e29 Atlas of Clinical Manifestations of Metabolic Diseases

J. Larry Jameson

The term *metabolism* is derived from the Greek *metabol,* to change. It includes the broad array of chemical pathways that are necessary for normal development and homeostasis. In practice, clinicians generally use the term *metabolism* in reference to energy utilization for anabolism or catabolism. Alternatively, intermediary metabolism describes the myriad cellular pathways that convert energy sources from one form to another (e.g., citric acid cycle). The emerging field of *metabolomics* is based on the premise that the identification and measurement of metabolic products will enhance our understanding of physiology and disease.

Over the years, the classification of metabolic diseases has extended beyond traditional pathways involved in fuel metabolism to include disorders such as lysosomal storage diseases or connective tissue diseases. Thus, metabolic diseases really reflect disorders of cell biology. For example, lysosomal storage diseases (Chap. 355) result from a variety of defects, usually in a lysosomal enzyme, causing accumulation of a substrate within the lysosome. Certain lipodystrophies and cardiomyopathies can be caused by mutations in lamin A, a structural protein in the nuclear envelope. Membrane defects (Chap. 359), usually involving transporters of amino acids, sugars, or ions, cause disorders such as cystinuria, Hartnup disease, or Wilson disease. Connective tissue diseases (Chap. 357) frequently involve defects in collagen synthesis or structure (osteogenesis imperfecta, Ehlers-Danlos syndrome, Alport syndrome) or in other extracellular matrix structural proteins such as fibrillin (Marfan syndrome). Many metabolic disorders originate from defects in enzymes involved in the synthesis or degradation of amino acids, carbohydrates, lipids, purines, or pyrimidines. (Chaps. 353, 356, 358). Lipoprotein disorders (Chap. 350) are caused by defects in a wide array of cellular pathways including membrane receptors (LDL-R), enzyme defects (lipoprotein lipase), carrier proteins (apoB100), or transporters (ABCA1). In some instances, metabolic abnormalities induce compensatory physiologic responses that reflect the interactions of multiple different metabolic pathways. For example, the metabolic syndrome (Chap. 236) includes a constellation of clinical features (central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension). It likely has multiple genetic and environmental origins. Cushing syndrome reflects the metabolic effects of excess cortisol on multiple tissues (Chap. 336).

This broader definition results in a plethora of metabolic diseases, numbering in the thousands. Fortunately, comprehensive reference sources exist, such as the Online Metabolic and Molecular Bases of Inherited Disease (OMMBID): (*http://genetics.accessmedicine.com/*) and the Online Mendelian Inheritance in Man (OMIM): (*http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM*). The study of metabolic diseases has been invaluable for advancing our understanding of human genetics by providing insight into principles such as patterns of inheritance, variable expressivity, phenotypic variation, and novel approaches to therapy, including screening programs, blood and organ transplantation, gene therapy, and enzyme replacement (Chap. 62).

This atlas provides a visual survey of selected metabolic disorders with references to the topics elsewhere in the text. The authors encourage submission of additional illustrations that might be used to facilitate learning among our peers and thereby enhance the recognition and care of patients with these disorders.

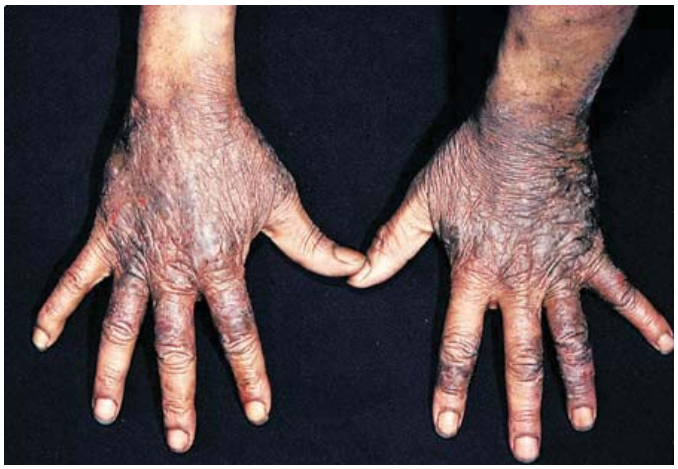


FIGURE e29-1 "Gauntlet" of pellagra (niacin deficiency). Indurated, lichenified, pigmented, and scaly skin on the dorsa of the hands. See Chap. 71.

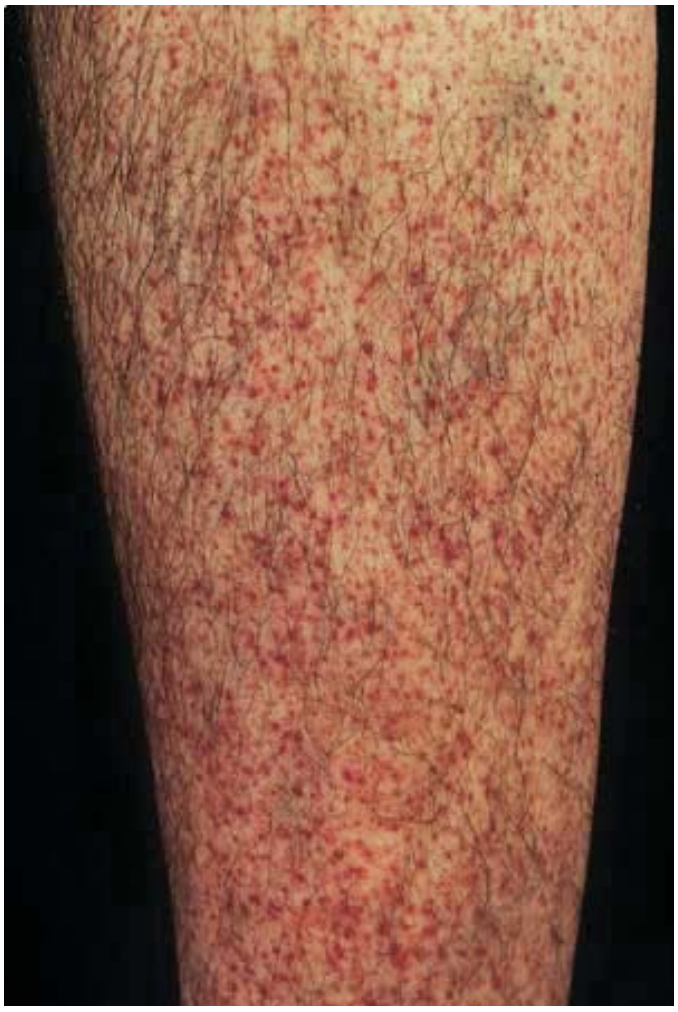


FIGURE e29-2 Scurvy (vitamin C deficiency). Perifollicular hemorrhage on the leg. The follicles are often plugged by keratin (perifollicular hyperkeratosis). This eruption occurred in a 46-year-old alcoholic, homeless male, who also had bleeding gums and loose teeth. See Chap. 71.

