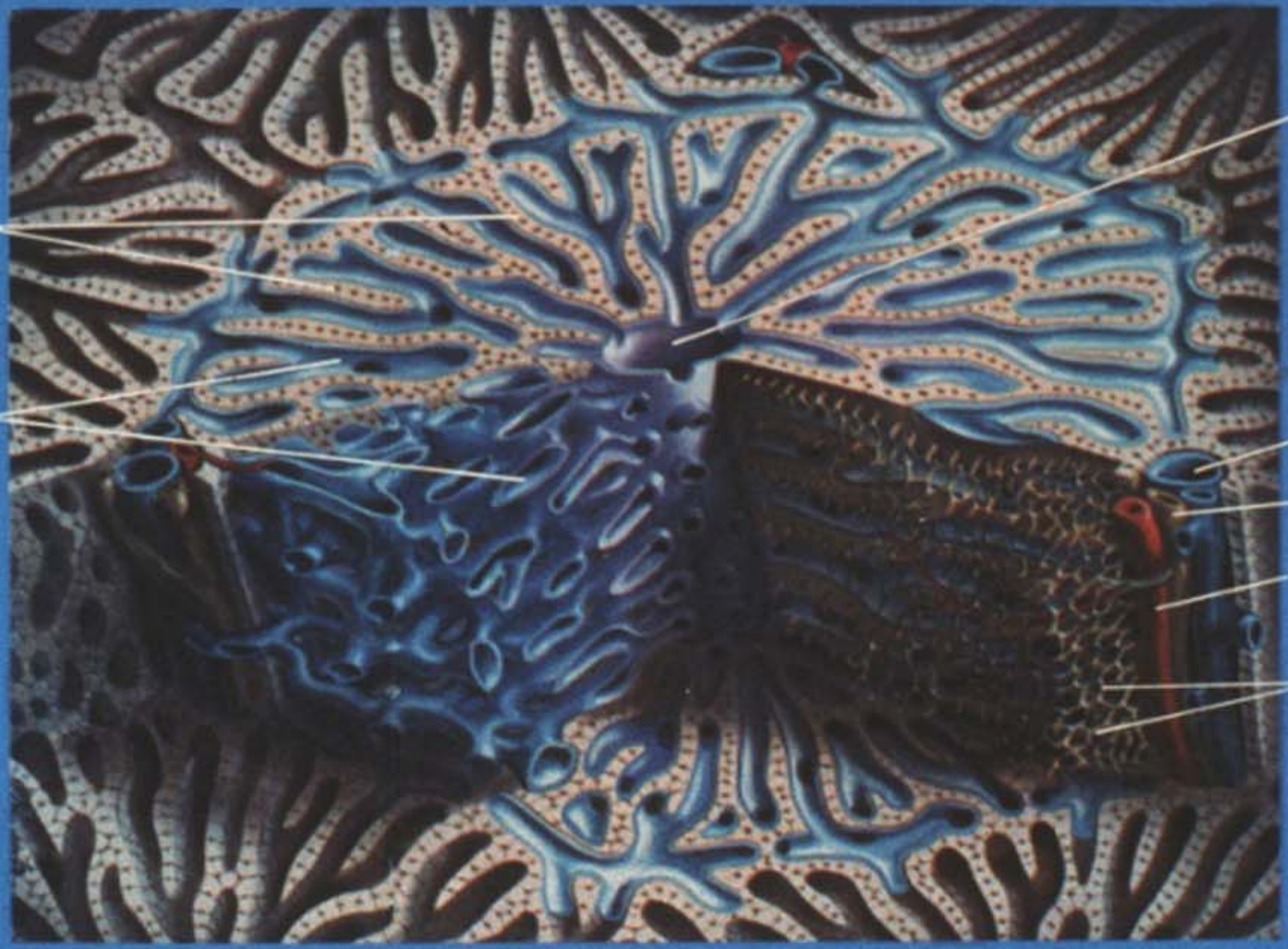
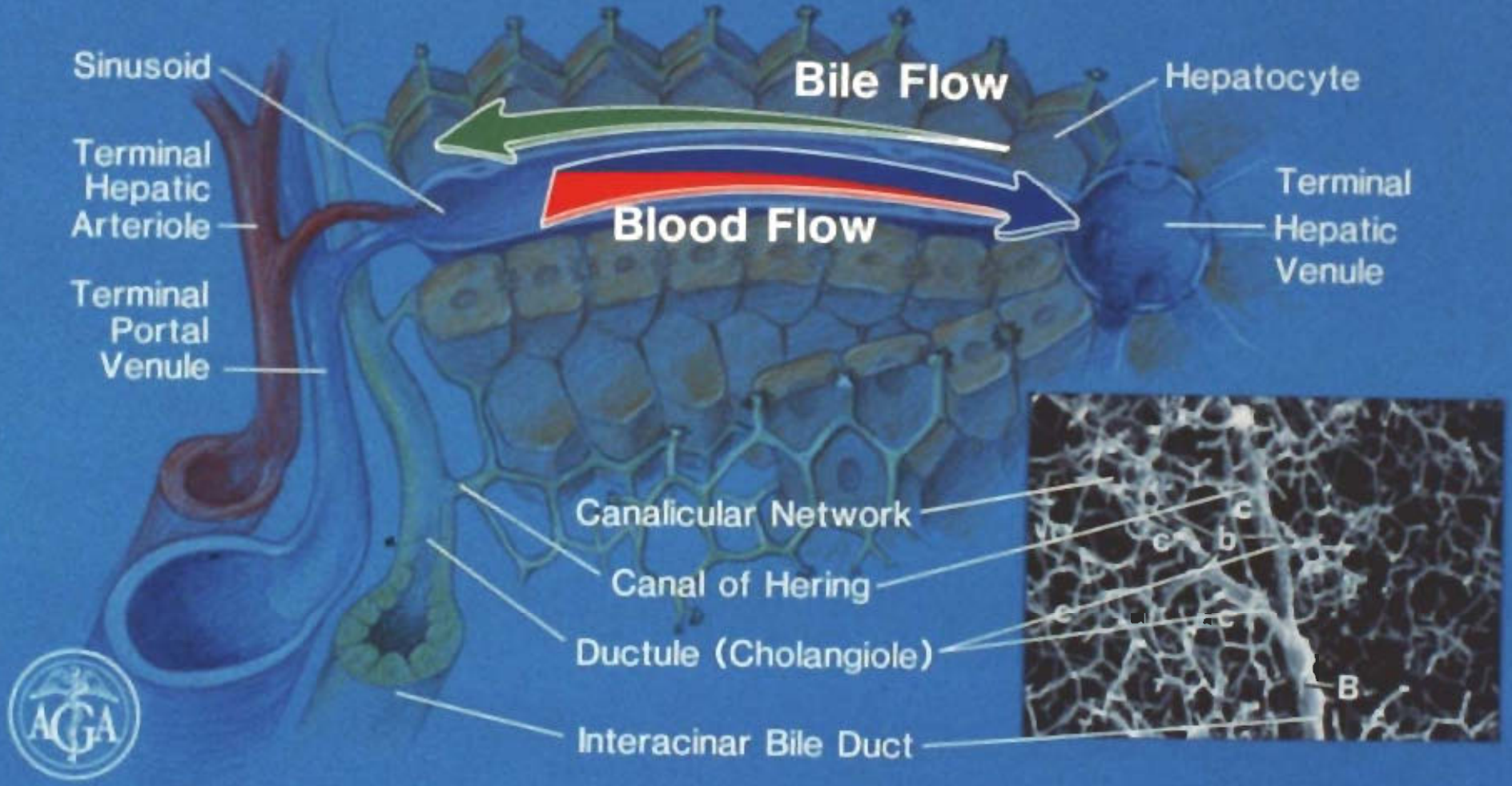
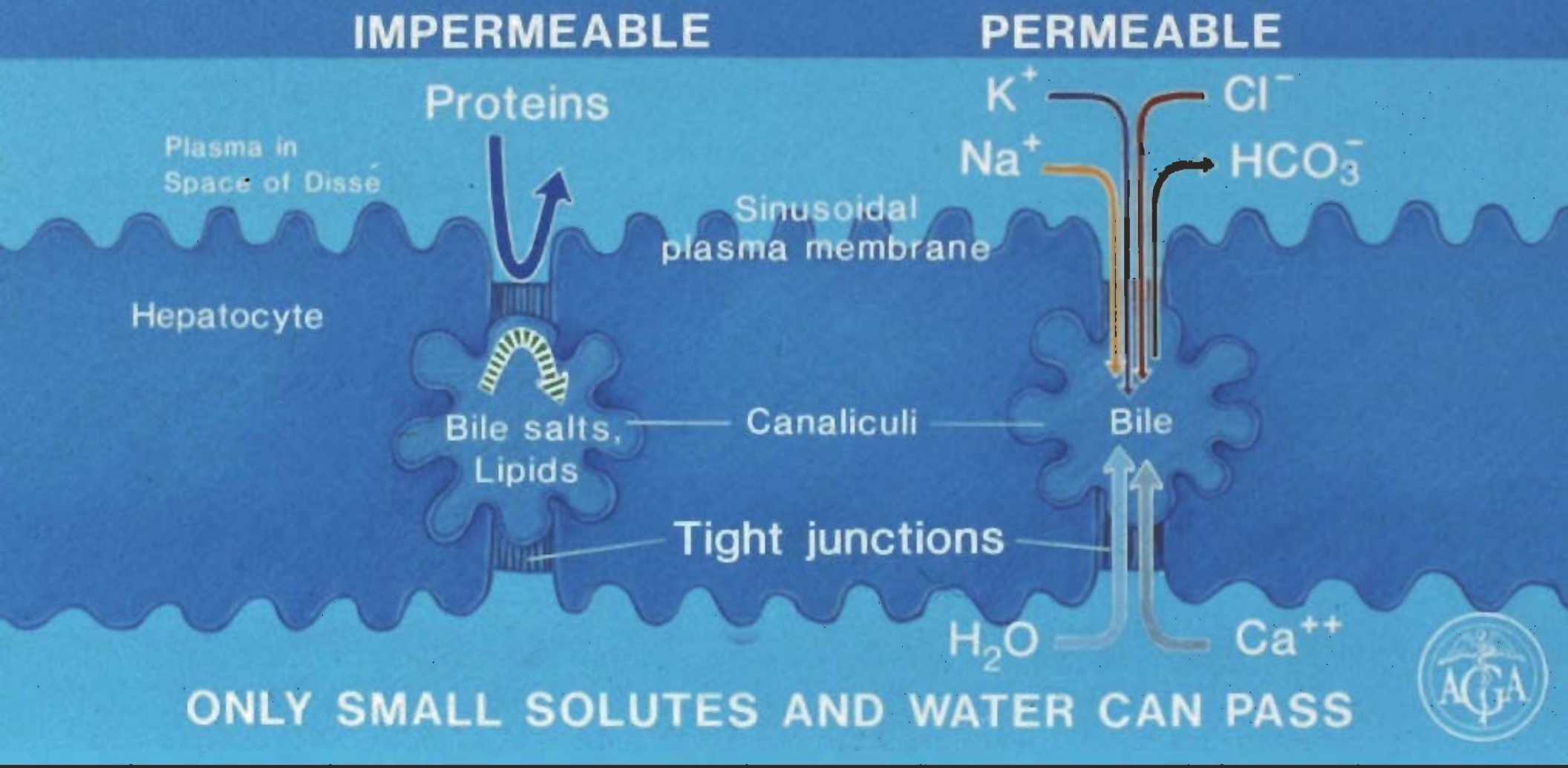
THE TRADITIONAL LIVER LOBULE IS RADIALLY ARRANGED AROUND A CENTRAL HEPATIC VENULE WITH PORTAL TRIADS AT THE PERIPHERY



