Disorders of porphyrin metabolism. Icterus

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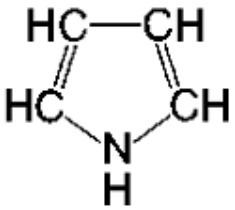
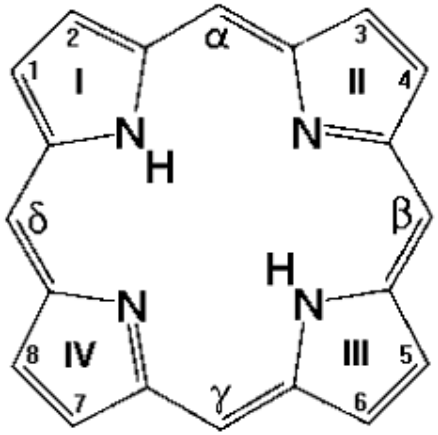
Porphyrins are macrocyclic tetrapyrroles containing a conjugated system of double bonds



pyrrole



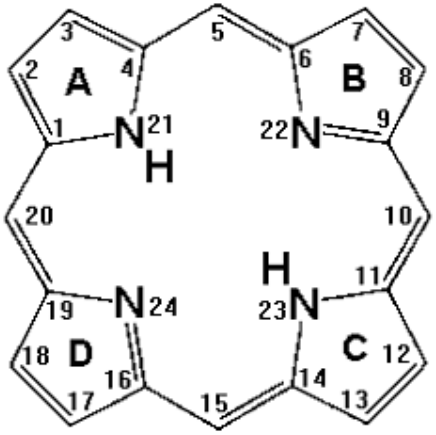
Fischer numbering (old) of porphin

pyrrole rings
I = A
II = B
III = C
IV = D

methenyl bridges
α = 5
β = 10
γ = 15
δ = 20

substituent positions

1 = 2	5 = 12
2 = 3	6 = 13
3 = 7	7 = 17
4 = 8	8 = 18



New numbering of porphin

Examples of some important human and animal hemoproteins.

Protein	Function
Hemoglobin	Transport of oxygen in blood
Myoglobin	Storage of oxygen in muscle
Cytochrome *c*	Involvement in electron transport chain
Cytochrome P450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrrolase	Oxidation of trypotophan

Heme biosynthesis

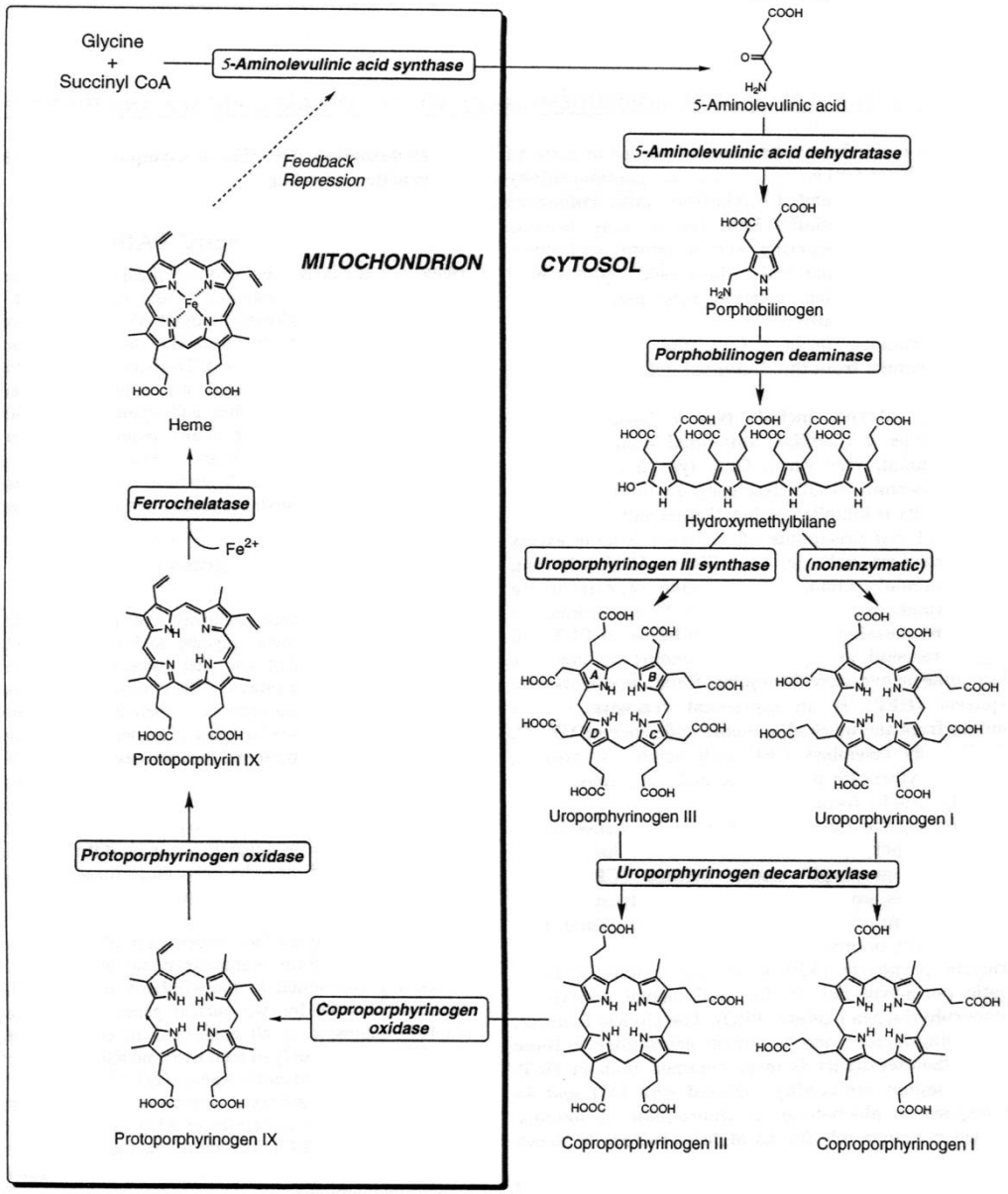


Fig. 124-1 The heme biosynthetic pathway. The pathway consists of eight enzymes, four localized in mitochondria and four in the cytosol. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are metabolized to heme. Heme is exported from mitochondria for incorporation into cellular hemoproteins and, particularly in liver, exerts feedback regulation on 5-aminolevulinic acid synthase.

Table 124-2 Human Heme Biosynthesis Enzymes and Genes

Enzyme	Gene symbol	Chromosomal location	cDNA (bp) protein (aa)	Genome	
				Size (kb)	Organization*
5-Aminolevulinate synthase:					
Housekeeping	*ALAS1*	3p21.1	2199 bp/640 aa	17 kb	11 exons
Erythroid-specific	*ALAS2*	Xp11.21	1937 bp/587 aa	22 kb	11 exons
5-Aminolevulinate dehydratase:	*ALAD*	9q34			13 exons
Housekeeping			1149 bp/330 aa	15.9 kb	Exons 1A + 2–12
Erythroid-specific			1154 bp/330 aa		Exons 1B + 2–12
Porphobilinogen deaminase:	*PBGD*	11q23.3		11 kb	15 exons
Housekeeping			1086 bp/361 aa		Exons 1 + 3–15
Erythroid-specific			1035 bp/344 aa		Exons 2–15
Uroporphyrinogen III synthase:	*UROS*	10q25.2 → q26.3		34 kb	10 exons
Housekeeping			1296 bp/265 aa		Exons 1 + 2B–10
Erythroid-specific			1216 bp/265 aa		Exons 2A + 2B–10
Uroporphyrinogen decarboxylase	*UROD*	1p34	1104 bp/367 aa	3 kb	10 exons
Corproporphyrinogen oxidase	*CPO*	3q12	1062 bp/354 aa	14 kb	7 exons
Protoporphyrinogen oxidase	*PPO*	1q23	1431 bp/477 aa	5.5 kb	13 exons
Ferrochelatase	*FECH*	18q21.3	1269 bp/423 aa	45 kb	11 exons

*Number of exons and those encoding housekeeping and erythroid-specific forms.

