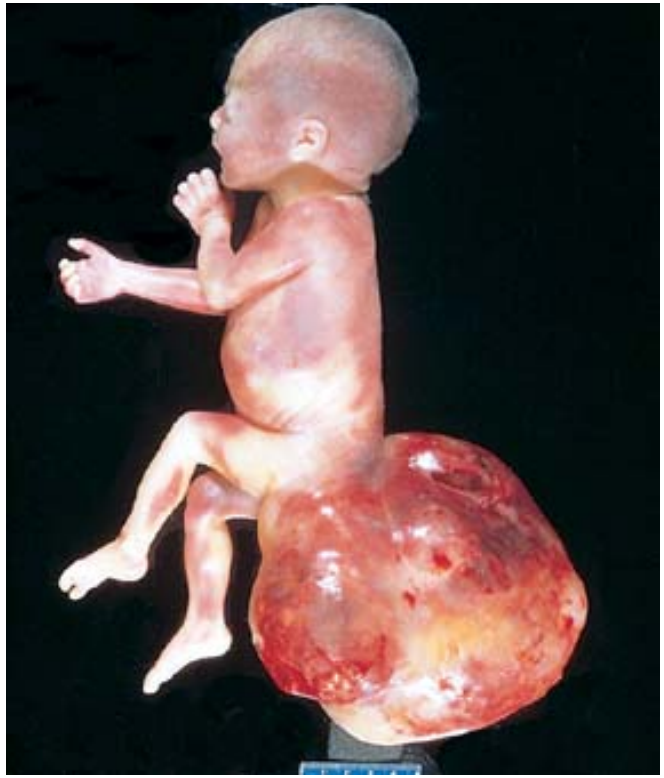


TABLE 10-9 -- Common Malignant Neoplasms of Infancy and Childhood

0 to 4 Years	5 to 9 Years	10 to 14 Years
Leukemia	Leukemia	
Retinoblastoma	Retinoblastoma	
Neuroblastoma	Neuroblastoma	
Wilms tumor		
Hepatoblastoma	Hepatocarcinoma	Hepatocarcinoma
Soft tissue sarcoma (especially rhabdomyosarcoma)	Soft tissue sarcoma	Soft tissue sarcoma
Teratomas		
Central nervous system tumors	Central nervous system tumors	
	Ewing sarcoma	
	Lymphoma	Osteogenic sarcoma
		Thyroid carcinoma
		Hodgkin disease

Histologically, many of the malignant pediatric neoplasms are unique. In general, they tend to have a more primitive *(embryonal)* rather than pleomorphic-anaplastic microscopic appearance, are often characterized by sheets of cells with small, round nuclei, and frequently exhibit features of organogenesis specific to the site of tumor origin. Because of this

TABLE 10-10 -- Genetic and Other Useful Markers of Small Round Cell Tumors of Childhood

Tumor Type	Genetic Markers	Other Diagnostically Useful Features
Neuroblastoma	17q gain, * 1p deletion *	Clinical elevation in level of urinary catecholamines
	N-*myc* amplification *	Neurosecretory granules by electron microscopy
	DNA hyperdiploidy, near triploidy †	Neuron-specific enolase expression
	t(11;22), ‡ t(21;22), t(7;22)	*MIC2* (CD99) gene expression
	EWS-FLI1 or *EWS-ERG* fusion transcript	
Rhabdomyosarcoma	t(2;13), ‡ * t(1;13)—alveolar rhabdomyosarcoma (ARMS)	Myogenin and Myo D1 expression (all subtypes)
	11p15.5 deletion—embryonal rhabdomyosarcoma (ERMS)	Alternating thick and thin filaments by electron microscopy
	PAX3-FKHR and *PAX7-FKHR* fusion transcript (ARMS)	
Burkitt lymphoma	t(8;14), ‡ t(2;8), t (8;22)	B-cell phenotype expressing CD19, CD20, CD10, IgM
		Epstein-Barr virus latent infection (endemic cases)
Lymphoblastic lymphoma/ acute lymphoblastic leukemia	Hyperdiploidy (>50), † Hypodiploidy(<46) *	Terminal deoxynucleotidyl transferase (TdT)+
	B-lineage: various translocations, including t(12;21) (*TEL-AML1*), ‡ , † t (9;22) (*BCR-ABL*, Philadelphia chromosome), * t(4;11) (AF4-MLL) * , t (1;19) (*PBX-E2A*) T-lineage: 1p32 abnormalities (*TAL1* gene)	Various B- and T-lineage antigens
Wilms tumor	11p13 (*WT1*) deletion/mutation	
	11p15.5 abnormalities of imprinting (e.g., *IGF2*, *H19*, $p57^{KIP2}$)	
	16q, * 1p, * 7p deletion	
Retinoblastoma	13q14 (*RB*) deletion/mutation	Retinal S antigen expression
Medulloblastoma	17p deletion	Evidence of neuronal differentiation (synaptophysin expression) or glial differentiation (glial fibrillary acid protein [GFAP] expression)
	Isochromosome 17q	

PNET, peripheral neuroectodermal tumor.

*Generally associated with a poorer prognosis.
†Generally associated with a better prognosis.

‡Most common translocation.

latter characteristic, these tumors are frequently designated by the suffix *-blastoma*, for example, nephroblastoma (Wilms tumor), hepatoblastoma, and neuroblastoma. Owing to their primitive histologic appearance, many childhood tumors have been collectively referred to as *small round blue cell tumors*. The differential diagnosis of such tumors includes neuroblastoma, Wilms tumor, lymphoma, rhabdomyosarcoma, and Ewing sarcoma/primitive neuroectodermal tumor. Rendering a definitive diagnosis is usually possible on histologic examination alone, or in combination with chromosome analysis, immunoperoxidase stains, and electron microscopy. The diagnostic features associated with the more common childhood neoplasms are summarized in Table 10-10 . Two of these tumors are particularly illustrative and are discussed here: the neuroblastic tumors, specifically neuroblastoma, and Wilms tumor. The remaining tumors are discussed in their respective organ-specific chapters.

The Neuroblastic Tumors

The term "neuroblastic tumor" includes tumors of the sympathetic ganglia and adrenal medulla that are derived from primordial neural crest cells populating these sites. As a family, neuroblastic tumors demonstrate certain characteristic features such as *spontaneous or therapy-induced differentiation of primitive neuroblasts into mature elements, spontaneous tumor regression*, and a *wide range of clinical behavior and prognosis*, which often mirror the extent of histologic differentiation. Neuroblastoma is the most important member of this family. It is the second most common solid malignancy of childhood

after brain tumors, accounting for 7% to 10% of all pediatric neoplasms, and as many as 50% of malignancies diagnosed in infancy.[108] Approximately 650 new cases are diagnosed in the United States each year, accounting for an incidence of approximately 9.5 cases per million children. The median age at diagnosis is 22 months; a little more than a third of the cases are diagnosed in infancy. There is a higher incidence of neuroblastoma in Caucasian as compared to African American populations, and males are at a marginally greater risk than females. Alone, it accounts for at least 15% of all childhood cancer deaths, although the 5-year survival rate has improved from 25% in the early 1960s to almost 55% in the mid-1990s. As will be evident later, age and stage have a remarkable effect on prognosis, and, in general, infants tend to have a significantly better prognosis than older individuals. Most occur sporadically, but a few are familial with autosomal dominant transmission, and in such cases the neoplasms may involve both of the adrenals or multiple primary autonomic sites.

Morophology.

In childhood, about 40% of neuroblastomas arise in the adrenal medulla. The remainder occur anywhere along the sympathetic chain, with the most common locations being the paravertebral region of the abdomen (25%) and posterior mediastinum (15%). Tumors may arise in numerous other sites, including the pelvis and neck and within the brain (cerebral neuroblastomas).

Macroscopically, neuroblastomas range in size from minute nodules (the **in situ lesions**) to large masses more than 1 kg in weight (Fig. 10-27). In situ neuroblastomas are reported to be 40 times more frequent than overt tumors. The great majority of these silent lesions spontaneously regress, leaving only a focus of fibrosis or calcification in the adult. Some neuroblastomas

Figure 10-27 Adrenal neuroblastoma in a 6-month-old child. The hemorrhagic, partially encapsulated tumor has displaced the opened left kidney and is impinging on the aorta and left renal artery. *(Courtesy of Dr. Arthur Weinberg, University of Texas Southwestern Medical School, Dallas, TX.)*

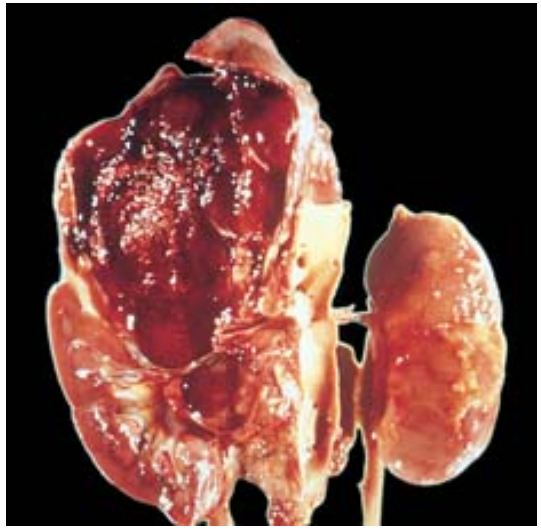


Figure 10-28 Adrenal neuroblastoma. This tumor is composed of small cells embedded in a finely fibrillar matrix.

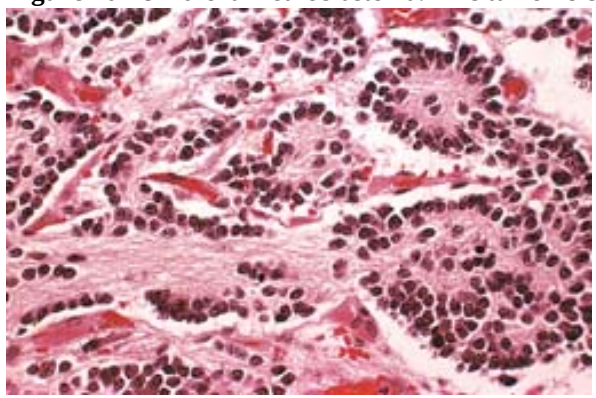
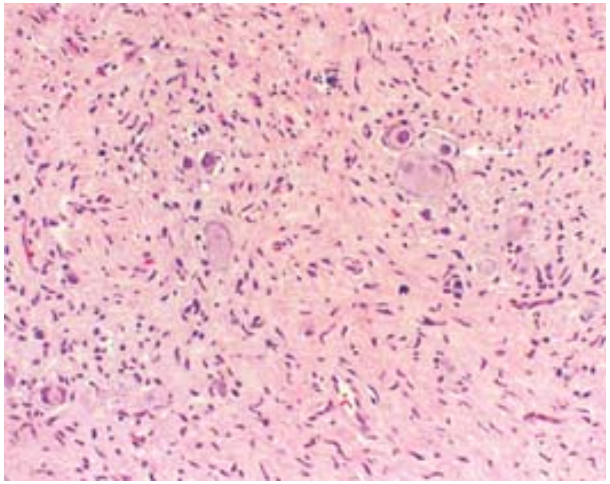


Figure 10-29 Ganglioneuromas, arising from spontaneous or therapy-induced maturation of neuroblastomas, are characterized by clusters of large cells with vesicular nuclei and abundant eosinophilic cytoplasm, representing neoplastic ganglion cells *(arrow)*. Spindle-shaped Schwann cells are present in the background stroma.



Stage 2A: Localized tumor with incomplete gross resection. Representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.

Stage 2B: Localized tumor with or without complete gross excision, ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes, which are negative for tumor microscopically.

Stage 3: Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement.

Stage 4: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs *(except as defined for stage 4S)*.

Stage 4S ("S" = special): Localized primary tumor (as defined for Stages 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow; *Stage 4S is limited to infants <1 yr*.

Unfortunately, most (60% to 80%) children present with Stage 3 or 4 tumors, and only 20% to 40% present with Stage 1, 2A, 2B, or 4S neuroblastomas. The staging system is of paramount importance in determining prognosis.

Clinical Course and Prognostic Features.

In young children, under age 2 years, neuroblastomas generally present with large abdominal masses, fever, and possibly weight loss. In older children, they may not come to attention until metastases produce manifestations, such as bone pain, respiratory symptoms, or gastrointestinal complaints. Neuroblastomas may metastasize widely through the hematogenous and lymphatic systems, particularly to liver, lungs, and bones, in addition to the bone marrow. Proptosis and ecchymosis may also be present because the periorbital region is a common metastatic site. Bladder and bowel dysfunction may be caused by paraspinal neuroblastomas that impinge on nerves. In neonates, disseminated neuroblastomas may present with multiple cutaneous metastases with deep blue discoloration to the skin (earning the rather unfortunate designation of "*blueberry muffin baby*"). *About 90% of neuroblastomas, regardless of location, produce catecholamines* (similar to the catecholamines associated with pheochromocytomas), which are an important diagnostic feature (i.e., elevated blood levels of catecholamines and elevated urine levels of metabolites, vanillylmandelic acid [VMA], and homovanillic acid [HVA]). Despite the elaboration of catecholamines, hypertension is much less frequent with these neoplasms than with pheochromocytomas (Chapter 24). Ganglioneuromas, unlike their malignant counterparts, tend to produce either asymptomatic mass lesions or symptoms related to compression.

The course of neuroblastomas is extremely variable. Several clinical, histopathologic, molecular, and biochemical factors have been identified in neuroblastomas that have a bearing on prognosis (see Table 10-11):

Age and stage are the most important determinants of outcome. Infants younger than age 1 year have an excellent prognosis regardless of the stage of the neoplasm. Most often in this age group, the neoplasms are Stage 1, 2A, or 2B, and therapy yields a greater than 90% 5-year survival.[114] At this early age, even when metastases are present, in about half the spread is limited to the liver, bone marrow, and skin (stage 4S), and such infants have at least an 80% 5-year survival with only minimal therapy. In fact, with Stage 4S disease, it is not uncommon for the primary or metastatic tumors to undergo spontaneous regression. [115] The biologic basis of this welcome behavior is not clear. Even when the dissemination is more widespread in the first year of life or the tumor is accompanied by unfavorable biologic characteristics such as N-*myc* amplification (see below), the survival is greater than 50%. Children between ages 1 and 5 years have an intermediate prognosis for low-stage tumors that have otherwise favorable

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TABLE 10-11 -- Prognostic Factors in Neuroblastomas

Variable	Favorable	Unfavorable
Stage *	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age *	≤ 1 year	>1 year
Histology *		
••Evidence of schwannian stroma and gangliocytic differentiation [a]	Present	Absent
••Mitotic rate [b]	Low	High
••Mitosis-karyorrhexis index [c]	≤200/5000 cells	>200/5000 cells
••Intratumoral calcification	Present	Absent
DNA ploidy *	Hyperdiploid or near-triploid	Diploid, near-diploid, or near-tetraploid
N-myc *	Not amplified	Amplified
Chromosome 17q Gain	Absent	Present
Chromosome 1p Loss	Absent	Present
Trk-A Expression	Present	Absent
Telomerase Expression	Low or absent	Highly expressed
MRP Expression	Absent	Present
CD44 Expression	Present	Absent
Serum Biochemical Markers		

••Ferritin	Normal	Elevated
••Lactate Dehydrogenase	≤1500 U/mL	> 1500 U/mL

Trk-A, tyrosine kinase receptor A; *MRP*, multidrug resistance-associated protein.

*Corresponds to the most commonly used parameters in clinical practice for assessment of prognosis and risk stratification.

[a] It is not only the presence but also the *amount* of schwannian stroma that confers the designation of a favorable histology. At least *50% or more schwannian stroma* is required before a neoplasm can be classified as ganglioneuroblastoma or ganglioneuroma.

[b] Mitotic rate is classified as *low* (≤10 mitoses/10 high power fields) or *high* (>10 mitoses/10 high power fields).

[c] Mitotic karyorrhexis index (MKI) is defined as the number of mitotic or karyorrhectic cells per 5000 tumor cells in random foci.

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biologic characteristics (see below), while those with advanced stage disease have <20% 5-year survival, irrespective of other prognostic variables. In contrast, children older than age 5 years usually have extremely poor outcomes irrespective of stage.

Morphology is an independent prognostic variable in neuroblastic tumors.[112] An age-linked morphologic classification of neuroblastic tumors has recently been proposed that divides them into *favorable* and *unfavorable* histologic subtypes. The specific morphologic features that bear in prognosis are listed in Table 10-11 .

