Clinical problems associated with heme metabolism are of two types. Disorders that arise from defects in the enzymes of heme biosynthesis are termed the **porphyrias** and cause elevations in the serum and urine content of intermediates in heme synthesis. Inherited disorders in bilirubin metabolism lead to **hyperbilirubinemia** .

Hyperbilirubinemias

Bilirubin levels are measured in the serum by an assay utilizing Ehrlich diazo reagent and results in the formation of an azobilirubin product. Conjugated bilirubin does not require addition of alcohol to promote the azotization reaction and thus, this is referred to as measurement of **direct bilirubin**. The reaction with unconjugated bilirubin requires the addition of alcohol and thus is referred to as the measurement of **indirect bilirubin**. Normal bilirubin measurements are 0.3–1.2md/dL for total (indirect + direct). Direct type bilirubin does not exist in the plasma, however, a small portion of indirect type bilirubin may present as direct reacting type and thus the serum measurement may show a direct bilirubin but this is never above 0.3mg/dL in a normal individual.

Excess circulation and accumulation of bilirubin (hyperbilirubinemia) results in a yellow-orange discoloration of the tissues and is most easily visible as icteric (yellowish) discoloration in the sclera of the eyes. Bilirubin toxicity (bilirubin encephalopathy) can be life threatening in neonates. Bilirubin encephalopathy is characterized by yellow discoloration of the basal ganglia in babies with intense jaundice and was first described over a century ago and the term "kernicterus" was coined to describe these physical changes. Any increase in plasma bilirubin above 20mg/dL is considered dangerous in neonates. However, individual differences in bilirubin sensitivity can result in kernicterus at lower bilirubin levels. Kernicterus occurs in infants with severe unconjugated hyperbilirubinemia and in young adults with high serum levels of unconjugated bilirubin. The latter is the result of inherited deficiencies in the enzyme responsible for bilirubin conjugation to glucuronic acid, bilirubin UDP glucuronosyltransferase (bilirubin-UGT).

Bilirubin has been shown to inhibit DNA synthesis, uncouple oxidative phosphorylation, and inhibit ATPase activity in brain mitochondria. Bilirubin also inhibits a variety of different classes of enzymes including dehydrogenases, electron transport proteins, hydrolyases, and enzymes of RNA synthesis, protein synthesis and carbohydrate metabolism. All of these toxic effects of bilirubin are reversed by binding to albumin. In fact, albumin plays a vital role in the disposition of bilirubin in the body by keeping the compound in solution and transporting it from its sites of production (primarily bone marrow and spleen) to its site of excretion which is the liver.

Several inherited disorders in bilirubin metabolism have been identified. **Gilbert syndrome and the Crigler-Najjar syndromes** result from predominantly unconjugated hyperbilirubinemia. **Dubin-Johnson syndrome and Rotor syndrome** result from conjugated hyperbilirubinemia. Once conjugated to glucuronate, bilirubin is water soluble, therefore, conjugated hyperbilirubinemias are less severe in their symptomology than are the unconjugated hyperbilirubinemias.

Porphyrias

The porphyrias are both inherited and acquired disorders in heme synthesis. These disorders are classified as either erythroid or hepatic, depending upon the principal site of expression of the enzyme defect. Eight different porphyrias have been classified encompassing defects in each of the enzymes of heme synthesis. Defects in the function of hepatic uroporhyrinogen decarboxylase (UROD) result in type I porphyria cutanea tarda (PCT I), whereas mutations in the UROD gene result in type II PCT (PCT II). PCT is the most commonly occurring type of porphyria. It should be noted that no porphyria has been identified resulting from defects in the house-keeping form of ALAS (ALAS1). The most commonly occurring hepatic porphyria is acute intermittent porphyria, AIP, which is caused by a defect in porphobilinogen deaminase, (PBG deaminase). This enzyme is also called hydroxymethylbilane synthase (official gene symbol: HMBS) or also but rarely, uroporphyrinogen I synthase.