Feedback regulation of expression of 5-aminolevulinate synthase 1 (ALAS1) in non-erythroid cells

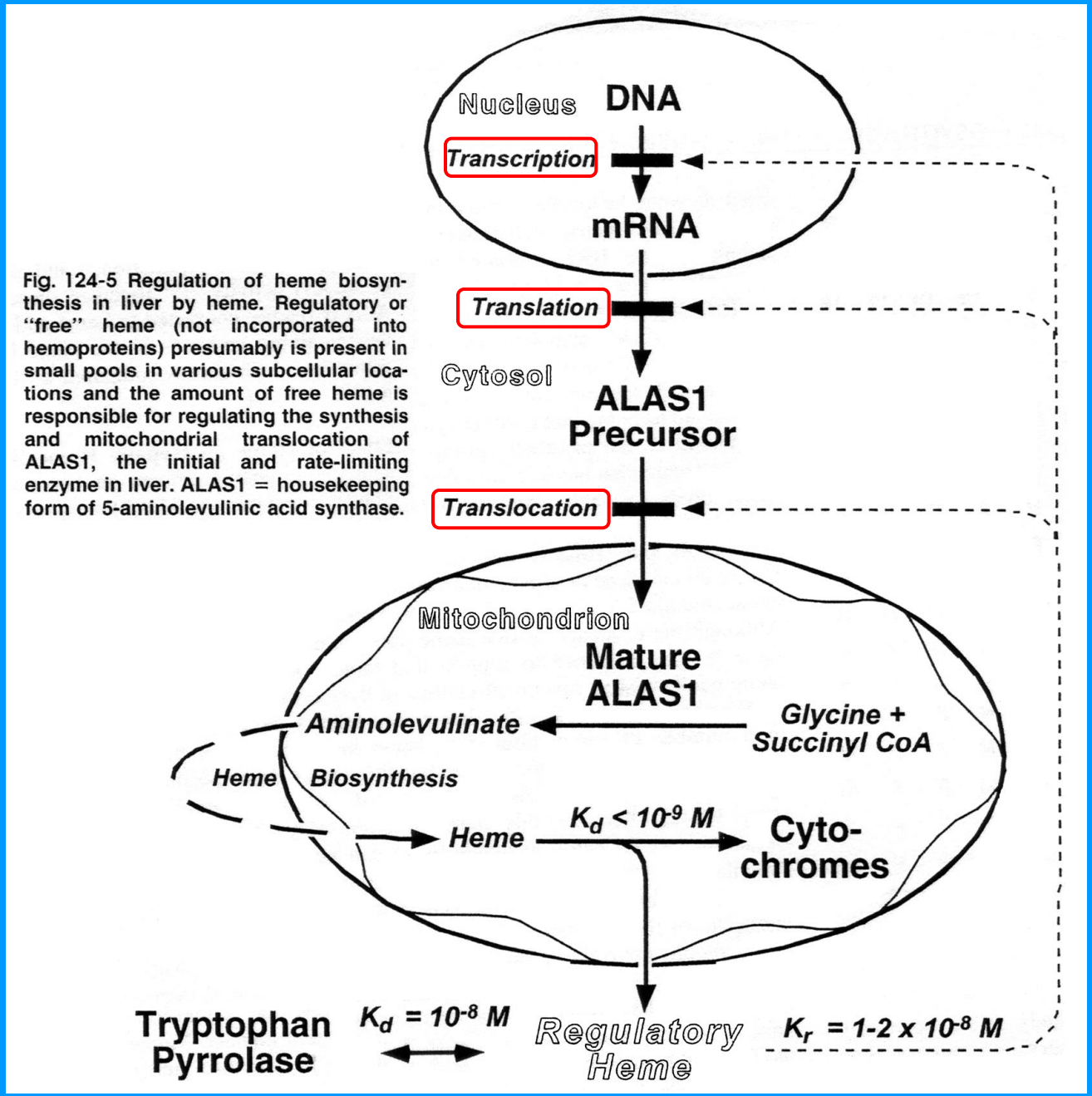


Fig. 124-5 Regulation of heme biosynthesis in liver by heme. Regulatory or "free" heme (not incorporated into hemoproteins) presumably is present in small pools in various subcellular locations and the amount of free heme is responsible for regulating the synthesis and mitochondrial translocation of ALAS1, the initial and rate-limiting enzyme in liver. ALAS1 = housekeeping form of 5-aminolevulinic acid synthase.

Classification of the Human Porphyrias Associated with Deficiencies of Specific Enzymes of the Heme Biosynthetic Pathway

Porphyria	Deficient enzyme	Enzyme activity (% normal)	Classification (Course)	Inheritance†	Principal symptomatology	Biochemical Findings*		
						Erythrocytes	Urine	Stool
5-Aminolevulinate dehydratase-deficient porphyria (ADP)	5-Aminolevulinate dehydratase (ALAD)	2	Hepatic‡ (Acute)	AR	Neurovisceral	Zn-protoporphyrin	ALA, coproporphyrin	
Acute intermittent porphyria(AIP)	Porphobilinogen deaminase (PBGD)	50	Hepatic (Acute)	AD	Neurovisceral		ALA, PBG, uroporphyrin	
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase (UROS)	<15	Erythropoietic (Chronic)	AR	Cutaneous photosensitivity	Uroporphyrin I; coproporphyrin I	Uroporphyrin I; Coproporphyrin I	Coproporphyrin I§
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase (UROD)	50	Hepatic (Chronic)	AD¶	Cutaneous photosensitivity		Uroporphyrin, Heptacarboxyl-porphyrin	Isocoproporphyrin
Hepatoerythropoietic porphyria (HEP)	Uroporphyrinogen decarboxylase (UROD)	<25	Hepatic‡ (Chronic)	AR	Cutaneous photosensitivity	Zn-protoporphrin	Uroporphyrin, Heptacarboxyl-porphyrin	Isocoproporphyrin
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase (CPO)	50	Hepatic (Acute)	AD	Neurovisceral & occasional cutaneous photosensitivity		ALA, PBG, coproporphyrin	
Variegate porphyria (VP)	Protoporphyrinogen oxidase (PPO)	50	Hepatic (Acute)	AD	Neurovisceral & cutaneous photosensitivity		ALA, PBG, coproporphyrin	Coproporphyrin; protoporphyrin
Erythropoietic protoporphyria (EPP)	Ferrochelatase	30	Erythropoietic (Chronic)	AD	Cutaneous photosensitivity	Free protoporphyrin		Protoporphyrin

*Only major increases are listed.
†AR = Autosomal recessive; AD = Autosomal dominant.
‡These porphyrias also have erythropoietic features including increased erythrocyte porphyrins.
§Type Isomers; ALA = 5′-aminolevulinic acid; PBG = porphobilinogen.
¶Inherited deficiency of UROD is partially responsible for familial (type II) PCT.

