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Environmental and Nutritional Diseases

Environment:

- The term "environment" encompasses the outdoor, indoor, and occupational environments shared by small and large populations , and our own personal environment.

- In each of these environments, the air we collectively breathe, the food and water we consume, and exposure to toxic agents are major determinants of our health.

- Our personal environment is greatly influenced by tobacco use, alcohol ingestion, therapeutic and non-therapeutic drug consumption, and diet.

- The term environmental diseases refers to conditions caused by exposure to chemical or physical agents in the ambient, workplace, and personal environment, including diseases of nutritional origin.

disasters, such as :

- the methyl mercury contamination of Minamata Bay in Japan in the 1960s

- Exposure to dioxin in Seveso, Italy, in 1976

- Leakage of methyl isocyanate gas in Bhopal, India, in 1984
- Chernobyl nuclear accident in 1986,
- Contamination of Tokyo subways by the organophosphate pesticide sarin

- Undernutrition is the single leading global cause of health loss (defined as morbidity and premature death

- In developing countries, infectious disease constitute 5 of the 10 leading causes of death: respiratory infections, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), diarrheal diseases, tuberculosis and malaria.

اثرات تغییر آب و هوا بر سلامت

- اندازه گیری دما نشان می دهد که زمین با یک سرعت فزاینده در طی ۵۰ سال گذشته گرم شده است.
- اثرات منفی تغییرات آب و هوایی روی سلامت انسان:
- تشدید بیماری های قلبی عروقی ،مغزی و تنفسی به وسیله گرما و آلودگی هوا
- گاستروانتریت ،وبا و سایر بیماری های عفونی برخاسته از آب و غذا
- بیماری های غفونی برخاسته از ناقلین(حشرات) مانند مالاریا و تب کنگو
- سوءتغذیه

Toxicity of Chemical and Physical agents

Toxicology : the science of poisons

- The definition of a poison is not straightforward. It is basically a quantitative concept strictly dependent on dosage.

- The quote from Paracelsus in the sixteenth century that "all Substances are poisons; the right dosage differentiates a poison from a remedy" is even more valid today given the proliferation of pharmaceutical drugs with potentially harmful effects.

Xenobiotics are exogenous chemicals in the environment
that may be absorbed by the body through inhalation,
ingestion, or skin contact

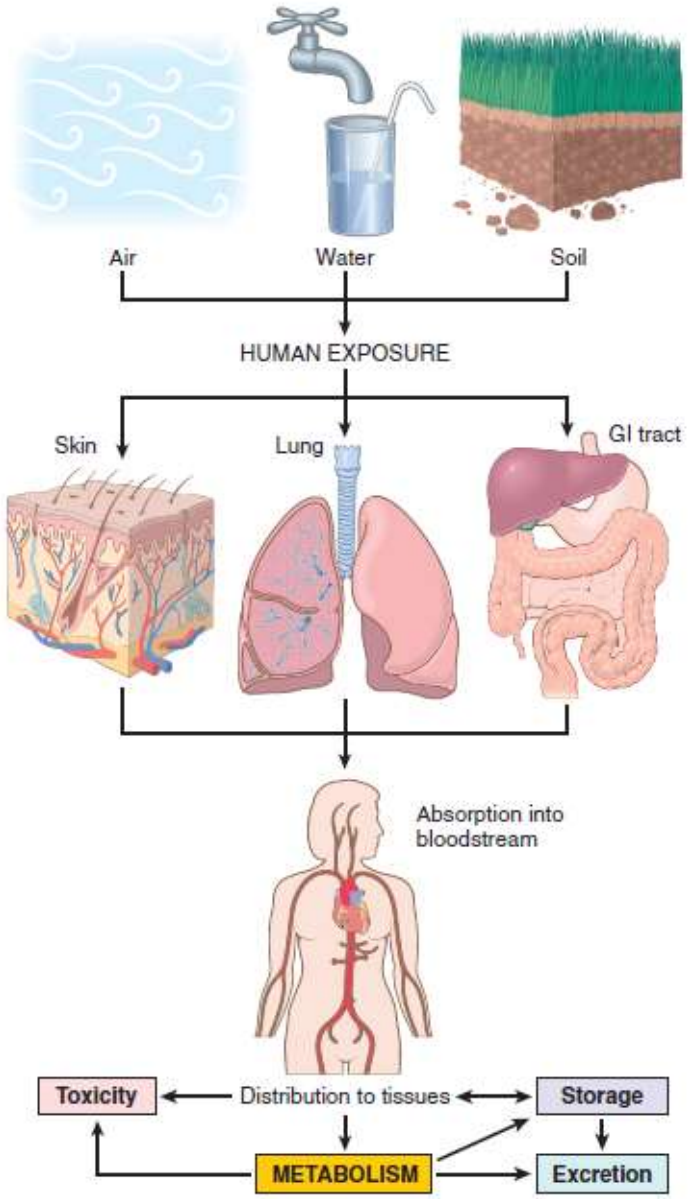
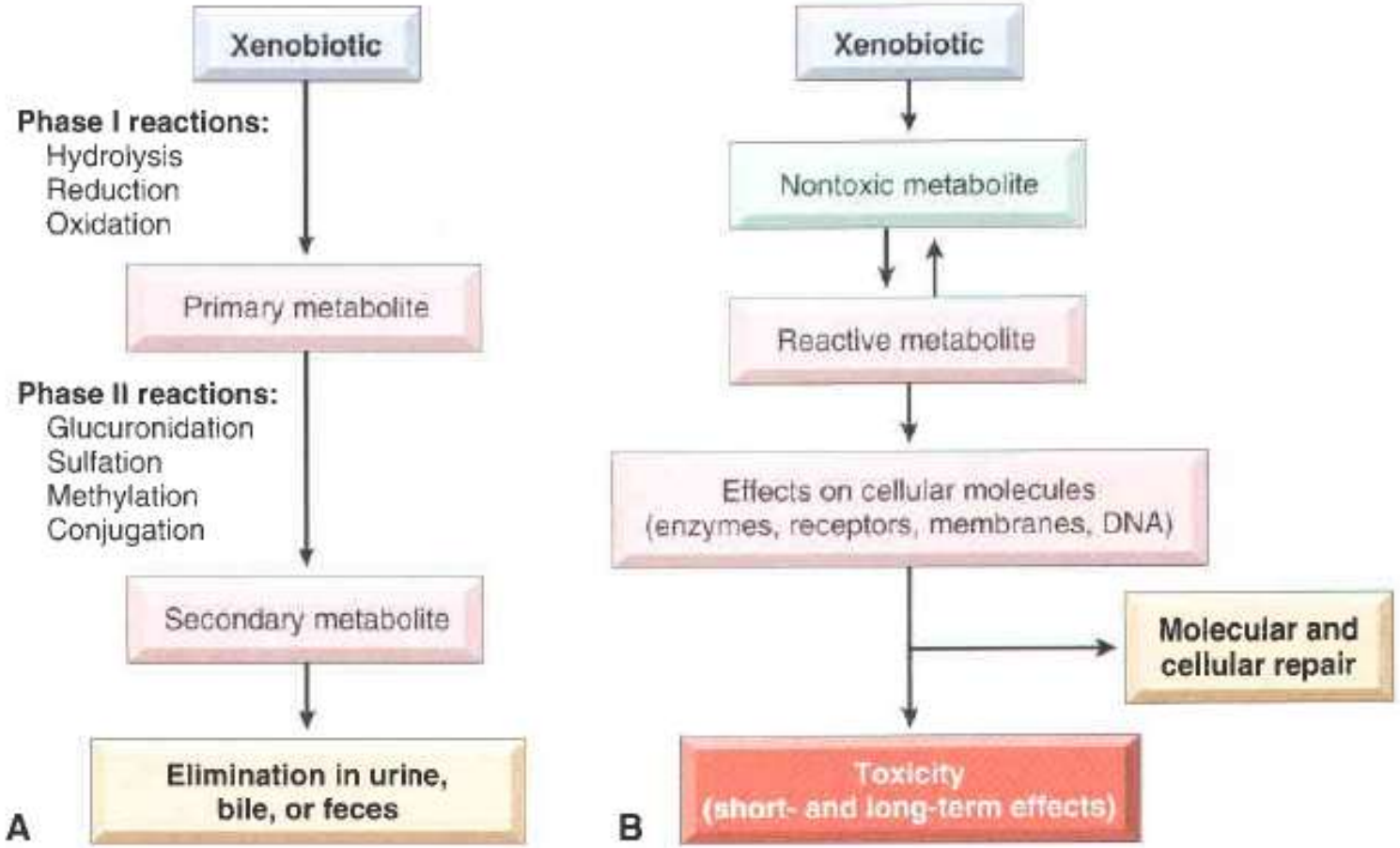


Figure 7–2 Human exposure to pollutants. Pollutants contained in air, water, and soil are absorbed through the lungs, gastrointestinal tract, and skin. In the body, they may act at the site of absorption, but they generally are transported through the bloodstream to various organs, where they may be stored or metabolized. Metabolism of xenobiotics may result in the formation of water-soluble compounds, which are excreted, or in activation of the agent, creating a toxic metabolite.

- Chemicals may be excreted in urine or feces or eliminated in expired air, or they may accumulate in bone, fat, brain, or other tissues

- بیشتر حلال ها و دارو ها لیپوفیل بوده و این امر انتقالشان را در خون به کمک لیپوپروتیین ها و نفوذشان به داخل اجزای لیپیدی غشای سلول را تسهیل می کند

- The reactions that metabolize xenobiotics into nontoxic products, or activate xenobiotics to generate toxic compounds occur in two phases:
- In phase I reactions, chemicals can undergo hydrolysis, oxidation, or reduction. Products of phase I reactions often are metabolized into water-soluble compounds through phase II reactions of glucuronidation, sulfation, methylation, and conjugation with glutathione (GSH). Water-soluble compounds are readily excreted.



Xenobiotic metabolism

A. , Xenobiotics can be metabolized to nontoxic metabolites and eliminated from the body (detoxification)

B. , Xenobiotic metabolism may also result in the formation of a reactive metabolite that is toxic to cellular components. If repair is not effective , short- and long-term effects develop.

- The most important cellular enzyme system involved in phase I reactions is the **cytochrome P-450 system**, located primarily in the endoplasmic reticulum (ER) of the **liver** but also present in **skin, lungs,** and **gastrointestinal (GI) mucosa** and in practically every organ.

- The system catalyzes reactions that either detoxify xenobiotics or activate xenobiotics into active compounds that cause cellular injury.

- P-450 enzymes vary widely in activity among different people, owing to both polymorphisms in the genes encoding the enzymes and interactions with drugs that are metabolized through the system.

- The activity of the enzymes also may be decreased by fasting or starvation, and increased by alcohol consumption and smoking

Environmental Pollution

Air pollution

- Outdoor
- Indoor

Out door air pollution

Pollutant	Populations at Risk	Effects
Ozone	Healthy adults and children	Decreased lung function Increased airway reactivity Lung inflammation
	Athletes, outdoor workers Asthmatics	Decreased exercise capacity Increased hospitalizations
Nitrogen dioxide	Healthy adults Asthmatics Children	Increased airway reactivity Decreased lung function Increased respiratory infections
Sulfur dioxide	Healthy adults Individuals with chronic lung disease Asthmatics	Increased respiratory symptoms Increased mortality Increased hospitalization Decreased lung function
Acid aerosols	Healthy adults Children Asthmatics	Altered mucociliary clearance Increased respiratory infections Decreased lung function Increased hospitalizations
Particulates	Children Individuals with chronic lung or heart disease Asthmatics	Increased respiratory infections Decreased lung function Excess mortality Increased attacks

- آلودگی هوای بیرون:
- **اوزون** : در اثر واکنش های ناشی از نور خورشید روی اکسید نیتروژن ناشی از اگزوز اتومبیل ها .سمیت آن مربوط به تولید رادیکال های آزاد است که به سلول های اپی تلیالی مجاری هوایی و سلول های آلوئولار آسیب می رساند.

- دی اکسید سولفور،ذرات معلق و آئروسل های اسیدی به وسیله کارخانه ها و صنایعی که از زغال سنگ و روغن به عنوان سوخت استفاده می کنند ،ایجاد می شود.

مونواکسید کربن

- گازی غیرمحرک،بی نگ، بی مزه و بی بو است که از اکسیداسیون ناقص مواد کربنی تولید می شود.

- COیک خفه کننده سیستمیک است و با اتصال به Hbو جلوگیری از انتقال اکسیژن فرد را می کشد .

- تمایل هموگلوبین بهCO، 200برابر اکسیژن است .کربوکسی هوگلوبین حاصل از آن توانایی حمل اکسیژن را ندارد.هیپوکسی موجب تضعیف CNSبه صورت تدریجی می شود.

- **مسمومیت حاد با CO:** به علت مواجهه تصادفی یا به قصد خودکشی،در بیماران با پوست روشن ،مسمومیت حاد با رنگ مخصوص قرمز گیلاسی منتشر پوست و غشاهای مخاطی ناشی از کربوکسی هموگلوبین مشخص می شود.

در صورت طولانی شدن بقا مغز می تواند کمی ادماتو و همراه با خونریزی نقطه ای و تغییرات نورونی ناشی از هیپوکسی باشد

- **مسمومیت مزمن:** از آنجایی ایجاد می شود که کربوکسی هموگلوبین ایجاد شده بسیار پایدار است .در نتیجه در اثر مواجهه مداوم با سطح کم CO،کربوکسی هموگلوبین می تواند تجمع پیدا کند و به غلظت تهدید کننده حیات برسد.

- در صورت خاتمه مواجهه فرد اغلب بهبود می یابد ولی ممکن است اختلالات عصبی،پایدار باقی بماند.
- تشخیص: تشخیص سطوح افزایش یافته ی کربوکسی هموگلوبین در خون

Outdoor air pollution

- Although the lungs bear the brunt of the adverse consequences, air pollutants can affect many organ systems.

Indoor Air Pollution

- **The commonest pollutant is tobacco smoke**
- **CO**
- **Nitrogen dioxideand carbon particulates (wood smoke)**
- **Asbestos**
- **Radon**
- **Bioaerosols** may contain pathogenic microbiologic agents, such as those that can cause Legionnaires' disease, viral pneumonia, and the common cold, as well as allergens derived from pet dander, dust mites, and fungi and molds, which can cause rhinitis, eye irritation, and even asthma

Metals as Environmental Pollutants

- Lead,
- Mercury,
- Arsenic, and
- Cadmium

Lead

- Lead exposure occurs through contaminated air and food and water
- lead-containing house paints and gasoline

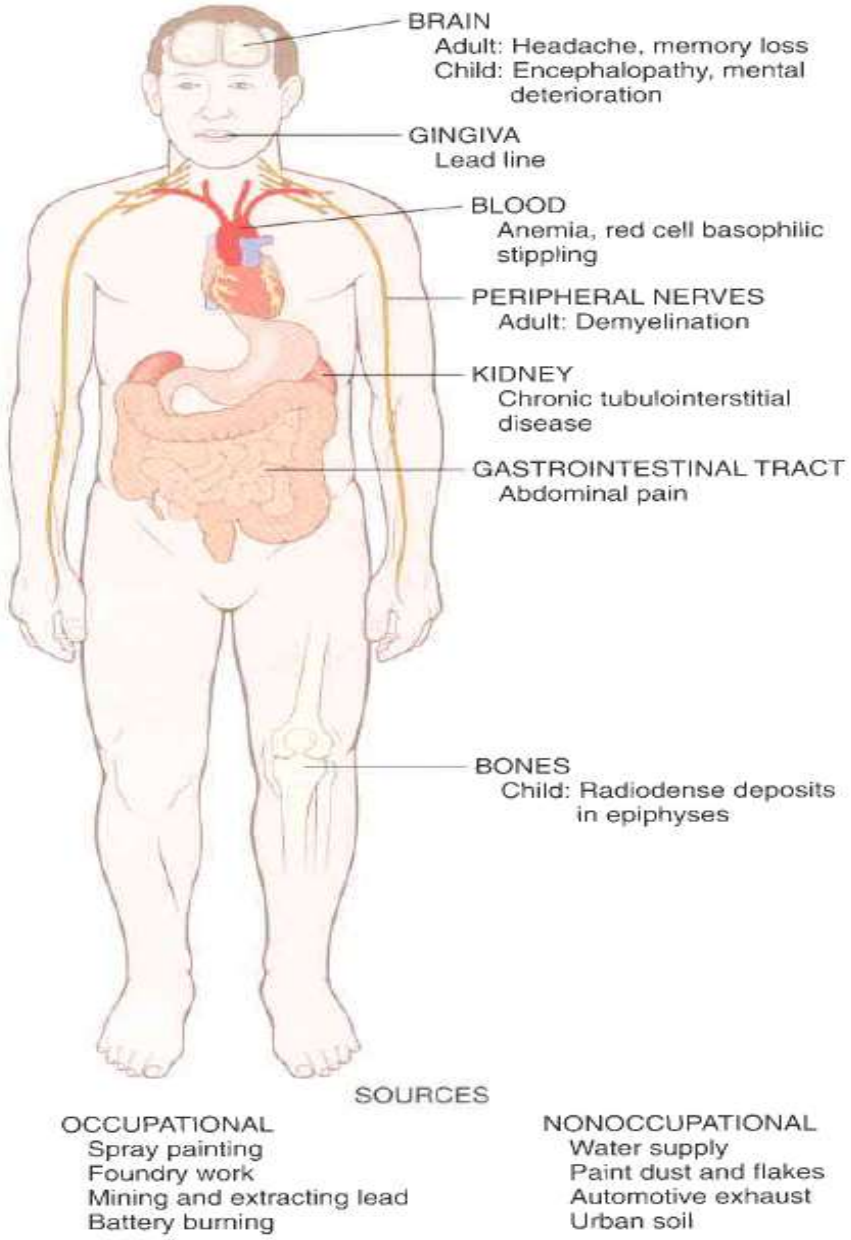
- کودکان بیش از ۵۰%سرب غذا را جذب می کنند در حالیکه بالغین تقریبا ۱۵% آنها را جذب می کنند.