Ploidy of the tumor cells correlates with outcome. In general, *hyperdiploidy* and *near-triploidy* have a correlation with young age, low stage, and a good prognosis, whereas *diploidy*, *near-diploidy*, and *near-tetraploidy* are associated with an unfavorable outcome irrespective of age. For example, in infants and children younger than age 2 years who have advanced disease, the presence of hyperdiploidy or near-triploidy correlates with response to chemotherapy and long-term disease-free survival, while corresponding diploid tumors have a significantly worse prognosis (the beneficial prognostic effects of ploidy tend to be negated in older children with advanced disease).

Amplification of the N-myc oncogene in neuroblastomas is a molecular event that has possibly the most profound impact on prognosis. [116] N-*myc* is located on the distal short arm of chromosome 2 (2p23-24). Amplification of N-*myc* does not karyotypically manifest at the resident 2p23-24 site, but rather as extrachromosomal *double minute chromatin bodies* or *homogeneously staining regions* on other chromosomes (Fig. 10-30). N-*myc* amplification is present in about 25% to 30% of primary tumors, most in advanced-stage disease. Up to 300 copies of N-*myc* have been observed in some tumors; the greater the number of copies, the worse the prognosis. N-*myc* amplification is currently the most important genetic abnormality used in risk stratification of neuroblastic tumors (see below).

Partial gain of the distal long arm of chromosome 17 is the most common karyotypic abnormality in neuroblastomas, present in up to 50% of tumors.[117] The mechanism of 17q gain is via an *unbalanced translocation*, where a portion of 17q is translocated to a partner chromosome (most commonly the distal short arm of chromosome 1, or the distal long arm of chromosome 11). Partial gain of 17q demonstrates significant association with adverse outcome in neuroblastomas, independent of other prognostic variables.

Deletion of the distal short arm of chromosome 1 in the region of band p36 has been demonstrated in 25% to 35% of primary tumors.[118] In addition, constitutional deletions of 1p36 have been demonstrated in a subset of patients with neuroblastomas. The loss of genetic material implies that one or more putative tumor suppressor genes in this region may be important in the pathogenesis of neuroblastomas, but their identity remains elusive. At least two distinct loci of deletions on 1p36 have been identified. The first, more distal region appears to demonstrate preferential loss of the maternal allele in tumors,

Figure 10-30 Fluorescence in situ hybridization using a fluorescein-labeled cosmid probe for N-*myc* on a tissue section. Note the neuroblastoma cells on the upper half of the photo with large areas of staining *(yellow-green)*; this corresponds to amplified N-*myc* in the form of homogeneously staining regions. Renal tubular epithelial cells in the lower half of the photograph show no nuclear staining and background *(green)* cytoplasmic staining. *(Courtesy of Dr. Timothy Triche, Children's Hospital, Los Angeles, CA.)*

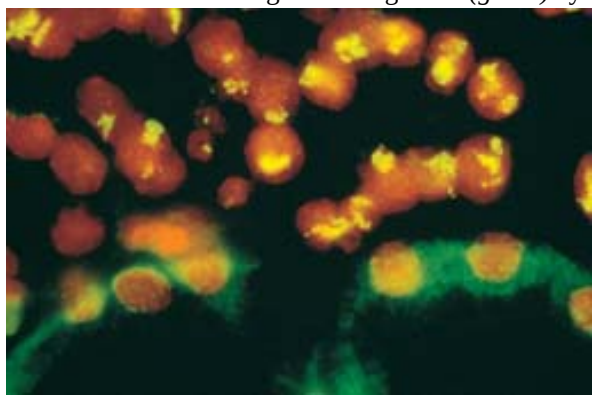


Figure 10-31 Wilms tumor in the lower pole of the kidney with the characteristic tan-to-gray color and well-circumscribed margins.

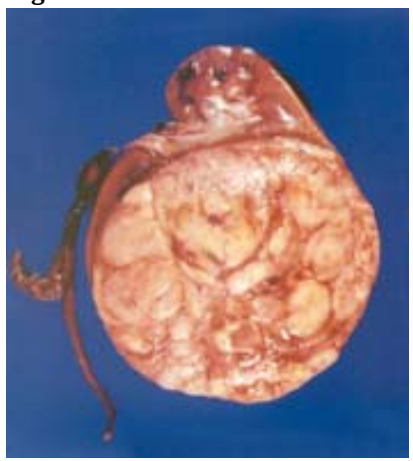
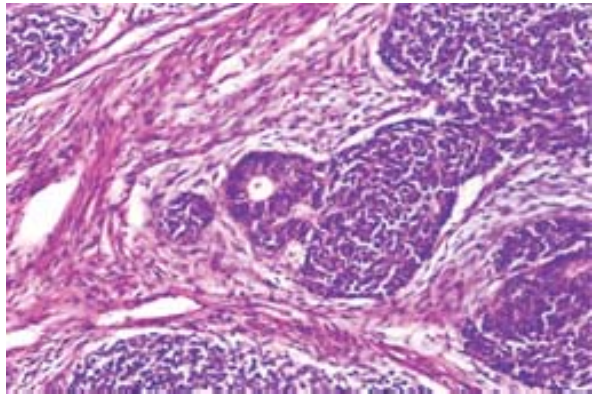


Figure 10-32 Triphasic histology of Wilms' tumor: the stromal component is comprised of spindle-shaped cells in the less cellular area on the left; the immature tubule in the center is an example of the epithelial component and the tightly packed blue cells, of the blastemal elements. *(Courtesy of Dr. Charles Timmons, Department of Pathology, University of Texas Southwestern Medical School, Dallas, TX.)* Anaplasia in Wilms' tumor is characterized by cells with large, hyperchromatic, pleomorphic nuclei and abnormal mitoses *(inset)*.



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Section II - Diseases of Organ Systems

Chapter 11 - Blood Vessels

Frederick J. Schoen MD, PhD

Diseases of arteries are responsible for more morbidity and mortality than any other type of human disease. Disorders of veins less commonly cause clinically significant problems. Vascular abnormalities cause clinical disease by two principal mechanisms:

- *Narrowing* or *completely obstructing* the lumens, either progressively (e.g., by atherosclerosis) or precipitously (e.g., by thrombosis or embolism).
- *Weakening* of the walls, leading to dilation or rupture.

To understand the diseases that affect blood vessels, we first consider some of the anatomic and functional characteristics of these highly specialized and dynamic tissues.

Normal

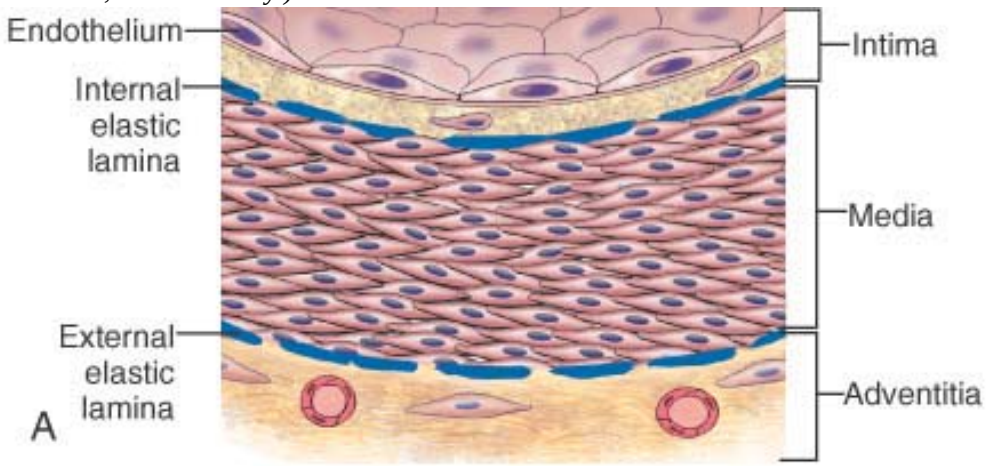
The general architecture and cellular composition of blood vessels are the same throughout the cardiovascular system. However, certain features of the vasculature vary with and reflect distinct functional requirements at different locations (see below). To withstand the pulsatile flow and higher blood pressures in arteries, arterial walls are generally thicker than the walls of veins. Arterial wall thickness gradually diminishes as the vessels become smaller, but the ratio of wall thickness to lumen diameter becomes greater.

The basic constituents of the walls of blood vessels are endothelial cells and smooth muscle cells, and extracellular matrix (ECM), including elastin, collagen, and glycosoaminoglycans. The three concentric layers—*intima*, *media*, and *adventitia*—are most clearly defined in the larger vessels, particularly arteries (Fig. 11-1). In normal arteries, the intima consists of a single layer of endothelial cells with minimal underlying subendothelial connective tissue. It is separated from the media by a dense elastic membrane called the *internal elastic lamina*. The smooth muscle cell layers of the media near the vessel lumen receive oxygen and nutrients by direct diffusion from the vessel lumen, facilitated by holes in the internal elastic membrane. However, diffusion from the lumen is inadequate for the outer portions of the media in large and medium-sized vessels, therefore these areas are nourished by small arterioles arising from outside the vessel (called *vasa vasorum*, literally "vessels of the vessels") coursing into the outer one half to two thirds of the media. The outer limit of the media of most arteries is a well-defined *external elastic lamina*. External to the media is the adventitia, consisting of connective tissue with nerve fibers and the vasa vasorum.

Based on their size and structural features, *arteries* are divided into three types: (1) large or *elastic arteries*, including the aorta, its large branches (particularly the innominate, subclavian, common carotid, and iliac), and pulmonary arteries; (2) medium-sized or *muscular arteries*, comprising other

Figure 11-1 The vascular wall. *A*, Graphic representation of the cross section of a small muscular artery (e.g., renal or coronary artery). *B*, Photomicrograph of histologic section containing a portion of an artery (A) and adjacent vein (V). Elastic membranes are stained black (internal elastic membrane of artery highlighted by *arrow*). Because it is exposed to higher pressures, the artery has a thicker wall that maintains an open, round lumen, even when blood is absent. Moreover, the elastin of the artery is more organized than in the corresponding vein. In contrast, the vein has a larger, but collapsed, lumen, and the elastin in its wall is diffusely distributed. *(B, Courtesy of Mark Flomenbaum, M.D., Ph.D., Office of the Chief Medical*

Examiner, New York City.)



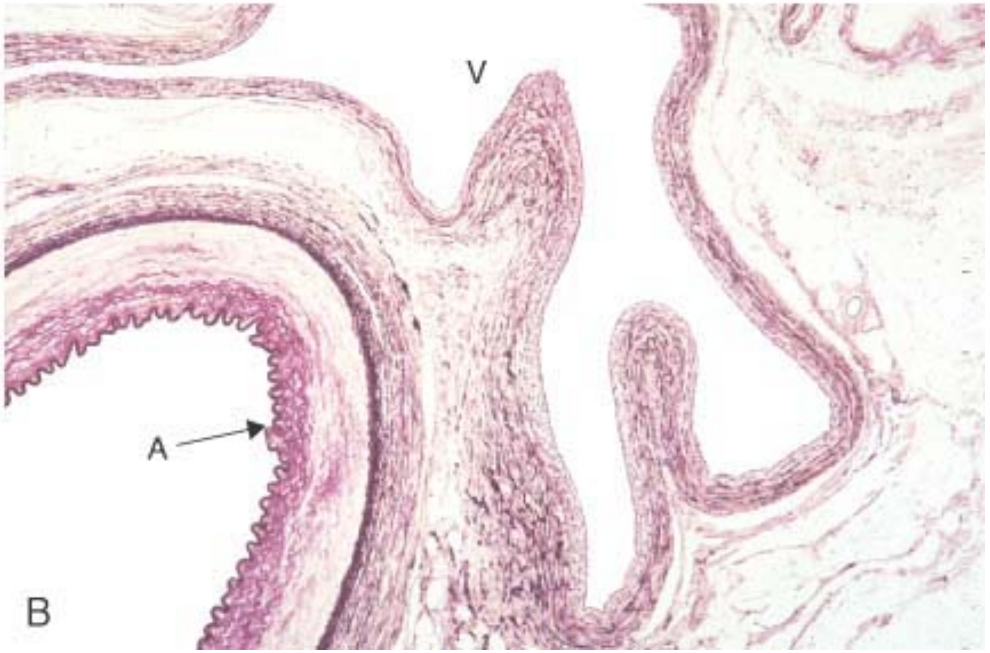


TABLE 11-1 -- Endothelial Cell Properties and Functions

Maintenance of Permeability Barrier
Elaboration of Anticoagulant, Antithrombotic, Fibrinolytic Regulators
Prostacyclin
Thrombomodulin
Heparin-like molecules

Plasminogen activator
Elaboration of Prothrombotic Molecules
Von Willebrand factor
Tissue factor
Plasminogen activator inhibitor
Extracellular Matrix Production (collagen, proteoglycans)
Modulation of Blood Flow and Vascular Reactivity
Vasconstrictors: endothelin, ACE
Vasodilators: NO, prostacyclin
Regulation of Inflammation and Immunity
IL-1, IL-6, chemokines
Adhesion molecules: VCAM-1, ICAM, E-selectin P-selectin
Histocompatibility antigens
Regulation of Cell Growth
Growth stimulators: PDGF, CSF, FGF
Growth inhibitors: heparin, TGF-β
Oxidation of LDL
ACE, angiotensin converting enzyme; NO, nitric oxide; IL, interleukin; PDGF, platelet-derived growth factor; CSF, colony-stimulating factor; FGF, fibroblast growth factor; TGF-β, transforming growth factor-beta; LDL, low-density lipoprotein.

Structurally intact ECs can respond to various pathophysiologic stimuli by adjusting their usual (constitutive) functions and by expressing newly acquired (inducible) properties—a process termed *endothelial activation* (Fig. 11-2). [4] [5] Inducers of endothelial activation include cytokines and bacterial products, which cause inflammation and septic shock (Chapter 2); hemodynamic stresses and lipid products, critical to the pathogenesis of atherosclerosis (see later); advanced glycosylation end products (important in diabetes, Chapter 24), as well as viruses, complement components, and hypoxia. Activated ECs, in turn, express adhesion molecules (Chapter 2), and produce other cytokines and chemokines, growth factors, vasoactive molecules that result either in vasoconstriction or in vasodilation, major histocompatibility complex molecules, procoagulant and anticoagulant moieties, and a variety of other biologically active products. ECs influence the vasoreactivity of the underlying smooth muscle cells through the production of both relaxing factors (e.g., nitric oxide [NO]) and contracting factors (e.g., endothelin). Normal endothelial function is characterized by a balance of these factors and the ability of the vessel to respond appropriately to various pharmacologic stimuli (e.g., vasorelaxation in response to acetylcholine).

Endothelial dysfunction, as defined by an altered phenotype that impairs vasoreactivity or induces a surface that is thrombogenic or abnormally adhesive to inflammatory cells, is responsible, at least in part, for the initiation of thrombus formation,

Figure 11-2 Endothelial cell response to environmental stimuli: causes (activators) and consequences (induced genes).