BILE FLOWS THROUGH A CANALICULAR NETWORK COUNTERCURRENT TO THE SINUSOIDAL BLOOD



TIGHT JUNCTIONS BETWEEN HEPATOCYTES FUNCTIONALLY SEPARATE CANALICULAR BILE FROM PLASMA IN THE SPACE OF DISSÉ

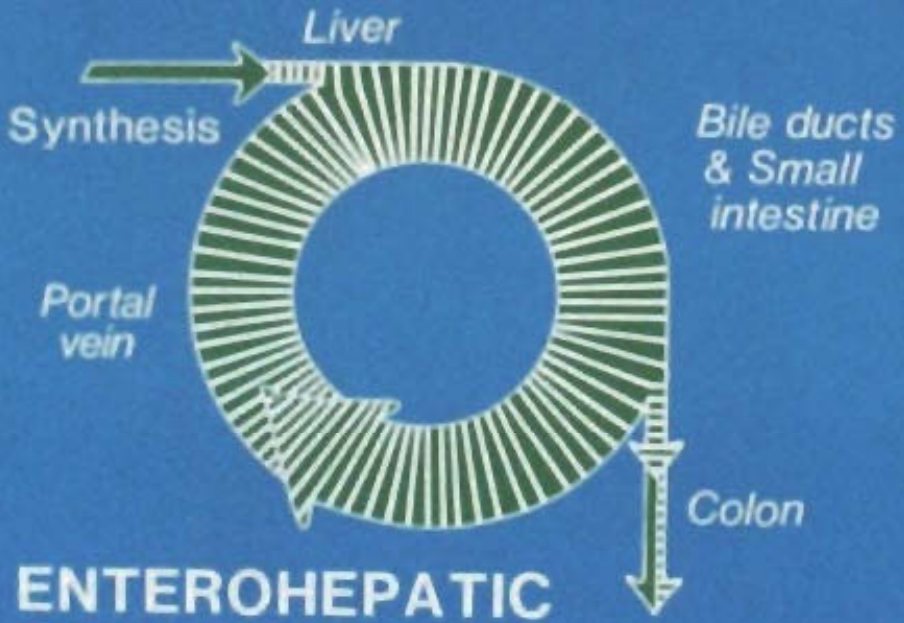


ONLY SMALL SOLUTES AND WATER CAN PASS

CONJUGATES SECRETED INTO BILE ARE NOT REABSORBED UNLESS ACTIVELY TRANSPORTED OR DEGRADED TO LIPOPHILIC PRODUCTS

Conjugated Bile Salts

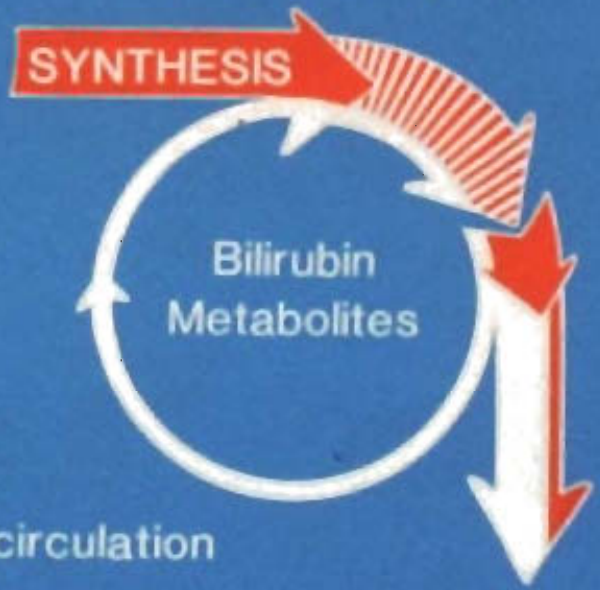
- Actively Transported by Ileum
- Mostly Reabsorbed



ENTEROHEPATIC RECIRCULATION

Conjugated Bilirubins

- NOT Actively Transported
- Deconjugated and Reduced
- Mostly Eliminated

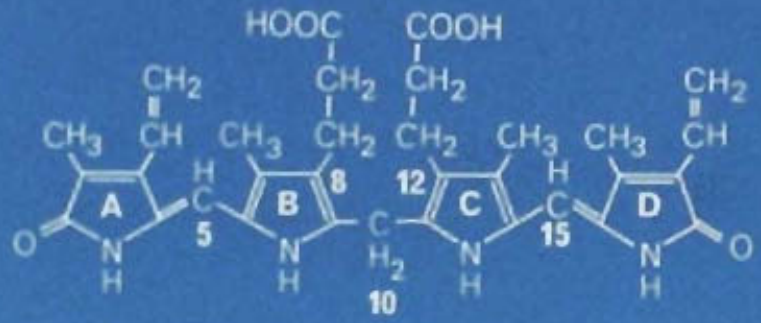


Recirculation

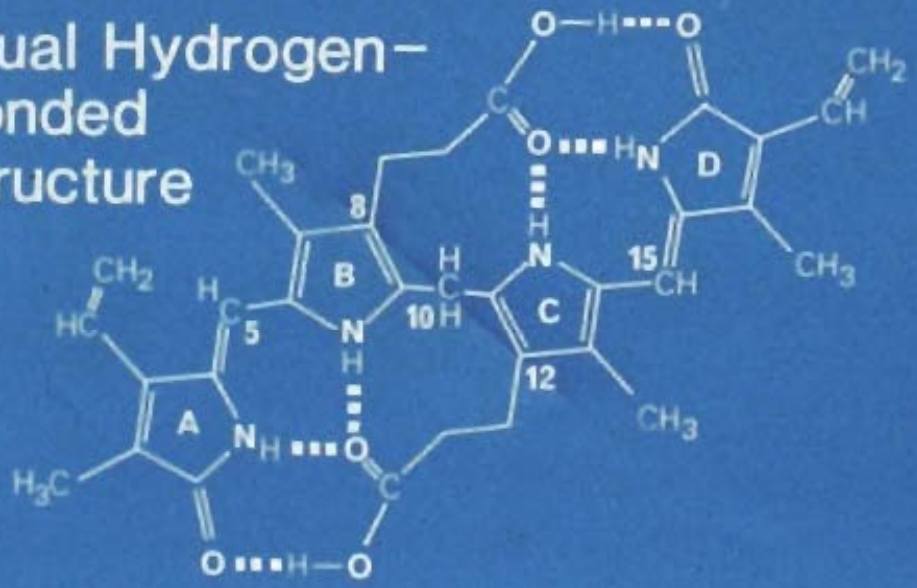
FECES

ALL POLAR GROUPS IN UNCONJUGATED BILIRUBIN ARE INTERNALLY HYDROGEN-BONDED

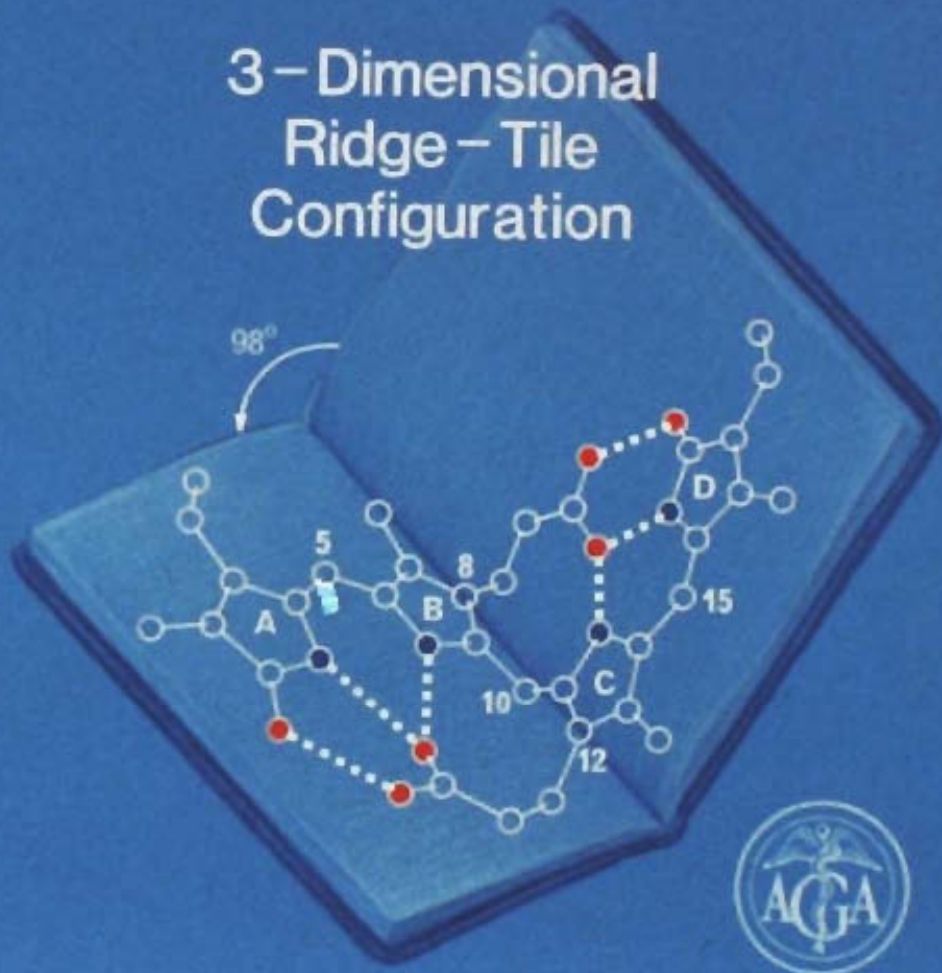
Conventional Representation
(A–D are four pyrrole rings)