- قسمت عمده ی سرب جذب شده (۸۵-۸۰%) توسط استخوان و دندان های در حال رشد جذب می شود ،سرب جهت اتصال به فسفات با کلسیم رقابت می کند و نیمه عمر آن در استخوان ۲۰ تا ۳۰ سال است.۵ تا ۱۰ درصد سرب جذب شده در خون باقی می ماند

The major anatomic targets of lead toxicity are:

- bone marrow
- blood,
- nervous system,
- Gastrointestinal tract, and
- kidneys

Lead effects on various organs



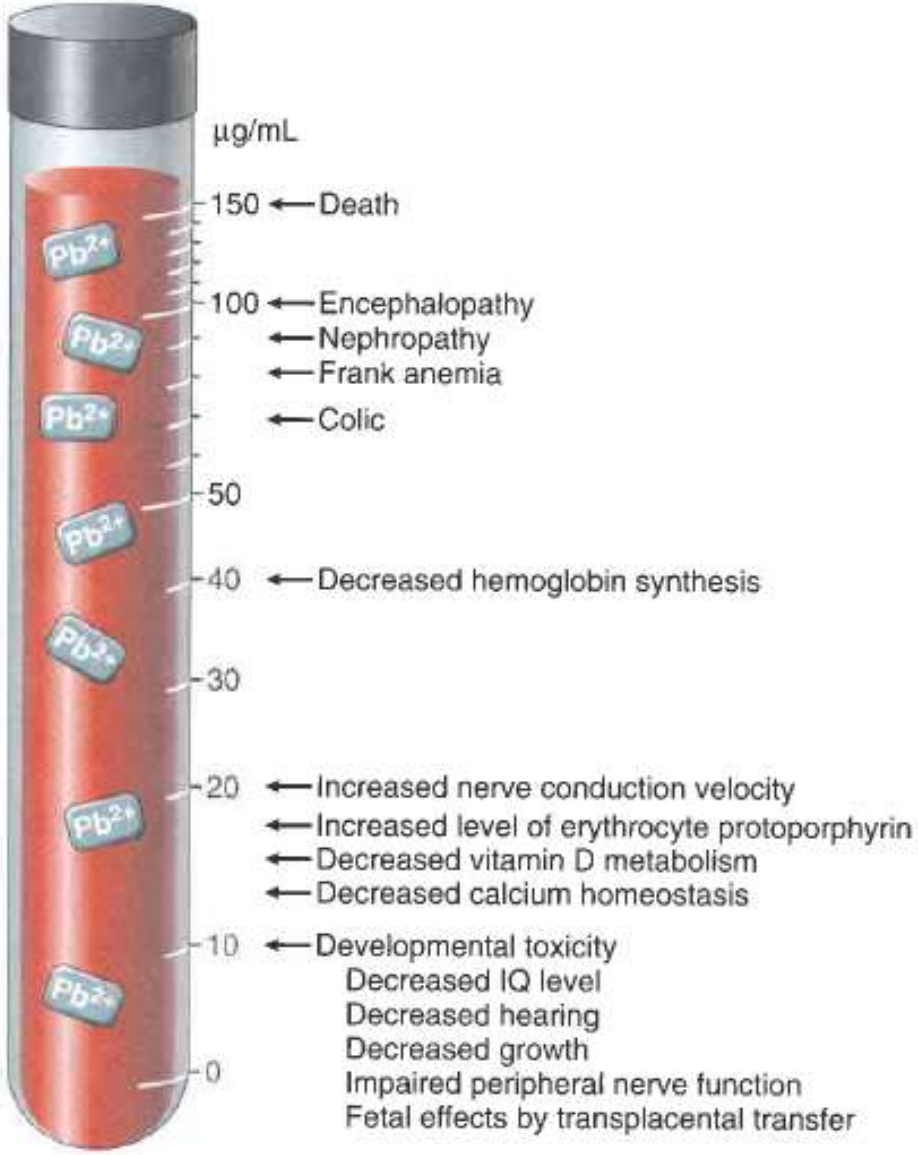
- its half-life in bone is 20 to 30 years.

- زیادی سرب باعث عوارض نورولوژیک در کودکان (اثرات مرکزی ،برگشت ناپذیر) و بالغین (نوروپاتی محیطی ،برگشت پذیر)می شود.
- The neurotoxic effects of lead are attributed to the inhibition of neurotransmitters caused by the disruption of calcium homeostasis.

- Brain damage is prone to occur in children. It can be very subtle, producing mild dysfunction, or it can be massive and lethal.
- In young children, sensory, motor, intellectual, and psychologic impairments including reduced IQ, learning disabilities, retarded psychomotor development, blindness, and, in more severe cases, psychoses, seizures, and coma

- In adults the CNS is less often affected, but frequently a peripheral demyelinating neuropathy appears, typically involving the motor nerves of the most commonly used muscles

Lead effects in different serum levels



- Lead interferes with the normal remodeling of cartilage and primary bone trabeculae in the epiphyses in children. This causes increased bone density detected as radiodense " **lead lines**“

- another type of lead line appears in the gums as a result of hyperpigmentation).
- Lead inhibits the healing of fractures

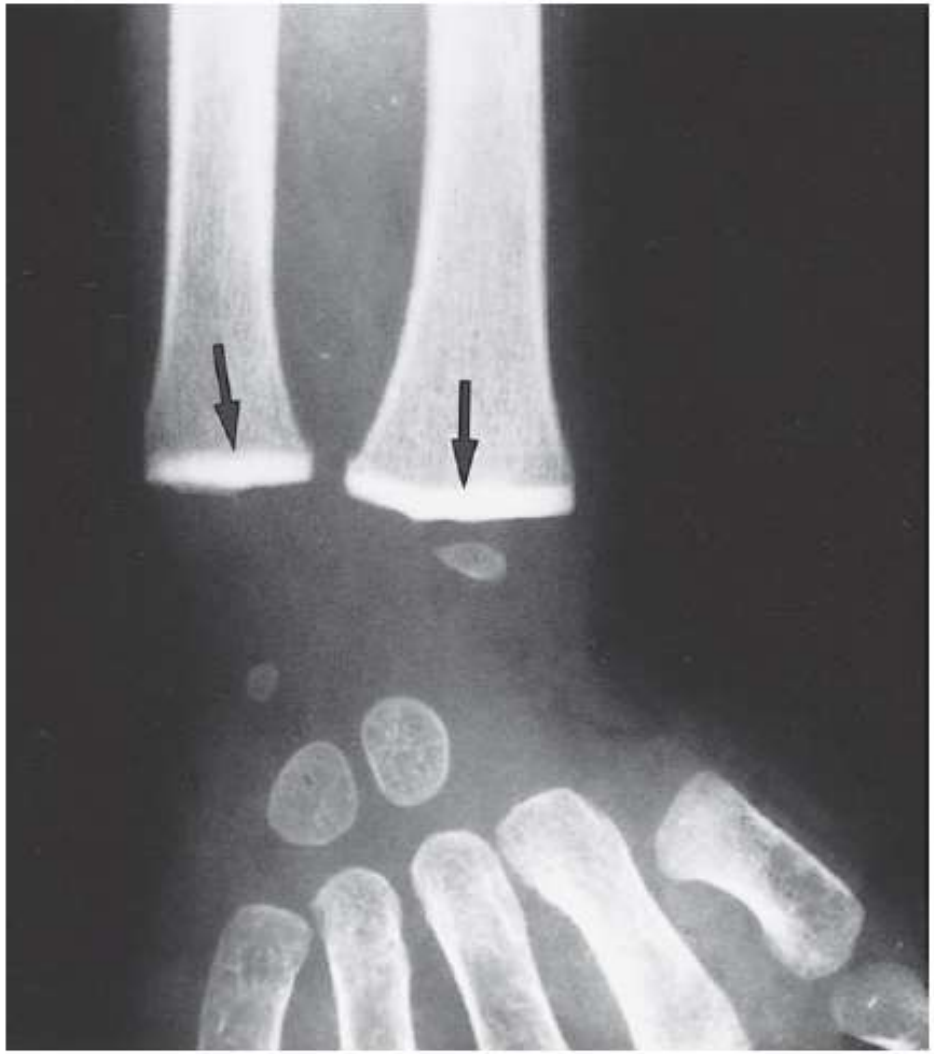


Figure 7–5 Lead poisoning. Impaired remodeling of calcified cartilage in the epiphyses (*arrows*) of the wrist has caused a marked increase in their radiodensity, so that they are as radiopaque as the cortical bone.
(Courtesy of Dr. G.W. Dietz, Department of Radiology, University of Texas Southwestern Medical School, Dallas, Texas.)

- The gastrointestinal tract is also a major source of clinical manifestations. Lead "colic" is characterized by extremely severe, poorly localized abdominal pain.

- Kidneys may develop proximal tubular damage with intranuclear lead inclusions.
- Chronic renal damage leads to interstitial fibrosis and possibly renal failure.
- Decreases in uric acid excretion can lead to gout (" saturnine gout ")

- Lead has a high affinity for sulfhydryl groups and interferes with two enzymes involved in heme Iron incorporation into heme is impaired, leading to anemia.

- Lead also inhibits sodium- and potassium-dependent ATPases in cell membranes, an effect that may increase the fragility of red cells, causing hemolysis

- Blood changes are one of the earliest signs of lead accumulation and are characteristic, consisting of a **microcytic**, **hypochromic anemia** associated with a distinctive punctate **basophilic stippling** of red cells.
- These changes in the blood stem from the inhibition of heme synthesis in marrow erythroid progenitors
- Another consequence of this blockade is that zinc-protoporphyrin is formed instead of heme.

Mercury

- Fish (swordfish, shark, and bluefish) and amalgam
- Power plants AND industrial sources
- Palsy ,deafness, blindness, mental retardation, and major CNS defects in children exposed in utero. بیماری (Minamata disease)
- For unclear reasons, **the developing brain is extremely sensitive to methyl mercury**
- Intracellular glutathione, acting as thiol donor, is the main protective mechanism against mercury-induced CNS and kidney damage.

Arsenic

- به طور طبیعی در خاک و آب یافت می شودو نیز در نگهدارنده های چوب ،علف کش ها و سایر ترکیبات کشاورزی
- تداخل با فسفوریلاسیون اکسیداتیو میتوکندری
- مسمومیت حاد:اختلالات شدید گوارشی،قلبی عروقی و سیستم عبی مرکزی
- مسمومیت مزمن:تغییرات پوستی(هیپرپیگمانتاسیون و هیپرکراتوز) و BCCو SCC
- تفاوت تومورهای ناشی از آرسنیک با نور آفتاب:متعدد بودن و ظهور ضایعات در کف دست وپا
- افزایش خطر کارسینوم ریه

- If ingested in large quantities, arsenic causes acute toxic effects consisting of severe disturbances of the gastrointestinal, cardiovascular and central nervous systems that are often fatal.
- These effects may be attributed to interference with mitochondrial oxidative phosphorylation, since trivalent arsenic can replace the phosphates in ATP

Cadmium

- In contrast to the other metals discussed, cadmium toxicity is a relatively modern problem.
- Nickel-cadmium batteries, which are usually disposed of as household waste
- Affects lung (obstructive disease & lung cancer) and kidney (tubular damage)

Industrial and Agricultural Exposures

Occupational exposure

TABLE 9–2 Human Diseases Associated with Occupational Exposures

Organ/System	Effect	Toxicant
Cardiovascular system	Heart disease	Carbon monoxide, lead, solvents, cobalt, cadmium
Respiratory system	Nasal cancer	Isopropyl alcohol, wood dust
	Lung cancer	Radon, asbestos, silica, bis(chloromethyl)ether, nickel, arsenic, chromium, mustard gas, uranium
	Chronic obstructive lung disease	Grain dust, coal dust, cadmium
	Hypersensitivity	Beryllium, isocyanates
	Irritation	Ammonia, sulfur oxides, formaldehyde
	Fibrosis	Silica, asbestos, cobalt
Nervous system	Peripheral neuropathies	Solvents, acrylamide, methyl chloride, mercury, lead, arsenic, DDT
	Ataxic gait	Chlordane, toluene, acrylamide, mercury
	Central nervous system depression	Alcohols, ketones, aldehydes, solvents
	Cataracts	Ultraviolet radiation
Urinary system	Toxicity	Mercury, lead, glycol ethers, solvents
	Bladder cancer	Naphthylamines, 4-aminobiphenyl, benzidine, rubber products
Reproductive system	Male infertility	Lead, phthalate plasticizers, cadmium
	Female infertility/stillbirths	Lead, mercury
	Teratogenesis	Mercury, polychlorinated biphenyls
Hematopoietic system	Leukemia	Benzene
Skin	Folliculitis and acneiform dermatosis	Polychlorinated biphenyls, dioxins, herbicides
	Cancer	Ultraviolet radiation
Gastrointestinal tract	Liver angiosarcoma	Vinyl chloride

- **Organic solvents:**

are widely used in huge quantities worldwide. Some, such as chloroform and carbon tetrachloride,are found in degreasing and dry cleaning agents and paint removers.

Acute exposure to high levels of vapors from these agents can cause dizziness and confusion,leading to CNS depression and even coma.

Lower levels have toxicity for the liver and kidneys

- Occupational exposure of rubber workers to **benzene** and **1,3-butadiene** : **increases the risk of leukemia.**

- Benzene is oxidized to an epoxide through hepatic CYP2E1, a component of the P-450 enzyme system already mentioned.
- The epoxide and other metabolites disrupt progenitor cell differentiation in the bone marrow, causing **marrow aplasia** and **acute myeloid leukemia**

- **Polycyclic hydrocarbons:**

Polycyclic hydrocarbons are among the most potent carcinogens, and industrial exposures have been implicated in the causation of lung and bladder cancer.

- **Organochlorines (and halogenated organic compounds in general) including DDT:**

Acute DDT poisoning in humans causes neurologic toxicity.

Most organochlorines are endocrine disruptors and have antiestrogenic or antiandrogenic activity in laboratory animals, but long-term health effects in humans have not been firmly established.

- **Dioxins and PCBs (polychlorinated biphenyl)**can cause skin disorders such as folliculitis and acneiform dermatosis known as **chloracne**, which consists of acne, cyst formation, hyperpigmentation, and hyperkeratosis, generally around the face and behind the ears. It can be accompanied by abnormalities in the liver and CNS.

- Because PCBs induce the P-450 enzyme system, workers exposed to these substances may show altered drug metabolism

Bisphenol A (BPA):

- is used in the synthesis of polycarbonate food and water containers and of epoxy resins that line almost all food bottles and cans; as a result, exposure to BPA is virtually ubiquitous in humans.
- BPA has long been known as a potential endocrine disruptor. Several large retrospective studies have linked elevated urinary BPA levels to heart disease in adult populations
- infants who drink from BPA-containing containers may be particularly susceptible to its endocrine effects.