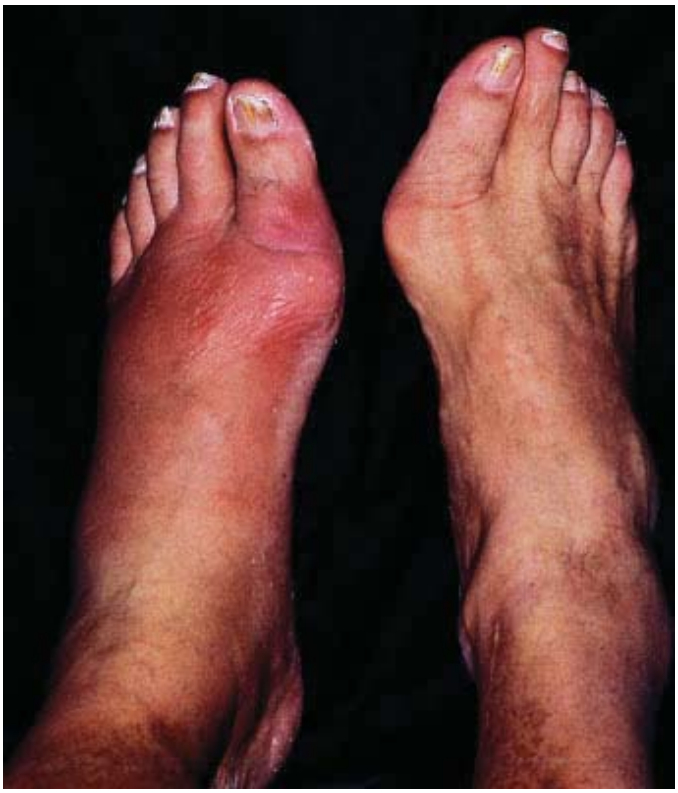


FIGURE e29-3 Podagra with gouty inflammation of the first metatarsophalangeal (MTP) joint. Note the swelling and erythema of the left first MTP. See Chaps. 327 and 353. (*Courtesy of Kevin J. Knoop, MD, MS; with permission.*)

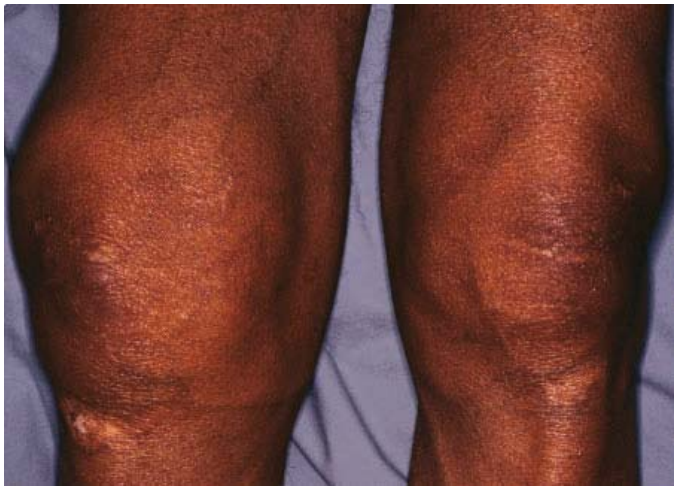


FIGURE e29-4 Gout. Large tophi of gout located in and around the right knee. See Chaps. 327 and 353. (*Courtesy of Daniel L. Savitt, MD; with permission.)*

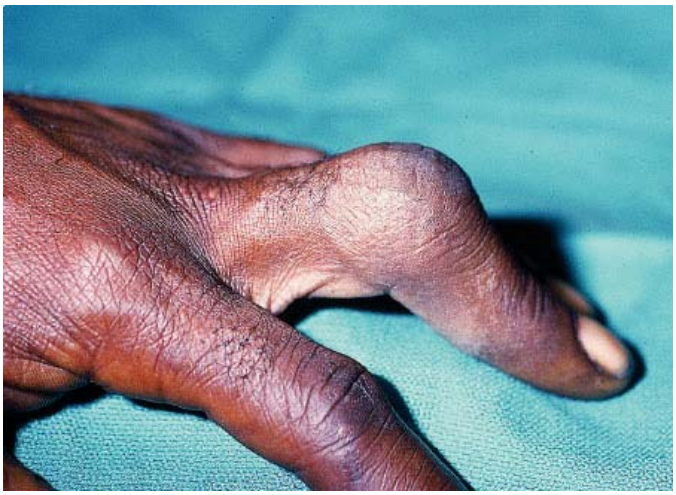


FIGURE e29-5 Gout. The finger is an unusual site for gouty arthritis. Examination of the synovial fluid confirmed the diagnosis. See Chaps. 327 and 353. (*Courtesy of Alan B. Storrow, MD; with permission.*)

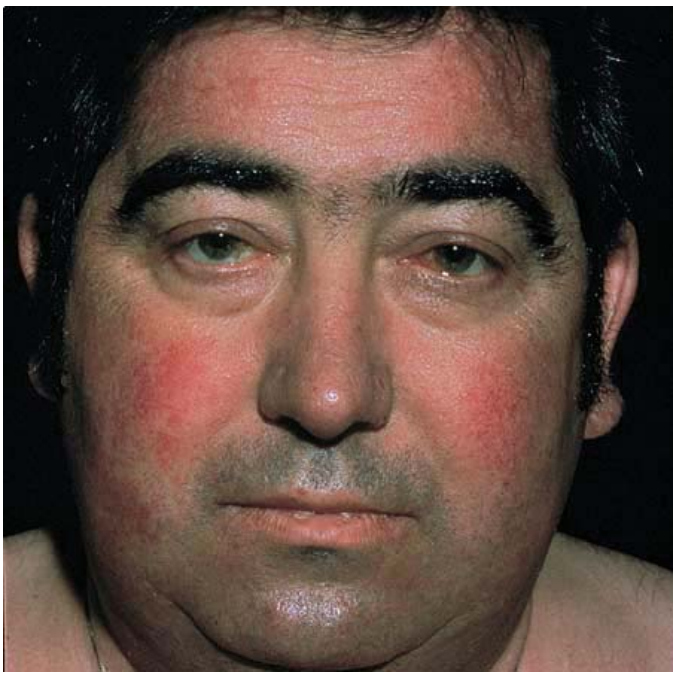


FIGURE e29-6 Cushing's syndrome. Plethoric moon facies with erythema and telangiectases of cheek and forehead; the face and neck and supraclavicular areas (not depicted here) show increased deposition of fat. See Chap. 336.