Actual Hydrogen-Bonded Structure



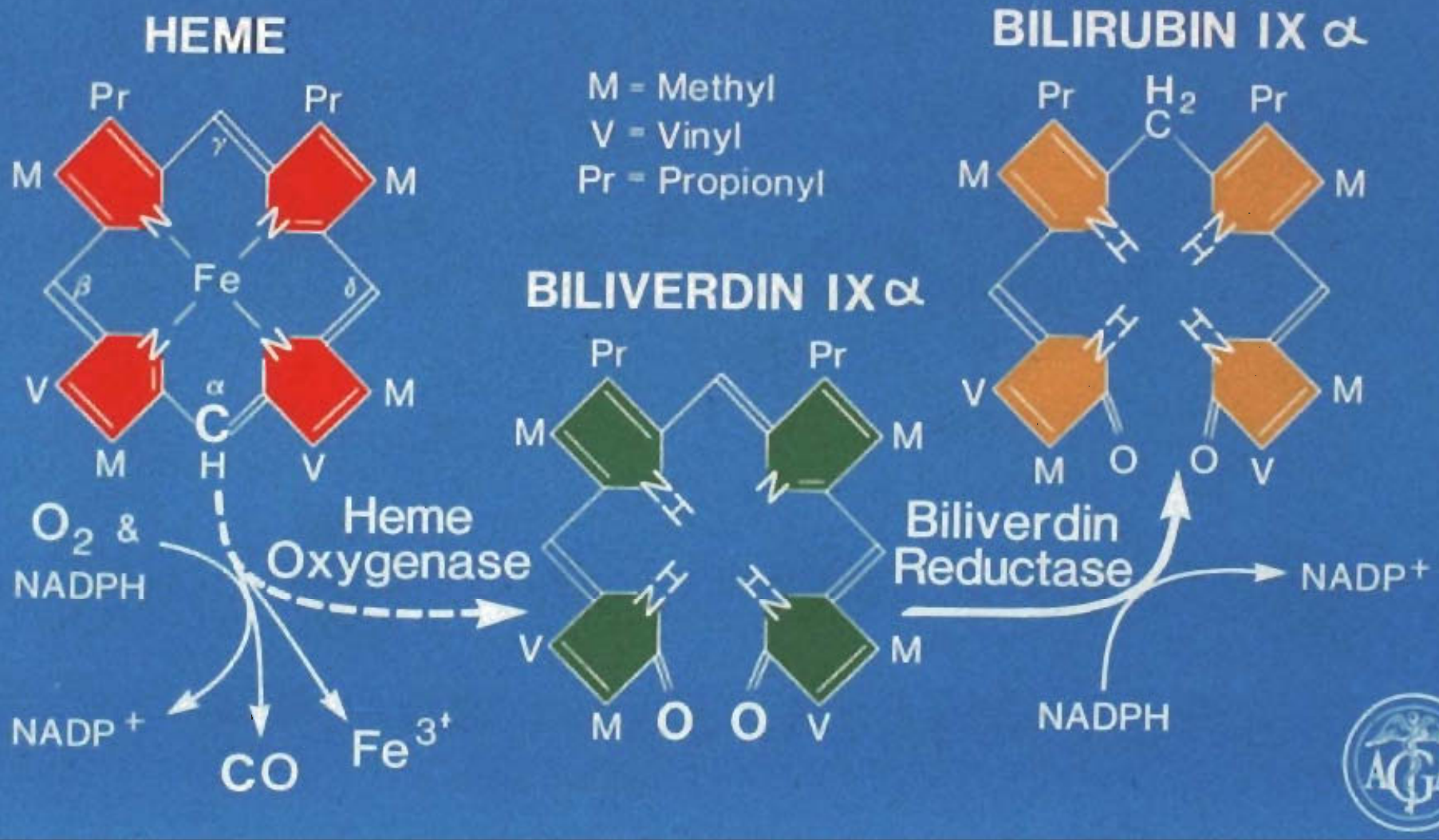
3-Dimensional Ridge-Tile Configuration



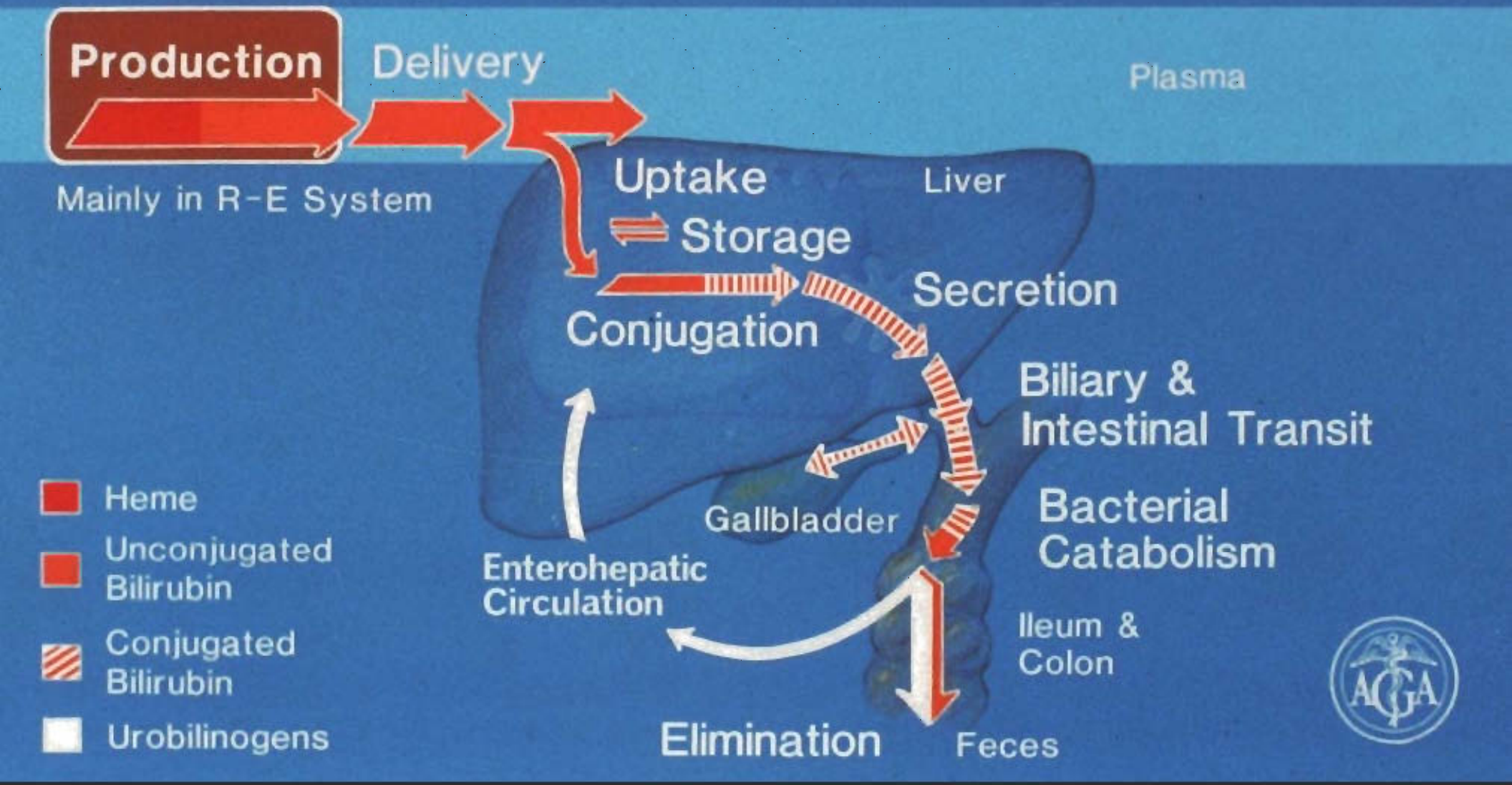
LOSS OF INTERNAL HYDROGEN-BONDS ALTERS THE PROPERTIES OF BILIRUBIN PHOTO-ISOMERS & CONJUGATES

Property	Unconjugated Bilirubin IX αZZ	Conjugates & EZ Photo-Isomers