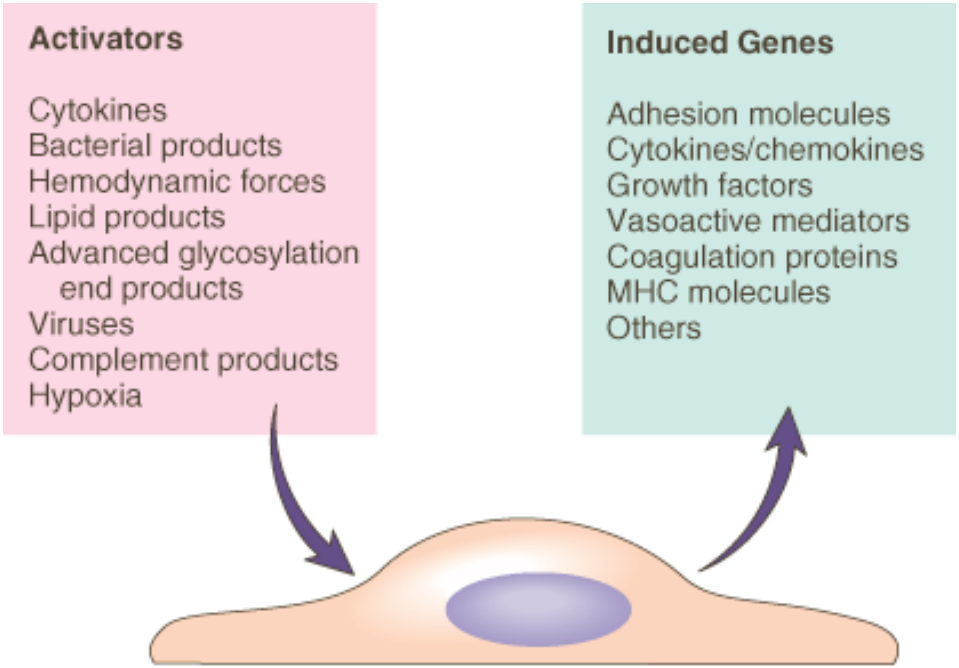


Figure 11-3 Schematic diagram of the mechanism of intimal thickening, emphasizing smooth muscle cell migration to, and proliferation and extracellular matrix elaboration in, the intima. *(Modified and redrawn from Schoen FJ: Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Philadelphia, W.B. Saunders Co., 1989, p. 254.)*

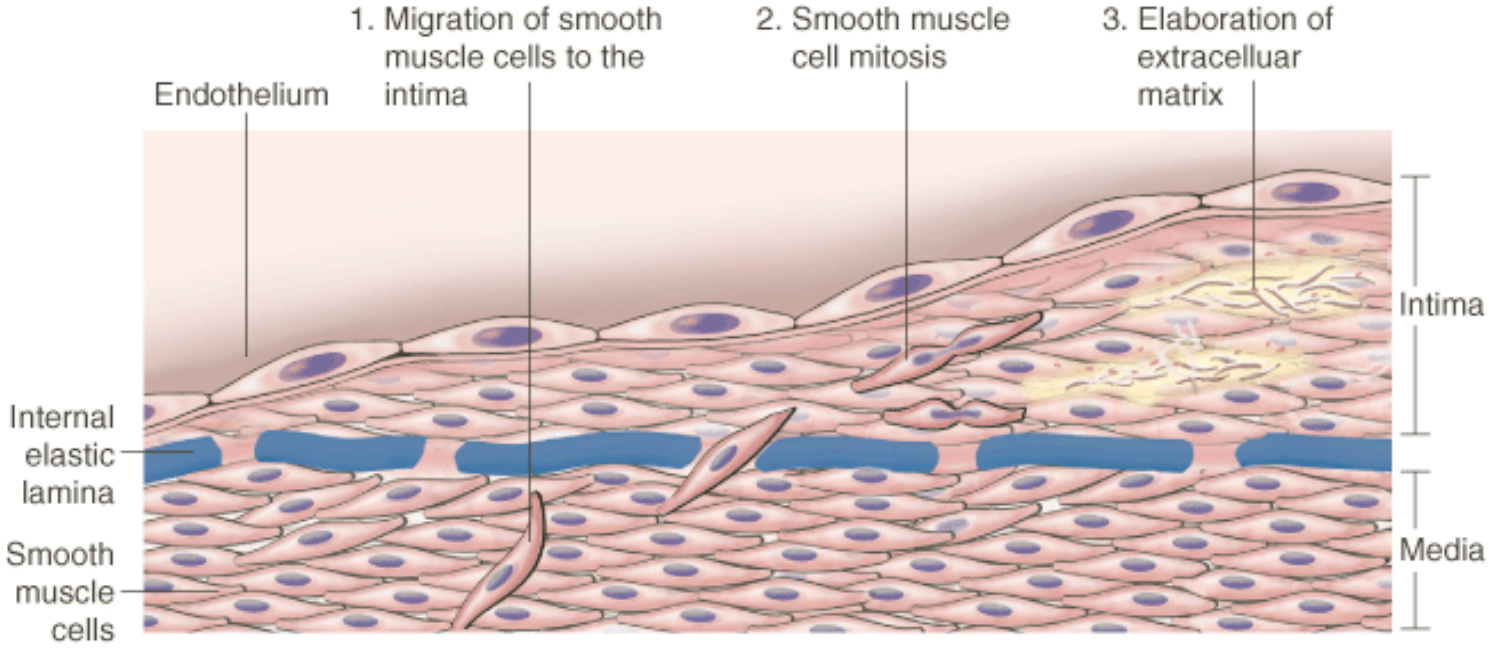


Figure 11-4 American Heart Association classification of human atherosclerotic lesions from the fatty dot (type I) to the complicated type VI lesion. The diagram also includes growth mechanisms and clinical correlations. *(Modified from Stary HC, et al: A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. Circulation 92:1355, 1995.)*

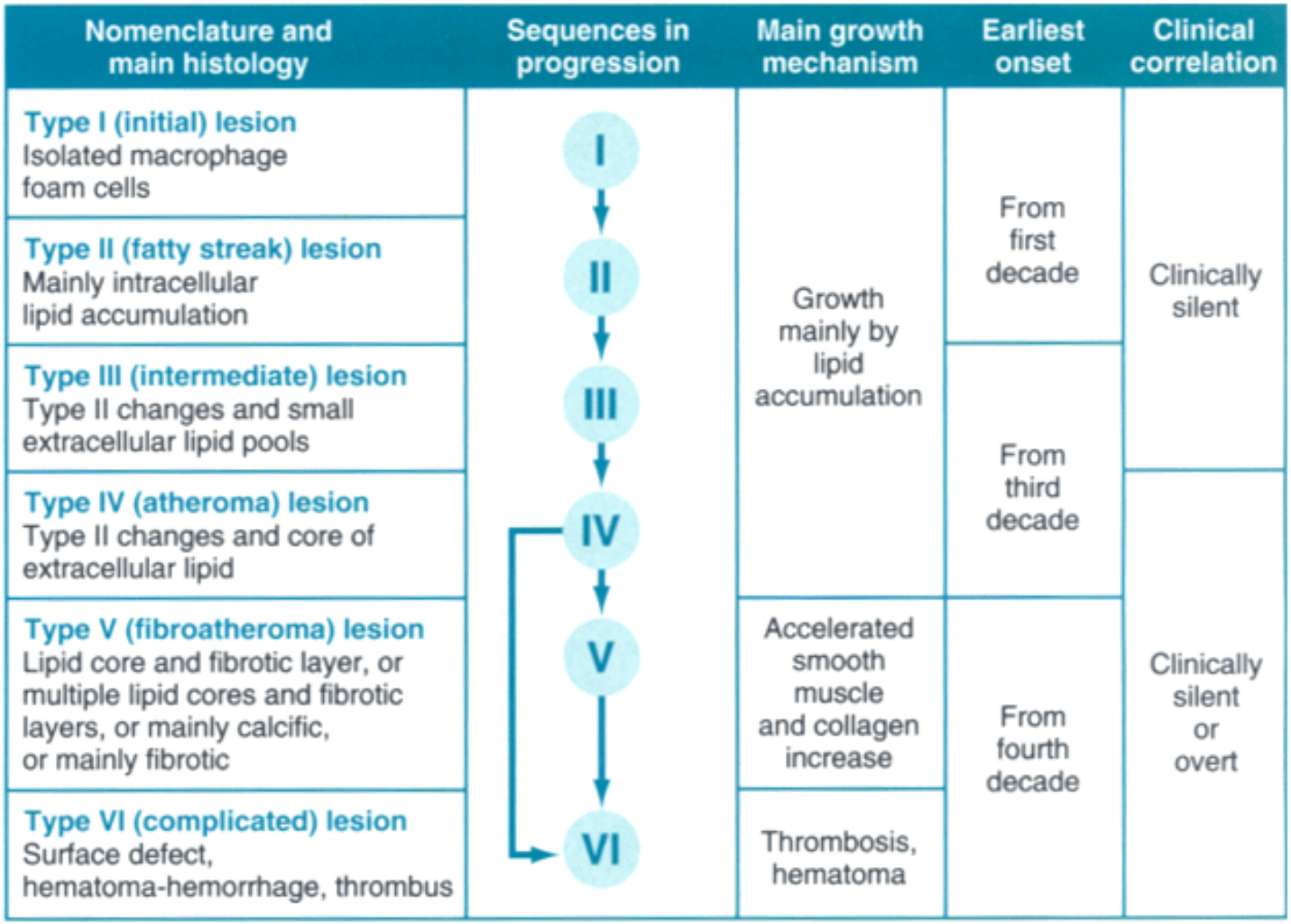


Figure 11-5 Schematic summary of the natural history, morphologic features, main pathogenetic events, and clinical complications of atherosclerosis in the coronary arteries.

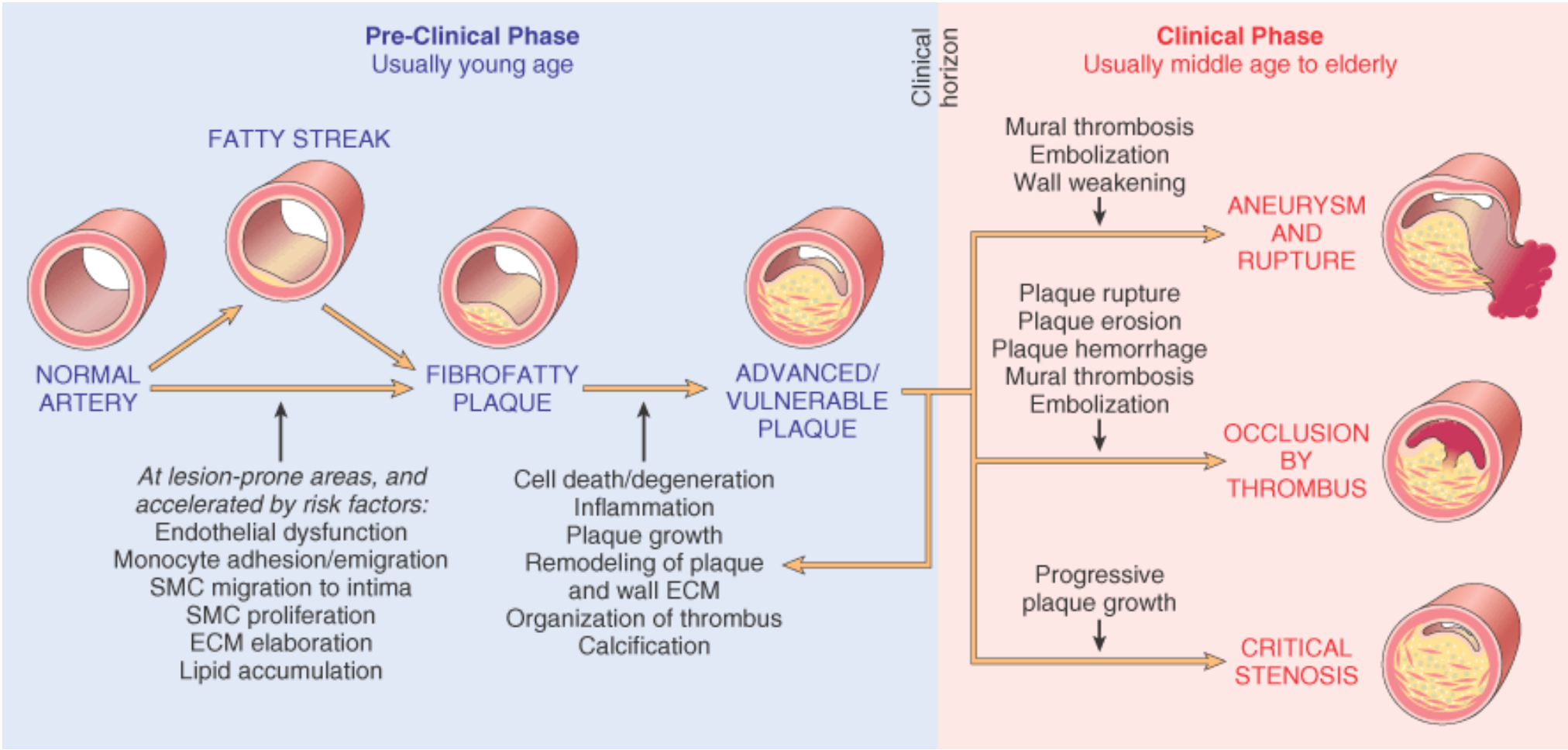


Figure 11-6 Fatty streak—a collection of foam cells in the intima. *A,* Aorta with fatty streaks (arrows), associated largely with the ostia of branch vessels. *B,* Close-up photograph of fatty streaks from aorta of experimental hypercholesterolemic rabbit shown following staining with Sudan red, a lipid-soluble dye, again illustrating the relationship of lesions to branch vessel ostia. *C,* Photomicrograph of fatty streak in experimental hypercholesterolemic rabbit, demonstrating intimal, macrophage-derived foam cells *(arrow). (B and C, Courtesy of Myron I. Cybulsky, M.D., University of Toronto, Canada).*

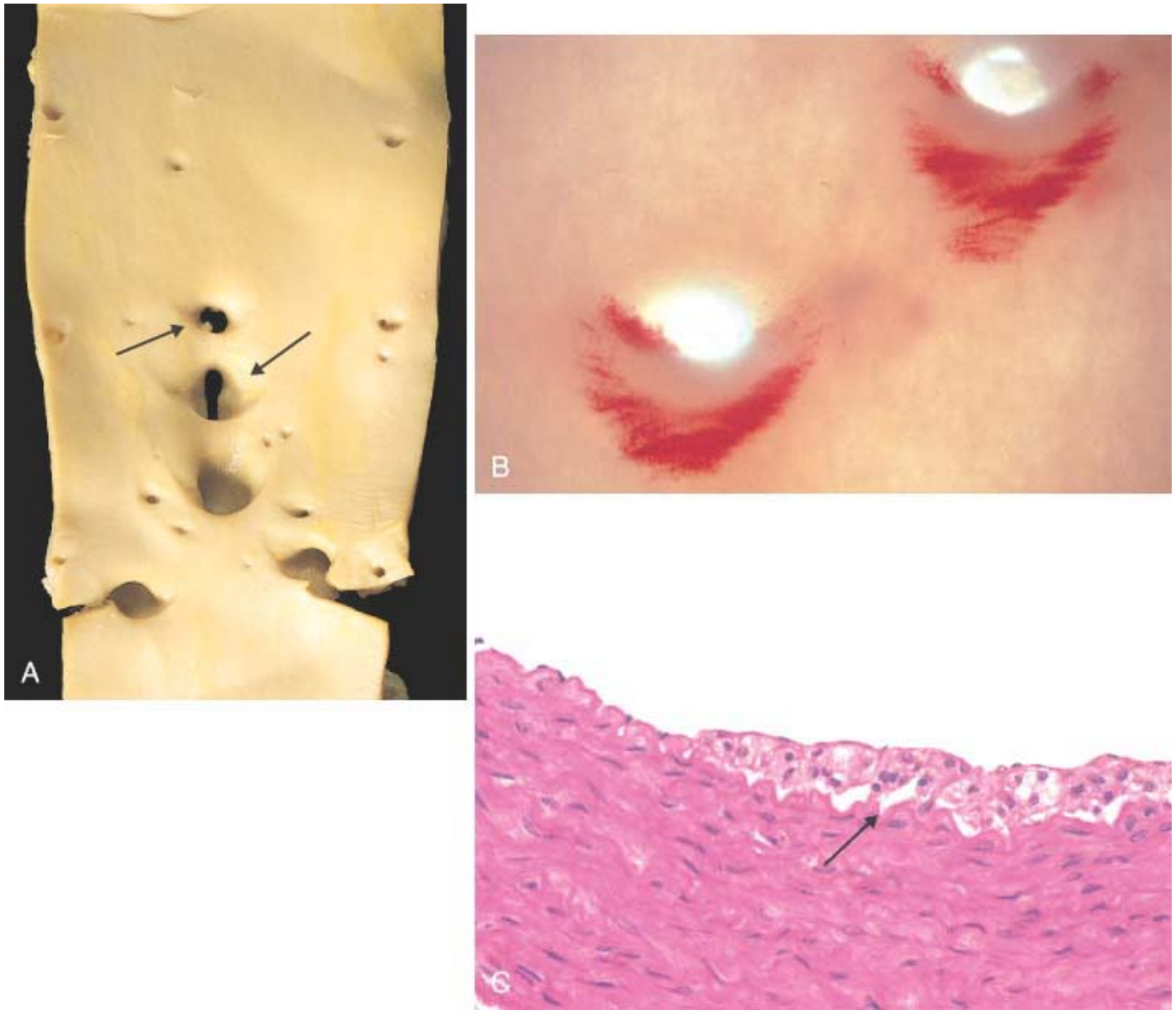


Figure 11-7 Schematic depiction of the major components of well-developed intimal atheromatous plaque overlying an intact media.