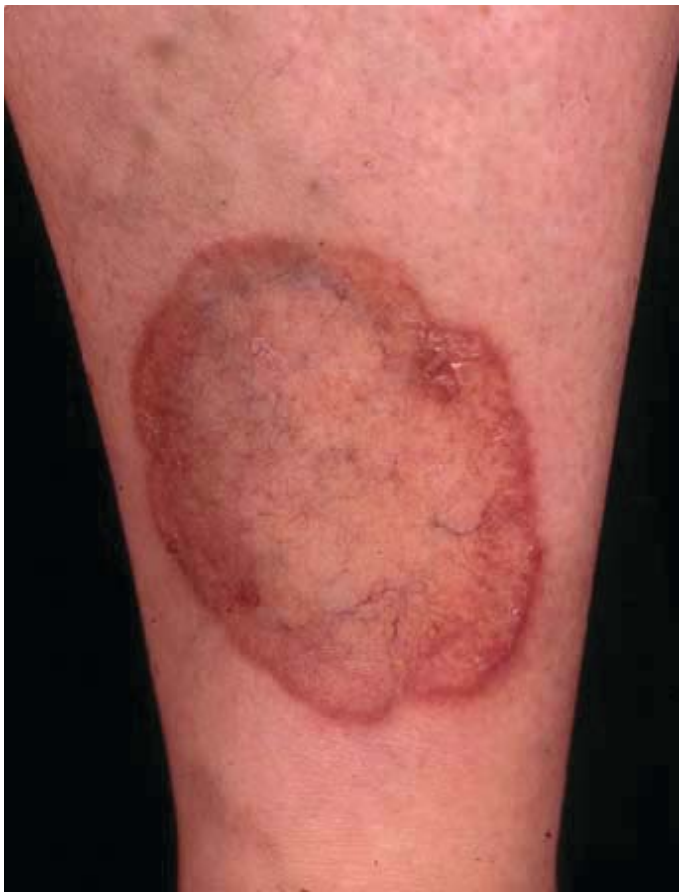


FIGURE e29-7 Necrobiosis lipoidica diabeticorum. A large, symmetric plaque with active tan-pink, well-demarcated, raised, firm borders and a yellow center in the pretibial regions of a 28-year-old diabetic female. The central parts of the lesions are depressed with atrophic changes of epidermal thinning and telangiectasis against yellow background. See Chap. 338.

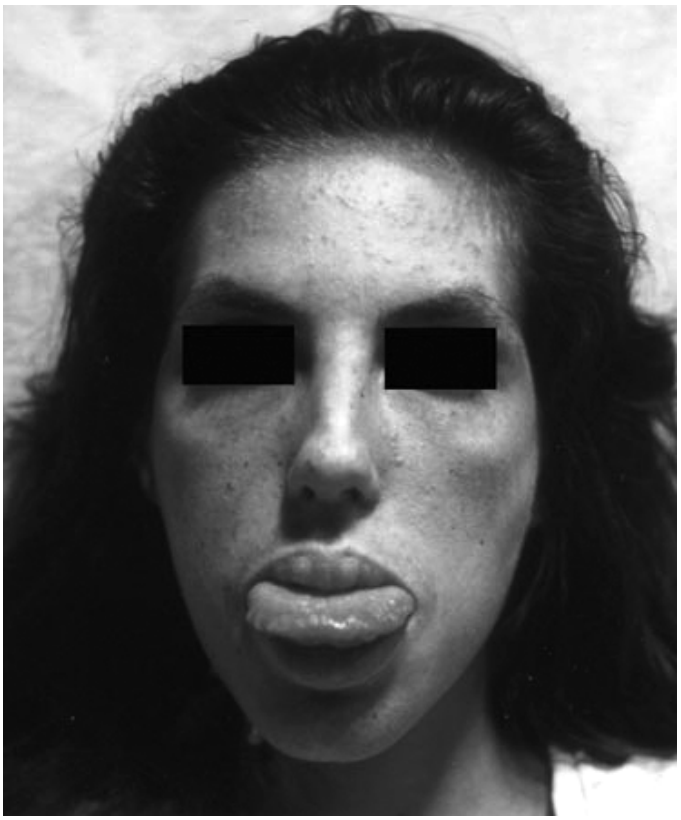


FIGURE e29-8 Patient with multiple endocrine neoplasia 2B syndrome. Note the multiple neuromas on the lips and tongue and the marfanoid facies. See Chap. 345.

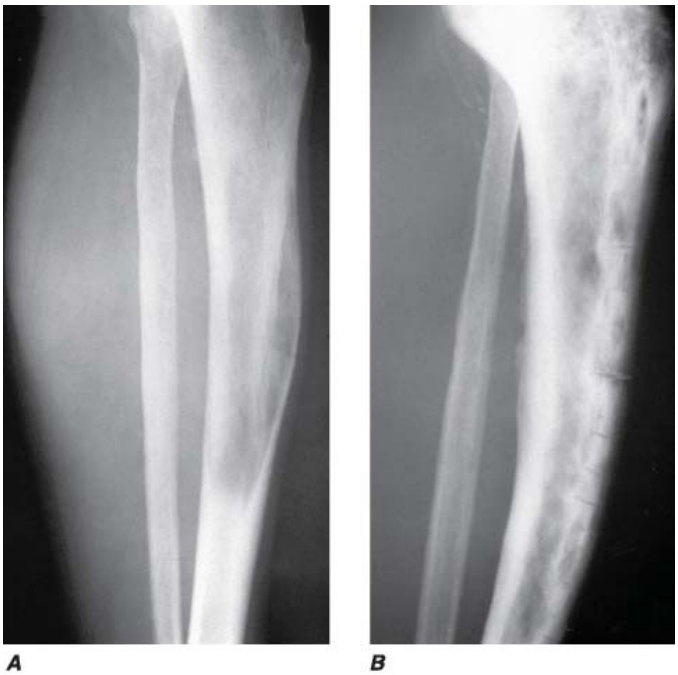


FIGURE e29-9 Early and late radiographs of Paget disease of the tibia, taken when the male patient was 45 years of age (***A***) and when he was 65 years of age (***B***). See Chap. 349.

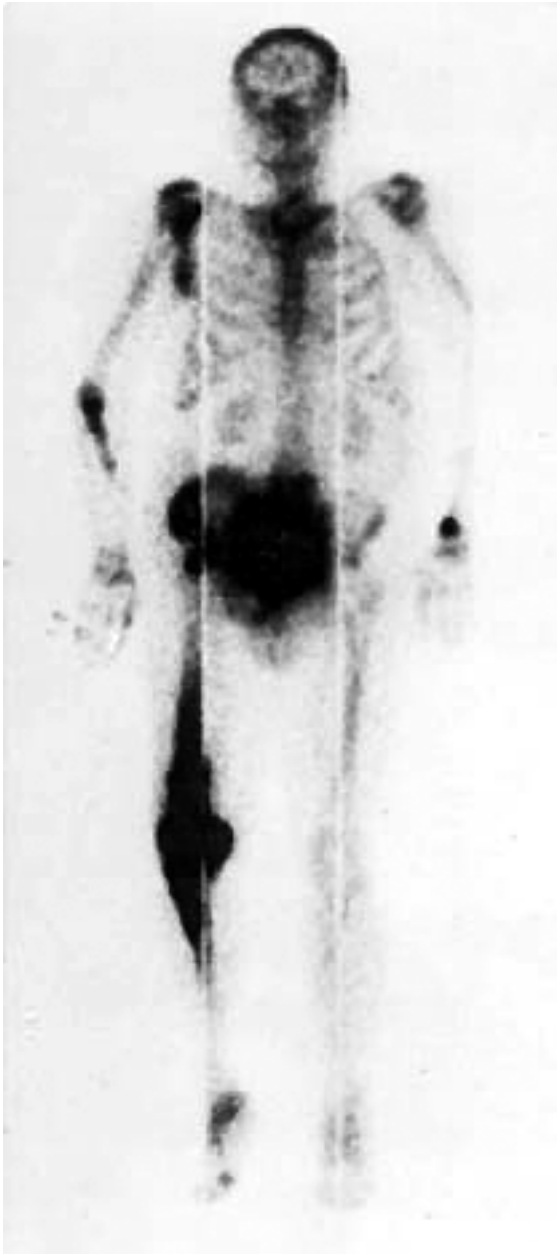


FIGURE e29-10 Bone scan of patient with severe Paget disease of the skull, ribs, spine, pelvis, right femur, and acetabulum. Note localization of bone-seeking isotope (99mTc-labeled bisphosphonate) in these areas. See Chap. 349.