Internal H-Bonding	Complete	Partial
Structure	Rigid, Ridge Tile	Flexible
Polar Groups	Shielded	Exposed
Water Solubility	Low (0.1 μM)	High
Diazo Reaction	Indirect	Direct
Biliary Secretion	Minimal	Extensive

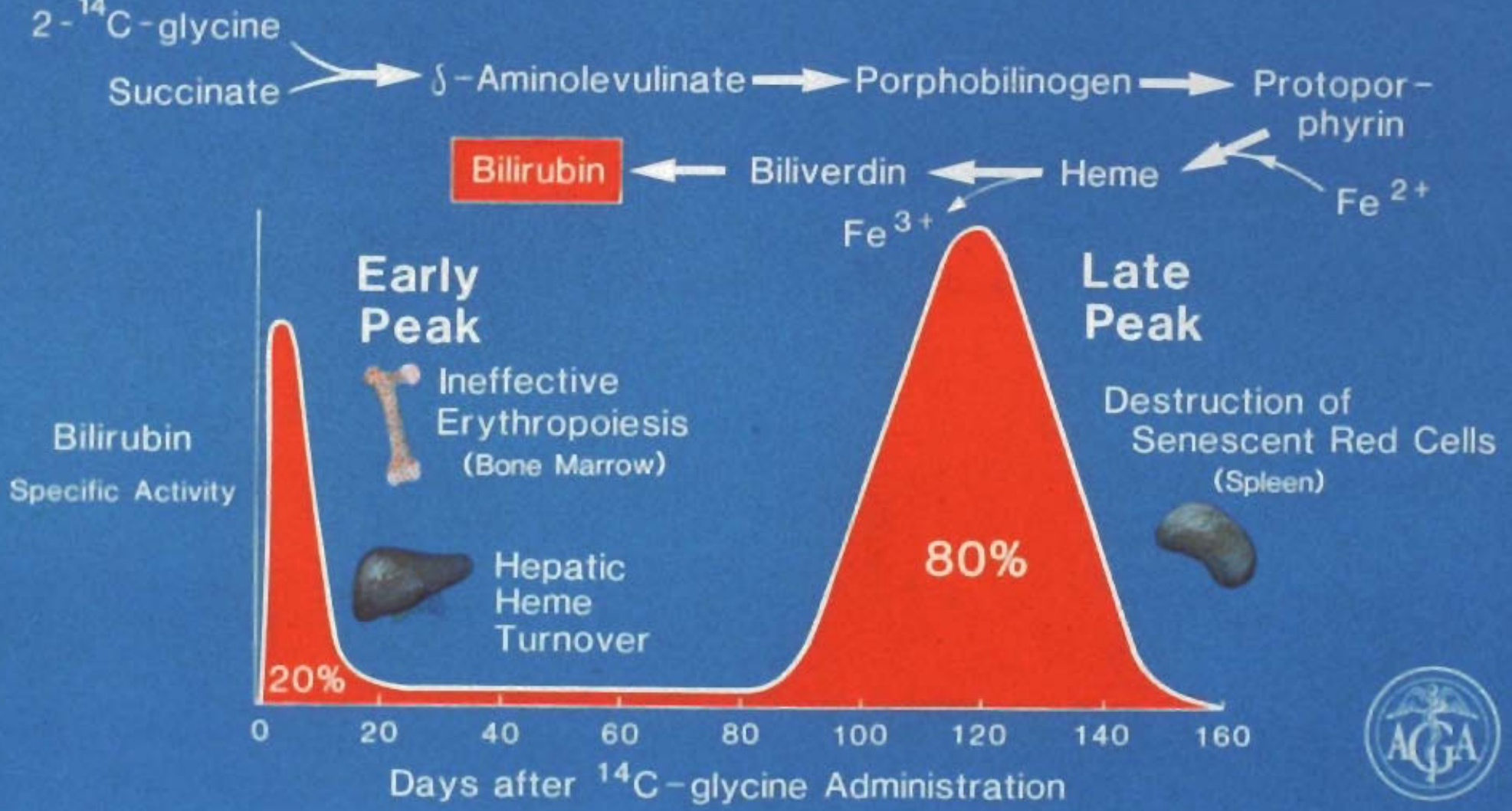
BILIRUBIN IS PRODUCED BY OXIDATION OF HEME AND REDUCTION OF THE RESULTANT BILIVERDIN