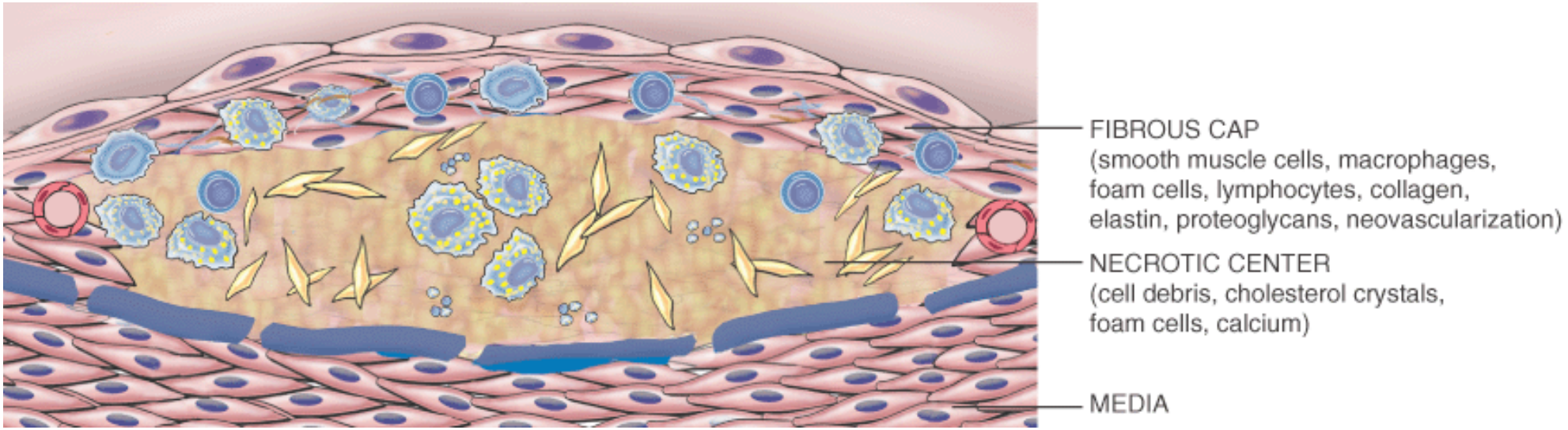


Figure 11-8 Gross views of atherosclerosis in the aorta. *A*, Mild atherosclerosis composed of fibrous plaques, one of which is denoted by the *arrow*. *B*, Severe disease with diffuse and complicated lesions.

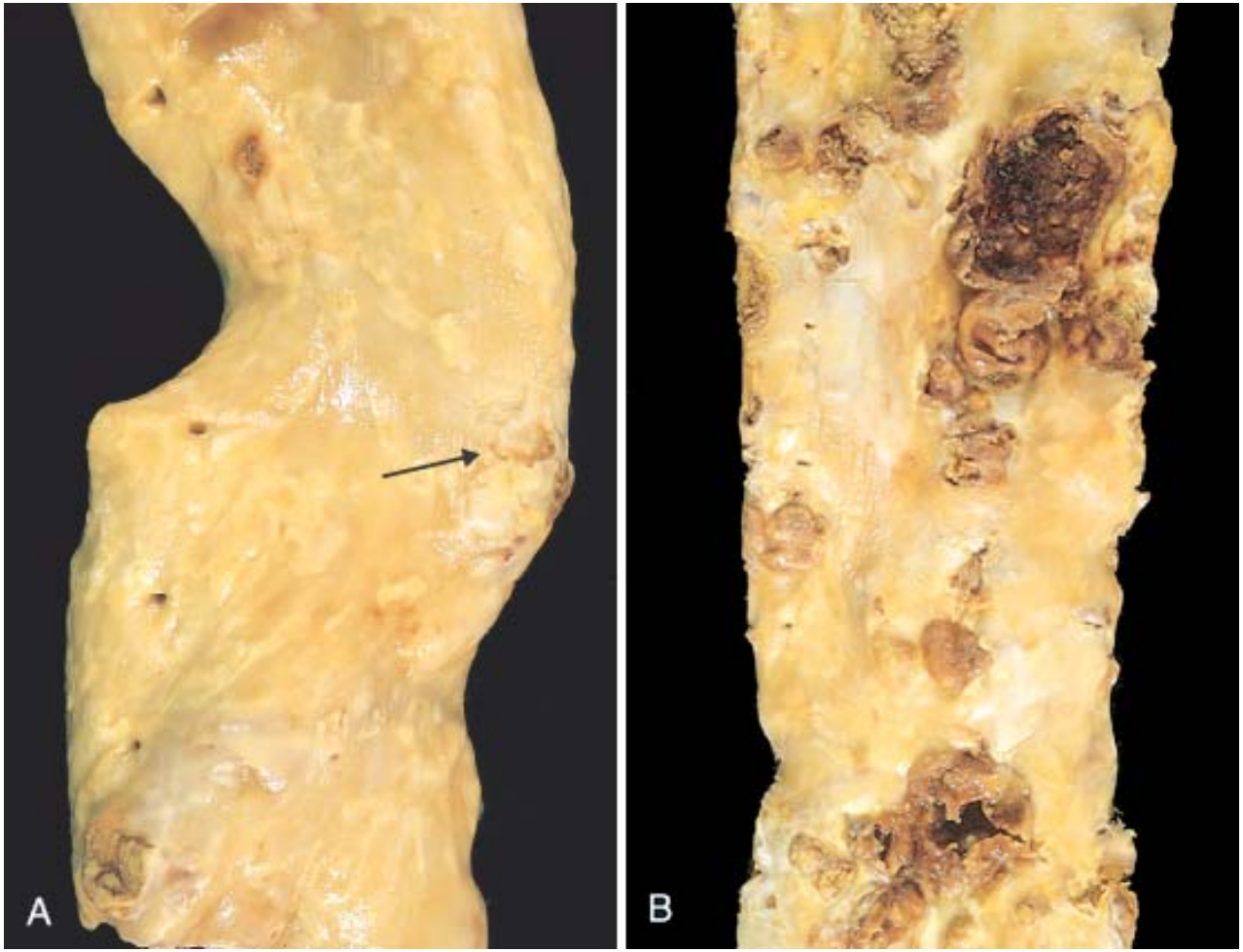


Figure 11-9 Histologic features of atheromatous plaque in the coronary artery. *A,* Overall architecture demonstrating fibrous cap (F) and a central necrotic (largely lipid) core (C). The lumen (L) has been moderately narrowed. Note that a segment of the wall is plaque free *(arrow).* In this section, collagen has been stained blue (Masson's trichrome stain). *B,* Higher-power photograph of a section of the plaque shown in *A,* stained for elastin (black), demonstrating that the internal and external elastic membranes are destroyed and the media of the artery is thinned under the most advanced plaque *(arrow). C,* Higher-magnification photomicrograph at the junction of the fibrous cap and core, showing scattered inflammatory cells, calcification *(broad arrow),* and neovascularization *(small arrows).*

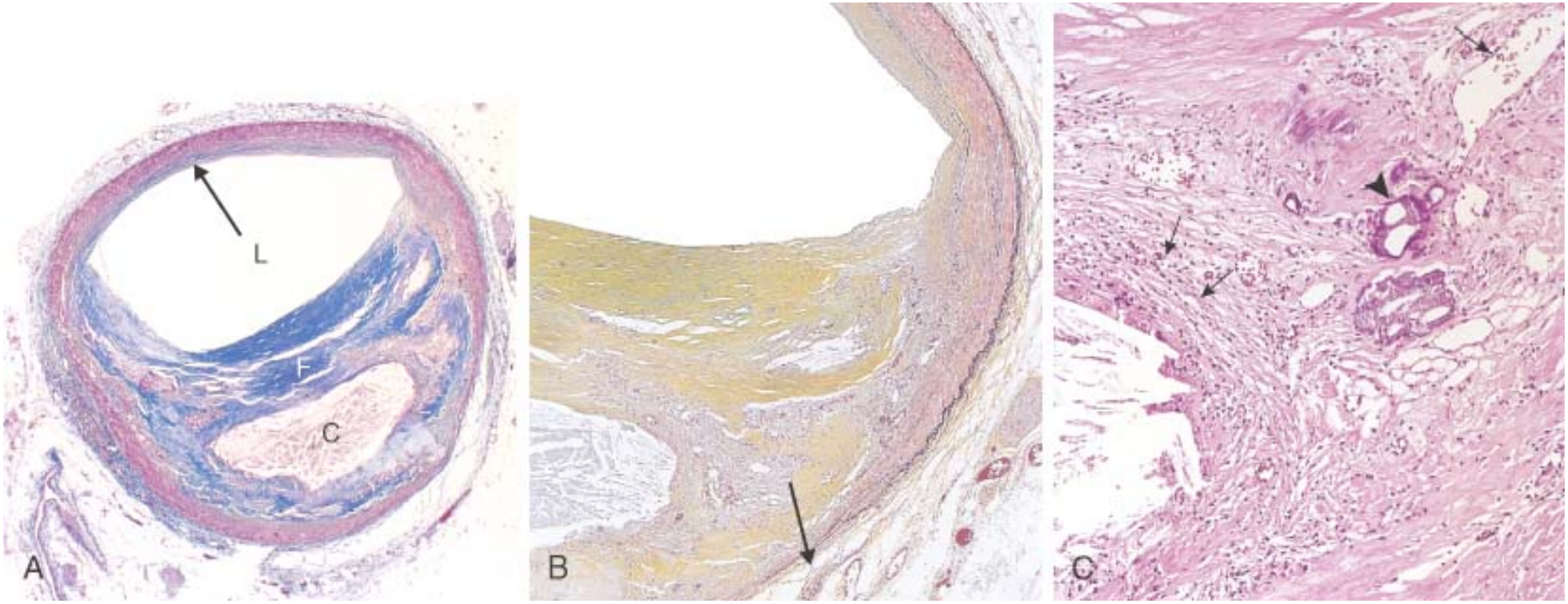


TABLE 11-2 -- Risk Factors for Atherosclerosis

Major	**Lesser, Uncertain, or Nonquantitated**
Nonmodifiable	
Increasing age	Obesity
Male gender	Physical inactivity
Family history	Stress ("type A" personality)
Genetic abnormalities	Postmenopausal estrogen deficiency
	High carbohydrate intake
Potentially Controllable	
Hyperlipidemia	Alcohol
Hypertension	Lipoprotein Lp(a)
Cigarette smoking	Hardened (trans)unsaturated fat intake
Diabetes	*Chlamydia pneumoniae*

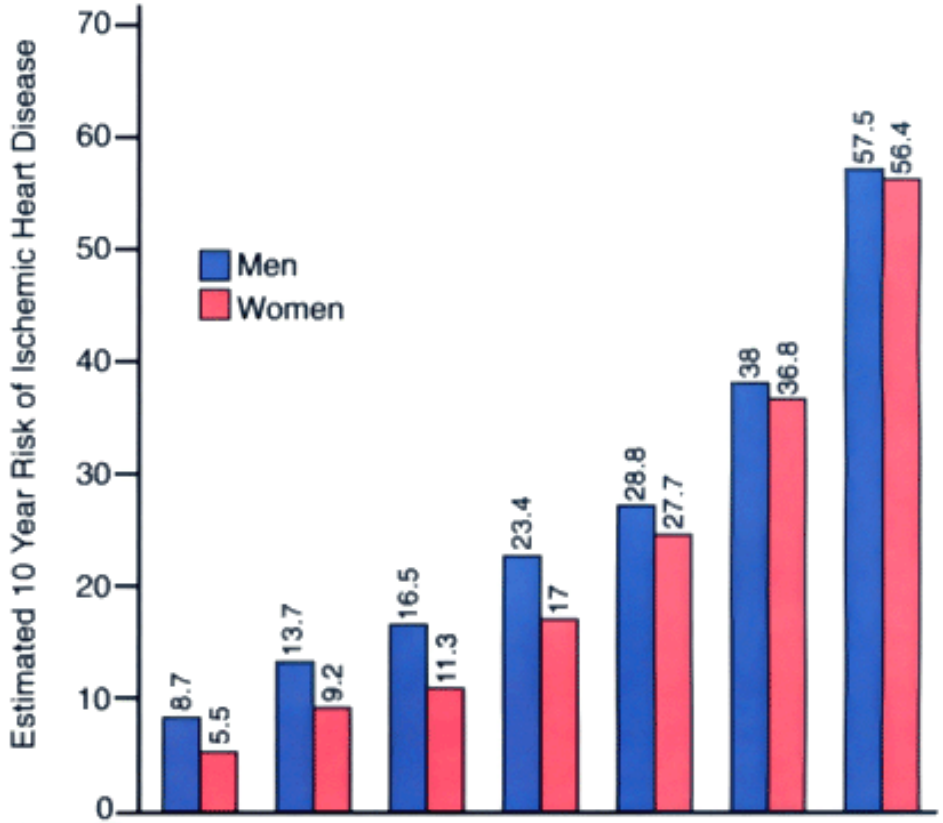
high blood lipid levels, such as familial hypercholesterolemia, which was discussed in Chapter 5 .

Other, nongenetic *risk factors, particularly diet, lifestyle, and personal habits, are to a large extent potentially reversible*. The four major risk factors potentially responsive to change are hyperlipidemia, hypertension, cigarette smoking, and diabetes.

Hyperlipidemia.

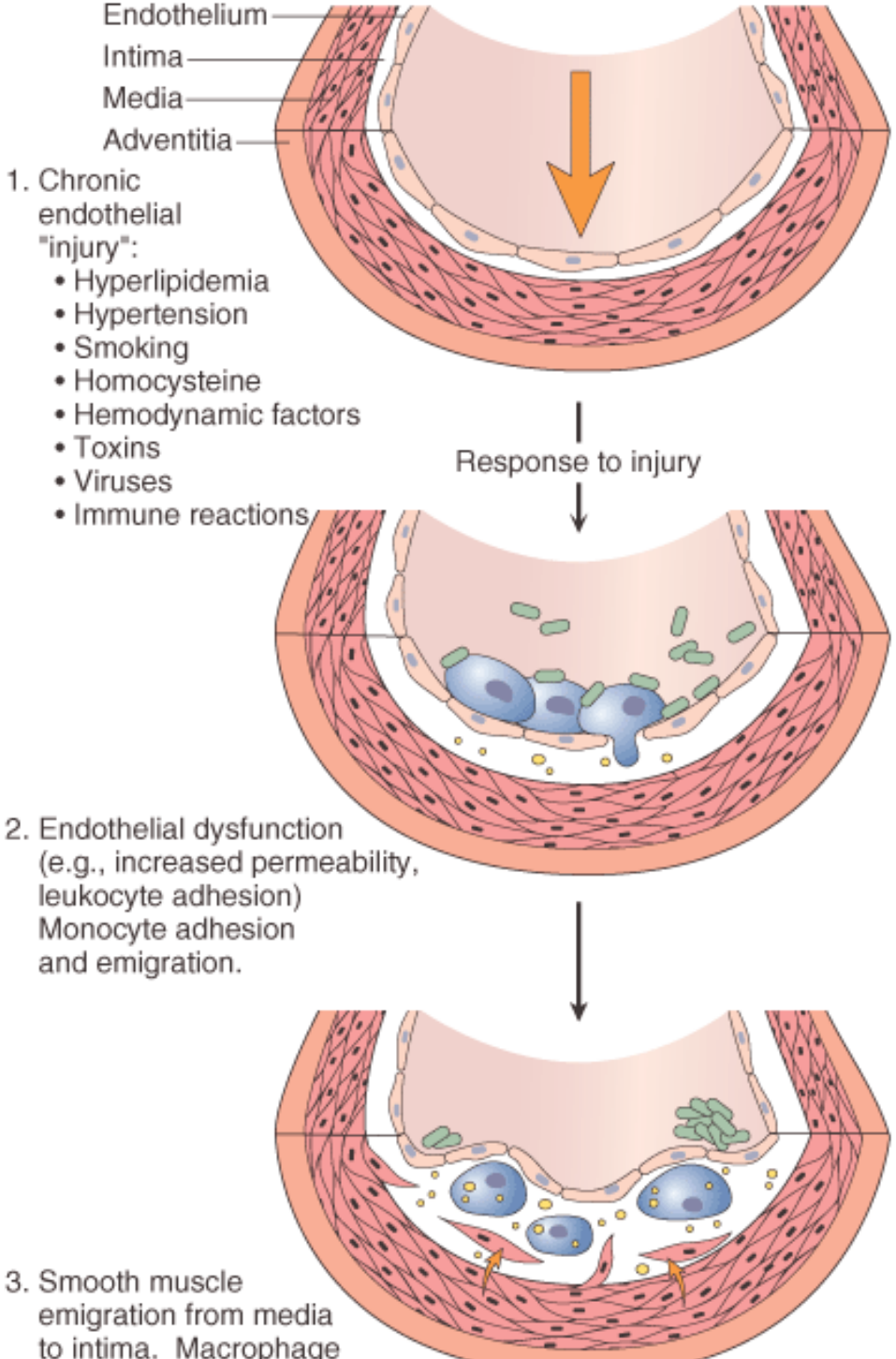
Hyperlipidemia is a major risk factor for atherosclerosis. Most of the evidence specifically implicates *hypercholesterolemia*. Elevated levels of serum cholesterol are sufficient to stimulate lesion development, even if other risk

Figure 11-10 Estimated 10-year risk of coronary artery disease according to various combinations of risk factor levels, expressed as the probability of an event in 10 years. HDL-C, high density lipoprotein cholesterol *(From Kannel WB, et al: An update on coronary risk factors. Med Clin North Am 79:951, 1995.)*



BP Systolic	120	160	160	160	160	160	160
Cholesterol	220	220	260	260	260	260	260
HDL-C	50	50	50	35	35	35	35
Diabetes	—	—	—	—	+	+	+
Cigarettes	—	—	—	—	—	+	+

Figure 11-11 Evolution of arterial wall changes in the response to injury hypothesis. *1*, Normal. *2*, Endothelial injury with adhesion of monocytes and platelets (the latter to denuded endothelium). *3*, Migration of monocytes (from the lumen) and smooth muscle cells (from the media) into the intima. *4*, Smooth muscle cell proliferation in the intima. *5*, Well-developed plaque (see Fig. 11-7 for details of mature plaque structure).