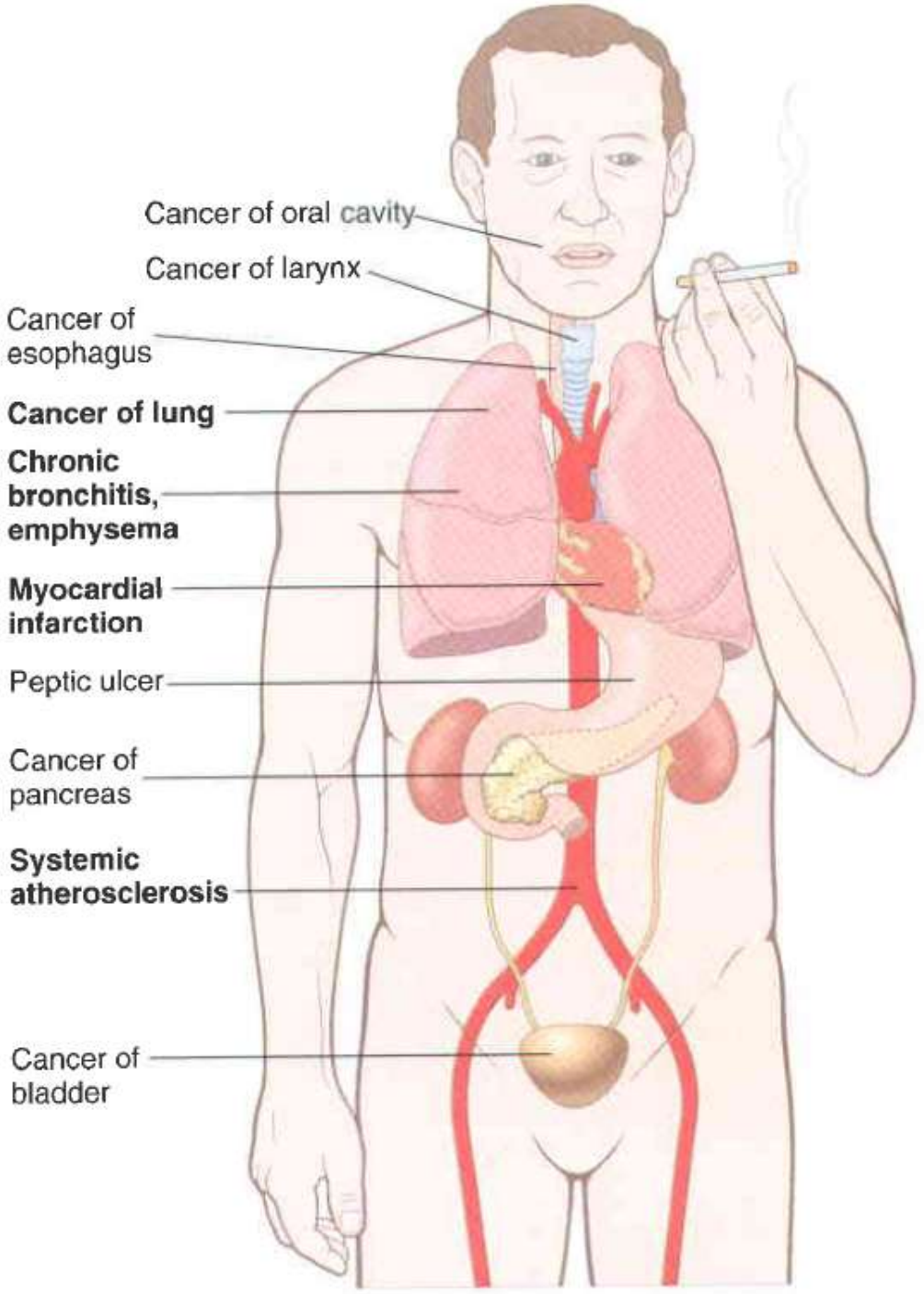
- Exposure to **vinyl chloride**, used in the synthesis of polyvinyl resins, was found to cause angiosarcoma of the liver, a rare type of liver tumor.

- Inhalation of mineral dusts causes chronic, non-neoplastic lung diseases called **pneumoconiosis**
- **The most common pneumoconioses are caused by exposures to mineral dust: coal dust (in mining of hard coal), silica (in sandblasting and stone cutting), asbestos (in mining, fabrication, and insulation work), and beryllium (in mining and fabrication).**

Effects of Tobacco

- The most common exogenous cause of human cancer
- The most common diseases caused by cigarette smoking involve the lung and include emphysema, chronic bronchitis, chronic obstructive pulmonary disease, and lung cancer.
- Smokeless tobacco is also harmful causing oral cancers
- Passive smoking
- **Smoking is the most preventable cause of human death**
- Cigarette smoking is also strongly associated with the development of atherosclerosis, MI, and cancers of the lip, mouth, pharynx, esophagus, pancreas, bladder, kidney, and cervix.

Smoking effects



- 80% of a population of nonsmokers is alive at age 70, only about 50% of smokers survive to that age.

- Cessation of smoking greatly reduces the risk of death from lung cancer, and it even has an effect, albeit reduced, on people who stop smoking at age 60.

Selected tobacco constituents

Substance	Effect
Tar	Carcinogenesis
Polycyclic aromatic hydrocarbons	Carcinogenesis
Nicotine	Ganglionic stimulation and depression; tumor promotion
Phenol	Tumor promotion; mucosal irritation
Benzopyrene	Carcinogenesis
Carbon monoxide	Impaired oxygen transport and utilization
Formaldehyde	Toxicity to cilia; mucosal irritation
Oxides of nitrogen	Toxicity to cilia; mucosal irritation
Nitrosamine	Carcinogenesis

Table 7–4 Organ-Specific Carcinogens in Tobacco Smoke

Organ	Carcinogen(s)
Lung, larynx	Polycyclic aromatic hydrocarbons 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) ^{210}Polonium
Esophagus	*N'*-Nitrosonornicotine (NNN)
Pancreas	NNK (?)
Bladder	4-Aminobiphenyl, 2-naphthylamine
Oral cavity: smoking	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity: snuff	NNK, NNN, ^{210}polonium

Data from Szczesny LB, Holbrook JH: Cigarette smoking. In Rom WH (ed): *Environmental and Occupational Medicine*, 2nd ed. Boston, Little, Brown, 1992, p 1211.

- The combination of tobacco (chewed or smoked) and alcohol consumption has multiplicative effects on the risks of oral, laryngeal, and esophageal cancers.

- Maternal smoking increases the risk of **spontaneous abortions** and **preterm births** and results in **intrauterine growth retardation** .
- however, birth weights of infants born to mothers who stopped smoking before pregnancy are normal.

- Children living in a household with an adult who smokes have an **increased frequency of respiratory illnesses and asthma.**

- **Passive smoke inhalation** in nonsmokers can be estimated by **measuring the blood levels of cotinine**, a metabolite of nicotine

- Pack/year


STOP
SMOKING
AND
STAY
HEALTHY


STOP SMOKING NOW

Effects of Alcohol

- Alcohol consumption is responsible for more than 100,000 deaths annually.

- After consumption, ethanol is absorbed unaltered in the stomach and small intestine and then distributes to all of the tissues and fluids of the body in direct proportion to the blood level.
- Less than 10% is excreted unchanged in the urine, sweat, and breath. The amount exhaled is proportional to the blood level and forms the basis for the breath test used by law enforcement agencies.

- A concentration of 80 mg/dL in the blood constitutes the legal definition of drunk driving in most states

- خواب آلودگی در200mg/dl و استوپور در 300mg/dl و اغما با ایست احتمالی تنفسی در سطوح بالاتر رخ می دهد.
- قسمت عمده الکل خون توسط سه سیستم آنزیمی شامل الکل دهیدروژناز،سیتوکروم p450و کاتالاز در کبد به استالدئید متابولیزه می شود.

- اکسیداسیون الکل توسط الکل دهیدروژناز منجر به کاهش NADمی شود که برای اکسیداسیون چربی ها در کبد مورد نیاز است وکمبود آن علت اصلی تجمع چربی در کبد افراد الکلی است.

- متابولیسم اتانل در کبد منجر به تولید گونه های واکنش دهنده اکسیژن و در نتیجه پراکسیداسون چربی های غشای سلولی میشوند

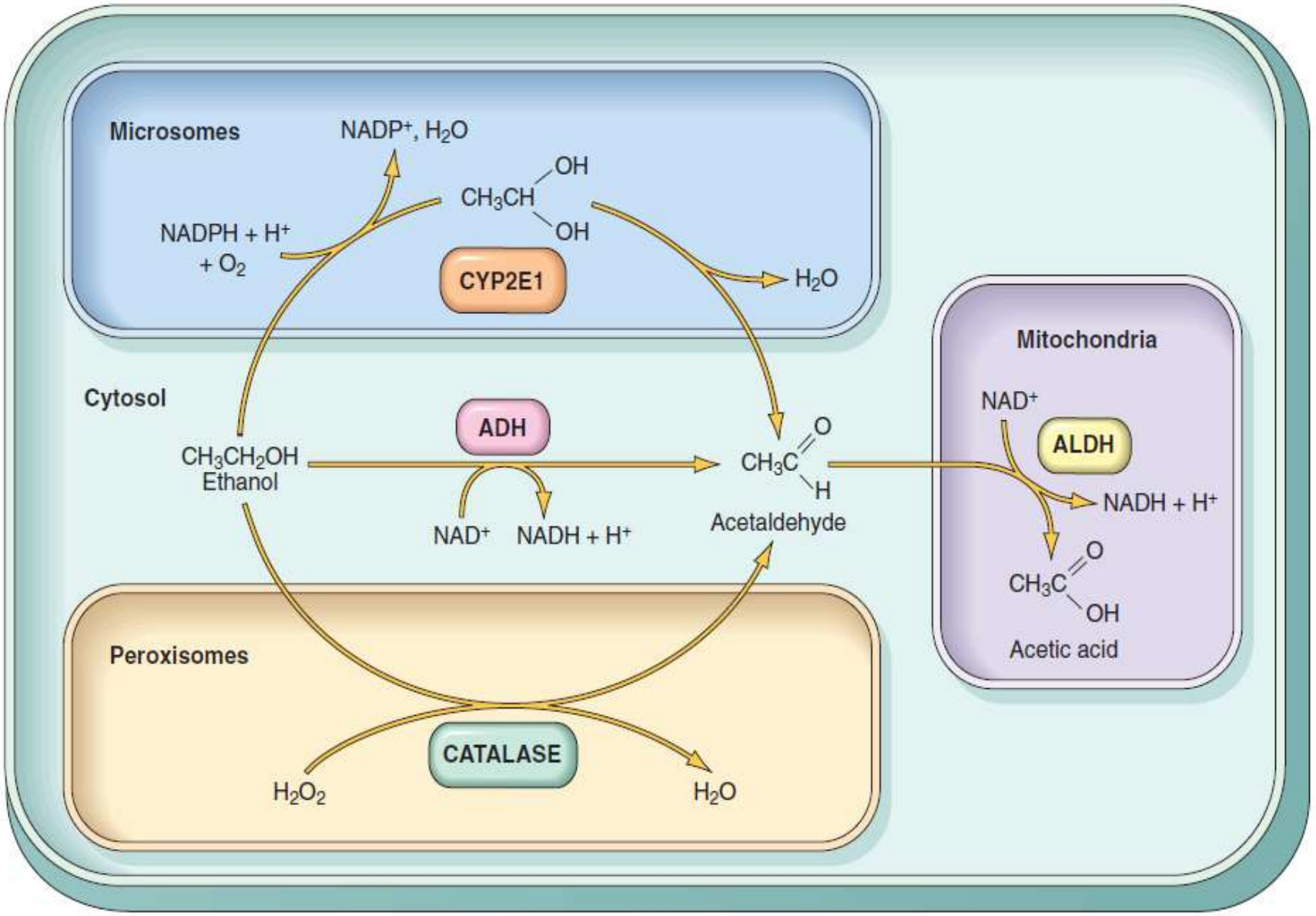


Figure 7–10 Metabolism of ethanol: oxidation of ethanol to acetaldehyde by three different routes, and the generation of acetic acid. Note that oxidation by alcohol dehydrogenase (ADH) takes place in the cytosol; the cytochrome P-450 system and its CYP2E1 isoform are located in the ER (microsomes), and catalase is located in peroxisomes. Oxidation of acetaldehyde by aldehyde dehydrogenase (ALDH) occurs in mitochondria. *(Data from Parkinson A: Biotransformation of xenobiotics. In Klassen CD [ed]: Casarett and Doull's Toxicology:* The Basic Science of Poisons, *6th ed. New York, McGraw-Hill, 2001, p 133.)*

- The adverse effects of ethanol can be classified as acute or chronic.

- Acute alcoholism exerts its effects mainly on the CNS, but it may induce hepatic and gastric changes that are reversible if alcohol consumption is discontinued.

- Chronic alcoholism affects not only the liver and stomach but virtually all other organs and tissues as well.
- Chronic alcoholics suffer significant morbidity and have a shortened life span, related principally to damage to the liver, GI tract, CNS, cardiovascular system, and pancreas

STOP ALCOHOL

- The liver is the main site of chronic injury. In addition to fatty change, mentioned earlier, chronic alcoholism causes **alcoholic hepatitis** and **cirrhosis** .Cirrhosis is associated with **portal hypertension** and **an increased risk of hepatocellular carcinoma.**

- In the GI tract, chronic alcoholism can cause massive bleeding from gastritis, gastric ulcer, or esophageal varices (associated with cirrhosis), which may prove fatal.

- **Thiamine deficiency** is common in chronic alcoholic patients; the principal lesions resulting from this deficiency are peripheral neuropathies and the Wernicke- Korsakoff syndrome Cerebral atrophy, cerebellar degeneration, and optic neuropathy may also occur.

- Alcohol has diverse effects on the cardiovascular system. Injury to the myocardium may produce dilated congestive cardiomyopathy (alcoholic cardiomyopathy)

- Excess alcohol intake increases the risk of acute and chronic pancreatitis

- The use of ethanol during pregnancy—reportedly even in low amounts—can cause **fetal alcohol syndrome**. It consists of **microcephaly, growth retardation and facial abnormalities in the newborn and reduction in mental functions in older children.**
- It is difficult to establish the amount of alcohol consumption that can cause fetal alcohol syndrome, but consumption during the first trimester of pregnancy is particularly harmful.

- Chronic alcohol consumption is associated with an increased incidence of cancers of the **oral cavity**, **esophagus** ,**liver**, and, possibly, **breast** in females.

- The mechanisms of the carcinogenic effect are uncertain.

Injury by Therapeutic Drugs and Drugs of Abuse

Adverse Drug Reactions

(ADR)

- Adverse drug reactions (ADRs) are untoward effects of drugs that are given in conventional therapeutic settings.

- affect almost 7-8% of patients admitted to a hospital.
- It is estimated that in about 10% of these patients, ADRs are fatal.

- the ADR is a calculated risk for the dosage assumed to achieve the maximum therapeutic effect.

Longacting tetracyclines, which are used to treat diverse conditions,including acne, may produce localized or systemic reactions

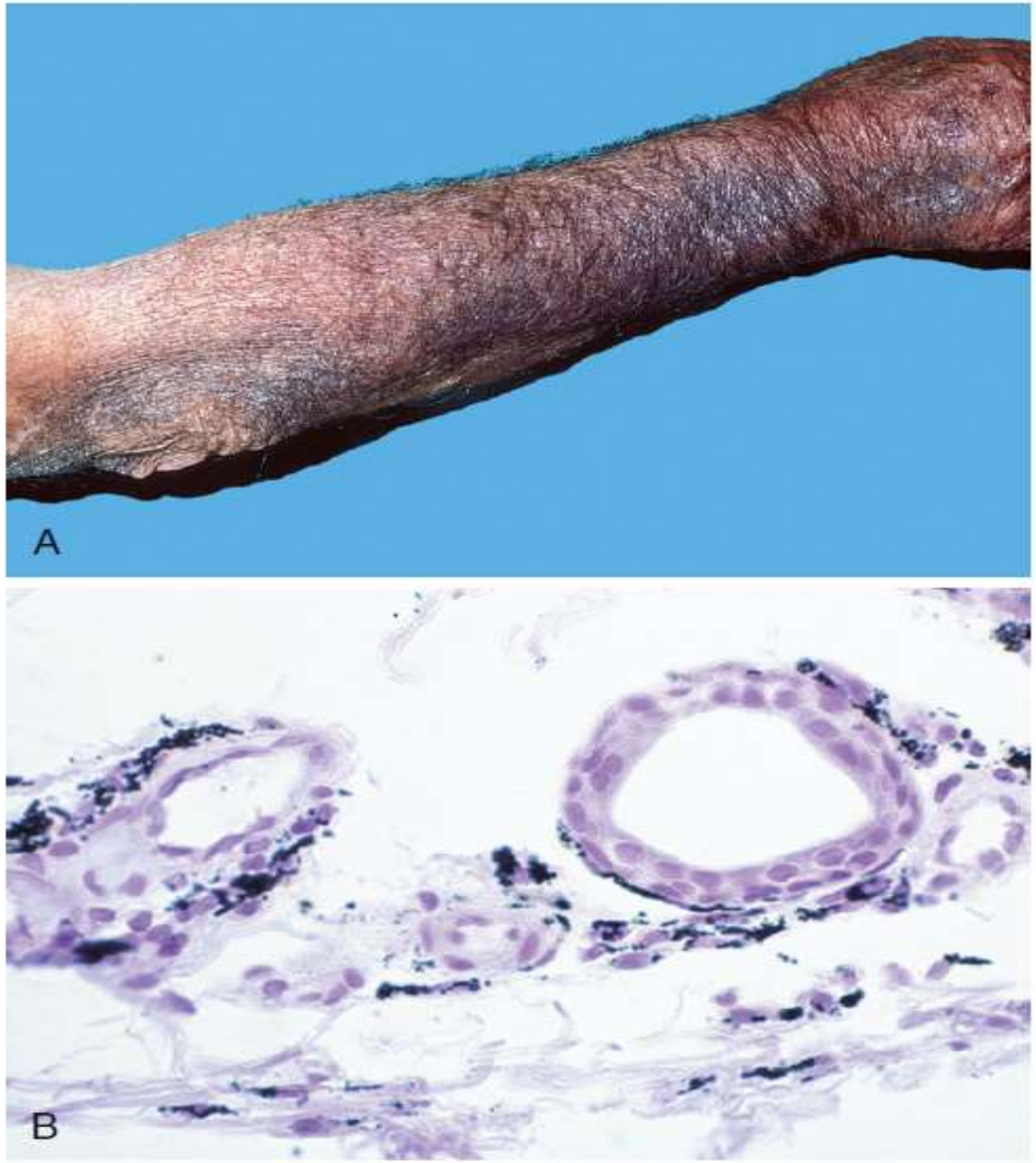


Figure 7–11 Adverse reaction to minocycline, a long-acting tetracycline derivative. **A,** Diffuse blue-gray pigmentation of the forearm, secondary to minocycline administration. **B,** Deposition of drug metabolite/iron/melanin pigment particles in the dermis.