All of the porphyrias lead to excretion of heme biosynthetic by products that turn the urine red and when deposited in the teeth turn them reddish brown. Accumulation of these byproducts in the skin renders it extremely sensitive to sunlight causing ulceration and disfiguring scars. Increased hair growth (hypertrichosis) is also a symptom of the porphyrias leading to appearance of fine hairs over the entire face and on the extremities. This latter symptom lends to the description of "werewolf syndrome" in many porphyria patients.

In many cases the treatment protocols for the intermittent attacks of the various porphyrias, in particular in the case of acute intermittent porphyria, include the use of hemin or hematin and glucose supplementation. Hemin is a form of iron protophorphyrin IX in which the associated iron has an additional chloride ligand. Hematin is similar except that instead of a chloride ion there is an hydroxide ion liganded to the iron. The rationale for the use of these agents is that they act as analogs of heme and strongly inhibit the activity of ALAS resulting in reductions in the heme biosynthetic intermediates that precipitate the porphyria attack. The use of glucose to treat porphyrias was a serendipitous observation but for a long time the mechanism by which glucose infusion alleviated the symptoms of a porphyria attack were not understood. Quite often there is an association between fasting, low serum glucose, and the precipitation of an acute porphyria attack which suggested the utility of glucose infusion. The molecular mechanism was ascertained when it was found the the transcription factor, PGC-1α, is activated in the liver in respone to hypoglycemia. Indeed, activation of PGC-1α is required to initiate hepatic gluconeogenesis via the activation of several genes in this metabolic pathway. In addiiton to gluconeogenic genes, the ALAS1 gene is activated in the liver via PGC-1α. Thus, hypoglycemia leads to increased ALAS1 activity and results in accumulation of heme intermediates that result in the precipitation of the attack.

The Porphyrias

Porphyria	Enzyme Defect - Gene	Primary Symptoms - Comments
Erythroid Class		
X-linked sideroblastic anemia, XLSA	δ-aminolevulinic acid synthase 2: ALAS2	microcytic hypochromic anemia; erythroblast present with sidersomes; wide variability in age of presentation; progressive iron accumulation, fatal if not treated
Congenital erythropoietic porphyria, CEP (Gunther disease)	uroporphyrinogen III synthase: UROS	photosensitivity evidenced by blistering on the back of the hands and other sun-exposed areas of skin, skin friability after minor trauma, facial hypertrichosis (excessive hair growth), skin hyperpigmentation, reddish disocoloration of the teeth (erythrodontia); mild to severe hemolytic anemia; wide variability in phenotypic presentation from fetal lethality to late onset
Erythropoietic protoporphyria, EPP	ferrochelatase: FECH	hypersensitivity to sunlight and fluorescent lighting resulting in burning and itching sensations in skin, severe blistering and scarring
Hepatic Class		
ALA dehydratase deficient porphyria, ADP	ALA dehydratase (also called porphobilinogen synthase): ALAD	neurovisceral symptoms that are very similar to those experienced by acute intermittent porphyria patients
Acute intermittent porphyria, AIP	PBG deaminase (also called hydroxymethylbilane synthase or rarely uroporphyrinogen I synthase): HMBS	neurovisceral symptoms including severe abdominal pain, nausea, vomiting, tachycardia, hypertension, anxiety, depression, convulsions, peripheral neuropathy; chronic complications include hepatocellular carcinoma