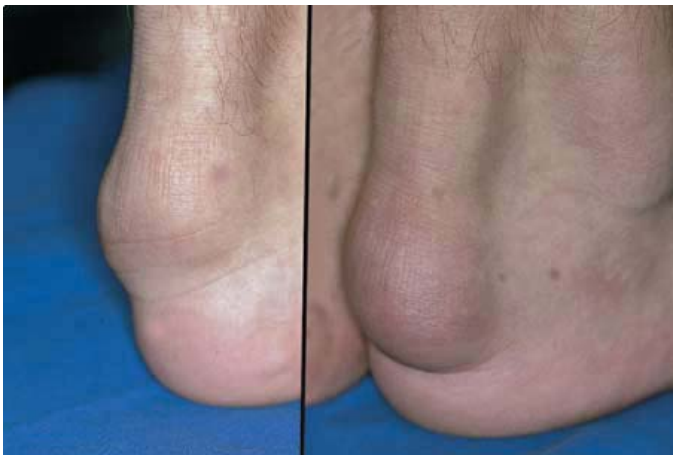
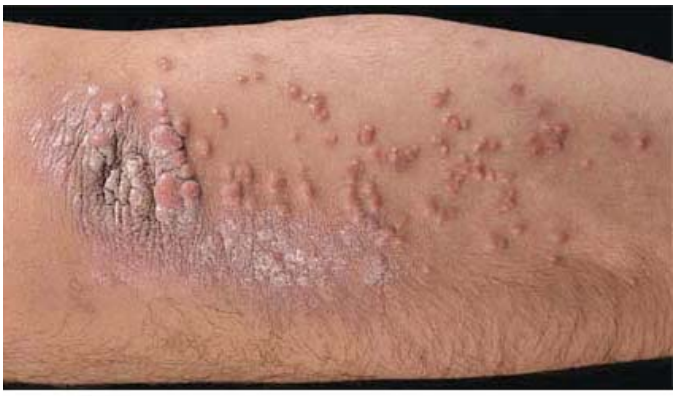


FIGURE e29-11 Tendinous xanthomas. Large subcutaneous tumors adherent to the Achilles tendons. See Chap. 350.



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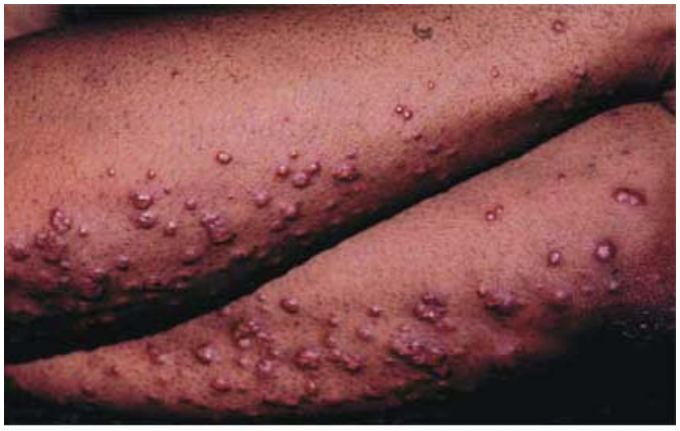


B

FIGURE e29-12 Papular eruptive xanthomas. *A.* Multiple, discrete, red-to-yellow papules becoming confluent on the elbow of an individual with uncontrolled diabetes mellitus; lesions were present on both elbows and buttocks. ***B.*** Papular eruptive xanthomas on the elbows and lower arms in an African American. This image is shown to demonstrate the color of xanthomas in black skin. See Chap. 350.

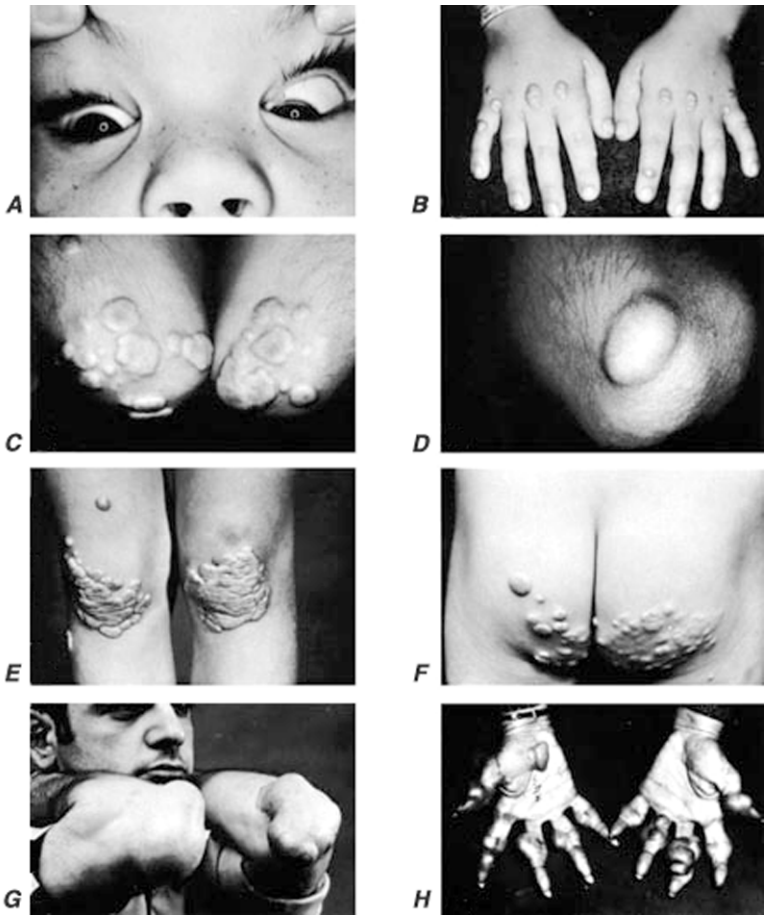


FIGURE e29-13 Forms of xanthomas and other lipid deposits frequently seen in familial hypercholesterolemia homozygotes. *A.* Arcus corneae. ***B, C, E,*** and ***F.*** Cutaneous planar xanthomas, which usually have a bright orange hue. ***C*** and ***D.*** Tuberous xanthomas on the elbows. ***H.*** Tendon and tuberous xanthomas. (*Panel H reproduced through the courtesy of Dr. A. Khachadurian; with permission.*) See Chap. 350.