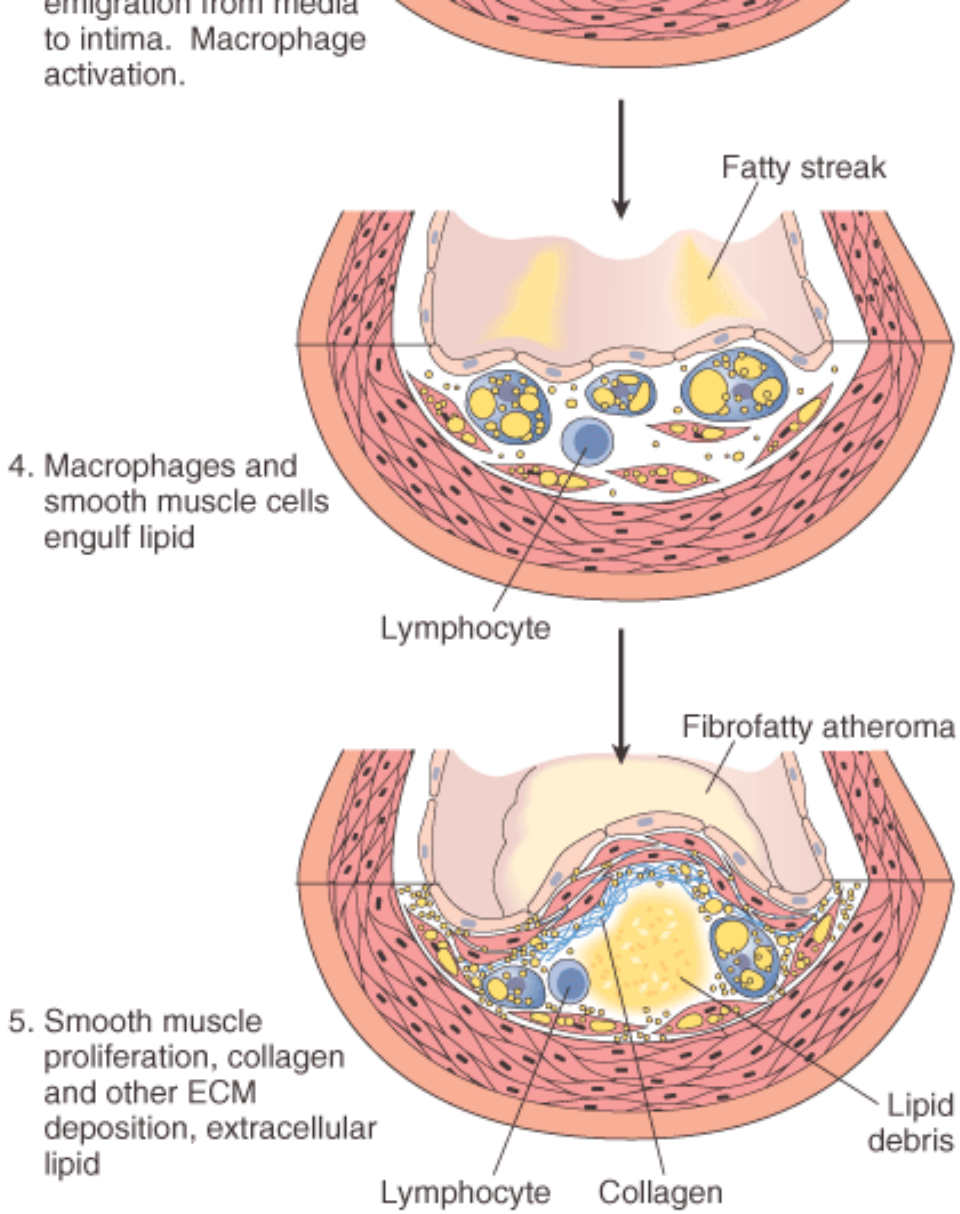


Figure 11-12 Schematic diagram of hypothetical sequence of cellular interactions in atherosclerosis. Hyperlipidemia and other risk factors are thought to cause endothelial injury, resulting in adhesion of platelets and monocytes and release of growth factors, including platelet-derived growth factor (PDGF), which lead to smooth muscle cell migration and proliferation. Foam cells of atheromatous plaques are derived from both macrophages and smooth muscle cells—from macrophages via the very-low-density lipoprotein (VLDL) receptor and low-density lipoprotein (LDL) modifications recognized by scavenger receptors (e.g., oxidized LDL), and from smooth muscle cells by less certain mechanisms. Extracellular lipid is derived from insudation from the vessel lumen, particularly in the presence of hypercholesterolemia, and also from degenerating foam cells. Cholesterol accumulation in the plaque reflects an imbalance between influx and efflux, and high-density lipoprotein (HDL) likely helps clear cholesterol from these accumulations. Smooth muscle cells migrate to the intima, proliferate, and produce extracellular matrix, including collagen and proteoglycans.

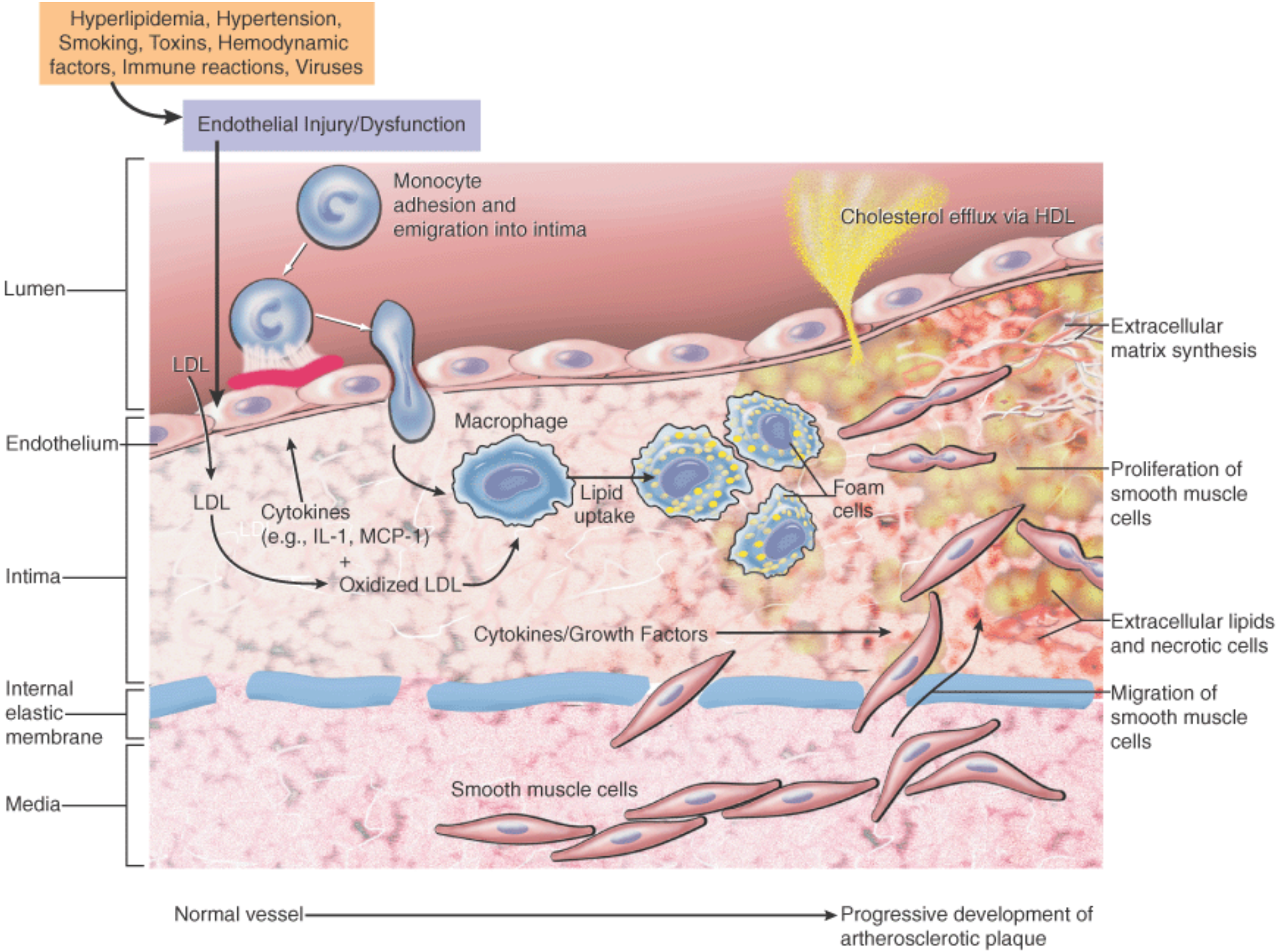

Hyperlipidemia, Hypertension, Smoking, Toxins, Hemodynamic factors, Immune reactions, Viruses
Endothelial Injury/Dysfunction
Monocyte adhesion and emigration into intima
Cholesterol efflux via HDL
Lumen
Endothelium
Intima
Internal elastic membrane
Media
LDL
LDL
Cytokines (e.g., IL-1, MCP-1) + Oxidized LDL
Macrophage
Lipid uptake
Foam cells
Extracellular matrix synthesis
Proliferation of smooth muscle cells
Extracellular lipids and necrotic cells
Migration of smooth muscle cells
Cytokines/Growth Factors
Smooth muscle cells
Normal vessel
Progressive development of artherosclerotic plaque

TABLE 11-3 -- Types and Causes of Hypertension

Essential Hypertension
Secondary Hypertension
••Renal
••••Acute glomerulonephritis
••••Chronic renal disease
••••Polycystic disease
••••Renal artery stenosis
••••Renal artery fibromuscular dysplasia
••••Renal vasculitis
••••Renin-producing tumors
••Endocrine
••••Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia, licorice ingestion)
••••Exogenous hormones (glucocorticoids, estrogen [including pregnancy-induced and oral contraceptives], sympathomimetics and tyramine-containing foods, monoamine oxidase inhibitors)
••••Pheochromocytoma
••••Acromegaly
••••Hypothyroidism (myxedema)
••••Hyperthyroidism (thyrotoxicosis)
••••Pregnancy-induced
••Cardiovascular
••••Coarctation of aorta
••••Polyarteritis nodosa (or other vasculitis)
••••Increased intravascular volume
••••Increased cardiac output
••••Rigidity of the aorta
••Neurologic
••••Psychogenic
••••Increased intracranial pressure
••••Sleep apnea

••••Acute stress, including surgery

Cushing syndrome, pheochromocytoma), narrowing of the renal artery, usually by an atheromatous plaque (renovascular hypertension) or other identifiable cause (secondary hypertension). *However, about 95% of hypertension is idiopathic (called essential hypertension). This form of hypertension generally does not cause short-term problems;* especially when controlled, is compatible with long life and is asymptomatic, unless a myocardial infarction, cerebrovascular accident, or other complication supervenes. Thus, this subgroup is often called *benign hypertension*.

A small percentage, perhaps 5%, of hypertensive persons show a rapidly rising blood pressure that if untreated, leads to death within a year or two. Called *accelerated* or *malignant hypertension*, the clinical syndrome is characterized by severe hypertension (i.e., systolic pressure over 200 mm Hg, diastolic pressure over 120 mm Hg), renal failure, and retinal hemorrhages and exudates, with or without papilledema. It may develop in previously normotensive persons but more often is superimposed on pre-existing benign hypertension, either essential or secondary.

Pathogenesis of Hypertension.

The multiple mechanisms of hypertension constitute aberrations of the normal physiologic regulation of blood pressure.[36] *Arterial hypertension occurs when the relationship between cardiac output and total peripheral resistance is altered.* For many of the secondary forms of hypertension, these factors are reasonably well understood. For example, in *renovascular hypertension*, renal artery stenosis causes decreased glomerular flow and pressure in the afferent arteriole of the glomerulus. This (1) induces renin secretion, initiating angiotensin II-mediated vasoconstriction and increased peripheral resistance, and (2) increases sodium reabsorption and therefore blood volume through the aldosterone mechanism. In pheochromocytoma, a tumor of the adrenal medulla (see Chapter 24), catecholamines produced by tumor cells cause episodic vasoconstriction and thus induce hypertension.

Regulation of Normal Blood Pressure.

Blood pressure is proportional to cardiac output and peripheral vascular resistance (Fig. 11-13). *Indeed, the blood pressure level is a complex trait that is determined by the interaction of multiple genetic, environmental, and demographic factors that influence cardiac output and vascular resistance.* The major factors that determine blood pressure variation within and between populations include age, gender, body mass index, and diet, principally sodium intake.

Cardiac output is highly dependent on blood volume, itself greatly influenced by the whole body sodium homeostasis. Peripheral vascular resistance is determined mainly at the level of the arterioles and is affected by neural and hormonal factors. Normal vascular tone reflects the balance between humoral vasoconstricting influences (including angiotensin II, catecholamines, and endothelin) and vasodilators (including kinins, prostaglandins, and NO). Resistance vessels also exhibit *autoregulation*, whereby increased blood flow induces vasoconstriction to protect against tissue hyperperfusion. Other local factors such as pH and hypoxia, and the α- and β-adrenergic systems, which influence heart rate, cardiac contraction, and vascular tone, may be important. The integrated function of these systems ensures adequate perfusion of all tissues, despite regional differences in demand.

The kidneys play an important role in blood pressure regulation as follows:

Figure 11-13 The critical roles of cardiac output and peripheral resistance in blood pressure regulation. NO, nitric oxide.