		(HCC) and renal failure
Hereditary coproporphyria, HCP	coproporphyrinogen III oxidase: CPOX	neurovisceral symptoms similar to those experienced by acute intermittent porphyria patients; seizures; peripheral neuropathy with ascending paralysis; some photosensitivity
Variegate porphyria, VP	protoporphyrinogen IX oxidase: PPOX	neurovisceral symptoms and photosensitivity; most commonly adult-onset; cutaneous blistering skin on photoexposed surfaces; crusty slowly healing skin lesions; occasional facial hypertrichosis (excessive hair growth) and hyperpigmentation; abdominal pain; constipation; back, chest, and extremity pain; anxiety; seizures; peripheral neuropathy associated with progressive muscle weakness that may progress to respiratory paralysis
Porphyria cutanea tarda type I, PCT type I, also called the sporadic type PCT	hepatic uroporphyrinogen decarboxylase activity	photosensitivity; referred to as the sporadic type of PCT; associated with reduced UROD activity in liver; not associated with direct mutations in the UROD gene; most likely due to multifactorial causes
Porphyria cutanea tarda type II, PCT type II, also called the familial type PCT, may also be referred to as hepatoerythropoietic porphyria, HEP	uroporphyrinogen decarboxylase in non-hepatic tissues: UROD	photosensitivity evidenced by blistering on the back of the hands and other sun-exposed areas of skin, skin friability after minor trauma, facial hypertrichosis (excessive hair growth), skin hyperpigmentation, severe thickening of affected skin areas (pseudoscleroderma)

Differential Diagnosis: Microcytic Anemias

Deficiency/Defect	Characteristics
B_6 Deficiency	Pyridoxal phosphate (PLP) required for the rate-limiting enzyme in heme biosynthesis: δ-aminolevulinic acid synthase (ALAS); deficiency results in loss of protoporphyrin IX synthesis, therefore, there will be a significant **reduction** in measurable ALAS product (δ-aminolevulinic acid, δ-ALA) and protoporphyrin in these patients; loss of heme production leads to hypochromic microcytic anemia; lack of protoporphyrin results in iron deposits on mitochondria in bone marrow erythroblasts resulting in the formation of **ringed sideroblasts**; loss of iron incorporation into protoporphyrin IX leads to **increased** serum and intracellular iron concentration; increase in intracellular iron results in **increased** translation of ferritin as a means to prevent iron toxicity
Iron Deficiency	iron deficiency is the leading cause of microcytic anemia; loss of iron results in reduced production of heme, thus, the result is a hypochromic microcytic anemia; lack of heme production results in loss of feed-back inhibition of ALAS, therefore these patients will have an associated **increase** in measurable protoporphyrin; loss of iron intake means **reduced** iron in the serum and reduced intracellular iron, the latter resulting in **reduced** ferritin translation; loss of iron for incorporation into protoporphyrin IX results in spontaneous, non-enzymatic incorporation of Zn^{2+} forming **Zn-protoporphyrin (ZPP)**, ZPP causes erythrocytes to fluoresce under ultraviolet illumination and is the basis of the ZPP test for iron deficiency or lead poisoning
Heavy Metal Poisoning	heavy metals, such as lead, inhibit several enzymes of heme biosynthesis and metabolism with the most significant toxic effects resulting from inhibition of ferrochelatase, the enzyme that incorporates iron into protoporphyrin IX generating heme; similar to B_6 deficiency, lead poisoning leads to **increased** intracellular iron in bone marrow erythroblasts causing the formation of **ringed sideroblasts**; because there is no heme, the ALAS reaction is not inhibited, as in the case of iron deficiency, this results in **increased** production of δ-ALA and protoporphyrin; lack of iron incorporation into protoporphyrin results in **increased** serum and intracellular iron concentrations, with the latter leading to **increased** ferritin synthesis as in the case of iron-deficient anemia; loss of iron for incorporation into protoporphyrin IX results in spontaneous, non-enzymatic incorporation of

	Zn^{2+} forming **ZPP** as in the case of iron-deficient anemia the ZPP test is diagnostic for lead poisoning

Disorders in Bilirubin Metabolism

Gilbert syndrome is an autosomal recessive disorder that belongs to a family of disorders that result as a consequence of defects in the metabolism and/or excretion of bilirubin. Bilirubin is the by-product of the catabolism of heme. Normal disposition of bilirubin involves its transport to the liver where it is conjugated to the sugar molecule, glucuronic acid. This conjugation reaction converts bilirubin to a water soluble compound that can be easily excreted in the feces. The conjugation of bilirubin to glucuronate is catalyzed by the enzyme bilirubin-UDP-glucuronosyltransferase (bilirubin-UGT).