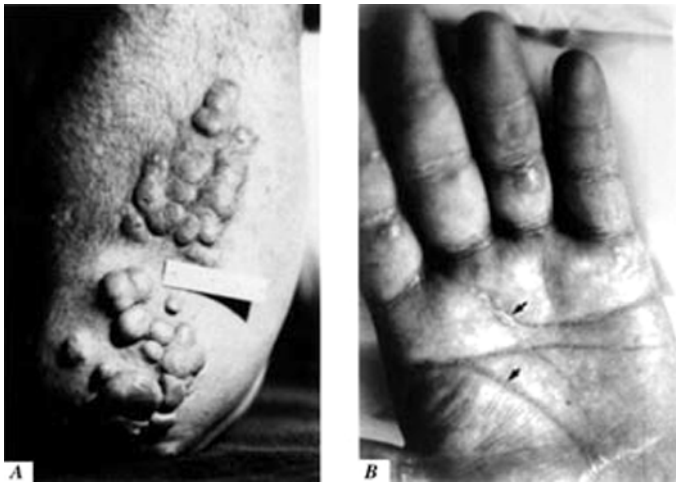


FIGURE e29-14 Examples of xanthomas in type III hyperlipoproteinemic subjects. *A.* Tuberoeruptive xanthomas of the elbows. ***B.*** Tuberous xanthomas of the digits and xanthomas of the palmar creases (xanthoma striata palmaris) (*arrows*). (*Courtesy of Dr. Thomas P. Bersot; with permission.*) See Chap. 350.

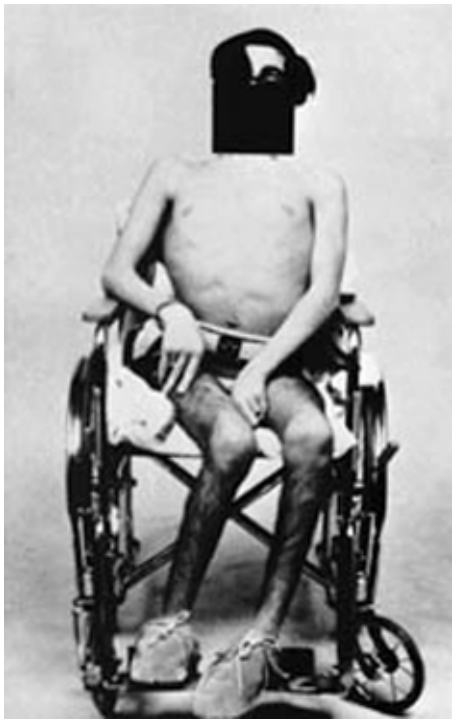


FIGURE e29-15 A 17-year-old patient with abetalipoproteinemia with generalized weakness, kyphoscoliosis, and lordosis. (*Courtesy of Drs. Peter Herbert, Gerd Assmann, Antonio M. Gotto, Jr., and Donald Fredrickson; with permission.*) See Chap. 350.

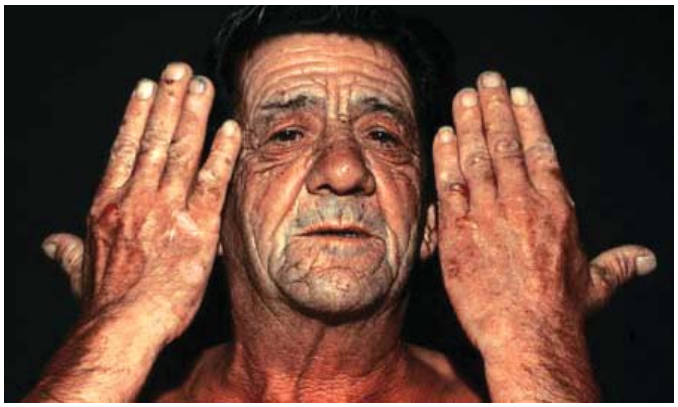


FIGURE e29-16 Porphyria cutanea tarda. Periorbital and malar violaceous coloration, hyperpigmentation, and hypertrichosis on the face; bullae, crusts, and scars on the dorsa of the hands. See Chap. 352.

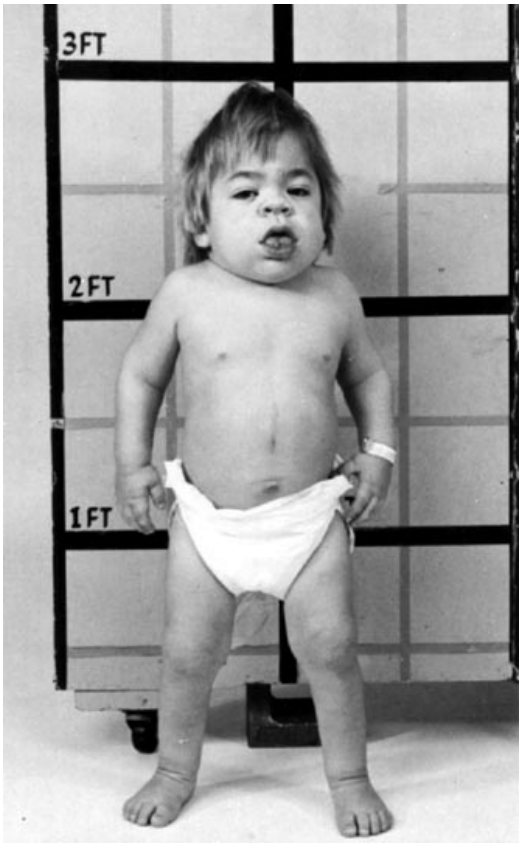


FIGURE e29-17 Mucopolysaccharidosis type IH (Hurler syndrome) in a 4-year-old boy. Diagnosis was made at the age of 15 months, at which time he had developmental delay, hepatomegaly, and skeletal involvement. At the time of the picture, the patient had short stature, an enlarged tongue, persistent nasal discharge, stiff joints, and hydrocephalus. Verbal language skills consisted of four to five words. The patient had a severe hearing loss and wore hearing aids. See Chap. 355.