Mutations of human heme biosynthesis enzyme genes causing porphyrias

Mutations of human heme biosynthesis enzyme genes causing porphyrias

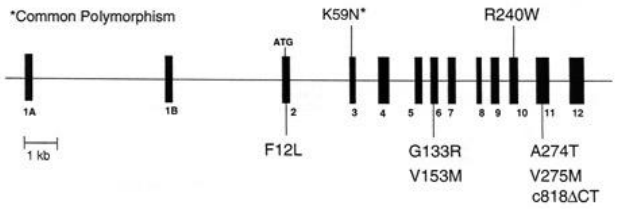


Fig. 124-12 The human *ALAD* gene and locations of mutations causing ADP. (*Courtesy of Dr. K. H. Astrin.*)

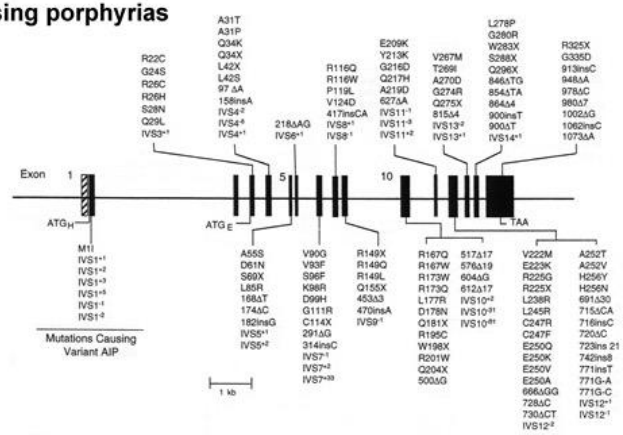


Fig. 124-17 The human *PBGD* gene, with locations of some of the many mutations causing AIP. (*Courtesy of Dr. K. H. Astrin.*)

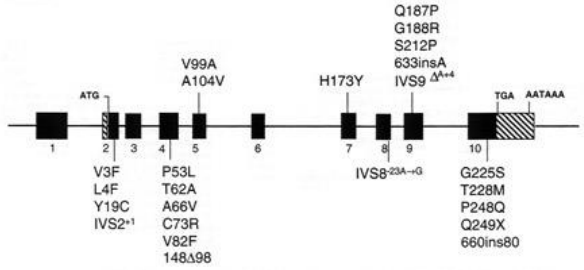


Fig. 124-19 The human *UROS* gene and locations of mutations causing CEP. (*Courtesy of Dr. K. H. Astrin.*)

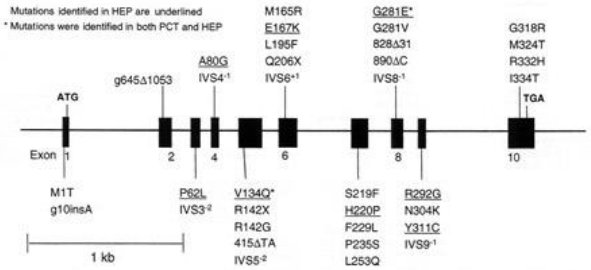


Fig. 124-23 The human *UROD* gene and locations of mutations causing familial (type 2) PCT and HEP. (*Courtesy of Dr. K. H. Astrin.*)

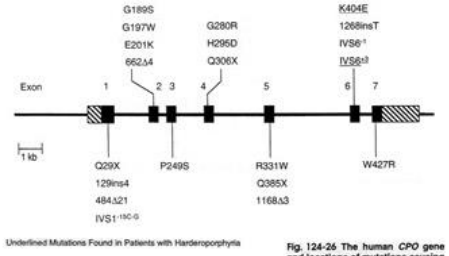


Fig. 124-26 The human *CPO* gene and locations of mutations causing HCP. (*Courtesy of Dr. K. H. Astrin.*)

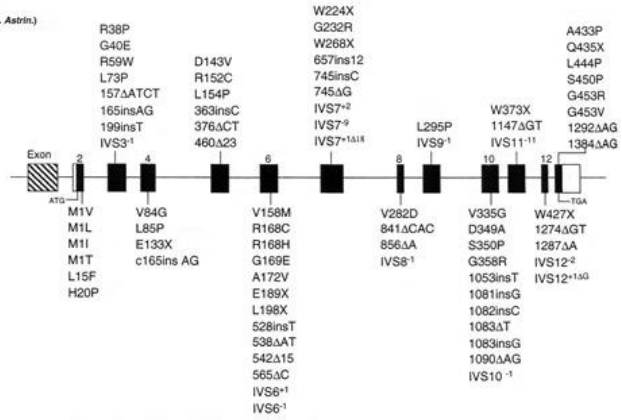


Fig. 124-27 The human *PPO* gene showing locations of mutations causing VP. (*Courtesy of Dr. K. H. Astrin.*)

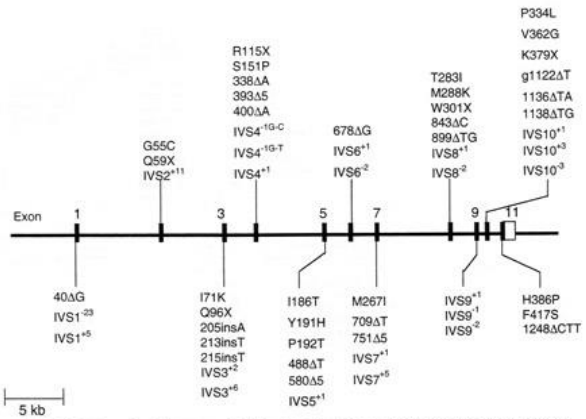


Fig. 124-29 The human ferrochelatase gene showing locations of mutations causing EPP. (*Courtesy of Dr. K. H. Astrin.*)