The human genome contains a complex locus on chromosome 2q37 that encodes several UDP-glucuronosyltransferase genes. This locus is referred to as the UDP-glucuronosyltransferase 1 family, polypeptide A complex locus (UGT1A). Several UGT1A enzymes, including bilirubin-UGT (identified as UGT1A1), are encoded by the UGT1A gene complex. The 5' region of the UGT1A complex contains 13 tandemly arrayed first exons, including 4 pseudo exons. These tandemly arrayed exons are identified as 1A1, 1A2, 1A3, etc. Exons 2, 3, 4, and 5 are located in the UGT1A 3' region. All UGT isoforms contain the same C-terminal domain encoded by exons 2 through 5. Each first exon has its own promoter element. The 9 viable first exons are independently spliced to the common exons 2 through 5 to generate 9 UGT1A transcripts with unique 5' ends and identical 3' ends. The N-terminal region encoded by each unique first exon determines acceptor substrate specificity, while the 246-amino acid C-terminal region encoded by the 4 common exons specifies interactions with the common donor substrate, UDP-glucuronic acid. The bilirubin-UGT isoform (UGT1A1) consists of 533 amino acids. The majority of patients with Gilbert syndrome inherit the disorder in an autosomal recessive manner. These individuals acquire the disorder as a result of mutations in the TATA-box of the promoter region upstream of exon 1 in the UGT1A1 gene which results in reduced levels of expression of a normal bilirubin-UGT enzyme. The normal sequence of the UGT1A TATA-box is $A(TA)_6TAA$ whereas in Gilbert syndrome individuals it is $A(TA)_7TAA$. This mutation is referred to as the UGT1A1*28 mutation. A small percentage of Gilbert syndrome individuals, particularly individuals of Asian heritage, inherited the disorder as an autosomal dominant trait. In these latter individuals the mutation in the UGT1A1 gene is a missense mutation that results in reduced levels of active bilirubin-UGT since the one normal allele is not capable of producing sufficient enzyme. Both types of UGT1A1 mutation found in Gilbert syndrome do not lead to the severity of reduced bilirubin-UGT activity seen in Crigler-Najjar syndromes.

Clinical Consequences of Hyperbilirubinemia

Excess circulation and accumulation of bilirubin (hyperbilirubinemia) results in a yellow-orange discoloration of the tissues and is most easily visible as icteric (yellowish) discoloration in the sclera of the eyes. Bilirubin toxicity (bilirubin encephalopathy) can be life threatening in neonates. Bilirubin encephalopathy is

characterized by yellow discoloration of the basal ganglia in babies with intense jaundice and was first described over a century ago and the term "kernicterus" was coined to describe these physical changes. Any increase in plasma bilirubin above 20mg/dL is considered dangerous in neonates. However, individual differences in bilirubin sensitivity can result in kernicterus at lower bilirubin levels. Kernicterus occurs in infants with severe unconjugated hyperbilirubinemia and in young adults with high serum levels of unconjugated bilirubin, with the latter the result of inherited deficiencies in bilirubin-UGT.

Bilirubin has been shown to inhibit DNA synthesis, uncouple oxidative phosphorylation, and inhibit ATPase activity in brain mitochondria. Bilirubin also inhibits a variety of different classes of enzymes including dehydrogenases, electron transport proteins, hydrolases, and enzymes of RNA synthesis, protein synthesis and carbohydrate metabolism. All of these toxic effects of bilirubin are reversed by binding to albumin. In fact, albumin plays a vital role in the disposition of bilirubin in the body by keeping the compound in solution and transporting it from its sites of production (primarily bone marrow and spleen) to its site of excretion which is the liver.

Bilirubin levels are measured in the serum by an assay utilizing Ehrlich diazo reagent and results in the formation of an azobilirubin product. Conjugated bilirubin does not require addition of alcohol to promote the azotization reaction and thus, this is referred to as measurement of **direct bilirubin**. The reaction with unconjugated bilirubin requires the addition of alcohol and thus is referred to as the measurement of **indirect bilirubin**. Normal bilirubin measurements are 0.3–1.2md/dL for total (indirect + direct). Direct type bilirubin does not exist in the plasma, however, a small portion of indirect type bilirubin may present as direct reacting type and thus the serum measurement may show a direct bilirubin but this is never above 0.3mg/dL in a normal individual.