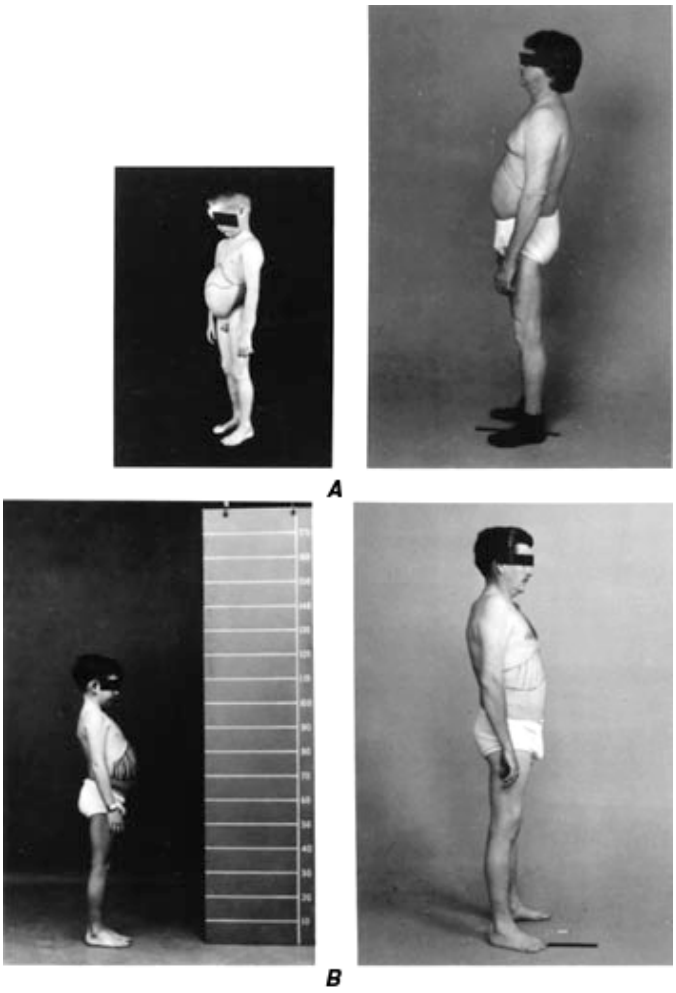


FIGURE e29-18 Growth and development in two patients with type Ia glycogen storage disease. *A.* Patient at age 7 years and at 39 years old. ***B.*** Another type Ia patient at age 10 years, and follow-up at age 33 years. Both patients survive despite their disease not being adequately treated. Note that the abdomen is less protuberant with age. Hypoglycemia also improves with age. In adulthood, however, both patients continue to be short, and both have gout, multiple liver adenomas, and a progressive renal disease. See Chap. 356.

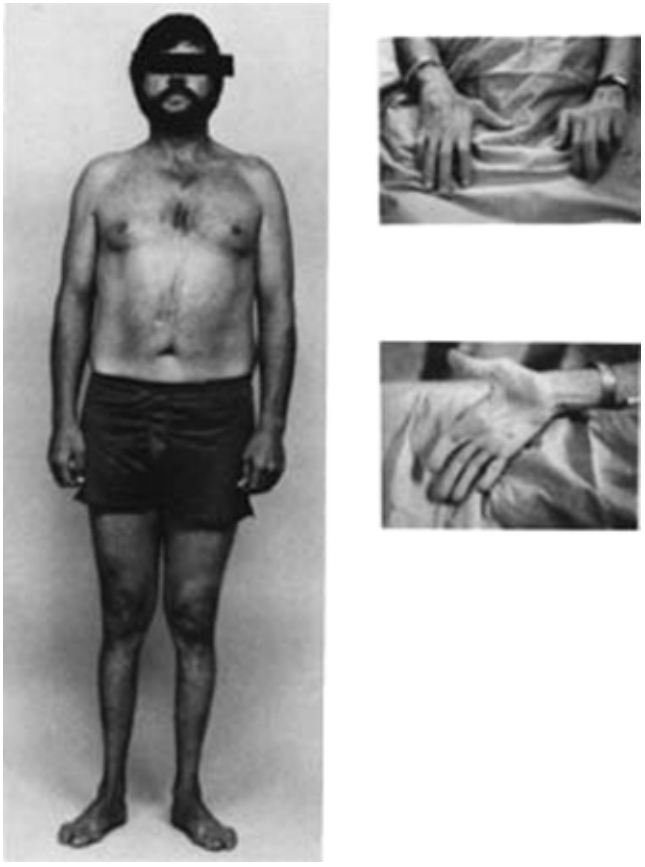


FIGURE e29-19 Progressive myopathy in a patient with type IIIa glycogen storage disease. The patient has a debrancher deficiency in both liver and muscle (subtype IIIa). As a child, he had hepatomegaly, hypoglycemia, and growth retardation. After puberty, he no longer had hepatomegaly, and his final height is normal. Note the muscle wasting in the lower legs and both hands at age 44 years (*left panel*); this progressed to a pronounced muscle atrophy at age 53 years (*two right panels*). See Chap. 356.

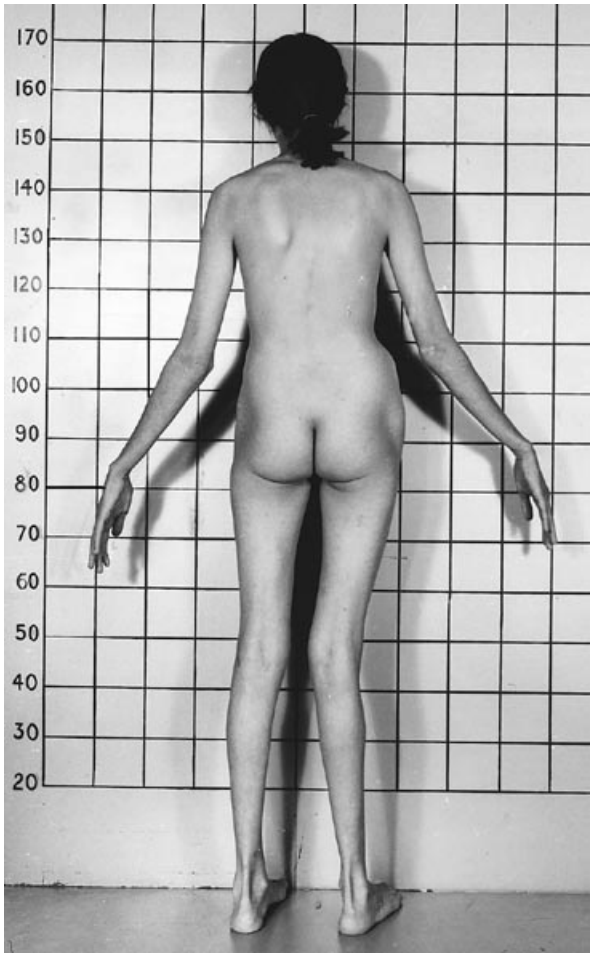
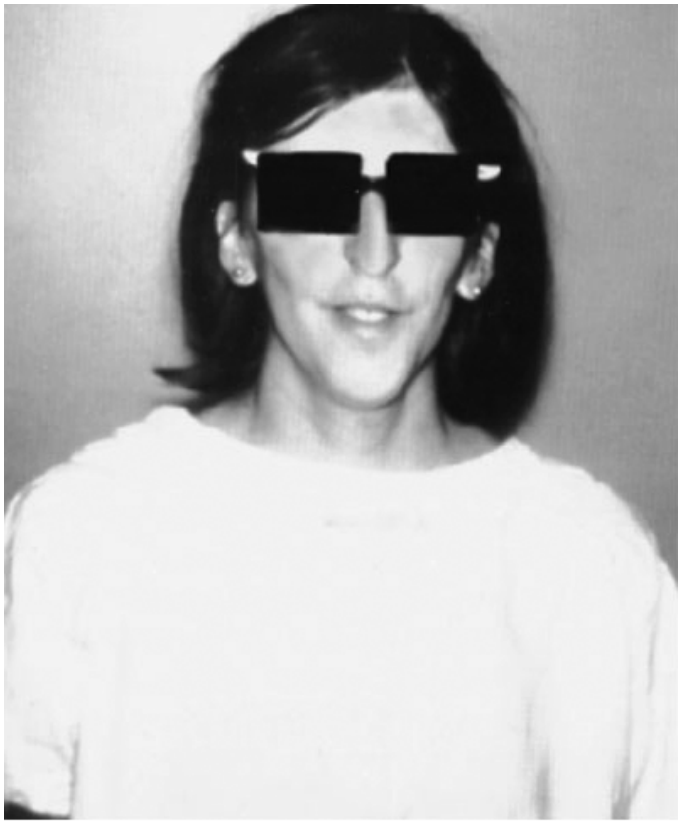


FIGURE e29-20 Skeletal features of Marfan syndrome in a 16-year-old girl. Note the long limbs that are associated with disproportionate tall stature, long fingers, scoliosis, and genu valgum. See Chap. 357.