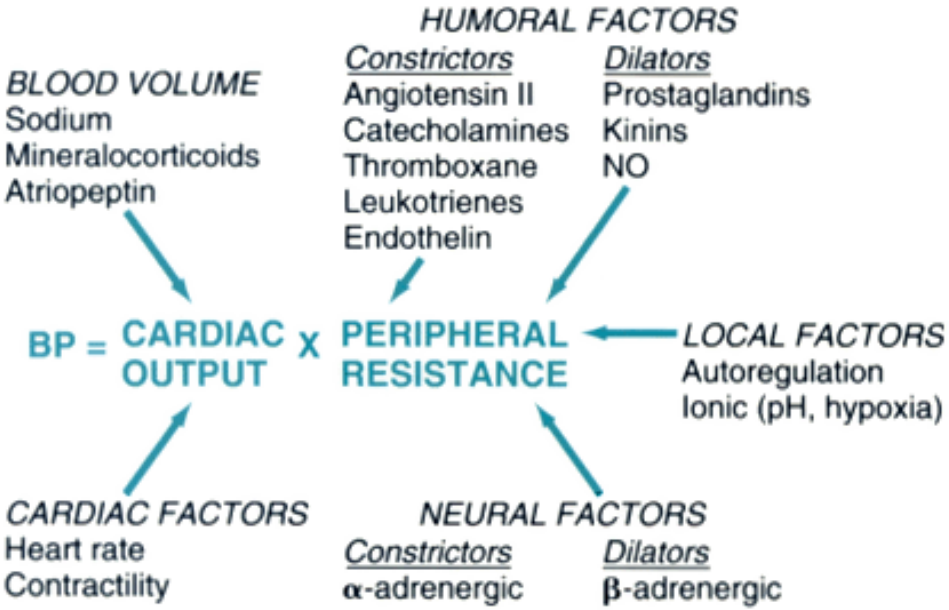


Figure 11-14 Blood pressure regulation by the renin-angiotensin system and the central roles of sodium metabolism in specific causes of inherited and acquired forms of hypertension. Components of the systemic renin-angiotensin system are shown in black. Genetic disorders that affect blood pressure by altering activity of this pathway are indicated in red; *arrows* indicate sites in the pathway altered by mutation. Genes that are mutated in these disorders are indicated in parentheses. Acquired disorders that alter blood pressure through effects on this pathway are indicated in blue. *(From Lifton RP, et al: Molecular genetics of human blood pressure variation. Science 272:676, 1996.)*

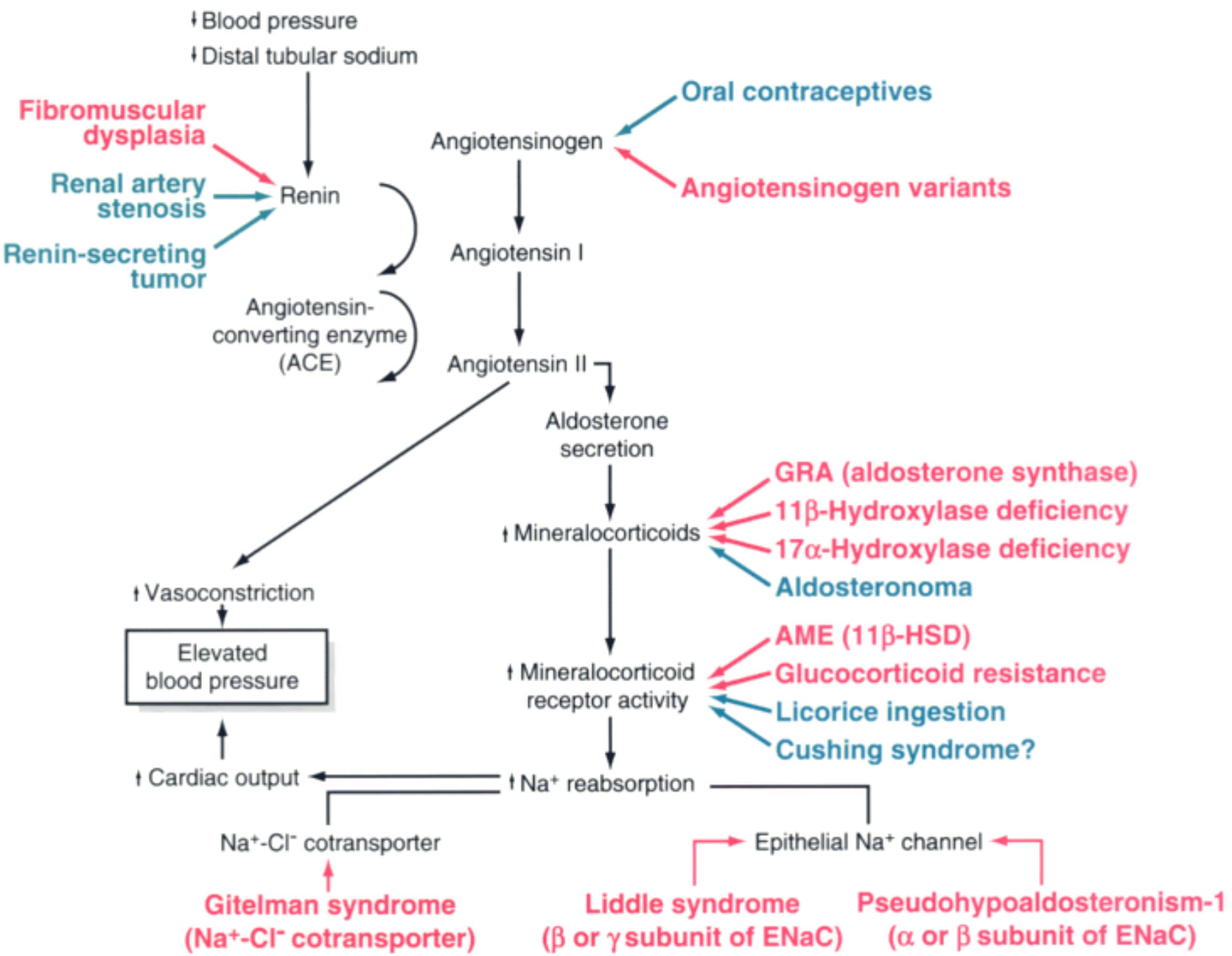


Figure 11-15 Hypothetical scheme for the pathogenesis of essential hypertension, implicating genetic defects in renal excretion of sodium, functional regulation of vascular tone, and structural regulation of vascular caliber. Environmental factors, especially increased salt intake, may potentiate the effects of genetic factors. The resultant increases in cardiac output and peripheral resistance contribute to hypertension. ECF, extracellular fluid.

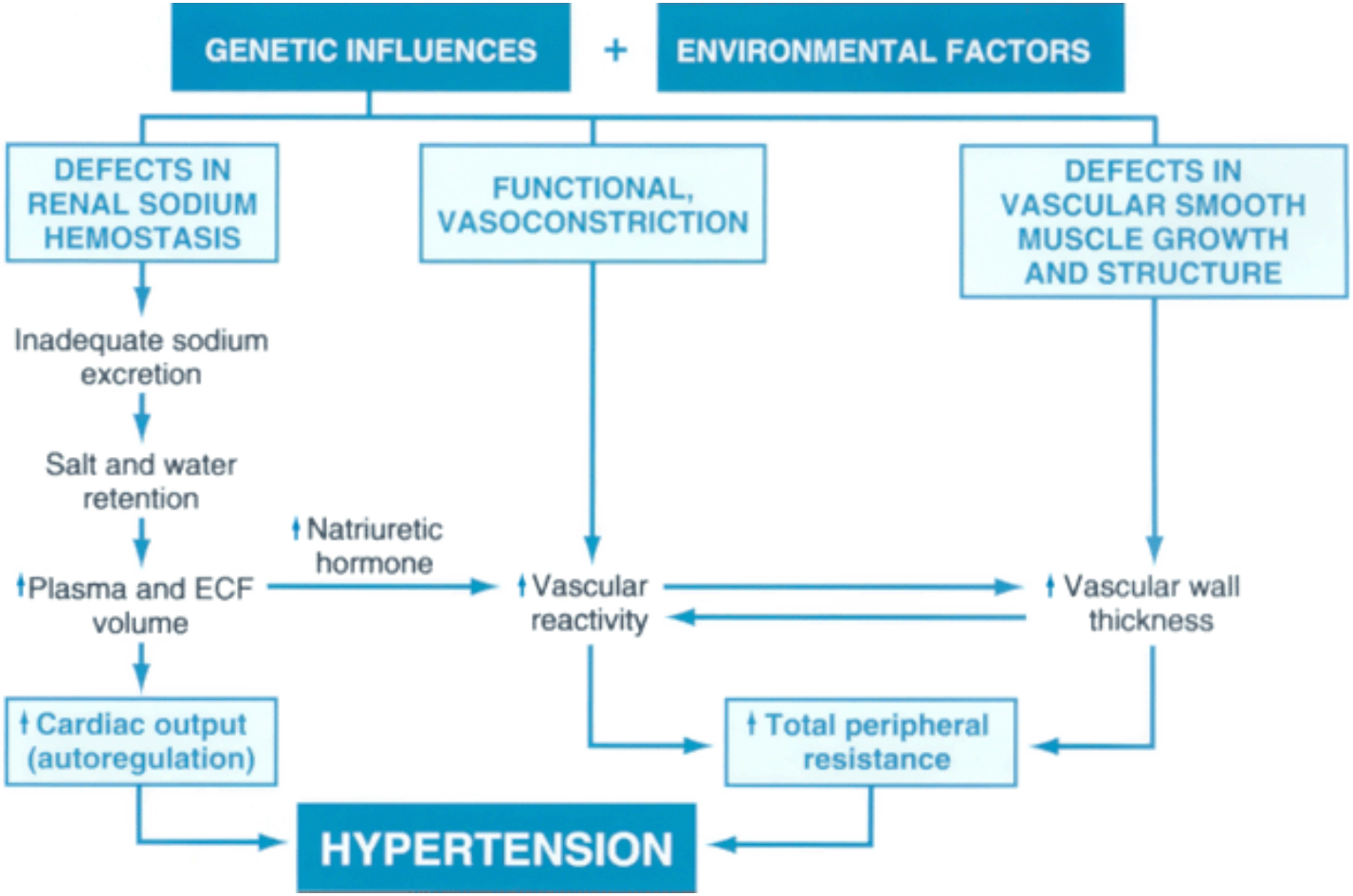


Figure 11-16 Mutations altering blood pressure in humans. A diagram of a nephron, the filtering unit of the kidney, is shown. The molecular pathways mediating NaCl reabsorption in individual renal cells in the thick ascending limb of the loop of Henle (TAL), distal convoluted tubule (DCT), and the cortical collecting tubule (CCT) are indicated, along with the pathway of the renin-angiotensin system, the major regulator of renal salt reabsorption. Single gene defects that manifest as inherited diseases affecting these pathways are indicated, with hypertensive disorders in red and hypotensive disorders in blue. Abbreviations: Al, angiotensin I; ACE, angiotensin converting enzyme; All, angiotensin II; MR, mineralocorticoid receptor; GRA, glucocorticoid-remediable aldosteronism; PHA1, pseudohypoaldosteronism, type 1; AME, apparent mineralocorticoid excess; 11β-HSD2, 11β-hydroxysteroid dehydrogenase-2; and DOC, deoxycorticosterone. *(From Lifton RP, et al: Molecular mechanisms of human hypertension. Cell 104:545, 2001.)*

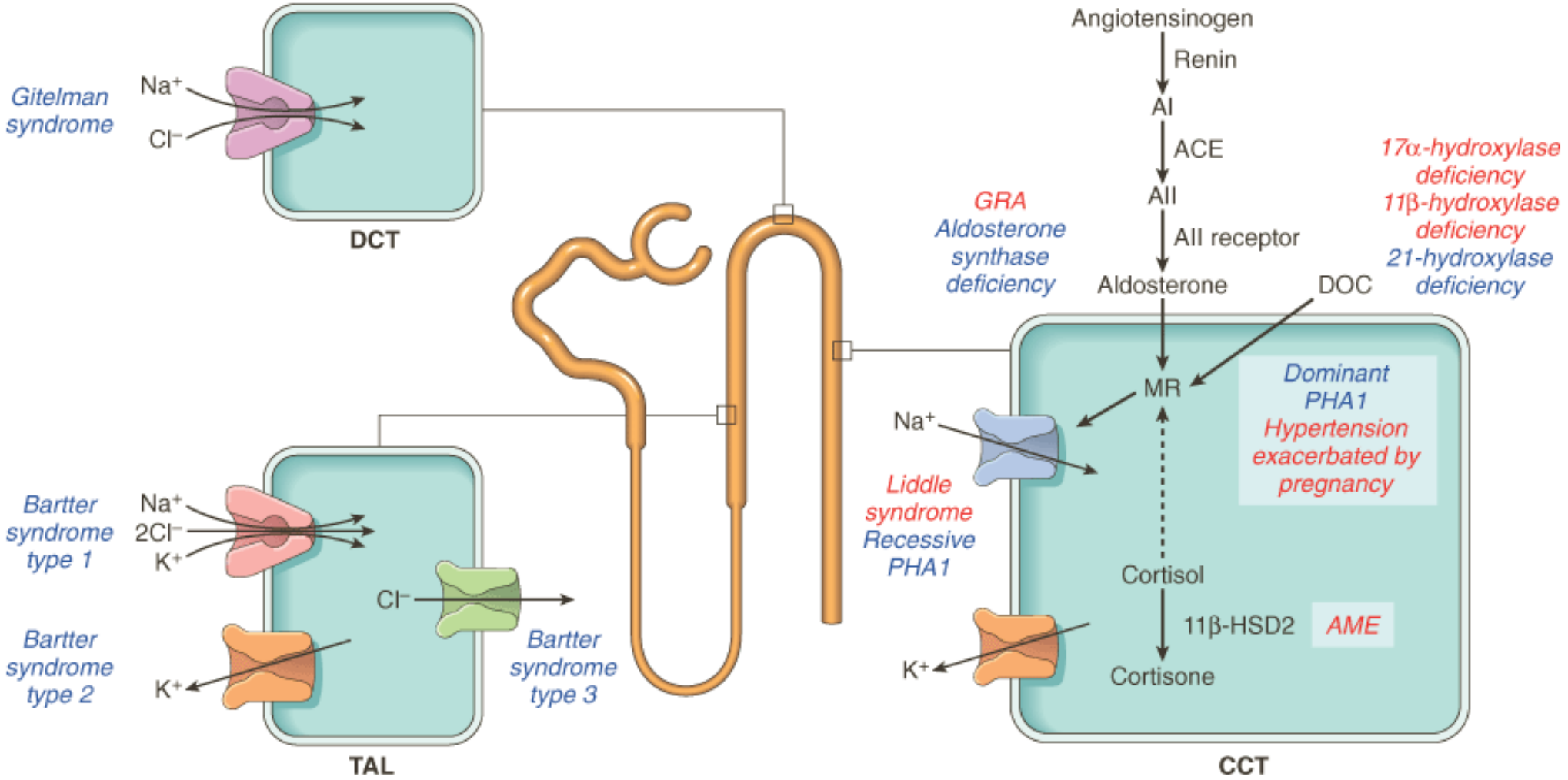


Figure 11-17 Vascular pathology in hypertension. *A,* Hyaline arteriolosclerosis. The arteriolar wall is hyalinized, and the lumen is markedly narrowed. *B,* Hyperplastic arteriolosclerosis (onionskinning) causing luminal obliteration *(arrow),* with secondary ischemic changes, manifested by wrinkling of the glomerular capillary vessels at the upper left (periodic acid-Schiff [PAS] stain). *(Courtesy of Helmut Rennke, M.D., Brigham and Women's Hospital, Boston, MA.)*

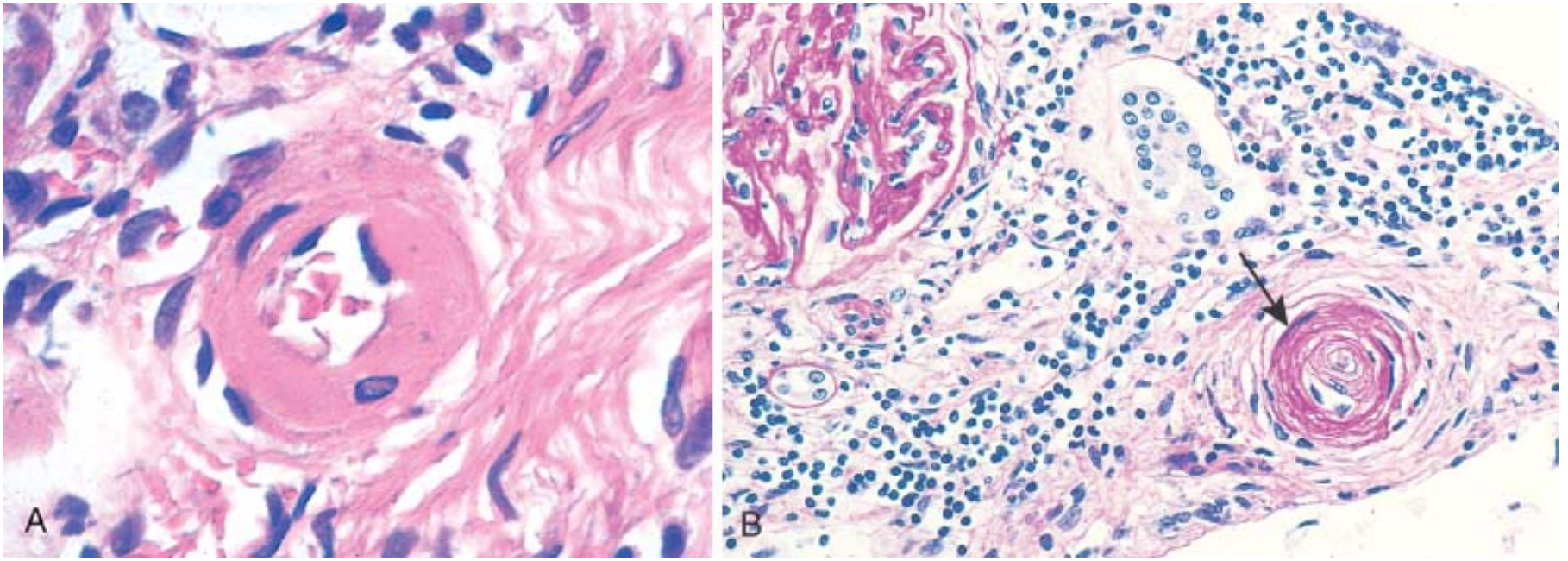


Figure 11-18 True and false aneurysms. *Center,* Normal vessel. *Left,* True aneurysm. The wall bulges outward and may be attenuated but is intact. *Right,* False aneurysm. The wall is ruptured, and there is a collection of blood (hematoma) that is bounded externally by adherent extravascular tissues.