Clinical Features of Gilbert Syndrome

Gilbert syndrome is also referred to as constitutional hepatic dysfunction and familial nonhemolytic jaundice. The syndrome is characterized by mild chronic, unconjugated hyperbilirubinemia. Almost all afflicted individuals have a degree of icteric discoloration in the eyes typical of jaundice. Serum bilirubin levels in Gilbert syndrome patients is usually less than 3mg/dL. Many patients manifest with fatigue and abdominal discomfort, symptoms that are ascribed to anxiety, but are not due to bilirubin metabolism. Expression of the Gilbert phenotype requires a relatively high level of bilirubin production. This is evident from the fact that persons homozygous for the UGT1A TATA-box mutation do not exhibit hyperbilirubinemia. Presentation of Gilbert syndrome symptoms also occurs more frequently in men than in women because the production of bilirubin in higher in males.

Introduction to Crigler-Najjar Syndromes

The Crigler-Najjar syndromes (CNS) belong to a family of disorders that result as a consequence of defects in the metabolism and/or excretion of bilirubin. Bilirubin is the by-product of the catabolism of heme. Normal disposition of bilirubin involves its transport to the liver where it is conjugated to the sugar molecule,

glucuronic acid. This conjugation reaction converts bilirubin to a water soluble compound that can be easily excreted in the feces. The conjugation of bilirubin to glucuronate is catalyzed by the enzyme bilirubin-UDP-glucuronosyltransferase (bilirubin-UGT). There are two forms of Crigler-Najjar syndrome: type I results from mutations in the bilirubin-UGT gene that result in complete loss of enzyme activity, whereas, type II is the result of mutations that cause incomplete loss of enzyme activity. The Crigler-Najjar syndromes are inherited as autosomal recessive disorders.

The human genome contains a complex locus on chromosome 2q37 that encodes several UDP-glucuronosyltransferase genes. This locus is referred to as the UDP-glucuronosyltransferase 1 family, polypeptide A complex locus (UGT1A). Several UGT1A enzymes, including bilirubin-UGT (identified as UGT1A1), are encoded by the UGT1A gene complex. The 5' region of the UGT1A complex contains 13 tandemly arrayed first exons, including 4 pseudo exons. These tandemly arrayed exons are identified as 1A1, 1A2, 1A3, etc. Exons 2, 3, 4, and 5 are located in the UGT1A 3' region. All UGT isoforms contain the same C-terminal domain encoded by exons 2 through 5. Each first exon has its own promoter element. The 9 viable first exons are independently spliced to the common exons 2 through 5 to generate 9 UGT1A transcripts with unique 5' ends and identical 3' ends. The N-terminal region encoded by each unique first exon determines acceptor substrate specificity, while the 246-amino acid C-terminal region encoded by the 4 common exons specifies interactions with the common donor substrate, UDP-glucuronic acid. The bilirubin-UGT isoform (UGT1A1) consists of 533 amino acids. Mutations in UGT1A resulting in type I Crigler-Najjar syndrome include deletions, insertions, missense mutations and premature stop codons in any of the 5 exons encoding the UGT1A1 mRNA. In type II Crigler-Najjar, mutation in one allele always results in a single amino acid substitution resulting in reduced but not eliminated activity.