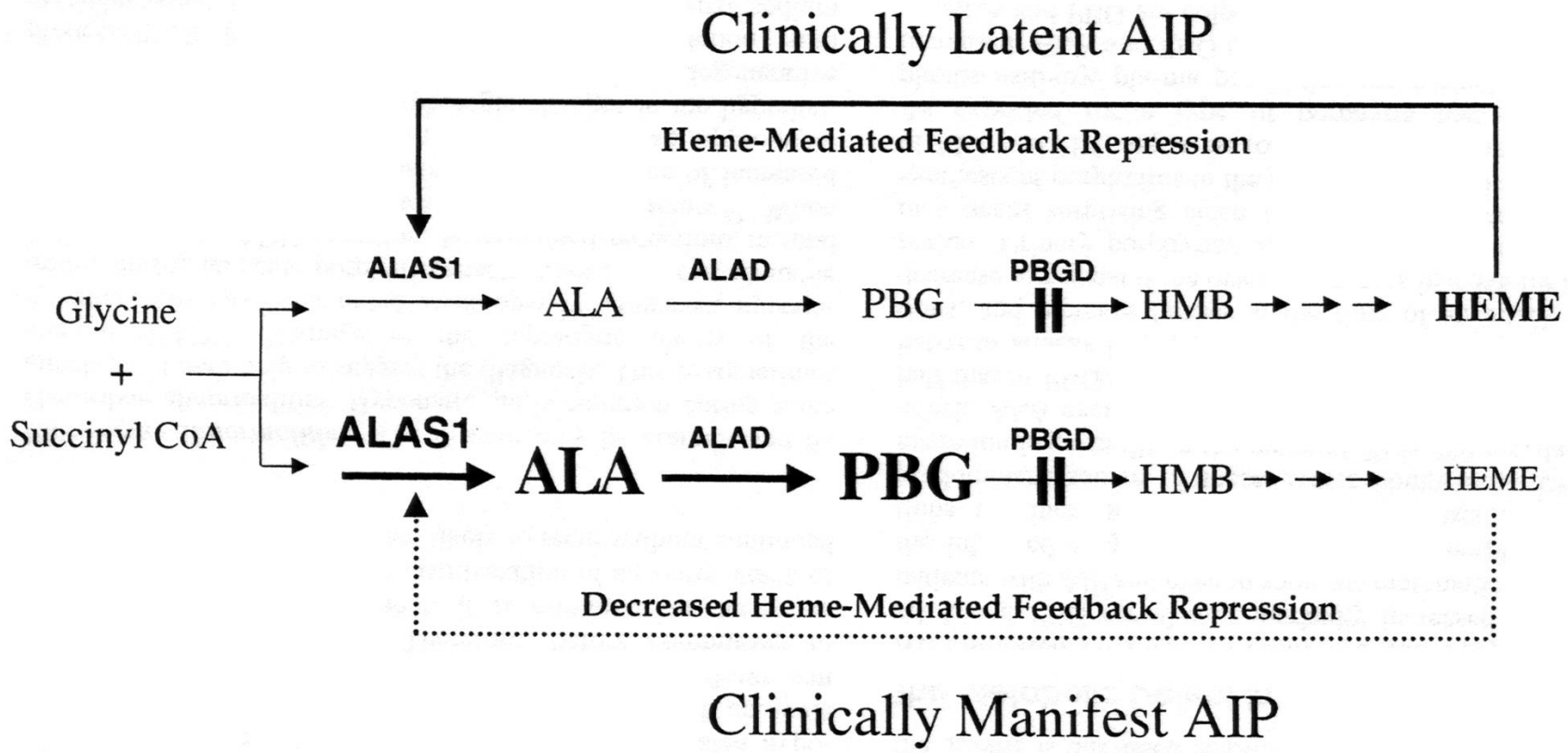


Fig. 124-13 Enzymatic block in AIP and loss of heme-mediated repression of hepatic ALAS1 when the disease is made clinically manifest by precipitating factors such as drugs, steroids, and dietary alterations. In the presence of PBGD deficiency, factors that stimulate heme synthesis result in decreased availability of heme for the regulatory heme pool in hepatocytes. ALA 5-aminolevulinic acid; ALAD = 5-aminolevulinic acid dehydratase; ALAS1 = ALA synthase, housekeeping form; HMB = hydroxymethylbilane; PBG = porphobilinogen; PBGD = porphobilinogen deaminase.

Table 124-4 Categories of Safe and Unsafe Drugs in the Acute Porphyrias*

Unsafe	Potentially Unsafe		Probably Safe	Safe
ACE inhibitors (especially enalapril)[380,383]	Alfadolone acetate[985,986]	Mifepristone (RU-486)[999,1000]	Adrenaline[383]	Acetaminophen (paracetamol)[383,968]
Antipyrine (phenazone)[383,967,968]	Alfaxolone[985,986]	Methyldopa[383,971]	Azathioprine[988,993]	Acetazolamide[383,386]
Aminopyrine (amidopyrine)[383,967,968]	Alkylating agents [cyclophosphamide, ifosfamide, busulphan, altretamine (hexamethylmelamine); dacarbazine, chlorambucil, and melphalan may be safer)][388,967,981,987,988]	Metyrapone[969]	Chloramphenicol[968,969]	Allopurinol[383,386]
Aminoglutethimide[383,969]		Nalidixic acid[383]	Cisapride[383]	Amiloride[383,386]
Barbiturates[248,254,256,383,968]		Nikethamide[383,967,969,970]	Colchicine[233,383]	Aspirin[383,968]
N-Butylscopolammonium bromide[383]		Nitrazepam[383,991]	Cytarabine[987]	Atropine[383,968]
Calcium channel blockers (especially nifedipine)[380–382,384]		Nitrofurantoin[279,383]	Chloroquine[233,383]	Bethanidine[383,384]
Carbamazepine[383,467]	Altretamine (hexamethylmelamine, see alkylating agents)	Nortriptyline (see tricyclic antidepressants)	Digoxin[383]	Bromides[466,974]
Carisoprodol[383]	Amitriptyline (see tricyclic antidepressants)	Pentazocine[380,383,971,986,1001]	Daunorubicin[987]	Bumetanide[386]
Chlorpropamide[383,967,970–972]	Benzodiazepines[383,989,990]	Phenoxybenzamine[39]	Doxazosin[384]	Chloral hydrate[39,255,383]
Danazol[475,476]	Busulphan (see alkylating agents)	Procarbazine[988]	Estrogens (natural/endogenous)[370,469,1006,1007]	Cimetidine[459]
Dapsone[383,973]	Captopril (see ACE inhibitors)	Pyrazinamide[967,1002]	Ibuprofen[383]	Corticosteroids[279,383]
Diclofenac[383]	Cephalosporins[383]	Spironolactone[39,383]	Indomethacin[383]	Coumarins[383]
Enalapril (see ACE inhibitors)	Chlorambucil (see alkylating agents)	Theophylline[383,967]	Labetalol[383]	Fluoxetine[383,386,387]
Diphenylhydantion[256,466,467,974]	Chlordiazepoxide[968,969,991]	Tiagabine[468]	Lithium[383]	Gabapentin[468]
Ethosuximide (see succinimides)	Clonidine[15,992]	Tramadol[380]	Losartan[380]	Gentamycin[383]
Ergot preparations[383,971]	Cyclophosphamide (see alkylating agents)	Tricyclic antidepressants[383,386,967,968,1003]	Methenamine[279]	Guanethidine[39,279,384]
Ethchlorvynol[967]	Cyclosporin[383,993]	Troglitazone[1004,1005]	Methylphenidate[383,969]	Insulin[383,967]
Ethinamate[970]	Diazepam[968,969,991]		Naproxen[383]	Narcotic analgesics[39,383]
Felbamate[468]	Diltiazem (see calcium channel blockers)		Neostigmine[279,383]	Ofloxacin[383]
Glutethimide[279,969,971]	Colistin[383]		Nitrous oxide[279,383]	Penicillin and derivatives[279,383,967]
Griseofulvin[49,975]	Dacarbazine (see alkylating agents)		Penicillamine[383]	Phenothiazines[39,383]
Ketoconazole[383]	Diphenhydramine[383,969]		Procaine[383]	Propranolol[279,1008]
Lamotrigine[468,976]	EDTA (see iron chelators)		Propanidid[279,383]	Streptomycin[279,383]
Mephenytoin[383,969,977]	Etomidate[383,986,994]		Propofol[383]	Succinylcholine[383,967]
Metoclopramide[368,369,978]	Estrogens (synthetic)[474,995]		Propoxyphene[279,383]	Tetracycline[279]
Meprobamate[39,383,969]	Erythromycin[383]		Rauwolfia alkaloids[279]	
Methyprylon[39,383,969]	5-Fluorouracil[988]		6-Thioguanine[987]	
Nefazadone[387]	Gold compounds (see heavy metals)		Thiouracils[383]	
Nifedipine (see calcium channel blockers)	Fluroxene[996,997]		Thyroxine[383]	
Novobiocin[383]	Heavy metals[383,967,971,998]		Tubocurarine[383]	
Phenylbutazone[34,383,967,968]	Hydralazine[39,383]		Vigabatrin[468]	
Primidone[383]	Hyoscine[383]		Vitamin B[279]	
Pargyline[39,383,969]	Ifosfamide (see alkylating agents)		Vitamin C[279]	
Progesterone & progestins[370,979]	Imipramine (see tricyclic antidepressants)			
Rifampin[383,980,981]	Iron chelators (DFO, EDTA)			
Succinimides[383,969]	Ketamine[383,390]			
Sulfasalazine[982]	Lisinopril (see ACE inhibitors)			
Sulfonamide antibiotics[256,383]	Mefenamic acid[383]			
Sulfonmethane (Sulfonal) & sulfonethylmethane(Trional)[983]	Melphalan (see alkylating agents)			
Sulfonylureas[383,970]				
Trimethadione[383,969,977]				
Valproic acid[466,984]				
Tranylcypromine[969]				

*Drugs (generic names) are listed in four categories, depending upon the weight of evidence as to their safety. There is considerable evidence for classification of drugs in the Safe and Unsafe categories, but much less evidence, or conflicting evidence, for drugs in the other two categories. This list is not comprehensive and does not reflect all information and opinions about drug safety in acute porphyrias. Some references cited may reflect conflicting opinions rather than supporting the classifications shown here.