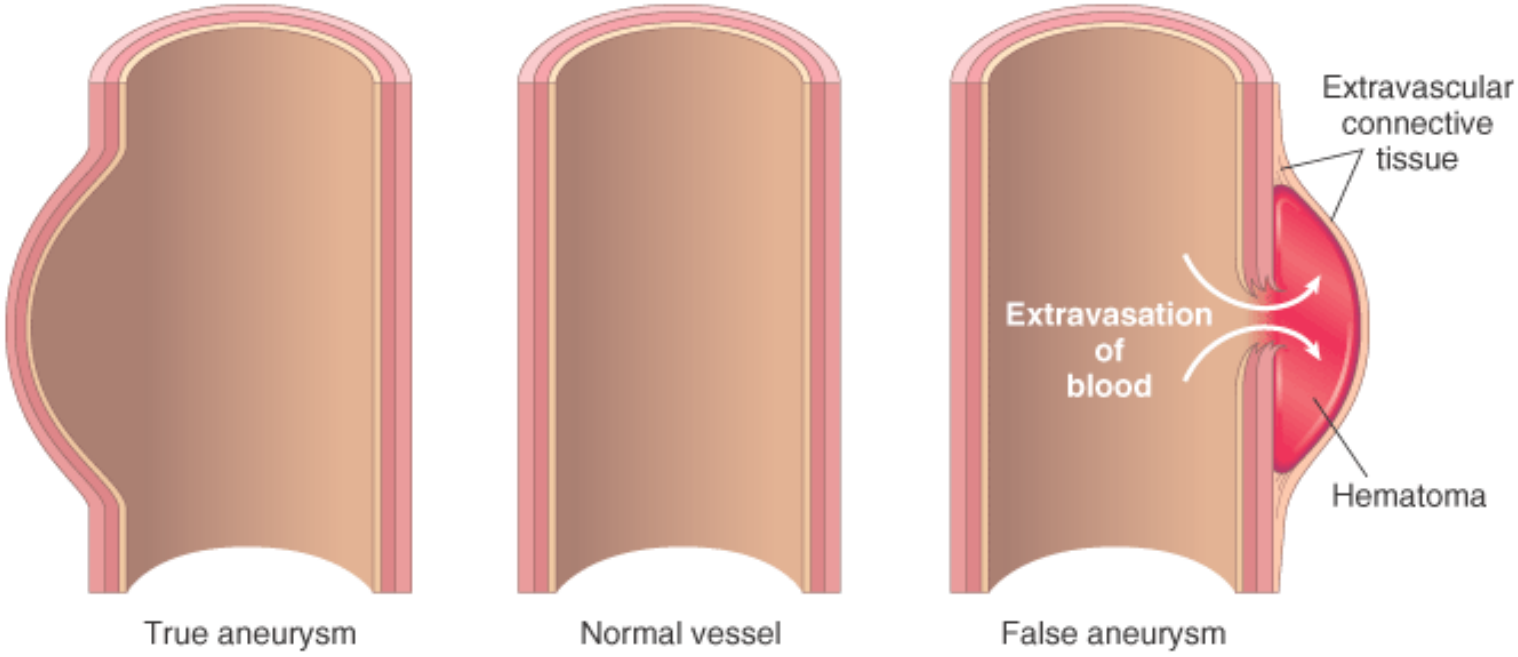


Figure 11-19 Abdominal aortic aneurysm. *A,* External view, gross photograph of a large aortic aneurysm that ruptured; the rupture site is indicated by the *arrow*. *B,* Opened view, with the location of the rupture tract indicated by a probe. The wall of the aneurysm is exceedingly thin, and the lumen is filled by a large quantity of layered but largely unorganized thrombus.

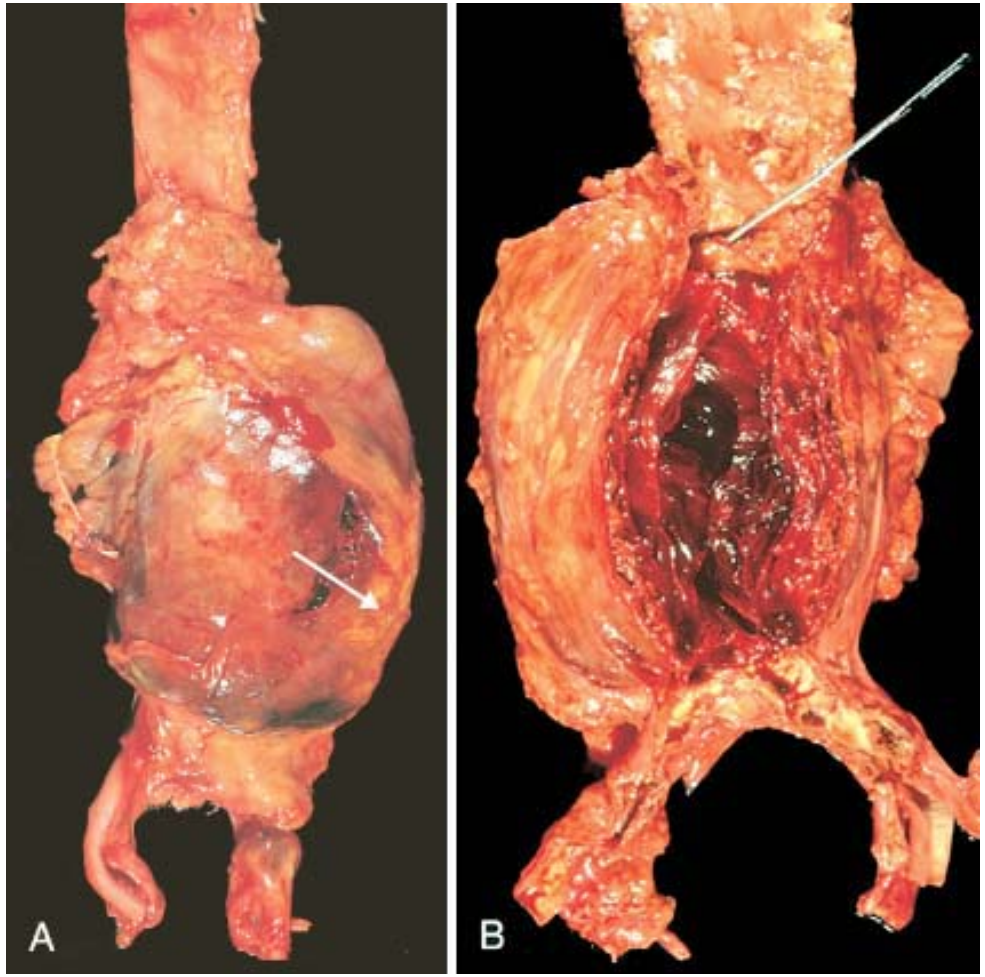


Figure 11-20 Aortic dissection. *A,* Gross photograph of opened aorta with proximal dissection, demonstrating a small, oblique intimal tear (demarcated by probe), allowing blood to enter the media, creating an intramural hematoma *(thin arrows)*. Note that the intimal tear has occurred in a region largely free from atherosclerotic plaque, and that propagation of the intramural hematoma was arrested at a site more distally, where atherosclerosis begins *(broad arrow). B,* Histologic view of the dissection demonstrating an aortic intramural hematoma *(asterisk)*. Aortic elastic layers are black, and blood is red in this section, stained with the Movat stain.

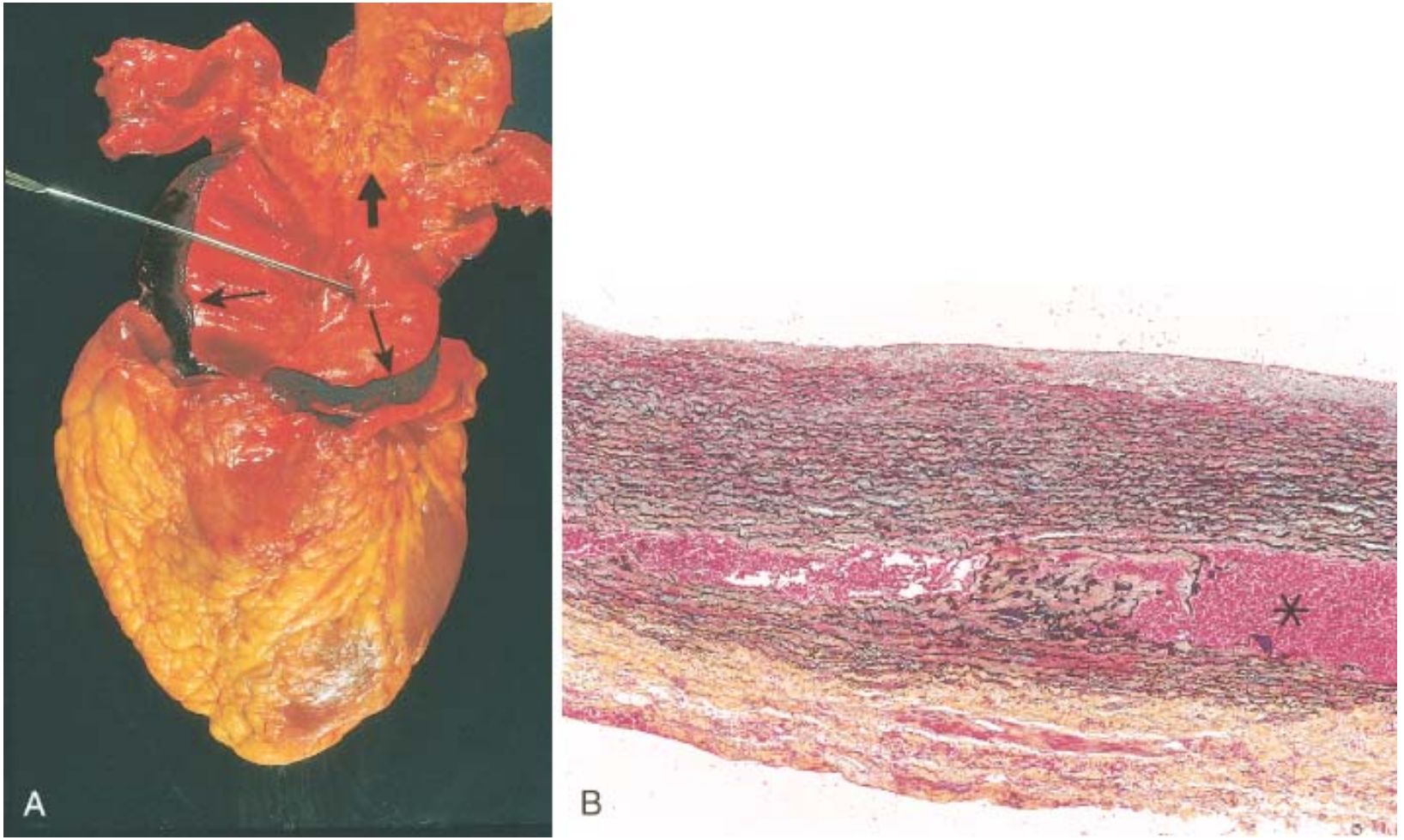


Figure 11-21 Medial degeneration. *A,* Cross-section of aortic media with marked elastin fragmentation and formation of areas devoid of elastin that resemble cystic spaces, from a patient with Marfan syndrome. *B,* Normal media for comparison, showing the regular layered pattern of elastic tissue. In both *A* and *B,* the tissue section is stained to highlight elastin as black.

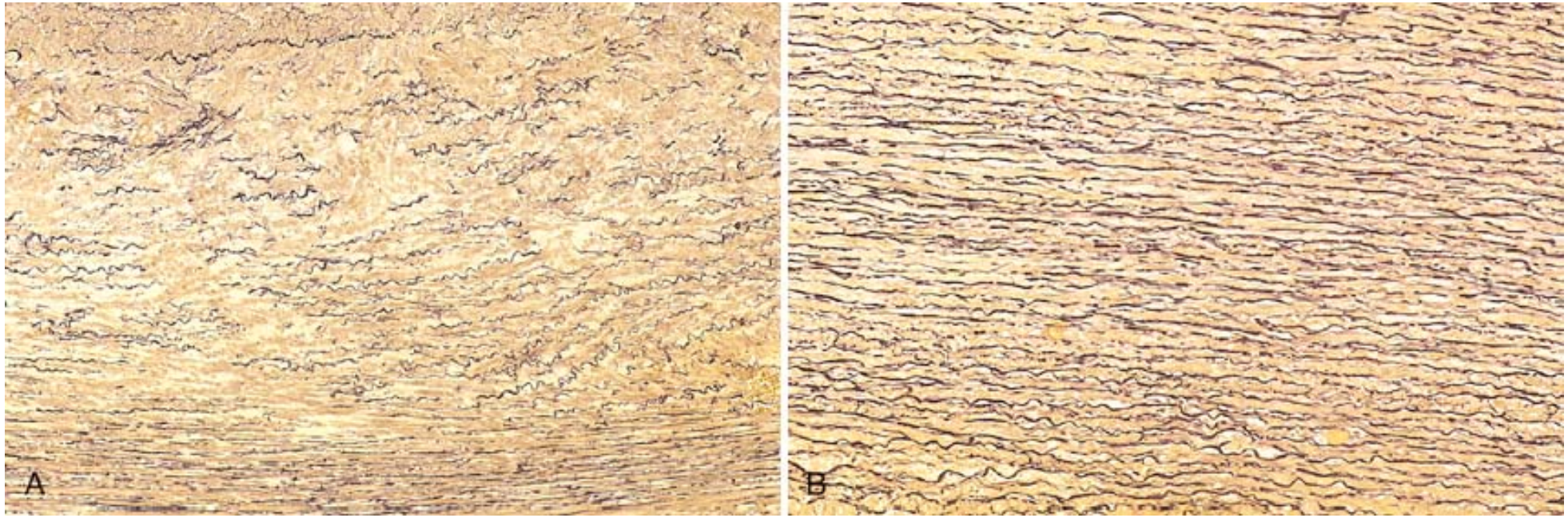


Figure 11-22 Classification of dissection into types A and B. Type A (proximal) involves the ascending aorta, whereas type B (distal) does not. The serious complications predominantly occur in the region from the aortic valve through the arch.