(A and B, Courtesy of Dr. Zsolt Argenyi, Department of Pathology, University of Washington, Seattle, Washington.)

Exogenous Estrogens and Oral Contraceptives

Hormonal Replacement Therapy (HRT)

- Estrogen therapy, once used primarily for distressing menopausal symptoms (e.g., hot flashes), has been widely used in postmenopausal women, with or without added progestins, to prevent or slow the progression of osteoporosis

- Recent data have confirmed the adverse effects of HRT on endometrial and breast cancers but do not support the view that HRT offers protection against ischemic heart disease.

- HRT with estrogen, with or without progestins, , including deep vein thrombosis, pulmonary embolism, and stroke, by several-fold. The increase is more pronounced during the first 2 years of treatment and in association with other risk factors such as immobilization or factor V or prothrombin mutations.

- Its effects depend on the type of estrogen/progesterone used, the mode of drug administration, the age of the person at the start of treatment, the duration of the treatment, and the presence of associate diseases

- Estrogens and progestins increase blood levels of highdensity lipoprotein and decrease levels of low-density lipoprotein.

- On the basis of retrospective epidemiologic data, it was thought that HRT would be beneficial in protecting against atherosclerosis and ischemic heart disease. However, large well-controlled prospective studies **did not demonstrate a protective effect of HRT against myocardial infarction**.

Oral Contraceptives (OCs)

- **Breast carcinoma**: The prevailing opinion is that OCs do not cause an increase in breast cancer risk.
- **Endometrial cancer** and **ovarian cancers**: OCs have a protective effect against these tumors
- **Thromboembolism**: approximately three-fold increased risk of venous thrombosis and pulmonary thrombo-embolism
- **Cardiovascular disease**. Increase the risk of myocardial infarction in smoking women at all ages and in nonsmoking women over age 35
- **Hepatic adenoma**: There is a well-defined association between OCs and this hepatic tumor

Acetaminophen

- At therapeutic doses, acetaminophen, a widely used nonprescription analgesic and antipyretic, is mostly conjugated in the liver with glucuronide or sulfate.
- Drug is ordinarily very safe (0.5 g) but if used in large doses can be toxic (15-25 g)
- About 5% or less is metabolized to **NAPQI** (N-acetyl-pbenzoquinoneimine) through the hepatic P-450 system. With very large doses, however, NAPQI accumulates, leading to **centrilobular hepatic necrosis**.

Aspirin (Acetylsalicylic Acid)

- Aspirin overdose may result from accidental ingestion in young children or suicide attempts in adults.
- The major untoward consequences are **metabolic**, with **few morphologic changes**.
- At first, respiratory alkalosis develops, followed by a metabolic acidosis that often proves fatal.
- Fatal doses may be as little as 2 to 4 gm in children and 10 to 30 gm in adults, but survival has been reported after doses five times larger.

- Chronic aspirin toxicity (salicylism) may develop in persons who take 3 gm or more daily (the dose used to treat chronic inflammatory conditions).
- Chronic salicylism is manifested by headache, dizziness, ringing in the ears (tinnitus), difficulty in hearing, mental confusion, drowsiness, nausea, vomiting, and diarrhea.

- The CNS changes may progress to convulsions and coma.
- The morphologic consequences of chronic salicylism are varied. Most often, there is an acute erosive ,which may produce overt or covert GI bleeding and lead to gastric ulceration.
- A bleeding tendency may appear concurrently with chronic toxicity, because aspirin irreversibly inhibits platelet cyclooxygenase and blocks the ability to make thromboxane A2,

- an activator of platelet aggregation. Petechial hemorrhages may appear in the skin and internal viscera, and bleeding from gastric ulcerations may be exaggerated.

- Proprietary analgesic mixtures of aspirin and phenacetin or its active metabolite, acetaminophen, when taken over several years, can cause tubulointerstitial nephritis with renal papillary necrosis. This clinical entity is referred to as analgesic nephropathy

Injury By Non-therapeutic Agents (DRUG ABUSE)

TABLE 9–6 Common Drugs of Abuse

Class	Molecular Target	Example
Opioid narcotics	Mu opioid receptor (agonist)	Heroin, hydromorphone (Dilaudid) Oxycodone (Percodan, Percocet, Oxycontin) Methadone (Dolophine) Meperidine (Demerol)
Sedative-hypnotics	$GABA_A$ receptor (agonist)	Barbiturates Ethanol Methaqualone (Quaalude) Glutethimide (Doriden) Ethchlorvynol (Placidyl)
Psychomotor stimulants	Dopamine transporter (antagonist) Serotonin receptors (toxicity)	Cocaine Amphetamines 3,4-methylenedioxymethamphetamine (MDMA, ecstasy)
Phencyclidine-like drugs	NMDA glutamate receptor channel (antagonist)	Phencyclidine (PCP, angel dust) Ketamine
Cannabinoids	CBI cannabinoid receptors (agonist)	Marijuana Hashish
Hallucinogens	Serotonin $5\text{-}HT_2$ receptors (agonist)	Lysergic acid diethylamide (LSD) Mescaline Psilocybin

Cocaine

- Use is highest among adults 18 to 25 years of age
- The pharmacologic actions of cocaine and crack are identical, but crack is far more potent. Both forms can be snorted, smoked after mixing with tobacco, ingested, or injected subcutaneously or intravenously
- Cocaine produces an intense euphoria and stimulation, making it one of the most addictive drugs.
- although physical dependence generally does not occur, the psychologic withdrawal is profound and can be extremely difficult to treat

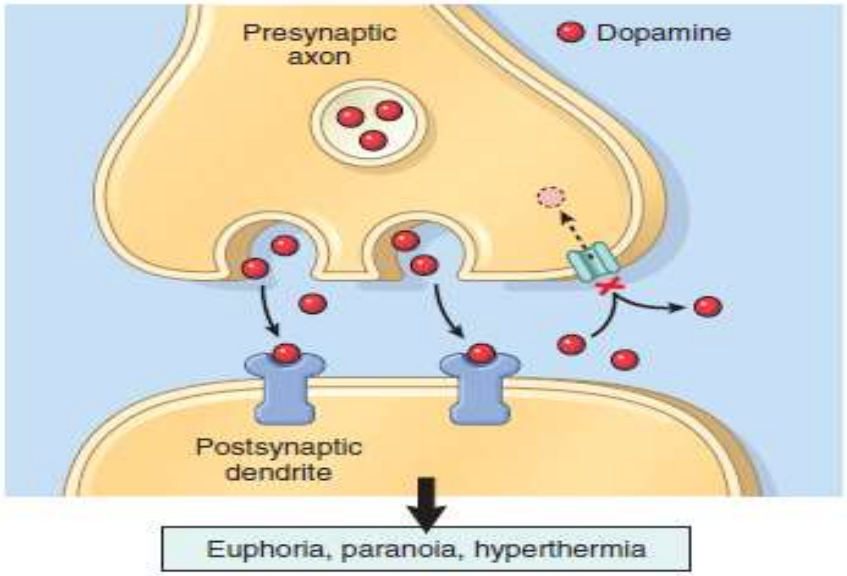
- **Acute overdose can produce seizures, cardiac arrhythmias, and respiratory arrest.**

- Following are the important manifestations of cocaine toxicity:

- **Cardiovascular effects**. The most serious physical effects of cocaine relate to its acute action on the cardiovascular system.

- Cocaine is a **sympathomimetic** agent, both in the CNS, where it blocks the reuptake of dopamine, and at adrenergic nerve endings, where it blocks the reuptake of both epinephrine and norepinephrine while stimulating the presynaptic release of norepinephrine.

CENTRAL NERVOUS SYSTEM SYNAPSE



SYMPATHETIC NEURON–TARGET CELL INTERFACE

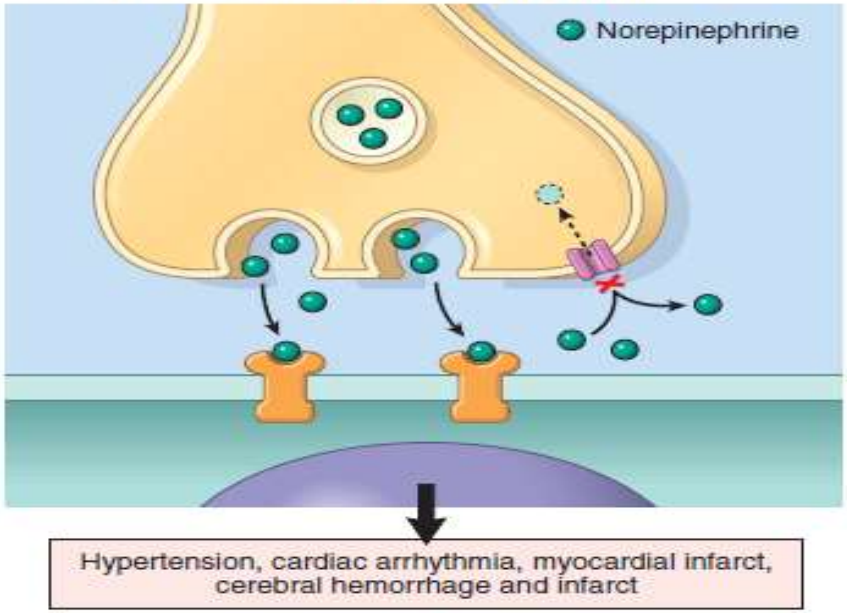


Figure 7–12 The effect of cocaine on neurotransmission. The drug inhibits reuptake of the neurotransmitters dopamine and norepinephrine in the central and peripheral nervous systems.

- The net effect is the accumulation of these neurotransmitters in synapses and excessive stimulation, manifested by **tachycardia, hypertension, and peripheral vasoconstriction**. Cocaine also induces myocardial ischemia, the basis for which is multifactorial.

- It causes coronary artery vasoconstriction and **promotes thrombus formation by facilitating platelet aggregation**.

- Cigarette smoking potentiates cocaine-induced coronary vasospasm. Thus, by increasing myocardial oxygen demand by its sympathomimetic action and, at the same time, reducing coronary blood flow, cocaine often triggers myocardial ischemia, which may lead to myocardial infarction.

- Cocaine also can precipitate **lethal arrhythmias** by enhanced sympathetic activity as well as by disrupting normal ion (K^+, Ca^{2+}, Na^+) transport in the myocardium.

- These toxic effects are not necessarily dose-related, and a fatal event may occur in a first-time user with what is a typical mood-altering dose.

- **CNS effects:** The most common CNS findings are **hyperpyrexia** (thought to be caused by aberrations of the dopaminergic pathways that control body temperature) and **seizures**.

- **Effects on the fetus**
- In pregnant women, cocaine may cause **decreased blood flow to the placenta**, resulting in **fetal hypoxia** and **spontaneous abortion**.
- Neurologic development may be impaired in the fetuses of pregnant women who are chronic drug users.

- **Chronic cocaine use**

Chronic use may cause:

(1) perforation of the nasal septum in snorters,

(2) decrease in lung diffusing capacity in users who inhale the smoke, and

(3) the development of dilated cardiomyopathy.

Heroin

- Heroin is an addictive opioid derived from the poppy plant and is closely related to morphine.
- As sold on the street, it is cut (diluted) with an agent (often talc or quinine); thus, the size of the dose not only is variable but also usually is unknown to the buyer.
- Heroin along with any contaminating substances usually is self-administered intravenously or subcutaneously.

- Effects are varied and include **euphoria, hallucinations**, **somnolence**, and **sedation**.

- Heroin has a wide range of adverse physical effects that can be categorized etiologically according to:

(1) the pharmacologic action of the agent,

(2) reactions to the cutting agents or contaminants,

(3) hypersensitivity reactions to the drug or its adulterants, and

(4) diseases contracted through sharing of needles.

- Some of the most important adverse effects of heroin are the following:

- **Sudden death**: Sudden death, usually related to overdose, is an ever-present risk, because drug purity generally is unknown and may range from 2% to 90%.
- The yearly incidence of sudden death among chronic users in the United States is estimated to be between 1% and 3%.
- Sudden death sometimes is due to loss of tolerance for the drug, such as after a period of incarceration. The mechanisms of death include profound respiratory depression, arrhythmia and cardiac arrest, and pulmonary edema.

- **Pulmonary disease :**

Pulmonary complications include edema, septic embolism, lung abscess, opportunistic infections, and foreign body granulomas from talc and other adulterants.

Although granulomas occur principally in the lung, they also are sometimes found in the **spleen, liver, and lymph nodes that drain the upper extremities**.

Examination under **polarized light** often highlights trapped talc crystals, sometimes enclosed within foreign body giant cells.

- **Infections:** Infectious complications are common. The sites most commonly affected are the **skin** and **subcutaneous tissue, heart valves, liver, and lungs**.

- In a series of addicted patients admitted to the hospital, more than 10% had endocarditis, which often takes a distinctive form involving **right-sided heart valves**, particularly the **tricuspid**.

- Most cases are caused by **Staphylococcus aureus**, but fungi and a multitude of other organisms have also been implicated.
- Viral hepatitis is the most common infection among addicts and is acquired by the sharing of dirty needles. In the United States, this practice has also led to a very high incidence of human immunodeficiency virus (HIV) infection in intravenous drug abusers.

- **Skin lesions**:
- Cutaneous lesions probably are the most frequent telltale sign of heroin addiction.
- Acute changes include **abscesses**, **cellulitis**, and **ulcerations due to subcutaneous injections**.
- Scarring at injection sites, hyperpigmentation over commonly used veins, and thrombosed veins are the usual sequelae of repeated intravenous inoculations

- **Renal problems**. Kidney disease is a relatively common hazard.
- The two forms most frequently encountered are **amyloidosis (generally secondary to skin infections)** and **focal glomerulosclerosis**;
- both induce heavy proteinuria and the nephrotic syndrome.

Marijuana

- Marijuana, or “pot,” is the most widely used illegal drug
- It is made from the leaves of the Cannabis sativa plant
- beneficial effects of THC include its capacity to decrease intraocular pressure in glaucoma and to combat intractable nausea secondary to cancer chemotherapy

- Marijuana use is well recognized to distort sensory perception and impair motor coordination, but these acute effects generally clear in 4 to 5 hours.

- With continued use, these changes may progress to **cognitive** and **psychomotor impairments**, such as inability to judge time, speed, and distance.
- Among adolescents, such impairment often leads to automobile accidents.