Clinical Consequences of Hyperbilirubinemia

Excess circulation and accumulation of bilirubin (hyperbilirubinemia) results in a yellow-orange discoloration of the tissues and is most easily visible as icteric (yellowish) discoloration in the sclera of the eyes. Bilirubin toxicity (bilirubin encephalopathy) can be life threatening in neonates. Bilirubin encephalopathy is characterized by yellow discoloration of the basal ganglia in babies with intense jaundice and was first described over a century ago and the term "kernicterus" was coined to describe these physical changes. Any increase in plasma bilirubin above 20mg/dL is considered dangerous in neonates. However, individual differences in bilirubin sensitivity can result in kernicterus at lower bilirubin levels. Kernicterus occurs in infants with severe unconjugated hyperbilirubinemia and in young adults with high serum levels of unconjugated bilirubin, with the latter the result of inherited deficiencies in bilirubin-UGT.

Bilirubin has been shown to inhibit DNA synthesis, uncouple oxidative phosphorylation, and inhibit ATPase activity in brain mitochondria. Bilirubin also inhibits a variety of different classes of enzymes including dehydrogenases, electron transport proteins, hydrolases, and enzymes of RNA synthesis, protein synthesis and carbohydrate metabolism. All of these toxic effects

of bilirubin are reversed by binding to albumin. In fact, albumin plays a vital role in the disposition of bilirubin in the body by keeping the compound in solution and transporting it from its sites of production (primarily bone marrow and spleen) to its site of excretion which is the liver.

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Clinical Features of Crigler-Najjar Syndromes

Type I: In patients with very high levels of unconjugated bilirubin, but with normal liver function tests, Crigler-Najjar syndrome type I is indicated. Almost all afflicted infants manifest with severe nonhemolytic icterus within the first few days of life. The jaundice in these patients is characterized by increased concentrations of indirect-reacting bilirubin in the plasma.

The advent of phototherapy has allowed for greater survival in type I patients, in fact without this therapy infants will succumb to kernicterus by the age of 15 months. Use of phototherapy and intermittent plasmapheresis has allowed many type I infants to survive until puberty without significant brain damage. The risk for kernicterus persists following puberty, however, because phototherapy is less effective at this age. Liver transplantation is considered the only definitive treatment for type I Crigler-Najjar syndrome.

Type II: The clinical manifestations of type II disease are similar to those of type I except that serum bilirubin levels are much lower, generally below 20mg/dL. The prognosis for type II patients is also much better than for type I patients. Induction of bilirubin-UGT by drugs such as phenobarbitol can lead to reductions in serum bilirubin levels in type II patients. Given that type I Crigler-Najjar results from complete loss of functional bilirubin-UGT it is not surprising that phenobarbitol has no effect in those patients. Type II Crigler-Najar syndrome was first described by I.M. Arias and thus, this form of the disease is also sometimes referred to as Arias syndrome.

Introduction to Dubin-Johnson Syndrome

Dubin-Johnson syndrome is an autosomal recessive disorder that belongs to a family of disorders that result as a consequence of defects in the metabolism and/or excretion of bilirubin. This disease is inherited as an autosomal recessive disorder. Bilirubin is the by-product of the catabolism of heme. Normal disposition of bilirubin involves its transport to the liver where it is conjugated to the sugar molecule, glucuronic acid. This conjugation reaction converts bilirubin to a water soluble compound that can be easily excreted in the feces. The conjugation of bilirubin to glucuronate is catalyzed by the enzyme bilirubin-UDP-

glucuronosyltransferase (bilirubin-UGT). Dubin-Johnson syndrome results from mutations in the gene encoding the bile canalicular multispecific organic anion transporter. This transporter is involved in the excretion of many non-bile organic anions by an ATP-requiring process.

The canalicular multispecific organic anion transporter (CMOAT) is encoded by the ABCC2 gene which is a member of the ATP-binding cassette family of transporter encoding genes. The CMOAT protein has also been called the multidrug resistance-associated protein 2 gene (MRP2). The ABCC2 gene is located on chromosome 10q24.2 spanning more than 200 kb and is comprised of 34 exons that encode a 1545 amino acid protein. Most of the mutations in the ABCC2 gene resulting in Dubin-Johnson syndrome are found in the exons encoding the cytoplasmic portion of the protein. This is the region that contains the ATP-binding cassettes.

