symptoms, such as fatigue and bone fracture. However, these are promptly improved by vitamin C supplementation.

**F. Porphyrias**

**Outline**

Porphyria is a general term for diseases caused by deposition of intermediate products such as porphyrins in the liver or skin, as a result of congenital or acquired impairment of an enzyme essential for heme synthesis.

- It is divided into hepatogenous porphyrias and myelogenous ones.
- The main cutaneous symptom is photosensitivity accompanied by blistering.

**Classification, Pathogenesis**

Porphyrin is a general term for molecules that have a porphyrin ring, which is an intermediate metabolite synthesized in the process of heme biosynthesis from glycine and succinyl-CoA. This biosynthesis occurs in various cells, particularly in the liver and bone marrow. Metabolic enzymes such as P450 occur as

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Fig. 17.21 Metabolic pathway of porphyrin and functional enzymes (arrows).
hemeproteins in the liver and are synthesized into the heme of hemoglobin. That is, there are hepatogenous porphyrias and erythropoietic (myelogenous) porphyrias. These are subclassified by the affected enzyme (Fig. 17.21). The major subtypes are shown in Table 17.3.

Porphyrians induce cutaneous and neurological symptoms. They become activated by light energy, which produces reactive oxygen that causes cytotoxicity and results in the cutaneous symptoms of photosensitive diseases. \( \delta \)-aminolevulinic acid (\( \delta \)-ALA) passes through the blood-brain barrier and acts neurotoxically.

1. **Congenital erythropoietic porphyria (CEP)**

**Clinical features**

Congenital erythropoietic porphyria (CEP) appears shortly after birth, first as photosensitivity (blistering, pustule formation, ulceration) and later as scarring. Wine-colored urine and purplish-black feces result from excretion of intermediate products. The intermediate products deposit in erythrocytes, teeth and bones. They fluoresce red under Wood’s lamp. Hemolytic anemia causes splenomegaly.

**Pathogenesis**

Large amounts of uroporphyrin I and coproporphyrin I are produced in the hematopoietic tissue as a result of congenital absence of uroporphyrinogen III synthase (Fig. 17.21). Uroporphyrin I and coproporphyrin I deposit in the skin and hemoglobin, where they absorb light energy and destroy cellular membranes. CEP is a rare, autosomal recessively inherited disease.

2. **Erythropoietic protoporphyria (EPP)**

**Clinical features**

Mild photosensitivity, heat sensation, pain, flash, edema or urticaria manifests in children age 10 or younger. Moderate hemolytic anemia occurs. Protoporphyrin deposited in the liver is crystallized and excreted in the bile; mild liver dysfunction and gallstones are present.
**F. Porphyrias**

Pathogenesis

Erythropoietic protoporphyria (EPP) is caused by congenital abnormality in the ferrochelatase (FECH) gene, the last gene in the heme synthesis pathway. Protoporphyrin IX is not transformed into heme and deposits in the body, particularly in the erythron of the bone marrow, causing EPP (Fig. 17.21). Protoporphyrin increases in the serum, bile and feces. EPP is the second most frequent porphyria subtype after PCT (described later). It is autosomal dominantly inherited.

Diagnosis, Treatment

Differential diagnosis of EPP can be made by photosensitivity in adolescents and increased protoporphyrin in the blood and feces. Administration of β-carotene and the protection from radiation afforded by tanning are effective treatments.

3. Acute intermittent porphyria (AIP)

Acute intermittent porphyria (AIP) is induced by drugs, sex hormones and stress, for example, and the symptoms appear acutely. It is autosomal dominantly inherited and most frequently occurs in women of adolescent age or older. Reduced activity of porphobilinogen deaminase (PBGD) leads to deposition of δ-ALA and porphobilinogen, precursors of porphyrins. Cutaneous symptoms are not seen; however, neurological symptoms, peripheral nervous symptoms and abdominal symptoms are present.

4. Variegate porphyria (VP)

Variegate porphyria (VP) is autosomal dominantly inherited hepatic porphyria caused by abnormality in protoporphyrinogen oxidase. It is clinically similar to PCT (described later), and the symptoms are less severe than those of hereditary coproporphyria.

5. Porphyria cutanea tarda (PCT)

Clinical features

Blistering is caused by injury and sun exposure on the face and dorsal hands during the spring and summer. It resolves with moderate scarring, atrophy and pigmentation; the course recurs (Fig. 17.22). Reddening of urine from excretion of uroporphyrin, abdominal symptoms resembling those of AIP, hypertrichosis of the face, and liver dysfunction may occur.

Pathogenesis

Uroporphrinogen decarboxylase activity decreases. Intermediate products such as uroporphyrin deposit in the liver and skin (Fig. 17.21). The condition is induced by chronic alcohol consumption, hepatitis, hepatocellular carcinoma, hemodialysis, or drugs such as estrogen, hexachlorobenzene, iron preparations or...
sulfonylurea drugs. Familial cases have been reported; these are autosomal dominantly inherited. Men in their middle ages and older and those who have habitually drunk alcohol for a long period of time are most commonly affected.

Pathology
Subcutaneous blistering is found. Endothelial cells are injured. PAS-positive substances are detected in the peripheral blood vessels.

Laboratory findings
Red fluorescence of porphyrins is observed by liver biopsy. There are elevated levels of uroporphyrins in the urine.

Treatment
Abstinence from alcohol consumption, shading from light, phlebotomy (300 ml to 500 ml of blood drawn over the course of 2 to 3 weeks), administration of an iron chelating agent, liver support therapy, and oral sodium hydrogen carbonate are effective.

G. Skin manifestations associated with diabetes

Various cutaneous lesions are induced by diabetes.

1. Diabetic gangrene

Gangrene occurs on the toes, soles, and fingers. It is associated with underlying diseases such as microangiopathy and arterial sclerosis. External factors such as injury, burn or secondary infection induce ulceration. Sharply circumscribed necrotic foci occur secondarily to ulceration, and these become intractable (Fig. 17.23). Circulatory stimulants, antibiotics, and surgical treatments including débridement, ablation and revascularization are conducted in combination with treatments for diabetes. Arteriosclerosis obliterans in the main artery is surgically treated.

2. Diabetic scleredema

Scleredema occurs in the nuchal region (Fig. 17.24). Although it is clinically similar to scleredema adulatorum, acute infection does not occur in diabetic scleredema as a prodrome nor is there spontaneous healing.

3. Diabetic xanthoma

Eruptive xanthoma occurs commonly on the extensor surfaces of the extremities and buttocks. When hyperlipemia is resolved by diabetic treatment such as administration of insulin, xanthoma also subsides.