- Marijuana **increases the heart rate** and sometimes blood pressure, and it may cause **angina** in a person with coronary artery disease

- The lungs are affected by chronic marijuana smoking; laryngitis, pharyngitis, bronchitis, cough, hoarseness, and asthma-like symptoms all have been described, along with mild but significant airway obstruction.
- Smoking a marijuana cigarette, compared with a tobacco cigarette, is associated with a **three-fold increase in the amount of tar inhaled** and retained in the lungs, as a consequence of deeper inhalation and longer breath holding

Other Illicit Drugs

- These drugs include various stimulants, depressants, analgesics, and hallucinogens.
- Among these are PCP (1-(1-phenylcyclohexyl) piperidine), or phenylcyclidine, and ketamine (related anesthetic agents); lysergic acid diethylamide (LSD), the most potent hallucinogenknown;“ecstasy”(3,4methylenedioxymethamphetamine [MDMA]); and oxycodone (an opiate).
- Not much is known about the long-time deleterious effects of any of these agents.
- Acutely, LSD has unpredictable effects on mood, affect, and thought, sometimes leading to bizarre and dangerous behaviors. Chronic use of ecstasy may **deplete the CNS of serotonin**, potentially leading to **sleep disorders, depression, anxiety, and aggressive behavior**.

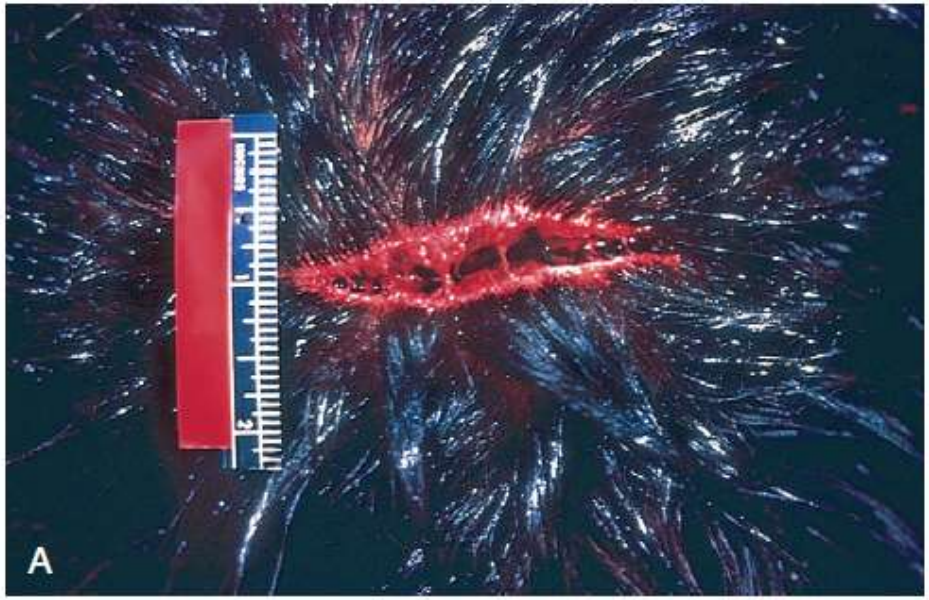
Injury by Physical Agents

- Mechanical Trauma
- Thermal Burns
- Electrical Injury
- Radiation injury

Mechanical Trauma

- Mechanical forces may inflict a variety of forms of damage.
- The type of injury depends on the shape of the colliding object, the amount of energy discharged at impact, and the tissues or organs that bear the impact.

- ترومای مکانیکی :الگوهای آسیب شامل:
- سابیدگی"abrasion"(زخمی که در اثر سایش یا مالش سطح پوستی ایجاد میشود و باعث آسیب لایه سطحی می شود.)
- کوفتگی contusion یا کبودی (آسیب توسط جسم غیرنوک تیز ،مشخصه آن صدمه به عروق خونی و خروج خون از عروق به داخل بافت)
- پارگی laceration :یک از هم گسیختگی یا کشش پاره کننده بافت است با یک جسم غیر نافذ
- زخم های برشیincised wound
- زخم های سوراخ شدگی penetrating:با یک وسیله بلند و باریک ایجاد می شود
- هرگاه وسیله مذکور بافت را سوراخ کند به آن نافذ و هرگاه از بافت عبور کرده و زخم خروجی ایجاد کند به آن سوراخ کننده(perforating)گویند.



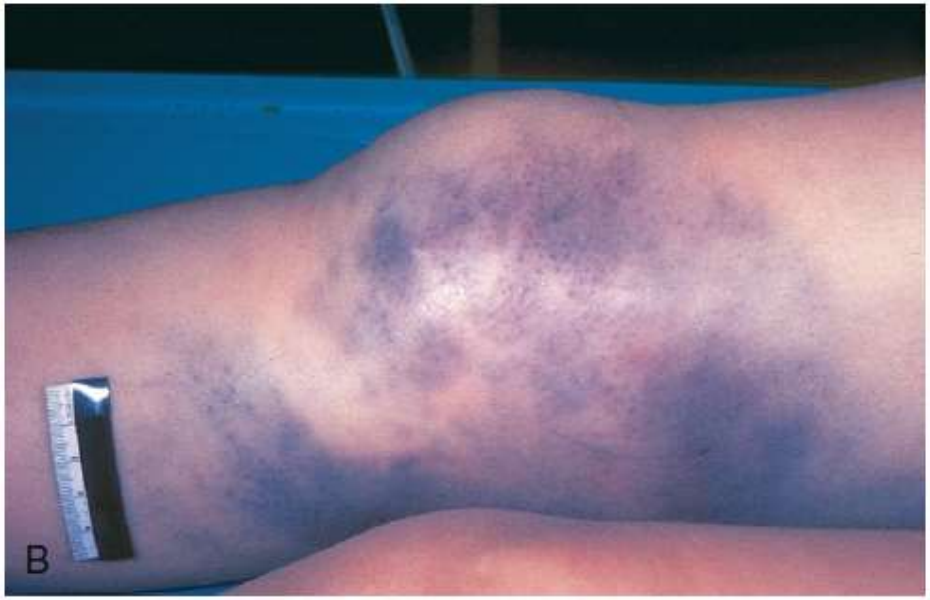


Figure 7–13 A, Laceration of the scalp: The bridging strands of fibrous tissues are evident. **B,** Contusion resulting from blunt trauma. The skin is intact, but hemorrhage of subcutaneous vessels has produced extensive discoloration.

(A, B, From the teaching collection of the Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

- **سوختگی حرارتی**:
- اهمیت بالینی سوختگی ها به عوامل زیر بستگی دارد:
  - ✓ عمق سوختگی
  - ✓ درصد سطح بدن درگیرشده،
  - ✓ وجود احتمالی آسیب های داخلی ناشی از استنشاق بخارات داغ و سمی،
  - ✓ درمان زودرس و موثر
- سوختگی با ضخامت کامل شامل تخریب کامل اپیدرم و درم همراه با از دست رفتن ضمائم درم (درجه ۳ و ۴)
- سوختگی با ضخامت ناکامل حداقل قسمت های عمقی ضمائم درم دست نخورده باقی می ماند
- درجه ۱(تنها درگیری اپی تلیال) و درجه ۲ (درگیری اپیدرم و درم سطحی)

MORPHOLOGY

- On gross inspection, **full-thickness burns** are **white or charred, dry, and anesthetic (as a result of destruction of nerve endings)**,
- partial-thickness burns, depending on the depth, are **pink or mottled, blistered and painful**.
- Histologic examination of devitalized tissue reveals coagulative necrosis adjacent to vital tissue, which quickly accumulates inflammatory cells and marked exudation.

- Another important consideration is the degree of injury to the airways and lungs.
- **Inhalation injury** is frequent in persons trapped in burning buildings and may result from the direct effect of heat on the mouth, nose, and upper airways or from the inhalation of heated air and gases in the smoke.

- **Water-soluble gases**, such as **chlorine, sulfur oxides, and ammonia**, may react with water to form acids or alkalis, particularly in the upper airways, resulting in inflammation and swelling, which may lead to partial or complete airway obstruction.
- **Lipid-soluble gases**, such as nitrous oxide and products of burning plastics, are more likely to reach deeper airways, producing pneumonitis. Unlike in sho**pulmonary manifestations may not develop for 24 to 48 hours**ck, which develops within hours,

- Organ system failure resulting from sepsis continues to be the leading cause of death in burned patients.

- The burn site is ideal for growth of microorganisms; the serum and debris provide nutrients, and the burn injury compromises blood flow, blocking effective inflammatory responses.
- The most common offender is the opportunist **Pseudomonas aeruginosa**, but antibiotic-resistant strains of other common hospital-acquired bacteria, such as **S. aureus**, and fungi, particularly **Candida**, also may be involved.

- **Pneumonia** or **septic shock** accompanied by **renal failure and/or the acute respiratory distress syndrome (ARDS)are the most common serious sequelae.**

- **Another very important pathophysiologic effect of burns is the development of a hypermetabolic state, with excess heat loss and an increased need for nutritional support.**
- **It is estimated that when more than 40% of the body surface is burned, the resting metabolic rate may approach twice normal.**

Hyperthermia

- Prolonged exposure to elevated ambient temperatures can result in:
- **heat cramps**
- **heat exhaustion**

or

- **heat stroke**.

- **Heat cramps**

result from loss of electrolytes through sweating.

Cramping of voluntary muscles, usually in association with vigorous exercise, is the hallmark sign.

Heat-dissipating mechanisms are able to maintain normal core body temperature.

- **Heat exhaustion** is probably the most common hyperthermic syndrome.
- Its onset is sudden, with prostration and collapse, and it results from a failure of the cardiovascular system to compensate for hypovolemia, secondary to water depletion.
- After a period of collapse, which is usually brief, equilibrium is spontaneously reestablished.

- **Heat stroke** is associated with high ambient temperatures and high humidity.
- Thermoregulatory mechanisms fail, sweating ceases, and core body temperature rises.
- In the clinical setting, a rectal temperature of **106°F or higher** is considered a grave prognostic sign, and the mortality rate for such patients exceeds 50%.
- The underlying mechanism is **marked generalized peripheral vasodilation** with peripheral pooling of blood and a decreased effective circulating blood volume.
- Necrosis of the muscles and myocardium may occur. Arrhythmias, disseminated intravascular coagulation, and other systemic effects are common. Elderly people, persons with cardiovascular disease, and otherwise healthy people undergoing physical stress (such as young athletes and military recruits) are prime candidates for heat stroke.

- **Malignant hyperthermia** :is not caused by exposure to high temperature.
- It is a genetic condition resulting from mutations in genes such as RYR1 that control calcium levels in skeletal muscle cells.
- In affected individuals, exposure to certain anesthetics during surgery may trigger a rapid rise in calcium levels in skeletal muscle, which in turn leads to muscle rigidity and increased heat production. The resulting hyperthermia has a mortality rate of approximately 80% if untreated, but this falls to less than 5% if the condition is recognized and muscle relaxants are given promptly.

Hypothermia

- Prolonged exposure to low ambient temperature leads to hypothermia.

- Chilling or freezing of cells and tissues causes injury by two mechanisms:

• Direct effects probably are mediated by physical disruptions within cells and high salt concentrations incidentnto the crystallization of the intra- and extracellular water.

• Indirect effects are the result of circulatory changes, which vary depending on the rate and the duration of the temperature drop

Electrical Injury

- Electrical injuries, which may be fatal, can arise from low voltage currents (i.e., in the home and workplace) or from high-voltage currents carried in power lines or by lightning.
- Injuries are of two types:
- (1)**burns** and (2) **ventricular fibrillation or cardiac and respiratory center failure resulting from disruption of normal electrical impulses.**

- An important characteristic of **alternating current(AC)**, the type available in most homes, is that it induces **tetanic muscle spasm**, so that when a live wire or switch is grasped, irreversible clutching is likely to occur, prolonging the period of current flow.

- This results in a greater likelihood of extensive electrical burns and, in some cases, spasm of the chest wall muscles, producing death from asphyxia.

Injury Produced by Ionizing Radiation

- Radiation is energy that travels in the form of waves or high-speed particles. Radiation has a wide range of energies that span the electromagnetic spectrum; it can be divided into nonionizing and ionizing radiation.
- Non ionizing:
  - UV, infrared, microwave, sound wave; moves atoms but not not sufficient to displace electrons from atoms.
  - Ionizing: remove electrons:

(1) X rays & Gamma rays

(2)high-energy neutrons, alpha particles (composed of two protons and two neutrons), and beta particles, which are essentially electrons.

- The relative biologic effectiveness depends on:

- **Rate of delivery**. The rate of delivery significantly modifies the biologic effect.
- Although the effect of radiant energy is **cumulative**, **delivery in divided doses may allow cells to repair some of the damage in the intervals.** Thus, fractional doses of radiant energy have a cumulative effect only to the extent that repair during the intervals is incomplete.
- Radiotherapy of tumors exploits the capability of normal cells to repair themselves and recover more rapidly than tumor cells.

- **Field size** The size of the field exposed to radiation has a great influence on its consequences.
- The body can sustain relatively high doses of radiation when they are delivered to small, carefully shielded fields, whereas smaller doses delivered to larger fields may be lethal.

- Cell proliferation :tissues with a high rate of cell turnover, such as gonads, bone marrow, lymphoid tissue, and the mucosa of the GI tract, are extremely vulnerable to radiation, and the injury is manifested early after exposure.

- **Hypoxia.** The production of reactive oxygen species by the radiolysis of water is the most important mechanism of DNA damage by ionizing radiation. Tissue hypoxia, such as may exist in the center of rapidly growing poorly vascularized tumors, may thus reduce the extent of damage and the effectiveness of radiotherapy directed against tumors.

- **Vascular damage.** Damage to endothelial cells, which are moderately sensitive to radiation, may cause narrowing or occlusion of blood vessels, leading to impaired healing, fibrosis, and chronic ischemic atrophy.

- These changes may appear months or years after exposure.
- Despite the low sensitivity of brain cells to radiation, vascular damage after irradiation can lead to late manifestations of radiation injury in this tissue.

- The most important cellular target of ionizing radiation is DNA.
- Damage to DNA caused by ionizing radiation that is not precisely repaired leads to mutations, which can manifest years or decades later as cancer. Ionizing radiation can cause many types of damage in DNA, including base damage, single- and double-strand breaks, and crosslinks between DNA and protein

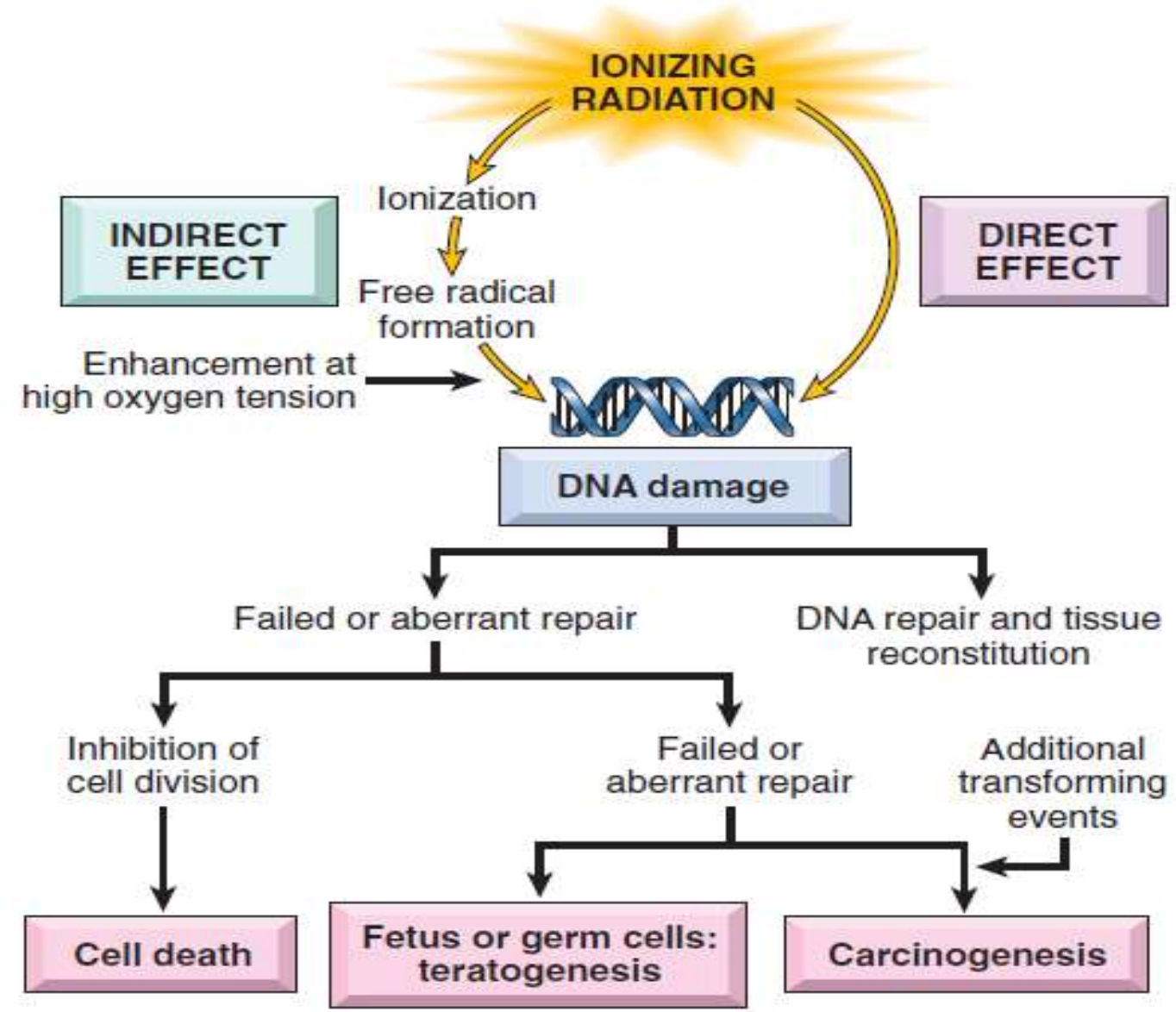


Figure 7–14 Effects of ionizing radiation on DNA and their consequences. The effects on DNA can be direct or, most important, indirect, through free radical formation.