Further information is available at the American Porphyria Foundation's Web site: www.enterprise.net.apf

Heme catabolism and hepatocellular bilirubin transport

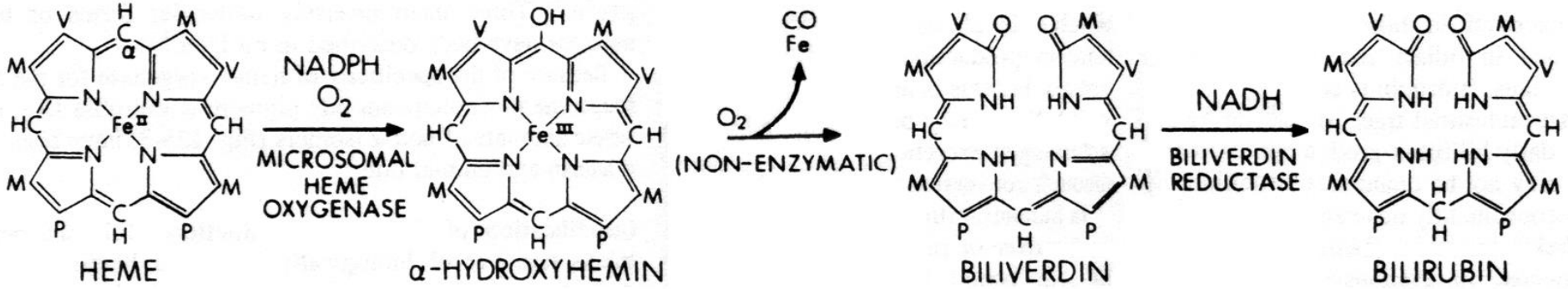


Fig. 125-2 Mechanism of heme ring opening and subsequent reduction of biliverdin to bilirubin.

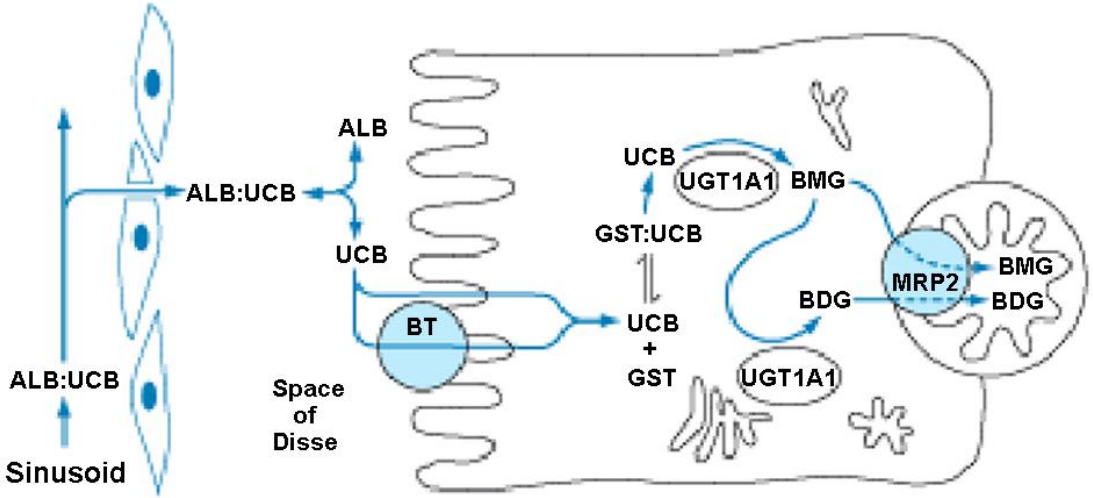
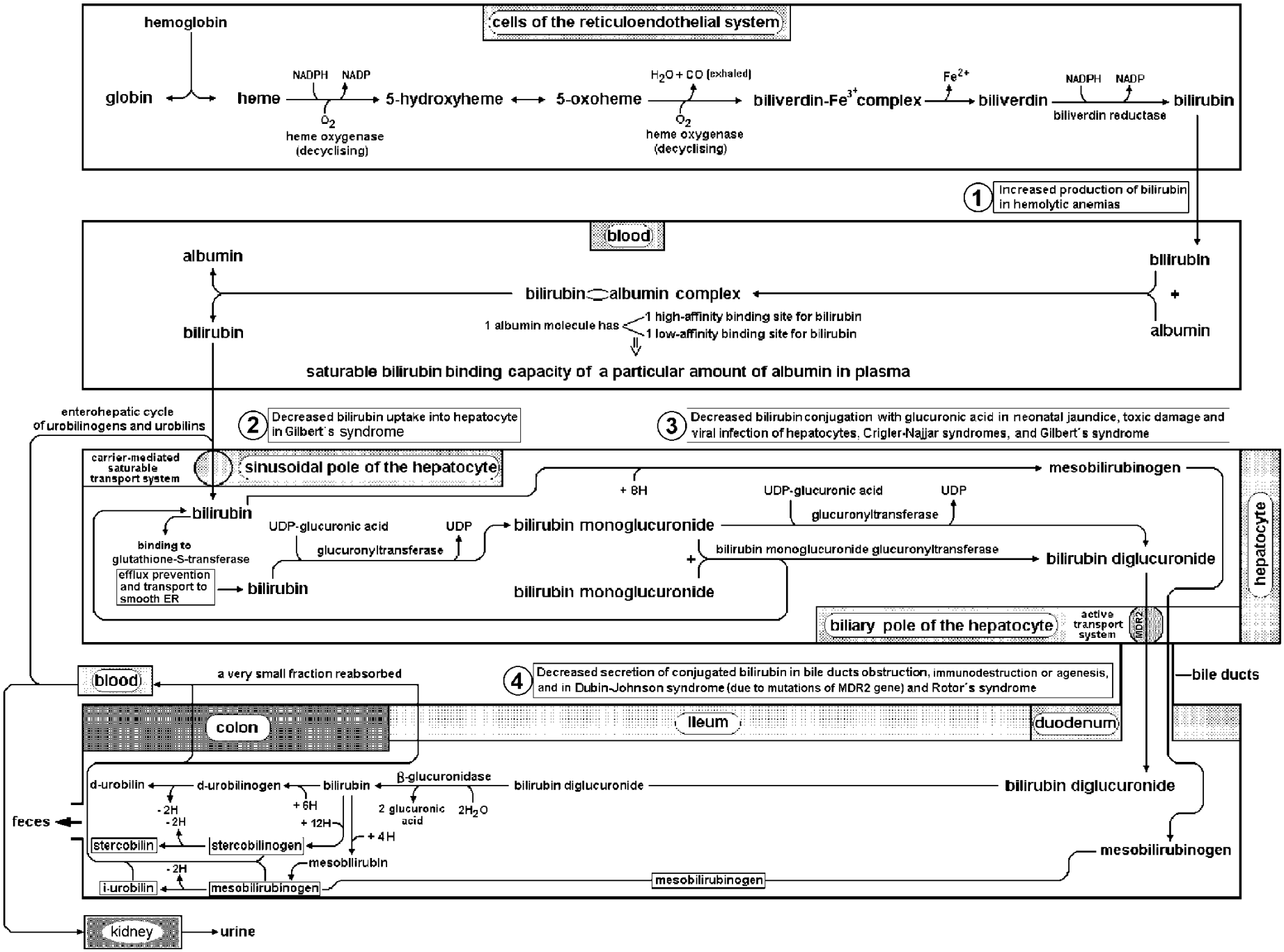