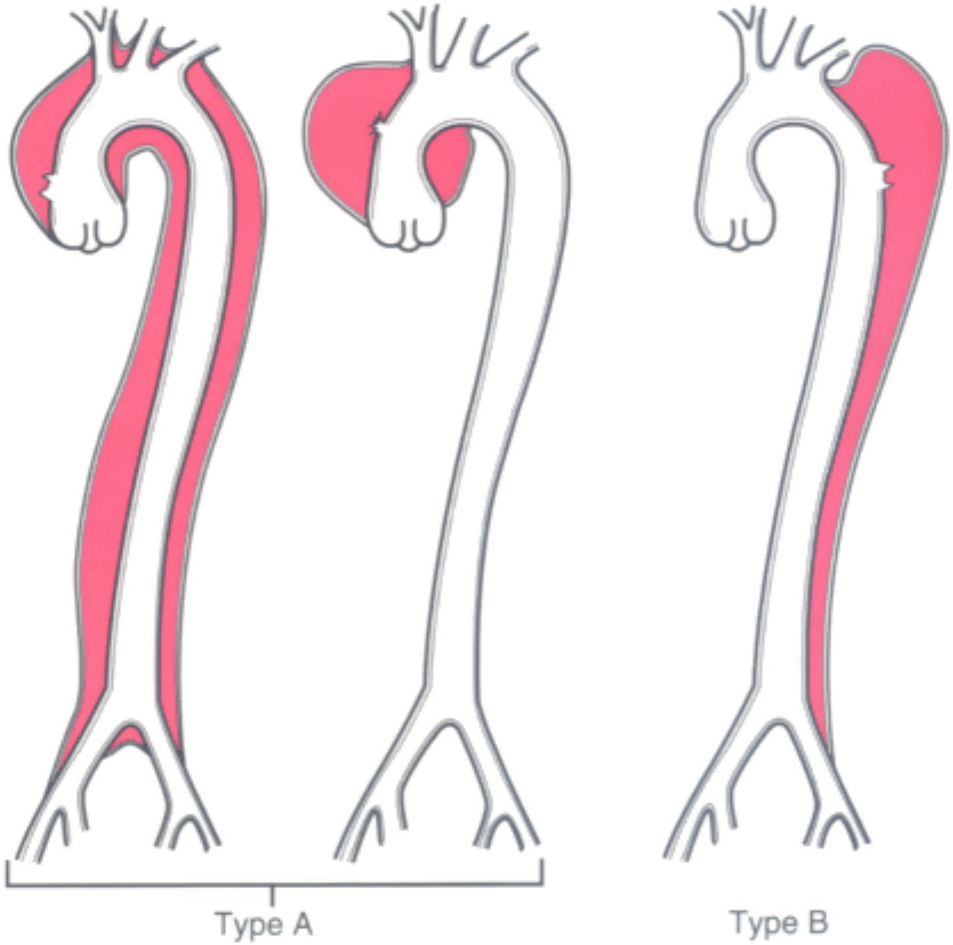


TABLE 11-4 -- Classification of Vasculitis Based on Pathogenesis

(Not Available)
Data from Jennette JC, Falk RJ: Update on the pathobiology of vasculitis. In Schoen FJ, Gimbrone MA (eds); Cardiovascular Pathology: Clinicopathologic Correlations and Pathogenetic Mechanisms. Baltimore, Williams & Wilkins, 1995, p 156.

chemical injury, such as irradiation, mechanical trauma, and toxins can also cause vascular damage.

Pathogenesis of Noninfectious Vasculitis.

The main immunologic mechanisms that initiate noninfectious vasculitis are: (1) immune complex deposition, (2) antineutrophil cytoplasmic antibodies, and (3) anti-endothelial cell antibodies.

Immune Complexes.

The evidence for involvement of immune complexes in vasculitides can be summarized as follows:

- The vascular lesions resemble those found in experimental immune complex-mediated conditions, such as the local Arthus phenomenon and serum sickness (Chapter 6). Immune reactants and complement can be detected in the serum or vessels of patients with vasculitis (e.g., DNA-anti-DNA complexes are present in the vascular lesions of systemic lupus erythematosus-associated vasculitis and IgG, IgM, and complement in cryoglobulinemic vasculitis).
- Hypersensitivity to drugs causes approximately 10% of vasculitic skin lesions, largely through vascular deposits of immune complexes. Some, such as penicillin, conjugate serum proteins; others, like streptokinase, are themselves foreign proteins. The manifestations vary and range from small-vessel hypersensitivity and leukocytoclastic vasculitis to polyarteritis nodosa, Wegener granulomatosis, and Churg-Strauss syndrome (see later for descriptions of these entities), and from mild and self-limiting to severe and even fatal. Identification of the disorder as a drug reaction is particularly important, as discontinuation of the offending agent is often followed by rapid improvement. [50]
- In vasculitis associated with viral infections, immune complexes can be found in the serum and in the vascular lesions of some patients, particularly in cases of polyarteritis nodosa (for example, HBsAg-anti-HbsAg in hepatitis-induced vasculitis).

Whether immune complexes deposit in vessel walls from the circulation, or are formed in situ, or both, is not known (see Chapter 6). However, many small vessel vasculitides show a paucity of vascular immune deposits and therefore other mechanisms have been sought for these so-called pauci-immune vasculitides.

Antineutrophil Cytoplasmic Antibodies.

Serum from many patients with vasculitis reacts with cytoplasmic antigens in neutrophils, indicating the presence of *antineutrophil cytoplasmic antibodies (ANCAs)*.[51] ANCAs are a heterogeneous group of autoantibodies directed against enzymes mainly found within the azurophil or primary granules in neutrophils, in the lysosomes of monocytes, and in ECs. The description of these autoantibodies is based on the immunofluorescent patterns of staining of ethanol-fixed neutrophils. Two main patterns are recognized: one shows cytoplasmic localization of the staining (c-ANCA), and the most common target antigen is proteinase-3 (PR3), a neutrophil granule constituent. The second shows perinuclear staining (p-ANCA) and is usually specific for myeloperoxidase (MPO). Either ANCA specificity may occur in a patient with ANCA-associated small-vessel vasculitis but c-ANCA is typically found in Wegener granulomatosis and p-ANCA is found in most cases of microscopic polyangiitis and Churg-Strauss syndrome. The disorders characterized by circulating ANCAs are called the *ANCA-associated vasculitides*.

ANCAs serve as useful quantitative diagnostic markers for these conditions, and their levels may reflect the degree of inflammatory activity.[52] ANCAs rise in episodes of recurrence, and thus are useful in management. In addition, the close association between ANCA titers and disease activity, particularly c-ANCA in Wegener granulomatosis, suggests that they may be important in the pathogenesis of this disease. Experimental data are consistent with a pathophysiologic mechanism for ANCA and/or ANCA antigen autoimmune responses in these diseases, but the precise mechanisms are unknown. However, there is yet no definitive proof that ANCAs play a causative role in the development of systemic vasculitis.

One plausible hypothesis for a causative role of ANCAs in vasculitis is summarized briefly as follows:[53] (1) An underlying disorder (e.g., an infection) elicits pro-inflammatory cytokines such as TNF, and granulocyte-macrophage colony-stimulating factor, and microbial products such as endotoxin, which together cause neutrophils and other inflammatory cells to express PR3 and MPO on their surfaces. (2) These stimulate the formation of ANCAs. (3) ANCAs react with circulating cytokine-primed neutrophils and cause them to degranulate (4) PMNs activated by ANCA cause endothelial

cell toxicity and other direct tissue injury. Interestingly, ANCAs directed against neutrophil constituents other than PR3 and MPO are also found in some patients with a wide range of inflammatory but nonvasculitic disorders such as inflammatory bowel disease, autoimmune liver disease, primary sclerosing cholangitis, and rheumatoid arthritis, and in some patients with malignancies and infections.

Anti-endothelial Cell Antibodies.

Antibodies to ECs, perhaps induced by defects in immune regulation, may predispose to certain vasculitides, such as those associated with SLE and Kawasaki disease.

Classification.

The systemic vasculitides are classified on the basis of the size and anatomic site of the involved blood vessels (Fig. 11-23), histologic characteristics of the lesion, and clinical manifestations. There is considerable clinical and pathologic overlap among these disorders summarized in Table 11-5 (Table Not Available) and discussed below.

GIANT CELL (TEMPORAL) ARTERITIS

Giant cell (temporal) arteritis, the most common form of systemic vasculitis in adults, is an acute and chronic, often granulomatous, inflammation of arteries of large to small size.[54] It affects principally the arteries in the head—especially the temporal arteries—but also the vertebral and ophthalmic arteries and the aorta, where it may cause thoracic aortic aneurysm. Ophthalmic arterial involvement may lead to permanent blindness. Therefore, visual loss caused by giant cell arteritis is a medical emergency that requires prompt recognition

Figure 11-23 Diagrammatic representation of the sites of the vasculature involved by the major forms of vasculitis. The widths of the trapezoids indicate the frequencies of involvement of various portions. LCA, leukocytoclastic angiitis. *(Reproduced from Jennette JC, and Falk RJ: Small-vessel vasculitis. New Engl J Med 337:1512, 1997.)*

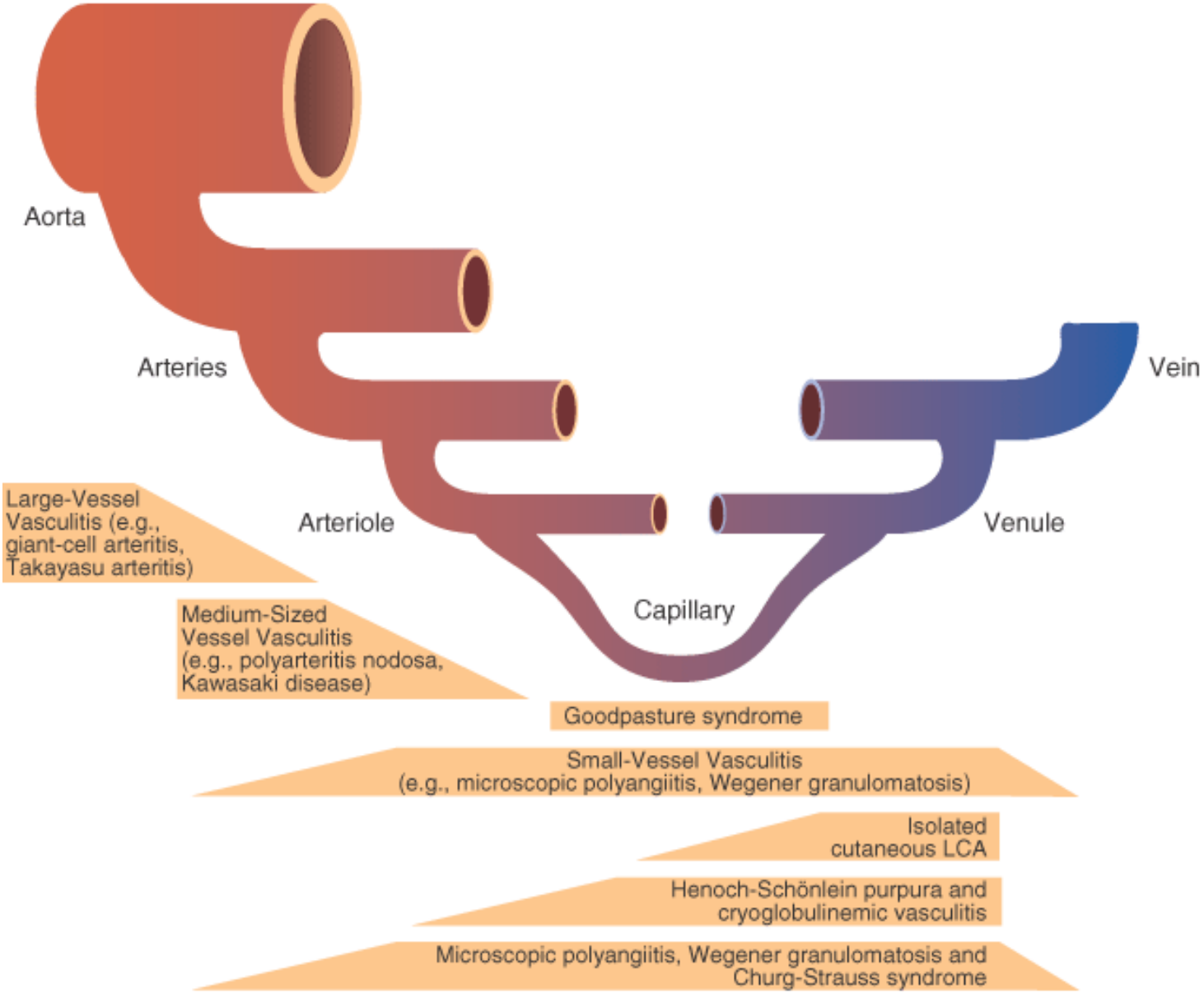


TABLE 11-5 -- Classification and Characteristics of Selected Vasculitis

(Not Available)
Modified from Jennette JC, et al: Nomenclature of systemic vasculitides: the proposal of an international consensus conference. Arthritis Rheum 37:187, 1994.

Figure 11-24 Temporal (giant cell) arteritis. *A*, H&E stain of section of temporal artery showing giant cells at the degenerated internal elastic membrane in active arteritis (*arrow*). *B,*

Elastic tissue stain demonstrating focal destruction of internal elastic membrane (*arrow*) and intimal thickening (IT) characteristic of long-standing or healed arteritis. *C,* Examination of the temporal artery of a patient with giant-cell arteritis shows a thickened, nodular, and tender segment of a vessel on the surface of head (*arrow*). *(C Reproduced from Salvarani C, et al. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 347:261, 2002.)*

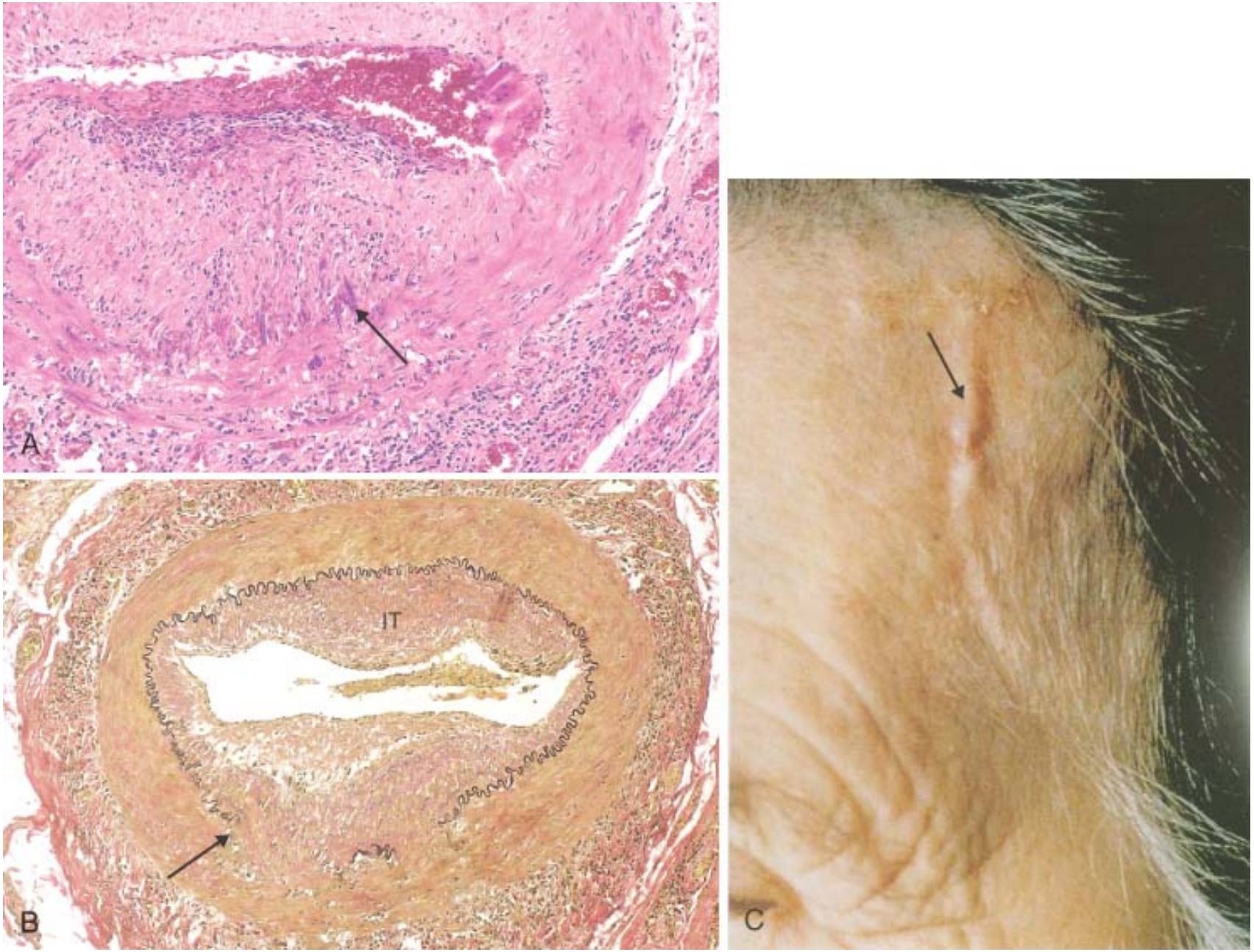


Figure 11-25 Takayasu arteritis. *A,* Aortic arch angiogram showing narrowing of brachiocephalic, carotid, and subclavian arteries *(arrows). B,* Gross photograph of two cross-sections of the right carotid artery taken at autopsy of the patient shown in *A,* demonstrating marked intimal thickening with minimal residual lumen. *C,* Histologic view of active Takayasu aortitis, illustrating destruction of the arterial media by mononuclear inflammation with giant cells.