- At the light microscopic level, vascular changes and interstitial fibrosis are prominent in irradiated tissues.

- During the immediate post-irradiation period, vessels may show only dilation.
- Later, or with higher doses, a variety of degenerative changes appear, including **endothelial cell swelling and vacuolation, or even dissolution with total necrosis of the walls of small vessels such as capillaries and venules**.

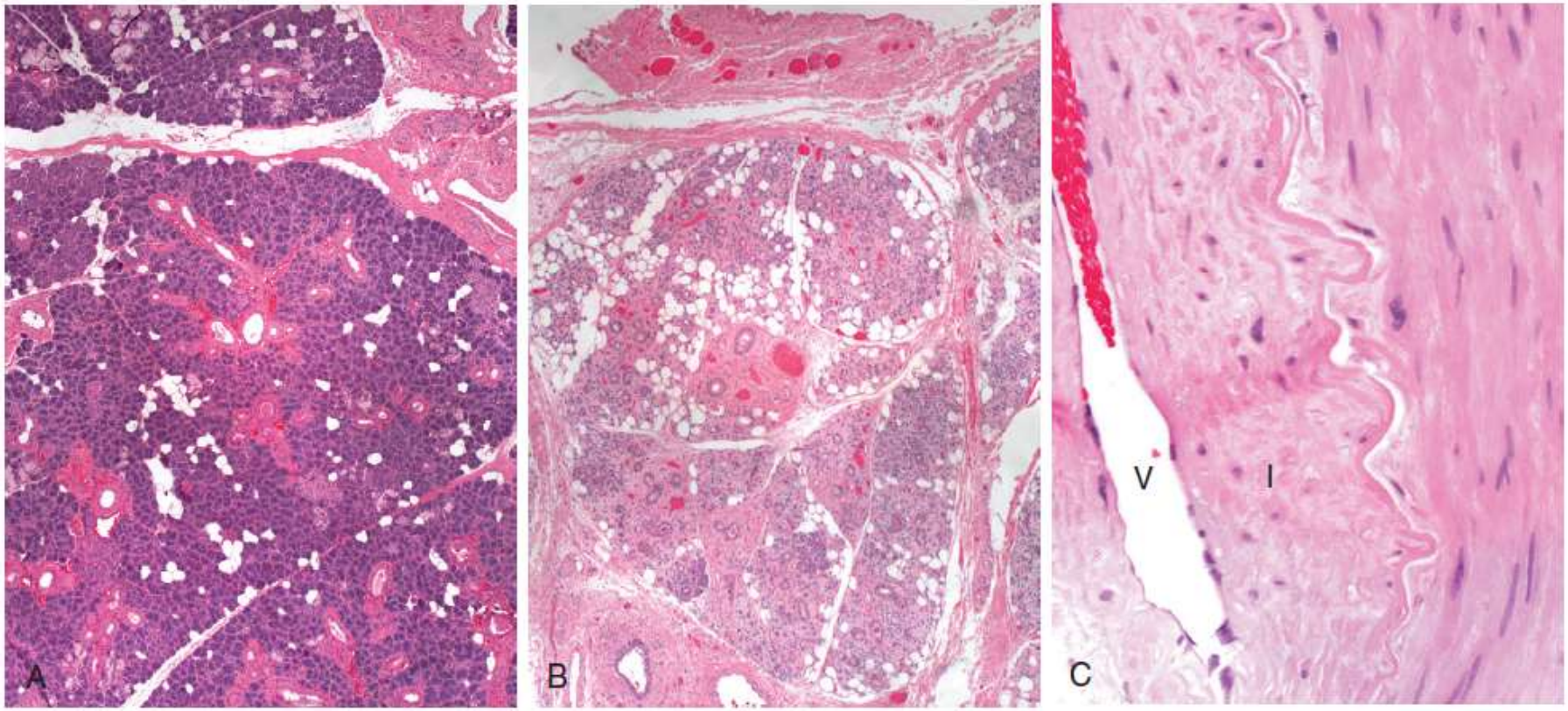


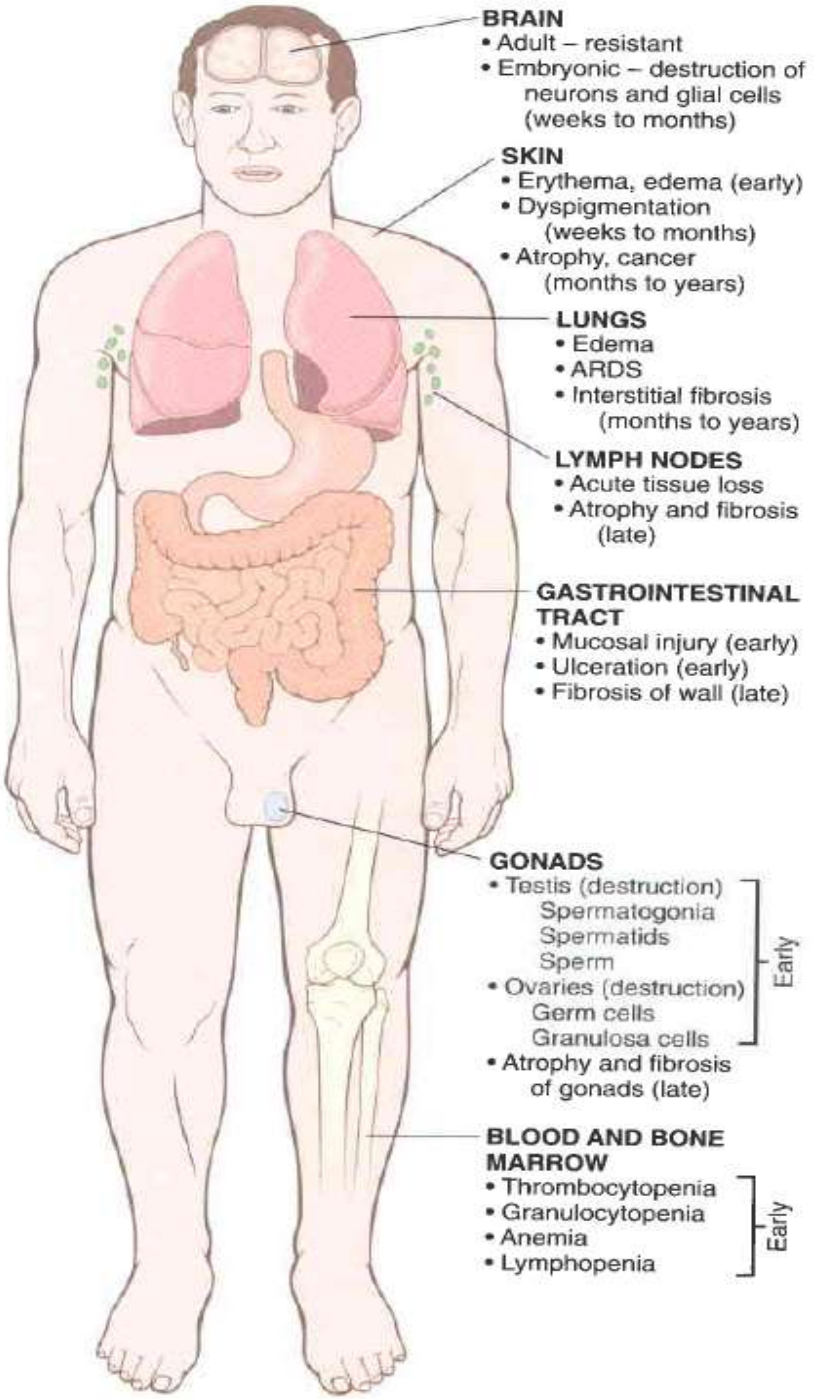
Figure 7–15 Vascular changes and fibrosis of salivary glands produced by radiation therapy of the neck region. **A,** Normal salivary gland; **B,** fibrosis caused by radiation; **C,** fibrosis and vascular changes consisting of fibrointimal thickening and arteriolar sclerosis. V, vessel lumen; I, thickened intima.

(A–C, Courtesy of Dr. Melissa Upton, Department of Pathology, University of Washington, Seattle, Washington.)

Radiation injury

Early effects occur within hours to weeks.

Late changes occur in months to years.



Hematopoietic and lymphoid systems

- The hematopoietic and lymphoid systems are extremely susceptible to radiation injury and deserve special mention.
- With **high dose** levels and large exposure fields, **severe lymphopenia may appear within hours of irradiation**, along with shrinkage of the lymph nodes and spleen.
- Radiation directly destroys lymphocytes, both in the circulating blood and in tissues (nodes, spleen, thymus, gut).
- With **sublethal doses** of radiation, regeneration from viable progenitors is prompt, leading to restoration of a normal lymphocyte count in the blood within weeks to months.

- The circulating granulocyte count may first rise but begins to fall toward the end of the first week.
- If the patient survives, **recovery of the normal granulocyte count** may require 2 to 3 months.
- Platelets are affected as well, with the nadir of the count occurring somewhat later than that for granulocytes; recovery is similarly delayed.

- Hematopoietic cells in the bone marrow, including red cell precursors, also are quite sensitive to radiant energy.
- **Red cells are radioresistant, but red cell progenitors are not; as a result, anemia appears after 2 to 3 weeks and may persist for months.**

Table 7–7 Estimated Threshold Doses for Acute Radiation Effects on Specific Organs

Health Effect	Organ/Structure	Dose (Sv)
Temporary sterility	Testes	0.15
Depression of hematopoiesis	Bone marrow	0.50
Reversible skin effects (e.g., erythema)	Skin	1.0–2.0
Permanent sterility	Ovaries	2.5–6.0
Temporary hair loss	Skin	3.0–5.0
Permanent sterility	Testis	3.5
Cataract	Lens of eye	5.0

Nutritional Diseases

Malnutrition

- An appropriate diet should provide:
- (1) sufficient energy, in the form of carbohydrates, fats, and proteins, for the body‘s daily metabolic needs;
- (2) amino acids and fatty acids to be used as building blocks for synthesis of structural and functional proteins and lipids; and
- (3) vitamins and minerals,

- In primary malnutrition, one or all of these components are missing from the diet.

- By contrast, in secondary, or conditional, malnutrition, the dietary intake of nutrients is adequate, and malnutrition results from nutrient malabsorption, impaired utilization or storage, excess losses, or increased requirements.

- The causes of **secondary malnutrition** can be grouped into three general but overlapping categories: GI diseases, chronic wasting diseases, and acute critical illness.

Leading conditions:

- Poverty: Homeless persons, aged individuals, and children of the poor
- Infection: infections have a negative effect on nutrition and malnutrition increases infection risk.
- Acute and chronic illness: patients with wasting diseases such as advanced cancers and AIDS

- Chronic alcoholism: Alcoholic persons may sometimes suffer PEM but more frequently have deficiency of several vitamins, especially thiamine, pyridoxine, folate, and vitamin A, as a result of dietary deficiency, defective gastrointestinal absorption, abnormal nutrient utilization and storage, increased metabolic needs, and an increased rate of loss.

- Self-impose dietary restriction: Anorexia nervosa, bulimia, and less overt eating disorders affect many individuals who are concerned about body image

PROTEIN-ENERGY MALNUTRITION (PEM)

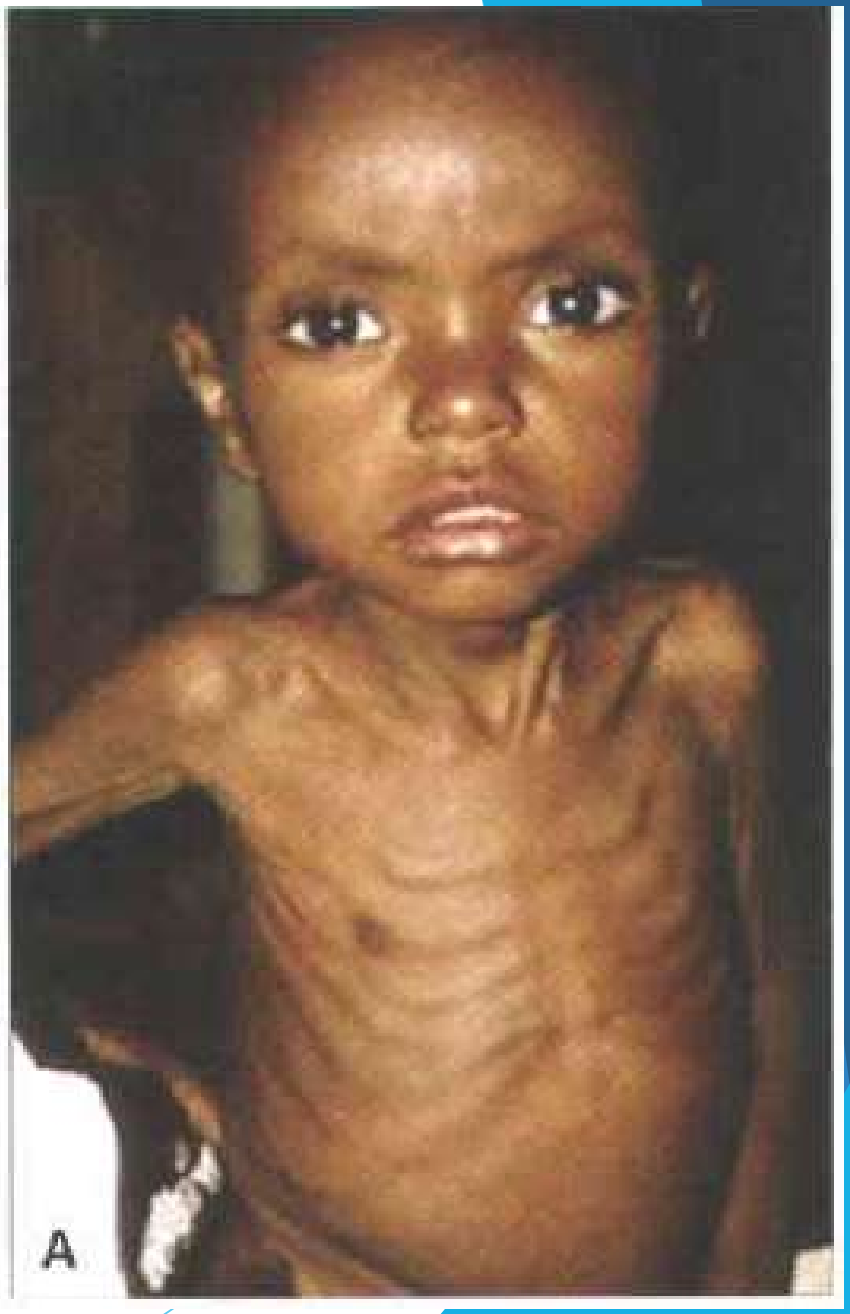
- Common in low income countries
- BMI <16
  - or
- child weight less than 80% normal

Marasmus

- Marasmus: dietary intake of protein and calories inadequate to meet the body's needs
- **child weight less than 60% normal**
  - Losses of muscle and subcutaneous fat, the extremities are emaciated, by comparison, the head appears too large for the body
  - Anemia and manifestations of multiple vitamin deficiencies are present, and there is evidence of immune deficiency

- the visceral protein compartment, which presumably is more precious and critical for survival, is depleted only marginally, so **serum albumin levels are either normal or only slightly reduced**

Loss of muscle mass and subcutaneous fat. The head looks too large for body



Kwashiorkor

- Kwashiorkor: occurs when protein deprivation is relatively greater than the reduction in total calories
- kwashiorkor, marked protein deprivation is associated with severe loss of the visceral protein compartment and the resultant **hypoalbuminemia** gives rise to generalized or dependent edema

- The loss of weight in these patients is masked by the increased fluid retention. In further contrast to Marasmus, there is relative sparing of subcutaneous fat and muscle mass

The infant shows generalized edema
Seen as ascites, puffiness of the face, hands
And legs

- Children with kwashiorkor have characteristic skin lesions, with alternating zones of hyperpigmentation, areas of desquamation, and hypopigmentation, giving a "flaky paint” appearance.
- Hair changes include overall loss of color or alternating bands of pale and darker hair.