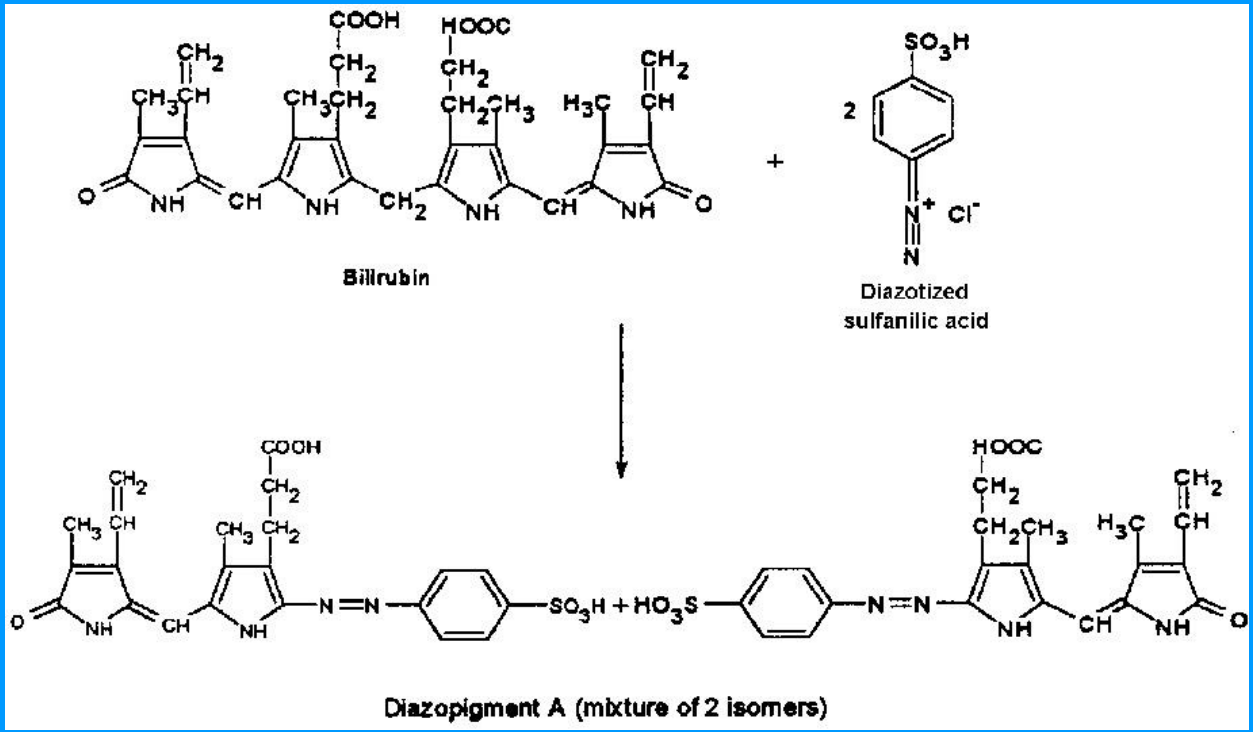
Figure 294-1. Hepatocellular bilirubin transport. Albumin-bound bilirubin in sinusoidal blood passes through endothelial cell fenestrae to reach the hepatocyte surface, entering the cell by both facilitated and simple diffusional processes. Within the cell it is bound to glutathione-S-transferases and conjugated by bilirubin-UDP-glucuronosyltransferase (UGT1A1) to mono- and diglucuronides, which are actively transported across the canalicular membrane into the bile. ALB, albumin; UCB, unconjugated bilirubin, UGT1A1, bilirubin-UDP-glucuronosyltransferase; BMG, bilirubin monoglucuronide; GST, glutathione-S-transferase; MRP2, multidrug resistance-associated protein 2; BDG, bilirubin diglucuronide; BT, proposed bilirubin transporter.

Summary of heme catabolism, bile pigments metabolism and hyperbilirubiemias



Determination of bilirubin as azo dye by the van den Bergh method

Direct-reacting bilirubin	Indirect-reacting bilirubin
Bilirubin esters (mainly bilirubin monoglucuronide and bilirubin diglucuronide)	Nonesterified bilirubin (mainly bilirubin–albumin and bilirubin–phospholipid–albumin complexes) (a) By denaturation with methanol (b) By displacement with acetate, benzoate, caffeine, diphylline



Interpretation of values of nonesterified plasma bilirubin (indirect-reacting fraction)

Bilirubin concentration μmol/L	Bilirubin clearance of liver	Bilirubin production rate
< 17	Usually normal	Usually normal
17-60	Normal or reduced	Increased or normal
> 60	Usually reduced	Increased or normal

Factors affecting the serum concentration of nonesterified bilirubin

Increase	Decrease*
Fasting◇ Physical activity Pregnancy Estrogens, oral contraceptives Alcoholic beverages Sepsis	Ultraviolet rays Cortisol Sulfonamides Phenobarbital

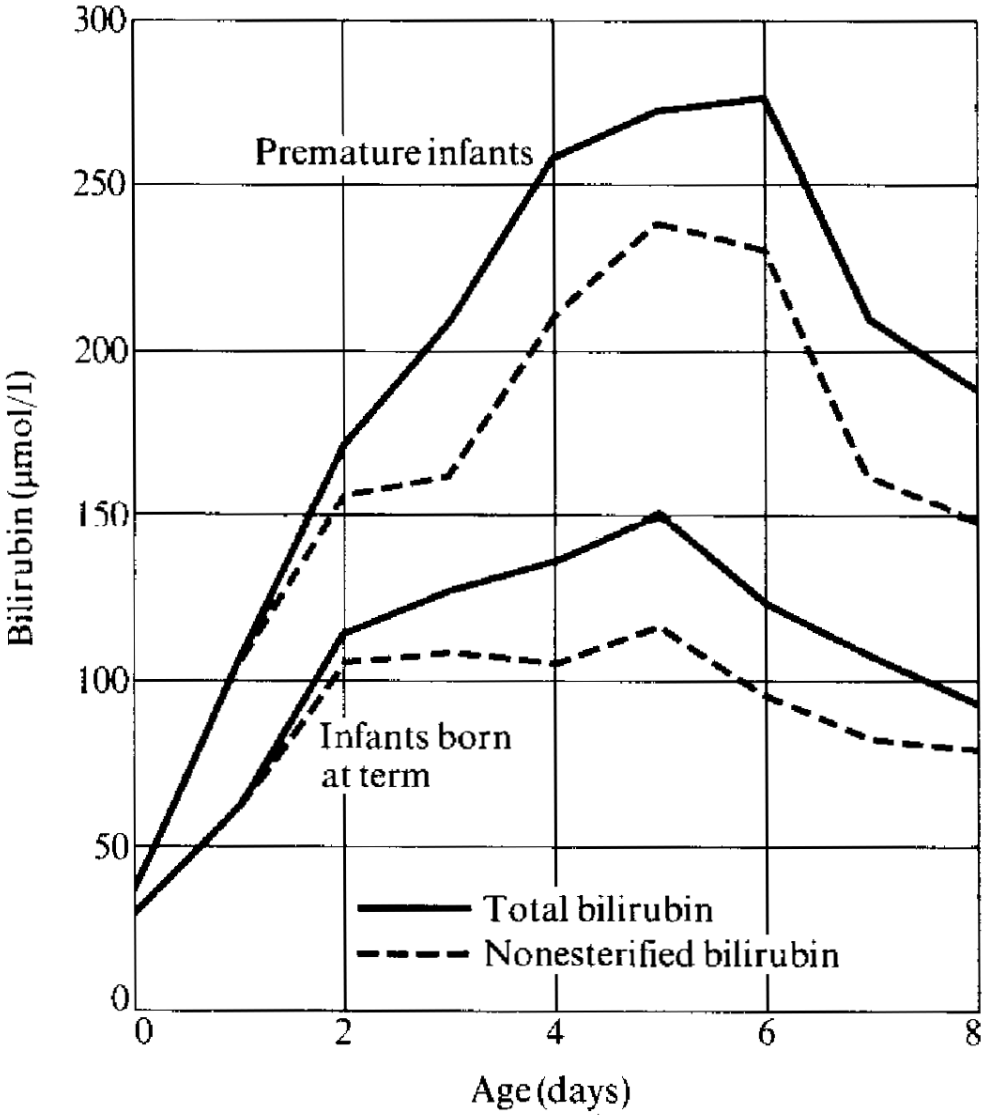
*Either through migration into tissue (creating hazard of kernicterus in the newborn, e.g. after administration of sulfonamides), or through intensification of bilirubin metabolism in the liver (e.g. due to phenobarbital).