EXCRETION OF BILIRUBIN INVOLVES MULTIPLE STEPS



THERE ARE MULTIPLE SOURCES OF BILIRUBIN



BILIRUBIN CONJUGATION IN MICROSOMES INVOLVES TWO STEPS, MEDIATED BY ONE BILIRUBIN-UDPGA TRANSFERASE

BILIRUBINS:

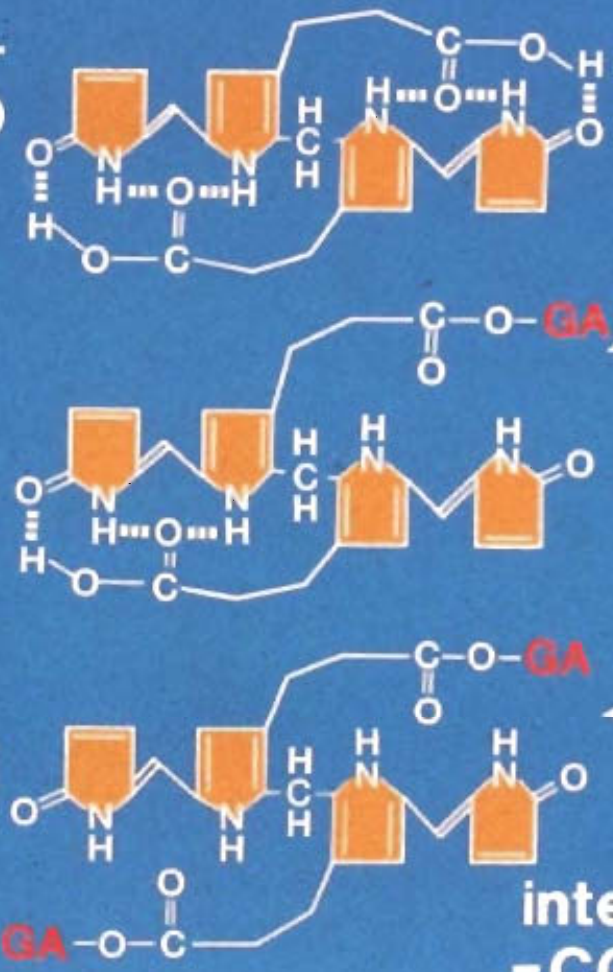
UNCONJUGATED (UCB)

①

MONO-GLUCURONIDE (BMG)

②

DIGLUCURONIDE (BDG)