- The hallmark anatomic changes in PEM are
- (1) growth failure,
- (2) peripheral edema in kwashiorkor, and
- (3) loss of body fat and atrophy of muscle, more marked in marasmus.

- The liver in kwashiorkor, but not in marasmus, is enlarged and fatty; superimposed cirrhosis is rare.

- In kwashiorkor (rarely in marasmus) the small bowel shows a decrease in the mitotic index in the crypts of the glands, associated with mucosal atrophy and loss of villi and microvilli.

- With treatment, the mucosal changes are reversible.

- The **bone marrow** in both kwashiorkor and marasmus may be hypoplastic, mainly as a result of decreased numbers of red cell precursors
- How much of this derangement is due to a deficiency of protein and folates and how much to reduced synthesis of transferrin and ceruloplasmin is uncertain.
- Thus, anemia is usually present, most often **hypochromic, microcytic anemia**, but a concurrent deficiency of folates may lead to a mixed microcytic-macrocytic anemia.

Secondary Protein-Energy Malnutrition

- Secondary PEM is common in chronically ill or hospitalized patients.
- A particularly severe form of secondary PEM, called cachexia, often develops in patients with advanced cancer

- The wasting is all too apparent and often presages death.
- Although loss of appetite may partly explain it, cachexia may appear before appetite decreases. The underlying mechanisms are complex, but appear to involve “cachectins” such as proteolysis-inducing factor, which are secreted by tumor cells, and cytokines, particularly **TNF**, which are released as part of the host response to advanced tumors.
- Both types of factors directly stimulate the degradation of skeletal muscle proteins, and cytokines such as TNF also stimulate fat mobilization from lipid stores.

Vitamin Deficiencies

- Thirteen vitamins are necessary for health; vitamins A, D, E, and K are fat-soluble, and all others are water-soluble.
- Certain vitamins can be synthesized endogenously:
  - vitamin D from precursor steroids,
  - vitamin K and biotin by the intestinal microflora,
  - niacin from tryptophan, an essential amino acid.

Vitamin A

- The generic term retinoids encompasses vitamin A in its various forms and both natural and synthetic chemicals
- Animal derived foods such as liver, fish, eggs, milk, and butter are important dietary sources
- Yellow and leafy, green vegetables such as carrots, spinach


Vitamin
A

- As with all fats, the digestion and absorption of carotenes and retinoids require bile and pancreatic enzymes.
- Retinol (generally ingested as retinol ester) and ß-carotene are absorbed through the intestinal wall, where ß-carotene is converted to retinol

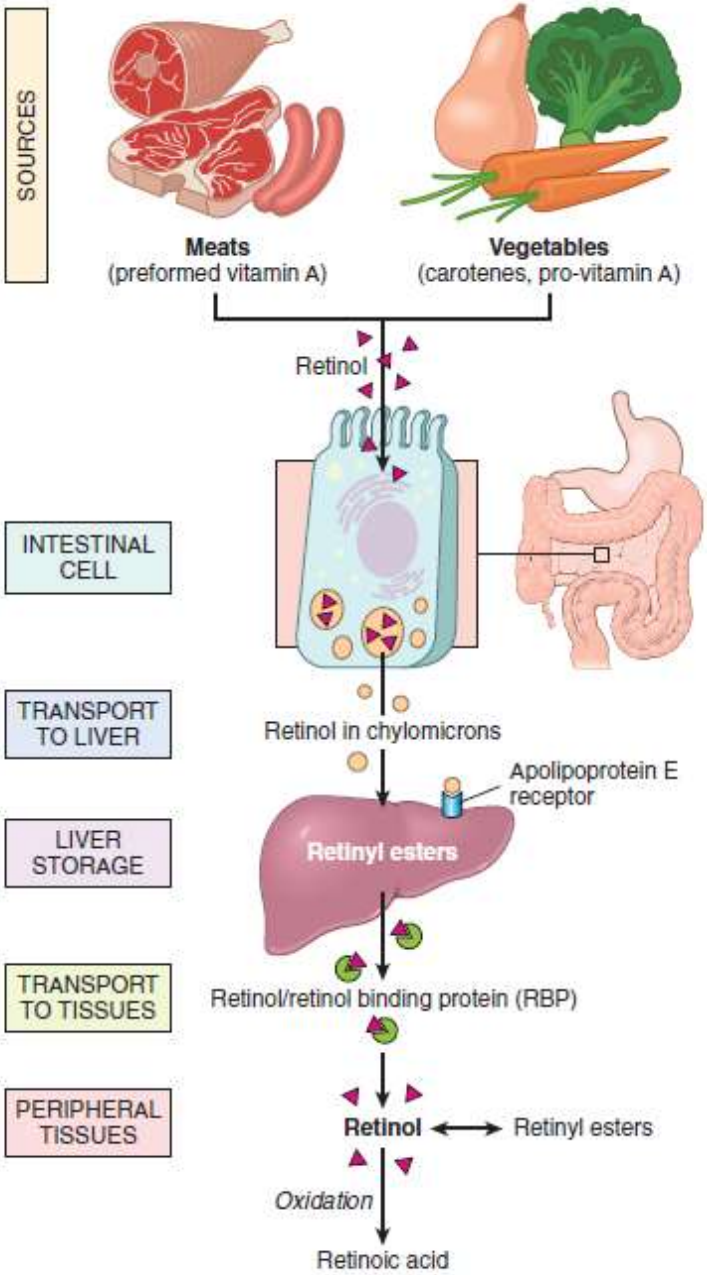


Figure 7–18 Vitamin A metabolism.

main functions of vitamin A

- Maintenance of **normal vision**
- **Cell growth and differentiation**
- **Host resistance to infections**

- Retinoids are used clinically for the treatment of skin disorders such as severe acne and certain forms of psoriasis,
- and also in the treatment of **acute promyelocytic leukemia (All-trans-retinoic acid (ATRA), a potent acid derivative of vitamin A, exerts its effects by binding to retinoic acid receptors (RARs), which regulate the differentiation of myeloid cells.**

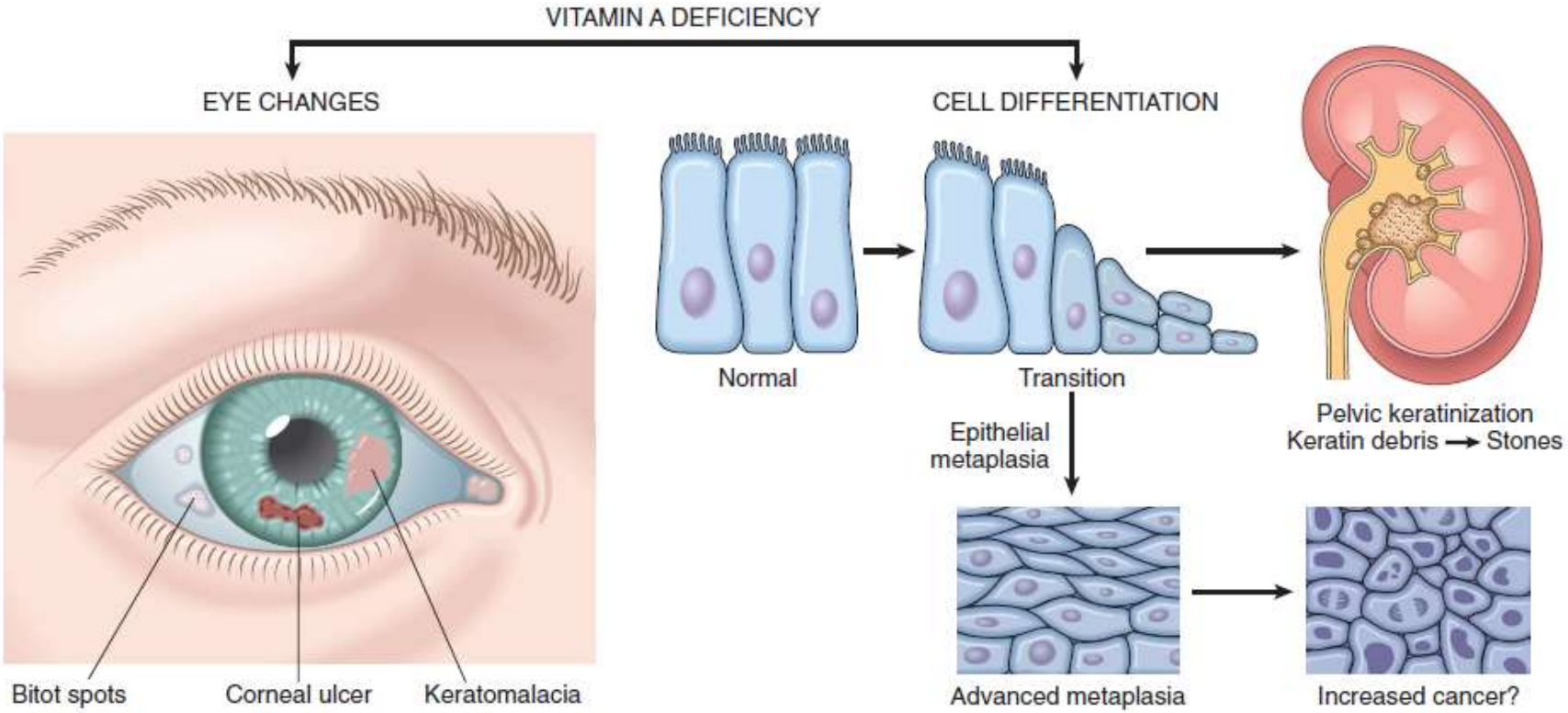


Figure 7–19 Vitamin A deficiency: major consequences in the eye and in the production of keratinizing metaplasia of specialized epithelial surfaces, and its possible role in epithelial metaplasia. Not depicted are night blindness and immune deficiency.

Vitamin A deficiency

- The most devastating changes occur in the eyes and are referred to as xerophthalmia

- immune deficiency

Vitamin A Toxicity

- The signs and symptoms of **acute toxicity** include **headache, dizziness, vomiting, stupor, and blurred vision**—all of which may be confused with those of a brain tumor

- **Chronic toxicity** is associated with **weight loss, anorexia, nausea, vomiting, and bone and joint pain**.
- Retinoic acid stimulates osteoclast production and activity, which lead to increased bone resorption and consequent high risk of fractures.

- Although synthetic retinoids used for the treatment of acne are not associated with these complications, their **use in pregnancy must be avoided** because of the well-established teratogenic effect of retinoids

Vitamin D

- Maintenance of adequate plasma levels of calcium and phosphorus
  - Stimulation of intestinal calcium absorption
  - Stimulation of calcium reabsorption in the kidney
  - Interaction with parathyroid hormone (PTH) in the regulation of blood calcium
- Mineralization of bone

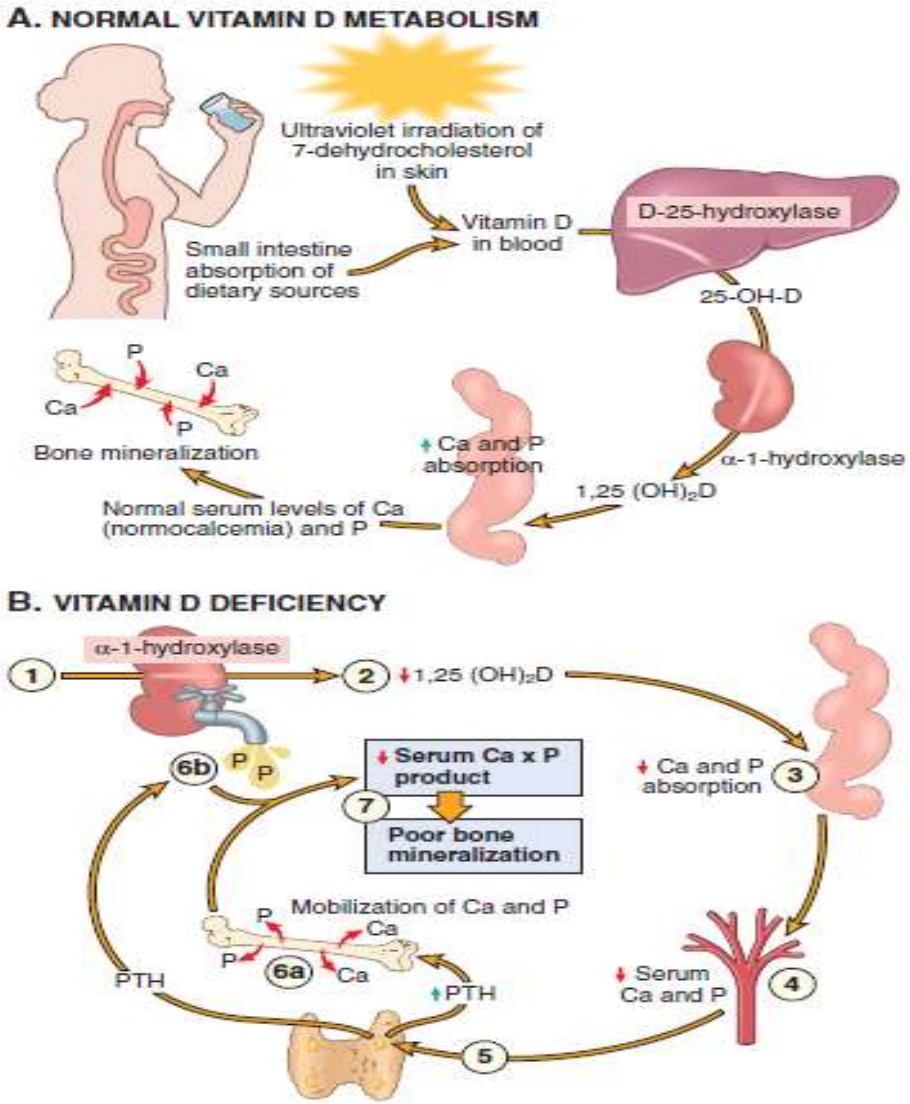


Figure 7–20 **A,** Normal vitamin D metabolism. **B,** Vitamin D deficiency. There is inadequate substrate for the renal hydroxylase (*1*), yielding a deficiency of 1,25-$(OH)_2D$ (*2*), and deficient absorption of calcium and phosphorus from the gut (*3*), with consequent depressed serum levels of both (*4*). The hypocalcemia activates the parathyroid glands (*5*), causing mobilization of calcium and phosphorus from bone (*6a*). Simultaneously, 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*).

- Of note, effects of vitamin D on bone **depend on the plasma levels of calcium**:
- On the one hand, in hypocalcemic states 1,25-(OH)2-D together with PTH increases the resorption of calcium and phosphorus from bone to support blood levels.
- On the other hand, in normocalcemic states vitamin D also is required for calcium deposition in epiphyseal cartilage and osteoid matrix.

Vitamin D deficiency

- Rickets and osteomalacia
- Nonskeletal effect:
- It has been reported that levels of l,25-dihydroxyvitamin D below 20 ng/mL are associated with a 30% to 50% increase in the incidence of colon, prostate, and breast cancers.