◇ Particularly in Gilbert's syndrome.

Results of laboratory investigation in healthy individuals and patients with three different causes of jaundice

Condition	Bilirubin in serum	Urobilinogen in urine	Bilirubin in urine	Urobilinogen in stool
Health	3 - 20 μmol/l (from this total bilirubin 95% is represented by non-esterified bilirubin)	0 - 4 mg/24 h	Absent	40 - 280 mg/24 h
Hemolytic anemia	Non-esterified is increased**	Increased	Absent	Increased
Bile ducts obstruction	Esterified is increased***	Absent	Present	Traces or absent
Acute viral hepatitis	Both esterified and non-esterified are increased	Increased in the pre-icteric phase Decreased or absent in the icteric phase (if microobstruction of bile canaliculi had occured)	Present (if microobstruction of bile canaliculi had occured)	Decreased or traces

Physiologic neonatal jaundice



Total bilirubin and nonesterified bilirubin in serum of 10 infants born at term and 23 premature infants.

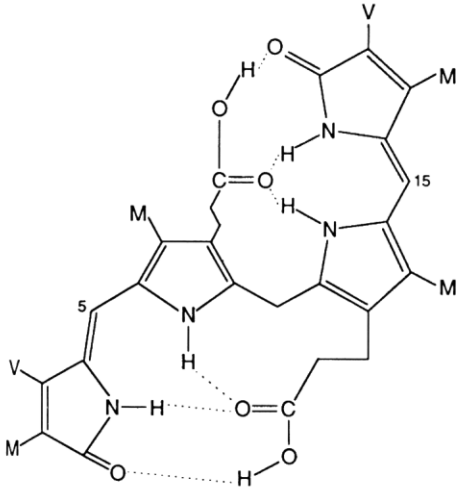


FIGURE 29-12
Conformation of bilirubin showing involuted hydrogen bonded-structure between NH/O and OH/O groups. Despite the presence of polar carboxyl groups, bilirubin is nonpolar and lipophilic. Disruption of hydrogen bonds by glucuronidation or by conversion of bilirubin to configurational or structural isomers yields water-soluble pigments.

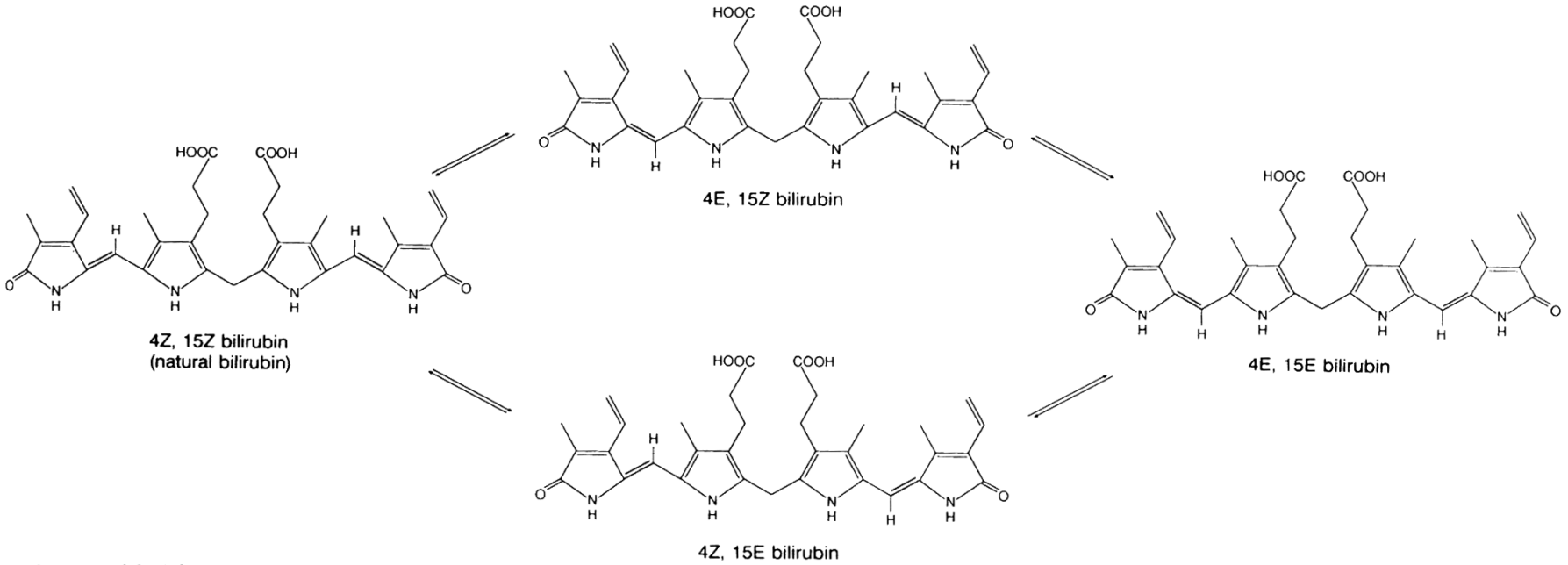


FIGURE 29-14
Photoisomers of bilirubin. The presence of two methene bridges containing double bonds (colored areas) gives rise to configurational (geometrical) isomers of bilirubin. Each double bond can exist in the Z or E configuration. The naturally occurring, most stable, water-insoluble form is the Z, Z isomer. It undergoes photoisomerization to configurational isomers (Z, E; E, Z; and E, E), which are more polar owing to inability to form intramolecular hydrogen bonds and are excretable from the liver without glucuronidation. Some excretion of photoisomers in urine also occurs.