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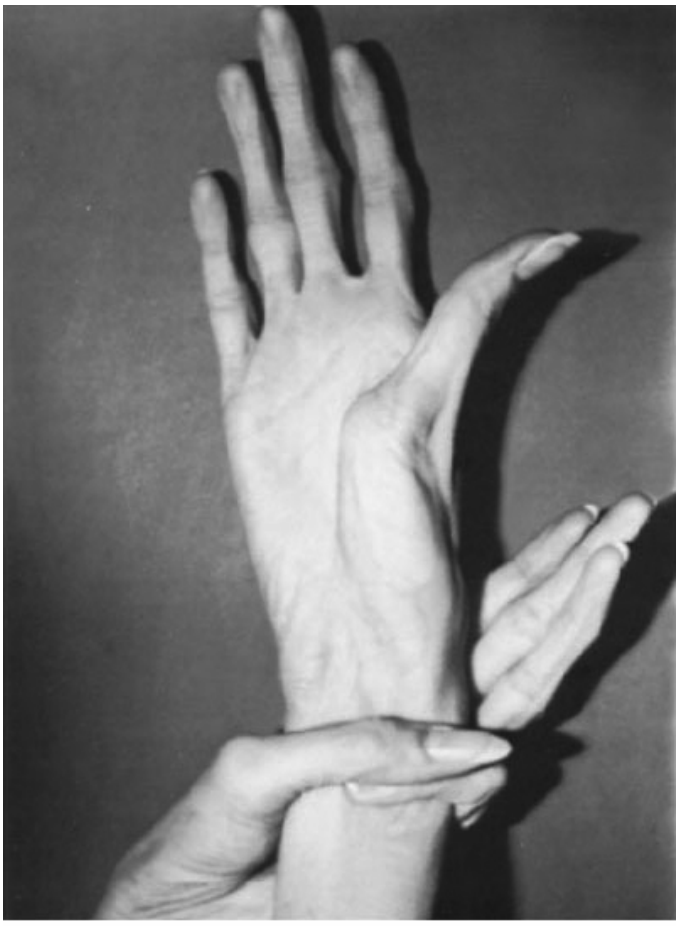

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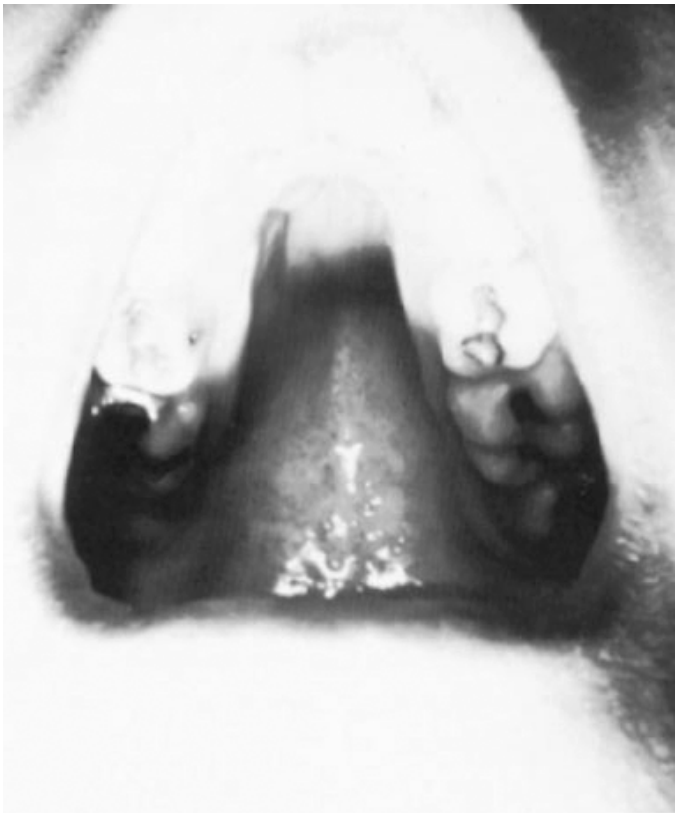

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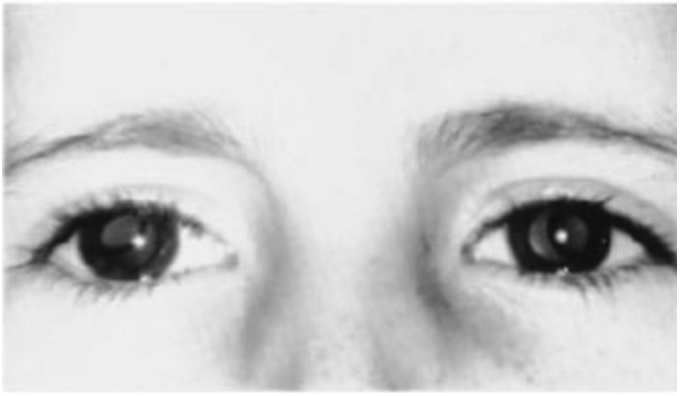
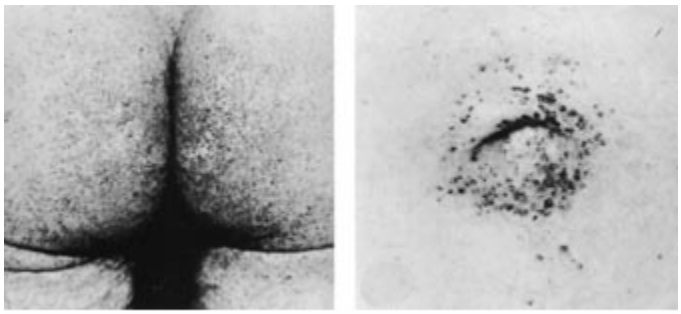