Clinical Consequences of Hyperbilirubinemia

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Clinical Features of Dubin-Johnson Syndrome

Dubin-Johnson syndrome is inherited as an autosomal recessive disorder characterized by mild, predominantly conjugated hyperbilirubinemia. The defect causing Dubin-Johnson syndrome leads to an abnormality in porphyrin metabolism such that more than 80% of the urinary compound from this pathway is coproporphyrin I, whereas in a normal individual it is usually less than 35%. Due to impaired transport of epinephrine metabolites to the bile canaliculi melanin-like pigments accumulate in the liver such that there is a characteristic black appearance to the organ but with normal histology. Jaundice is usually the only physical symptom detected in this disease. Most patients remain asymptomatic although some complain of weakness and abdominal pains. Only occasionally do patients develop hepatosplenomegaly. In many cases individuals with the disorder remain undiagnosed due to lack of obvious signs and symptoms. Women may exhibit overt symptoms for the first time when taking oral contraceptives or when pregnant.

Introduction to Rotor Syndrome

Rotor syndrome is an autosomal recessive condition that belongs to a family of disorders that result as a consequence of defects in the metabolism and/or excretion of bilirubin. Bilirubin is the by-product of the catabolism of heme. Normal disposition of bilirubin involves its transport to the liver where it is conjugated to the sugar molecule, glucuronic acid. This conjugation reaction converts bilirubin to a water soluble compound that can be easily excreted in the feces. The conjugation of bilirubin to glucuronate is catalyzed by the enzyme bilirubin-UDP-glucuronosyltransferase (bilirubin-UGT). Rotor syndrome is related to Dubin-Johnson syndrome in that it is a disorder characterized by conjugated hyperbilirubinema.

The molecular causes of Rotor syndrome are mutations in two gene. Mutations in both genes have to occur for an individual to manifest the symptoms of Rotor syndrome. These two genes encode proteins that are members of the solute carrier family of membrane transporters. The two genes are SLCO1B1 and SLCO1B3. The SCLO1B1 gene encodes the protein identifed as organic anion transporting polypeptide 1B1 (OATP1B1), while the SLCO1B3 gene encodes the protein, organic anion transporting polypeptide 1B3 (OATP1B3). These two transport proteins are responsible for the uptake of bilirubin by the liver. The SLCO1B1 gene is located on chromosome 12p12.1 and is composed of 15 exons that encode a 691 amino acid protein. Expression of the SLCO1B1 gene occurs only within hepatocytes. The SLCO1B3 gene is located on chromosome 12p12.2 and is composed of 17 exons that generate two alternatively spliced mRNAs encoding proteins of 702 amino acids (isoform 1) and 674 amino acids (isoform 2). Expresion of the SLCO1B3 gene is very nearly restricted to hepatocytes with extremely low level expression seen in testes and prostate.

Clinical Consequences of Hyperbilirubinemia

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encephalopathy) can be life threatening in neonates. Bilirubin encephalopathy is characterized by yellow discoloration of the basal ganglia in babies with intense jaundice and was first described over a century ago and the term "kernicterus" was coined to describe these physical changes. Any increase in plasma bilirubin above 20mg/dL is considered dangerous in neonates. However, individual differences in bilirubin sensitivity can result in kernicterus at lower bilirubin levels. Kernicterus occurs in infants with severe unconjugated hyperbilirubinemia and in young adults with high serum levels of unconjugated bilirubin, with the latter the result of inherited deficiencies in bilirubin-UGT.

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Clinical Features of Rotor Syndrome

Whereas, Rotor syndrome and Dubin-Johnson syndrome were originally thought to be variants of a single disorder they are now known to be different entities. Unlike Dubin-Johnson syndrome, Rotor syndrome shows no abnormal hepatic pigmentation. Although total coproporphyrin excretion in the urine of Rotor syndrome patients is markedly increased it is not to the same degree as in Dubin-Johnson patients. In Rotor syndrome homozygotes the level of coproporphyrin in the urine is around 65% and in heterozygotes it is around 40%, as compared to nearly 90% in Dubin-Johnson syndrome.