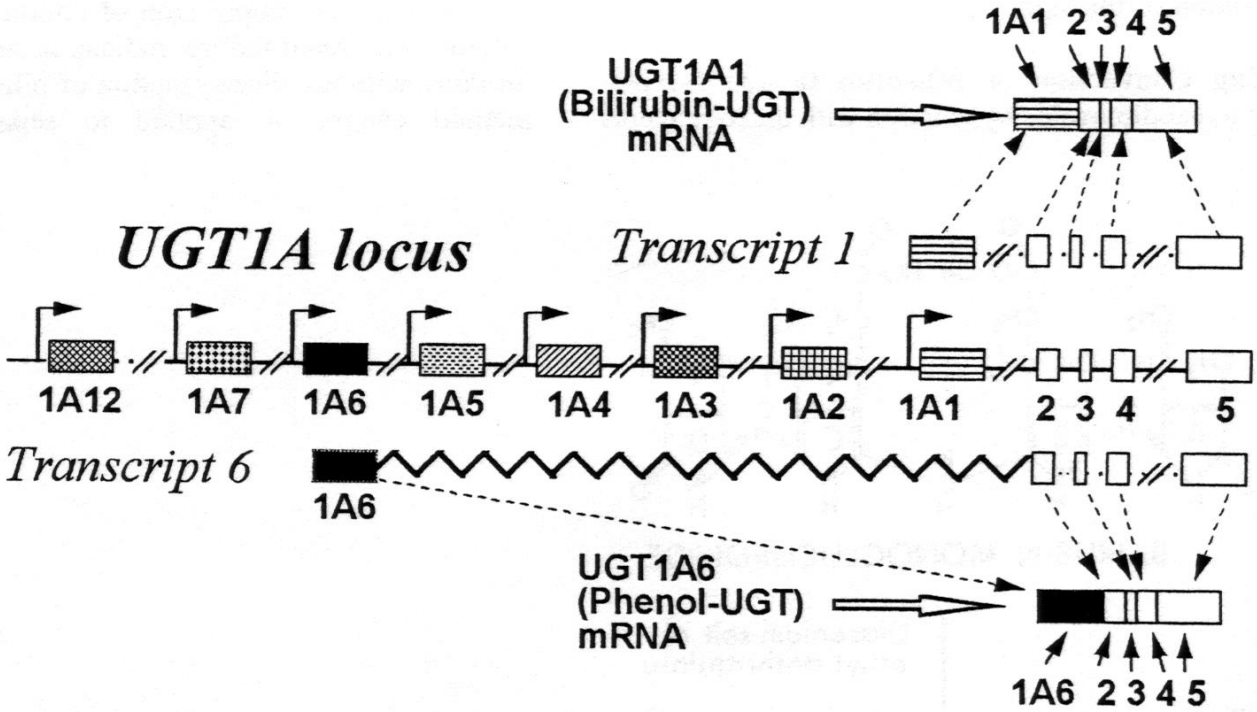


Fig. 125-10 Schematic representation of the human *UGT1A* locus, located at 2q37. This locus contains multiple genes that express bilirubin-UGT and several other UGT isoforms. Exons 2, 3, 4, and 5, located at the 3′ end of *UGT1A*, encode the identical C-terminal domains of all UGT isoforms expressed from this locus. Upstream to these common region exons are a series of unique exons (exons 1A1 through 1A12), each of which encodes the variable N-terminal domain of a different UGT isoform expressed from this locus. Each unique region exon is preceded by a separate promoter region (shown by arrows), permitting independent regulation of gene expression. Transcription can start from any of the promoters, producing transcripts of varying lengths. The unique exon located at the 5′ end of the transcript is spliced to the 3′ end of exon 2, and other unique region exons present in the transcript are spliced out. Thus, based on differential promoter usage, several mRNAs, each encoding a different member of the UGT1A subfamily, are generated. Genes belonging to this locus are named according the unique exon used in the expressed mRNA. Thus, when the transcription starts 5′ to exon 1A1 (transcript 1 in the figure), the mRNA encoding bilirubin-UGT is generated. This gene, which consists of exon 1A1 plus the common region exons 2 to 5, is termed *UGT1A1*, and the expressed enzyme is termed UGT1A1. If, on the other hand, the transcription starts 5′ to exon 1A6 (Transcript 6 in the figure), an mRNA consisting of exon 1A6 plus exons 2 to 5 is generated. This mRNA encodes a UGT isoform that accepts simple phenolic substrates, but not bilirubin. According to the current system of terminology, this gene is named *UGT1A6*, and the expressed isoform is termed UGT1A6.

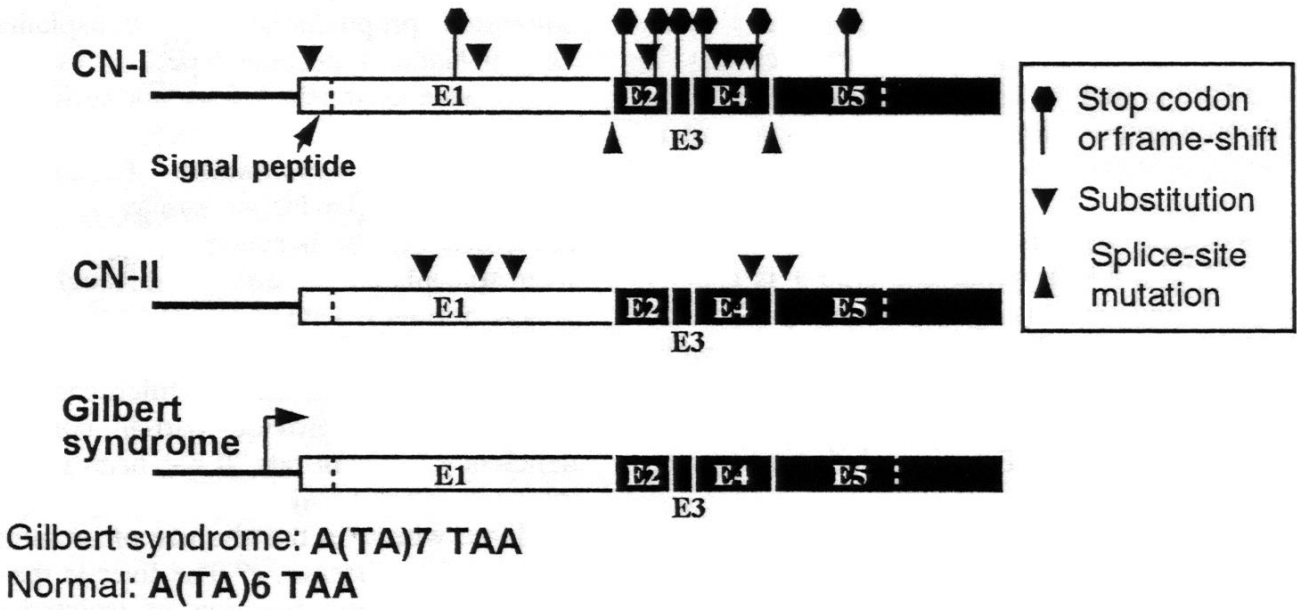


Fig. 125-16 Genetic lesions causing Crigler-Najjar syndrome type I, Crigler-Najjar syndrome type II, and Gilbert syndrome. Crigler-Najjar syndrome type I is produced by mutations, deletions, or insertions within the five exons that constitute the UGT1A1 mRNA. These genetic lesions may cause premature stop codons or substitution of a single amino acid. In two cases, there were mutations in the splice donor sequences on intron 1 and splice acceptor region of intron 4, respectively, resulting in the utilization of cryptic splice sites within exons, with consequent deletion of a segment of an exon from the mRNA. Crigler-Najjar syndrome type II is also caused by genetic lesions within the coding region of *UGT1A1*. In these cases, however, the mutations result in single amino acid substitutions that reduce the catalytic activity of the enzyme, but does not abolish it. In contrast to the two types of Crigler-Najjar syndrome, Gilbert syndrome is associated with a variant TATAA box, which contains two extra nucleotides, TA. This results in reduced expression of structurally normal UGT1A1.

Table 294-1. Principal Differential Characteristics of Gilbert's and Crigler-Najjar Syndromes

Feature	Crigler-Najjar Syndrome		Gilbert's Syndrome
	Type I	Type II	
Total serum bilirubin, μmol/L	310-755 (usually >345)	100-430 (usually ≤345)	Typically ≤70 μmol/L in absence of fasting or hemolysis
Routine liver tests	Normal	Normal	Normal
Response to phenobarbital	None	Decreases bilirubin by >25%	Decreases bilirubin to normal
Kernicterus	Usual	Rare	No
Hepatic histology	Normal	Normal	Usually normal; increased lipofuscin pigment in some
Bile characteristics			
Color:	Pale or colorless	Pigmented	Normal dark color
Bilirubin fractions:	>90% unconjugated	Largest fraction (mean:57%) monoconjugates	Mainly diconjugates but monoconjugates increased (mean 23%)
Bilirubin UDP-glucuronosyl-transferase activity	Typically absent; traces in some patients.	Markedly reduced: 0 to 10% of normal	Reduced: typically 10-33% of normal
Inheritance (all autosomal)	Recessive	Predominantly recessive	Promoter mutation: recessive Missense mutations: 7 of 8 dominant; 1 reportedly recessive