MORPHOLOGY

- The basic derangement in both rickets and osteomalacia is an excess of unmineralized bone matrix
- The following sequence ensues in rickets:

• Overgrowth of epiphyseal cartilage due to inadequate provisional calcification and failure of the cartilage cells to mature and disintegrate

• Persistence of distorted, irregular masses of cartilage, many of which project into the marrow cavity

• Deposition of osteoid matrix on inadequately mineralized cartilaginous remnants

• Disruption of the orderly replacement of cartilage by osteoid matrix, with enlargement and lateral expansion of the osteochondral junction

• Abnormal overgrowth of capillaries and fibroblasts in the disorganized zone resulting from microfractures and stresses on the inadequately mineralized, weak, poorly formed bone

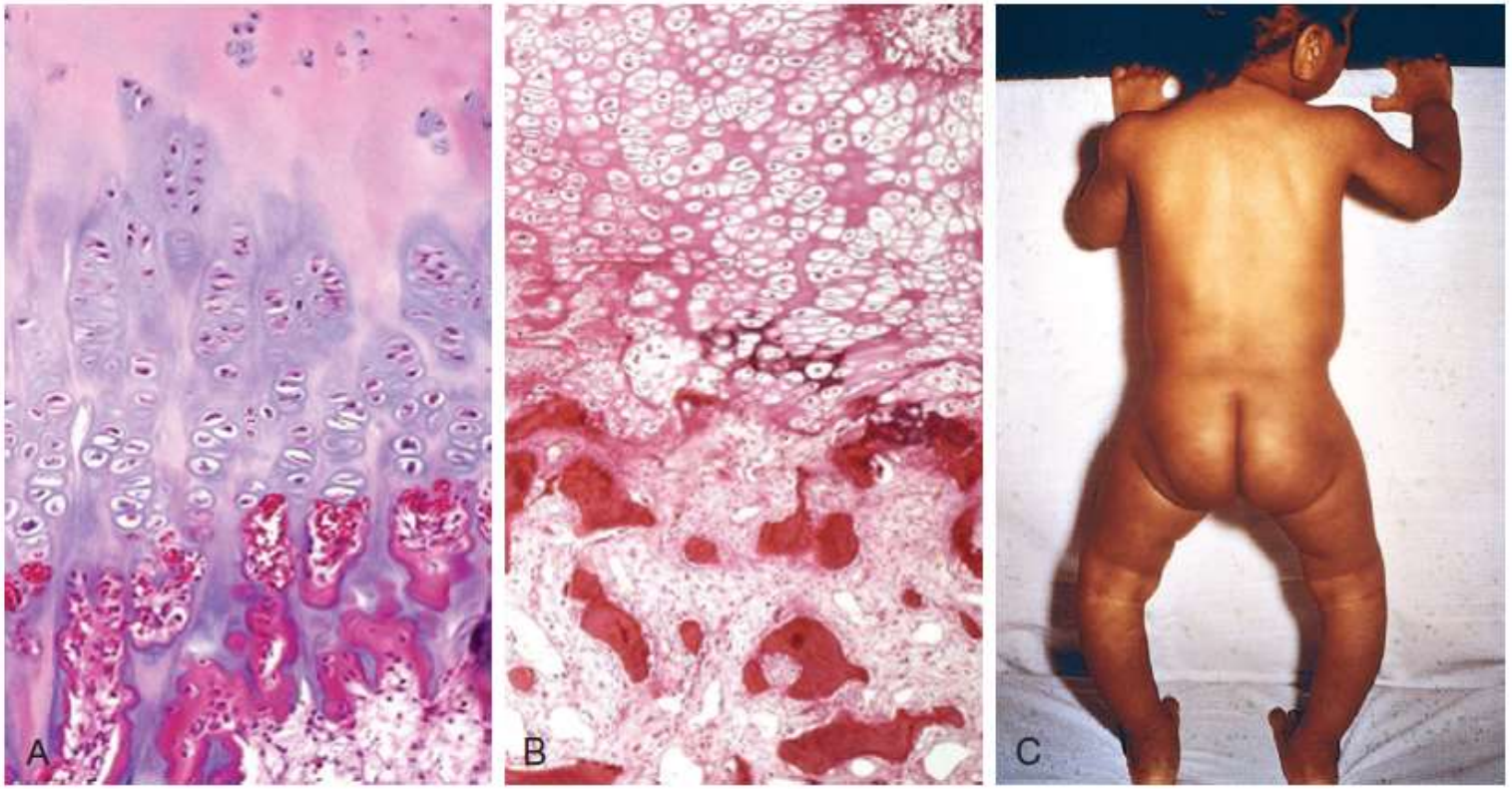


Figure 7–21 Rickets. **A,** Normal costochondral junction of a young child. Note cartilage palisade formation and orderly transition from cartilage to new bone. **B,** Rachitic costochondral junction in which the palisade of cartilage is absent. Darker trabeculae are well-formed bone; paler trabeculae consist of uncalcified osteoid. **C,** Note bowing of legs as a consequence of the formation of poorly mineralized bone in a child with rickets.
(B, Courtesy of Dr. Andrew E. Rosenberg, Massachusetts General Hospital, Boston, Massachusetts.)

- The gross skeletal changes depend on the **severity** of the rachitic process; its **duration**; and, in particular, the stresses to which individual bones are subjected

- **Craniotabes**
- **frontal bossing AND squared appearance to the head**
- **rachitic rosary**
- **pigeon breast deformity**
- **Harrison groove**
- **lumbar lordosis**
- **and bowing of the legs**

- In adults, the lack of vitamin D deranges the normal bone remodeling that occurs throughout life.
- The newly formed osteoid matrix laid down by osteoblasts is inadequately mineralized, producing the **excess of persistent osteoid** that is characteristic of osteomalacia.
- Although the contours of the bone are not affected, the **bone is weak and vulnerable to gross fractures or microfractures**, which are most likely to affect vertebral bodies and femoral necks.
- On histologic examination, the unmineralized osteoid can be visualized as a **thickened layer of matrix** (which stains pink in hematoxylin and eosin preparations) arranged about the more basophilic, normally mineralized trabeculae.

Vitamin C (Ascorbic Acid)

- Collagen
- Antioxidant effect


VITAMIN
C

Vitamin C deficiency

- Scurvy: hemorrhage and healing defects

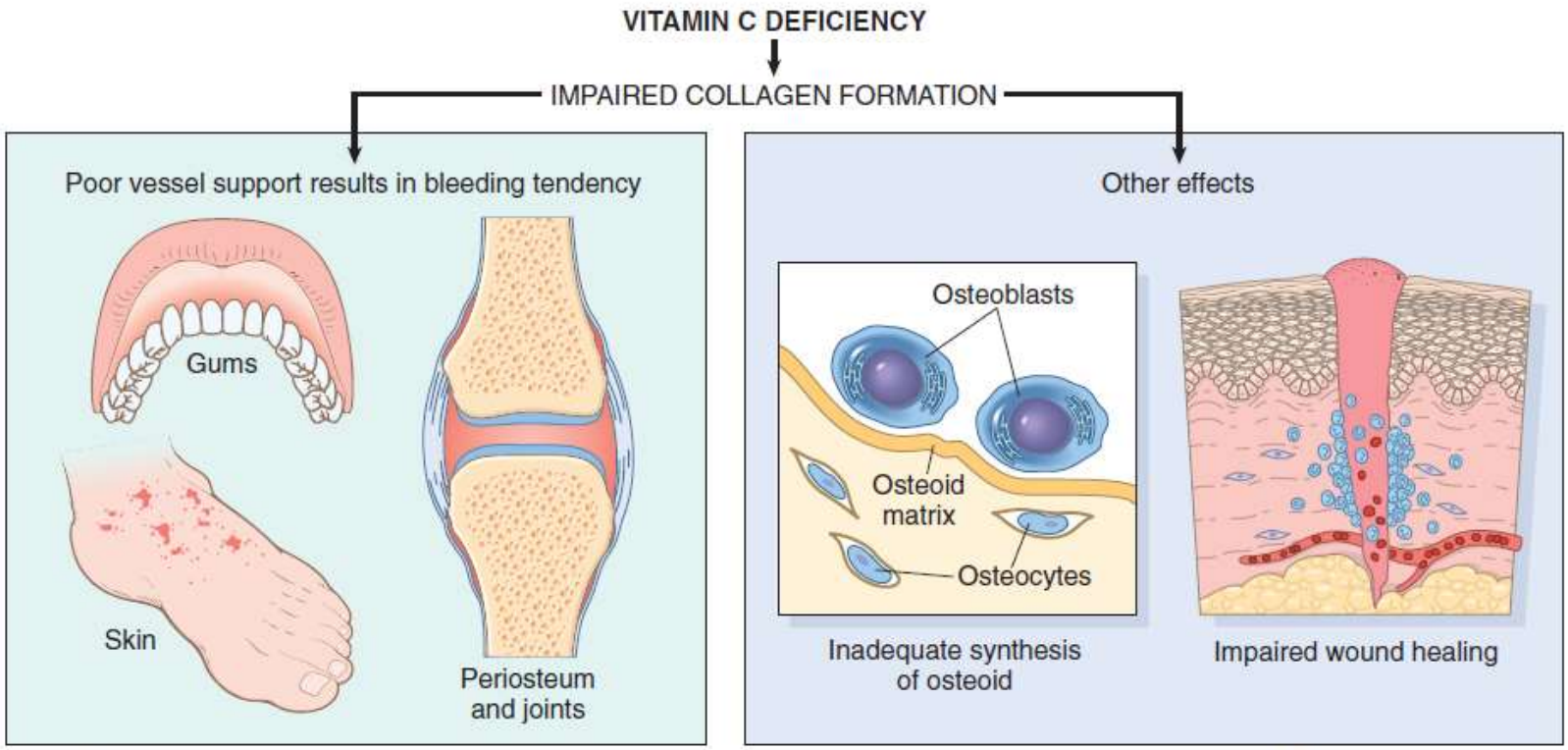


Figure 7–22 Major consequences of vitamin C deficiency caused by impaired formation of collagen. They include bleeding tendency due to poor vascular support, inadequate formation of osteoid matrix, and impaired wound healing.

Toxicity

- The popular notion that megadoses of vitamin C protect against the common cold or at least allay the symptoms has not been borne out by controlled clinical studies.
- Such slight relief as may be experienced probably is a result of the mild antihistamine action of ascorbic acid.
- The large excess of vitamin C is promptly excreted in the urine but may cause **uricosuria and increased absorption of iron**, with the potential for iron overload.

Vitamin	Functions	Deficiency Syndromes
FAT-SOLUBLE		
Vitamin A	A component of visual pigment Maintenance of specialized epithelia Maintenance of resistance to infection	Night blindness, xerophthalmia, blindness Squamous metaplasia Vulnerability to infection, particularly measles
Vitamin D	Facilitates intestinal absorption of calcium and phosphorus and mineralization of bone	Riskets in children Osteomalacia in adults
Vitamin E	Major antioxidant; scavenges free radicals	Spinocerebellar degeneration
Vitamin K	Cofactor in hepatic carboxylation of procoagulants—factors II (prothrombin), VII, IX, and X; and protein C and protein S	Bleeding diathesis (Chapter 14)
WATER-SOLUBLE		
Vitamin B_1 (thiamine)	As pyrophosphate, is coenzyme in decarboxylation reactions	Dry and wet beriberi, Wernicke syndrome, Korsakoff syndrome (Chapter 28)
Vitamin B_2 (riboflavin)	Converted to coenzymes flavin mononucleotide and flavin adenine dinucleotide, cofactors for many enzymes in intermediary metabolism	Ariboflavinosis, cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization
Niacin	Incorporated into nicotinamide adenine dinucleotide (NAD) and NAD phosphate, involved in a variety of redox reactions	Pellagra—"three Ds": dementia, dermatitis, diarrhea
Vitamin B_6 (pyridoxine)	Derivatives serve as coenzymes in many intermediary reactions	Cheilosis, glossitis, dermatitis, peripheral neuropathy (Chapter 28)
Vitamin B_{12}	Required for normal folate metabolism and DNA synthesis Maintenance of myelinization of spinal cord tracts	Megaloblastic pernicious anemia and degeneration of posterolateral spinal cord tracts (Chapter 14)
Vitamin C	Serves in many oxidation-reduction (redox) reactions and hydroxylation of collagen	Scurvy
Folate	Essential for transfer and use of one-carbon units in DNA synthesis	Megaloblastic anemia, neural tube defects (Chapter 14)
Pantothenic acid	Incorporated in coenzyme A	No nonexperimental syndrome recognized
Biotin	Cofactor in carboxylation reactions	No clearly defined clinical syndrome

Obesity

- BMI more than 25
- Associated with the increased incidence of several of the most important diseases of humans, including type 2 diabetes, dyslipidemias, cardiovascular disease, hypertension, and cancer.

- Not only the total body weight but also the distribution of the stored fat is of importance in obesity.
- Central, or visceral obesity, in which fat accumulates in the trunk and in the abdominal cavity (in the mesentery and around viscera), is associated with a much higher risk for several diseases than is excess accumulation of fat diffusely in subcutaneous tissue.

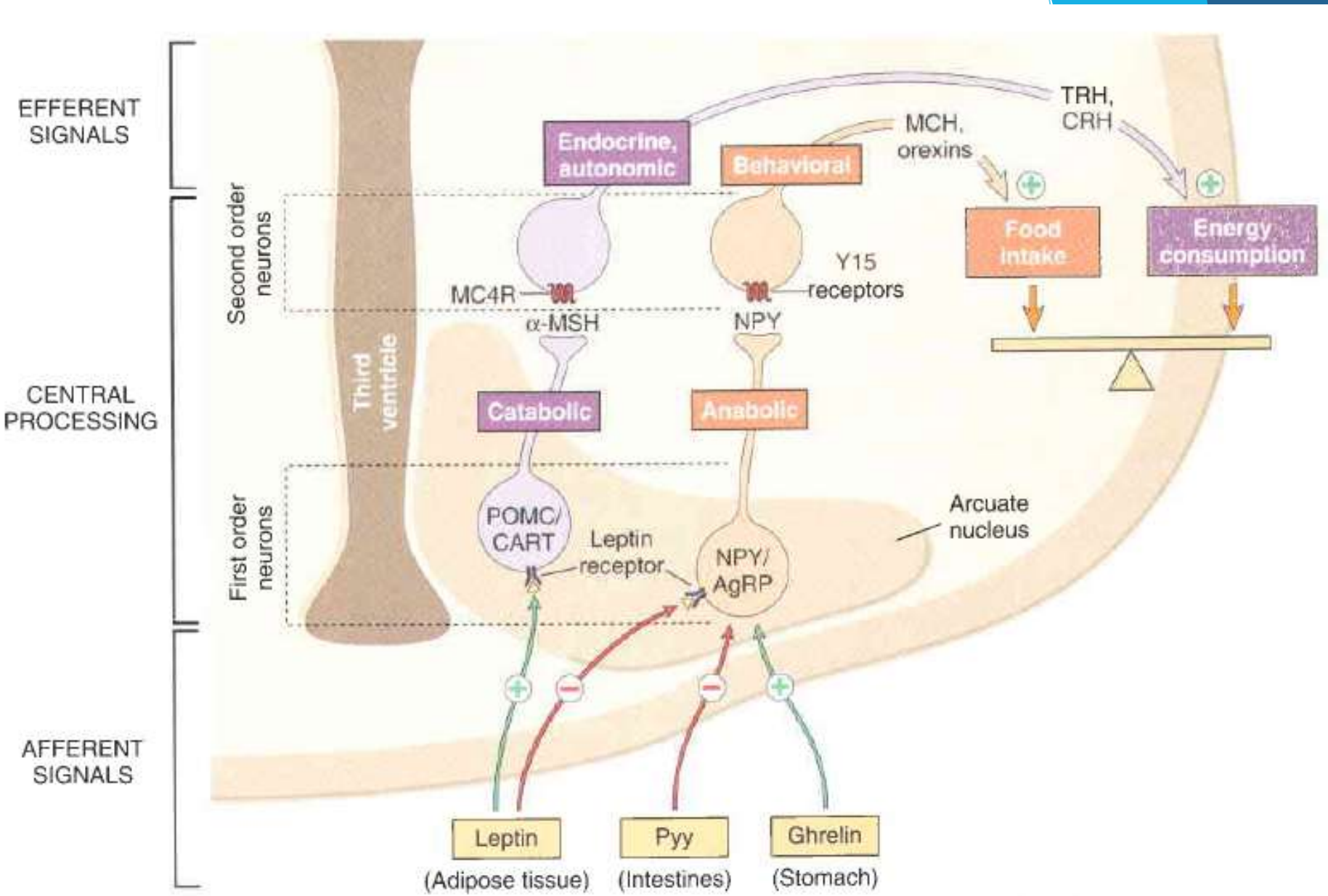
- At its simplest level, obesity is a disease of caloric imbalance that results from an excess intake of calories above their consumption by the body.
- However, the pathogenesis of obesity is exceedingly complex and not yet completely understood.
- Ongoing research has identified complex humoral and neural mechanisms that control appetite and satiety.

- the neurohumoral mechanisms that regulate energy balance can be subdivided into three components:

- A) The peripheral or afferent system generates signals from various sites. Its main components are leptin and adiponectin produced by fat cells, ghrelin from the stomach, peptide YY (PYY) from the ileum and colon, and insulin from the pancreas.

- B) The arcuate nucleus in the hypothalamus processes and integrates neurohumoral peripheral signals. These first order neurons communicate with second order neurons.

- C) The efferent system that carries the signals generated in the second order neurons of the hypothalamus to control food intake and energy expenditure.


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
Y15 receptors
NPY
Catabolic
Anabolic
POMC/ CART
Leptin receptor
NPY/ AgRP
Arcuate nucleus
Leptin
(Adipose tissue)
Pyy
(Intestines)
Ghrelin
(Stomach)

- Leptin= weight loss
- Adiponectin= weight loss

Obesity

- In men, a BMI greater than 25 kg/m2 correlated strongly with an increased incidence of adenocarcinoma of the esophagus, and cancers of the thyroid, colon,and kidney.
- In women, a BMI greater than 25 kg/m2 correlated strongly with an increased incidence of adenocarcinoma of the esophagus, and of endometrial, gallbladder, and kidney cancers.

Thank you