D

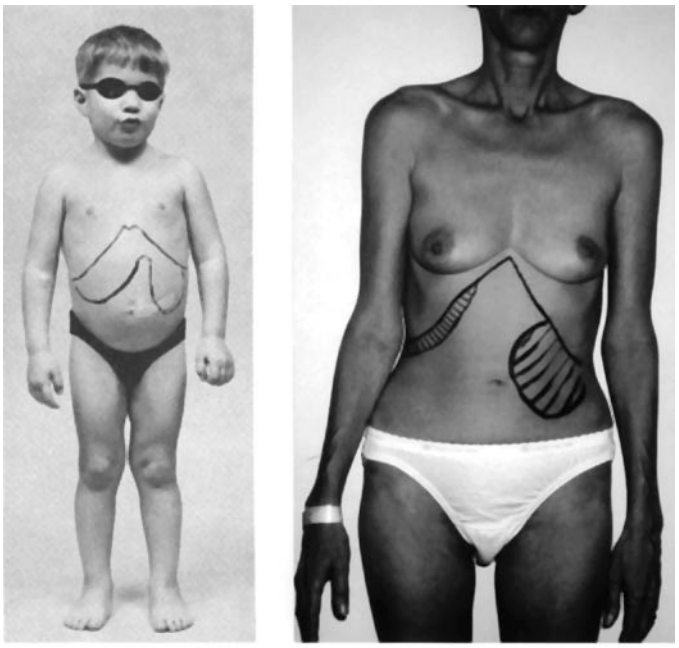
FIGURE e29-21 Marfan's syndrome. ***A.*** Long, narrow face. ***B.*** Arachnodactyly and positive wrist sign. ***C.*** High-arched palate. ***D.*** Ectopia lentis associated with aortic aneurysm and severe aortic regurgitation in a teenage girl. See Chap. 357.

FIGURE e29-22 Ochronotic pigmentation of the femur of a 56-year-old alkaptonuric patient. *(Courtesy of Dr. H. W. Edmonds of the Washington Hospital Center, Washington, DC; with permission.)* See Chap. 358.



A ***B***

FIGURE e29-23 Clusters of dark-red to blue angiokeratomas (telangiectases) on the buttocks (***A***) and in the umbilical area (***B***) of a hemizygote with Fabry disease. See Chap. 355.



A ***B***

FIGURE e29-24 Two patients with type B Niemann-Pick disease (NPD). *A.* A 4.7-year-old patient with type B NPD. (*From DS Fredrickson, HR Sloan, in JB Stanbury et al: The Metabolic Basis of Inherited Disease, 3d ed. New York, McGraw-Hill, 1972. Used by permission.*) ***B.*** A 44-year-old patient with type B NPD. See Chap. 355.

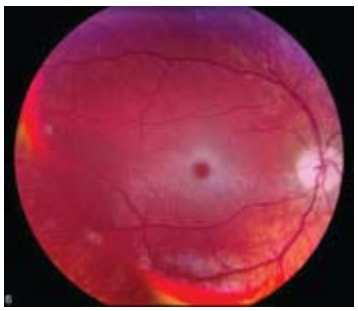


FIGURE e29-25 "Cherry red" spot in the eye of a Tay-Sachs patient. See Chap. 355. (*From http://www.nei.nih.gov/resources/eyegene.asp.*)

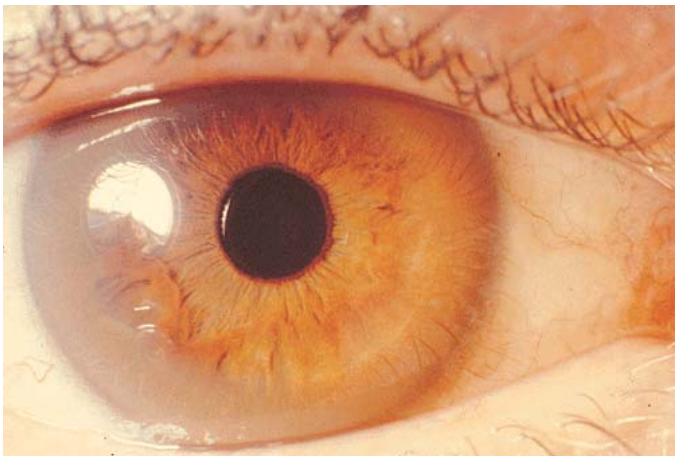


FIGURE e29-26 Kayser-Fleischer ring. This develops in Wilson's disease from copper deposition in Descemet's membrane, producing brownish discoloration of the peripheral cornea. It should not be confused with the yellow-white lipid ring of arcus senilis, which is common in the elderly and occasionally signifies hyperlipidemia, especially when it appears at a young age. See Chap. 354. (*Courtesy of Jonathan C. Horton, MD, PhD; with permission.*)

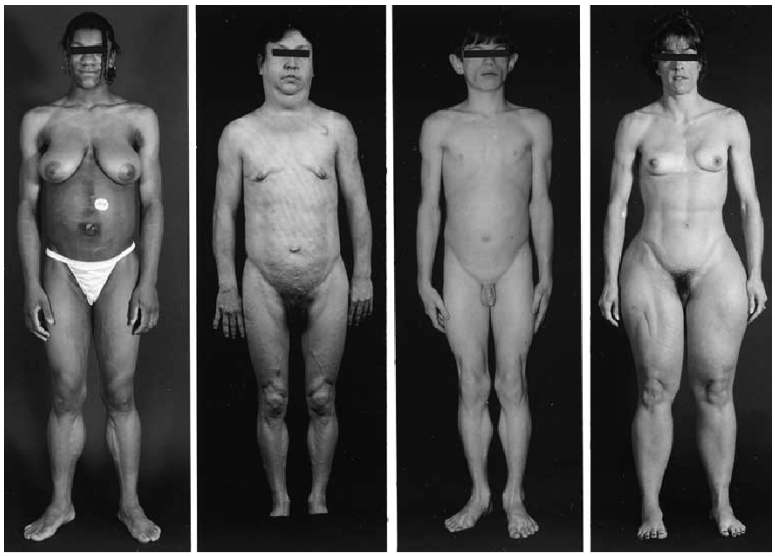


FIGURE e29-27 Anterior view of patients with different forms of lipodystrophy. *A.* Congenital generalized lipodystrophy: a 16-year-old girl with generalized loss of fat, acromegaloid features, severe acanthosis nigricans affecting axillae and abdomen, umbilical hernia. ***B.*** Familial partial lipodystrophy, Dunnigan variety: a 43-year-old woman with marked loss of subcutaneous fat from both the limbs and trunk and excess fat deposition in the face, chin, supraclavicular area, and labia majora. ***C.*** Acquired generalized lipodystrophy: a 10-year-old boy who developed generalized loss of fat that also affected the palms and soles after panniculitis at the age of 3 months. ***D.*** Acquired partial lipodystrophy: a 30-year-old woman with onset of lipodystrophy at age 14 years shows loss of fat from the face, neck, upper limbs, trunk, and anterior thighs. There is accumulation of excess fat in the hips and other regions of lower limbs. *(**A** from A Garg et al: J Clin Endocrinol Metab 84:3390, 1999; with permission. **B**, from JM Peters et al: Nat Genet 18;292, 1998; with permission.)*

SOURCES FOR FIGURES

Figures e29-1; e29-2; e29-6; e29-7; e29-11; e29-12; e29-16: K Wolff, RA Johnson, D Suurmond: *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York, McGraw-Hill, 2005. *www.accessmedicine.com*

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