UDPGA

UDP

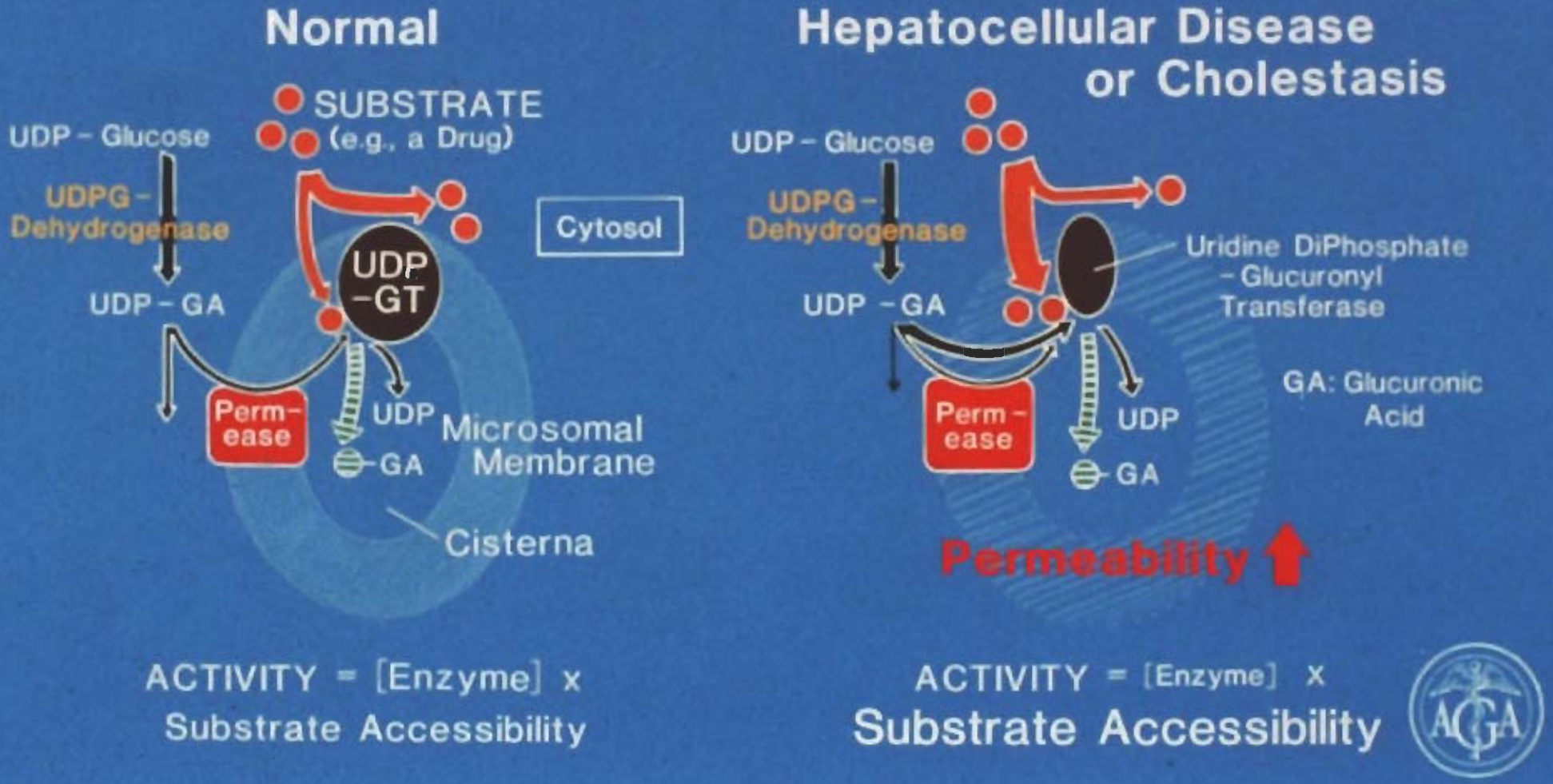
UDPGA

UDP

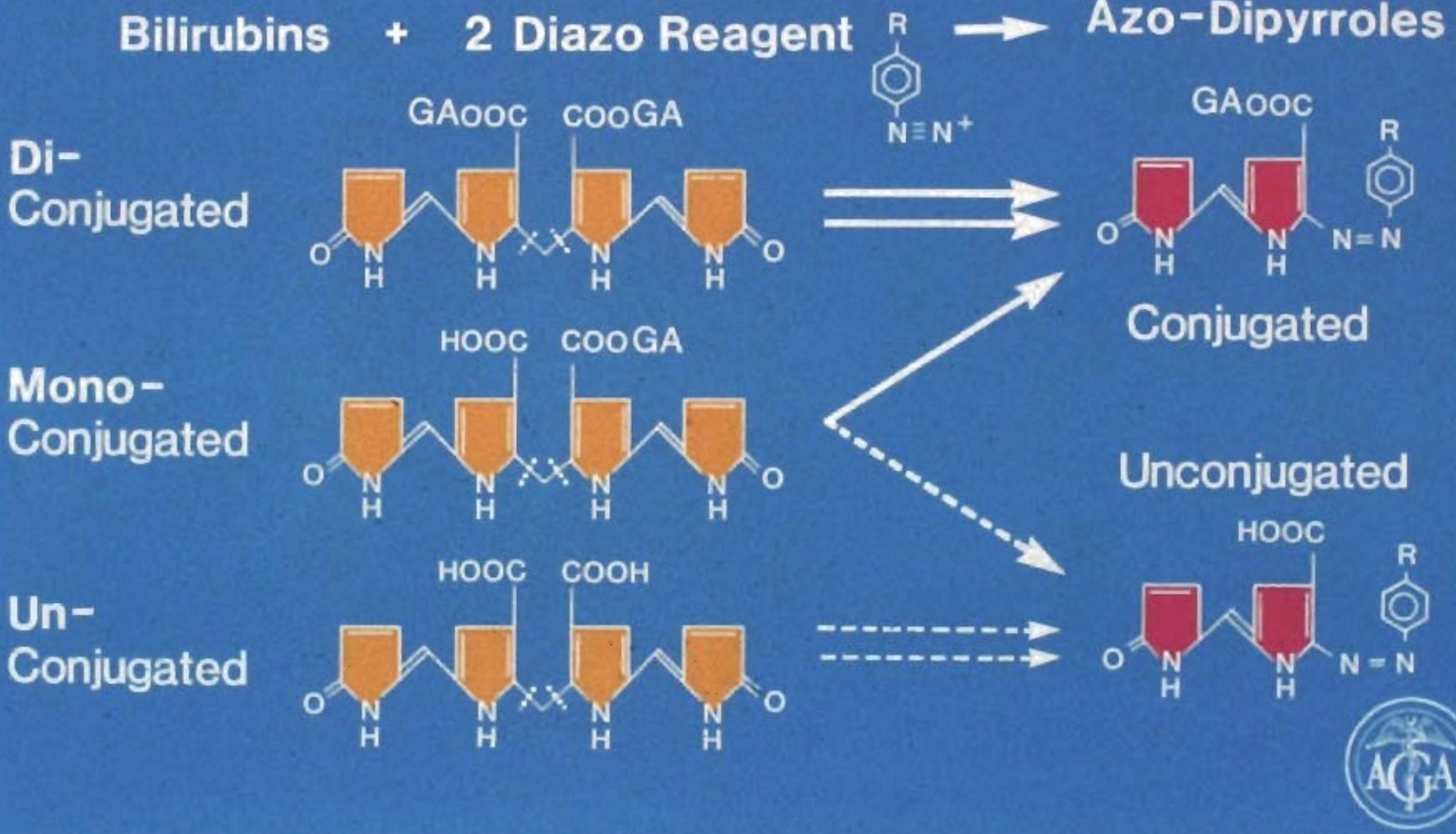
UDPGA Trans-ferase

Conjugation prevents internal H-bonding by the -COOH groups of Bilirubin

GLUCURONIDE CONJUGATION IS PRESERVED IN HEPATOBILIARY DISEASES, DUE TO INCREASED MICROSOMAL PERMEABILITY TO SUBSTRATES



THE DIAZO REACTION SPLITS BILIRUBINS INTO PAIRS OF AZODIPYRROLES THAT RETAIN THE CONJUGATION PATTERN OF THE BILIRUBINS



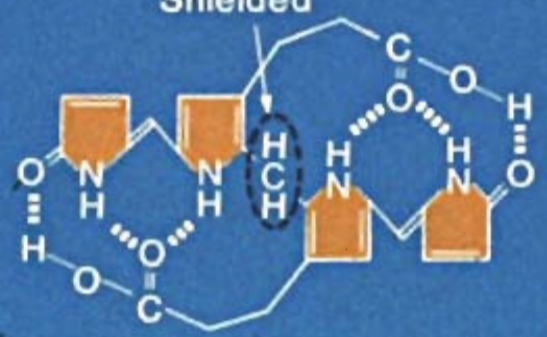
DIRECT AND TOTAL BILIRUBINS ARE MEASURED BY DIAZOTIZATION BEFORE AND AFTER ADDITION OF H-BOND BREAKERS

Bilirubins

Type of Diazo Reaction

UN-Conjugated
H-Bonded

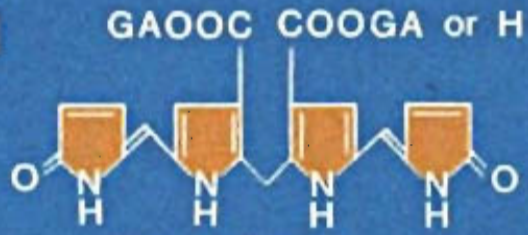
Sterically Shielded



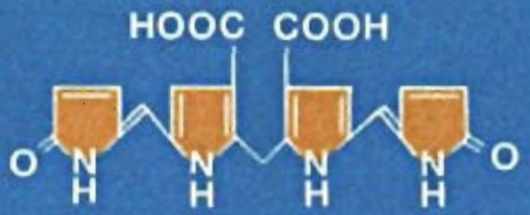
No Added Accelerator

DIRECT
(Mostly Conjugated)

Conjugated
No H-Bonds



UN-Conjugated
With H-Bonds Broken

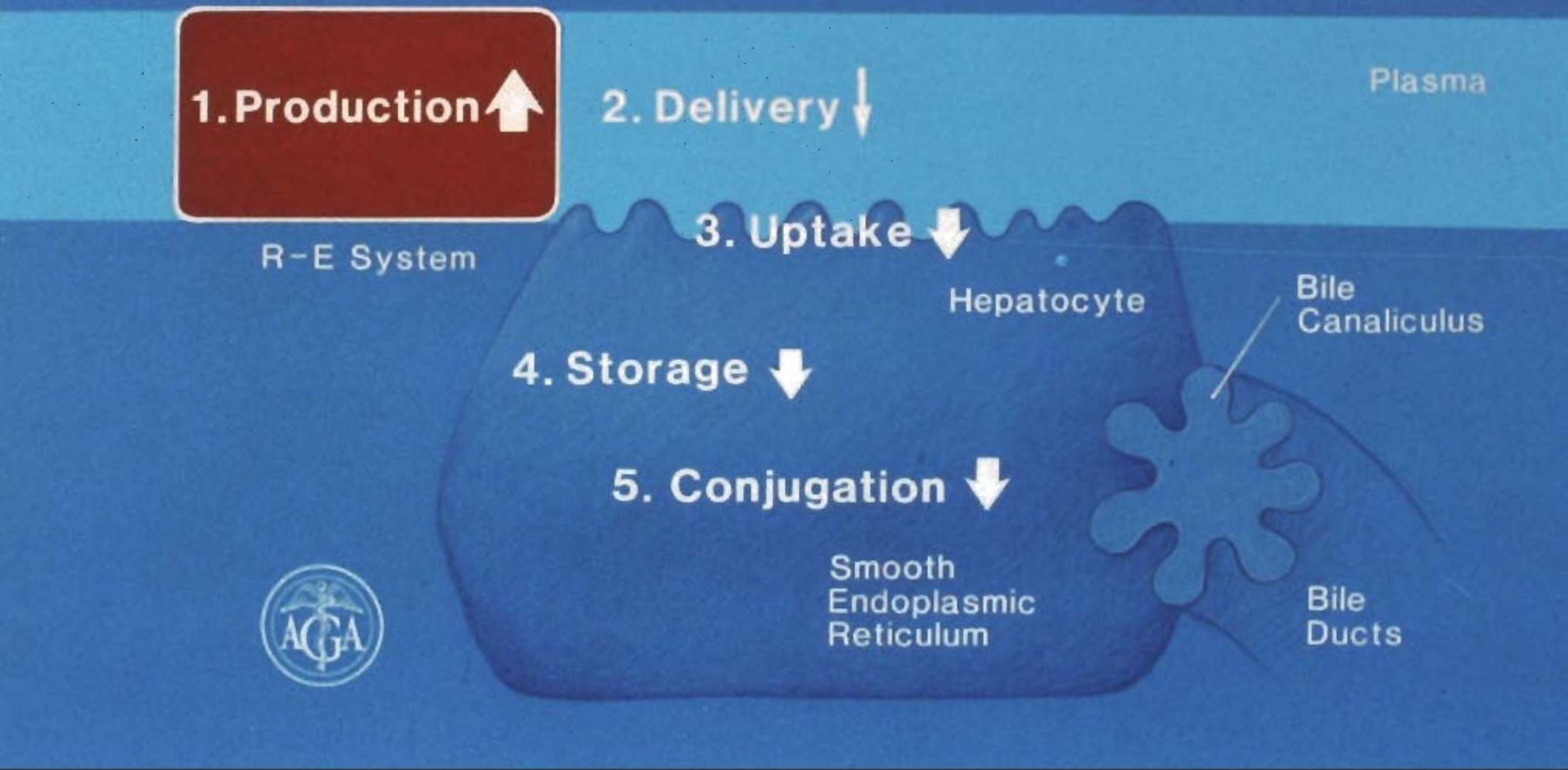


+ H-Bond Breakers

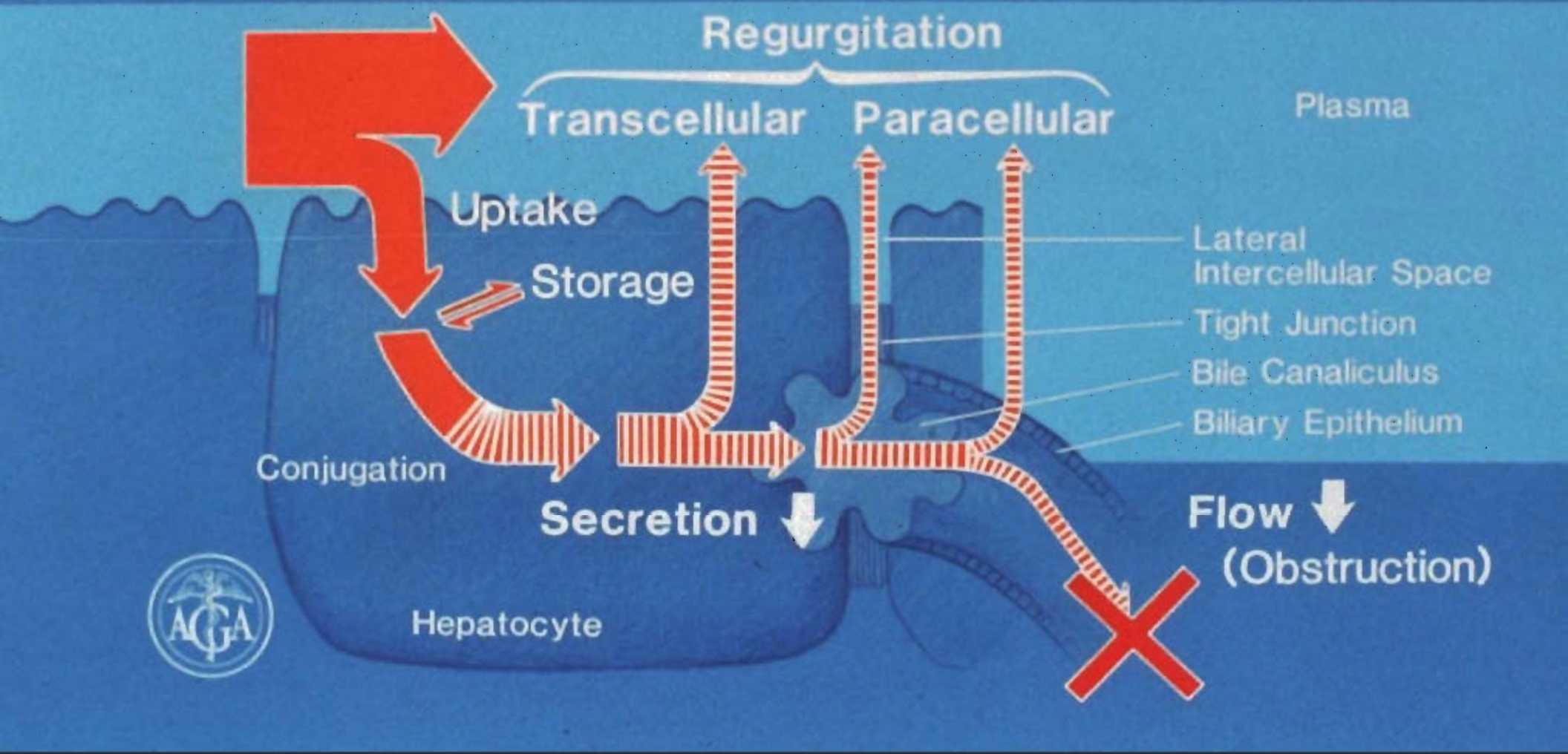
TOTAL
(Conjugated plus Unconjugated)

TOTAL - DIRECT = INDIRECT (Mostly Unconjugated)

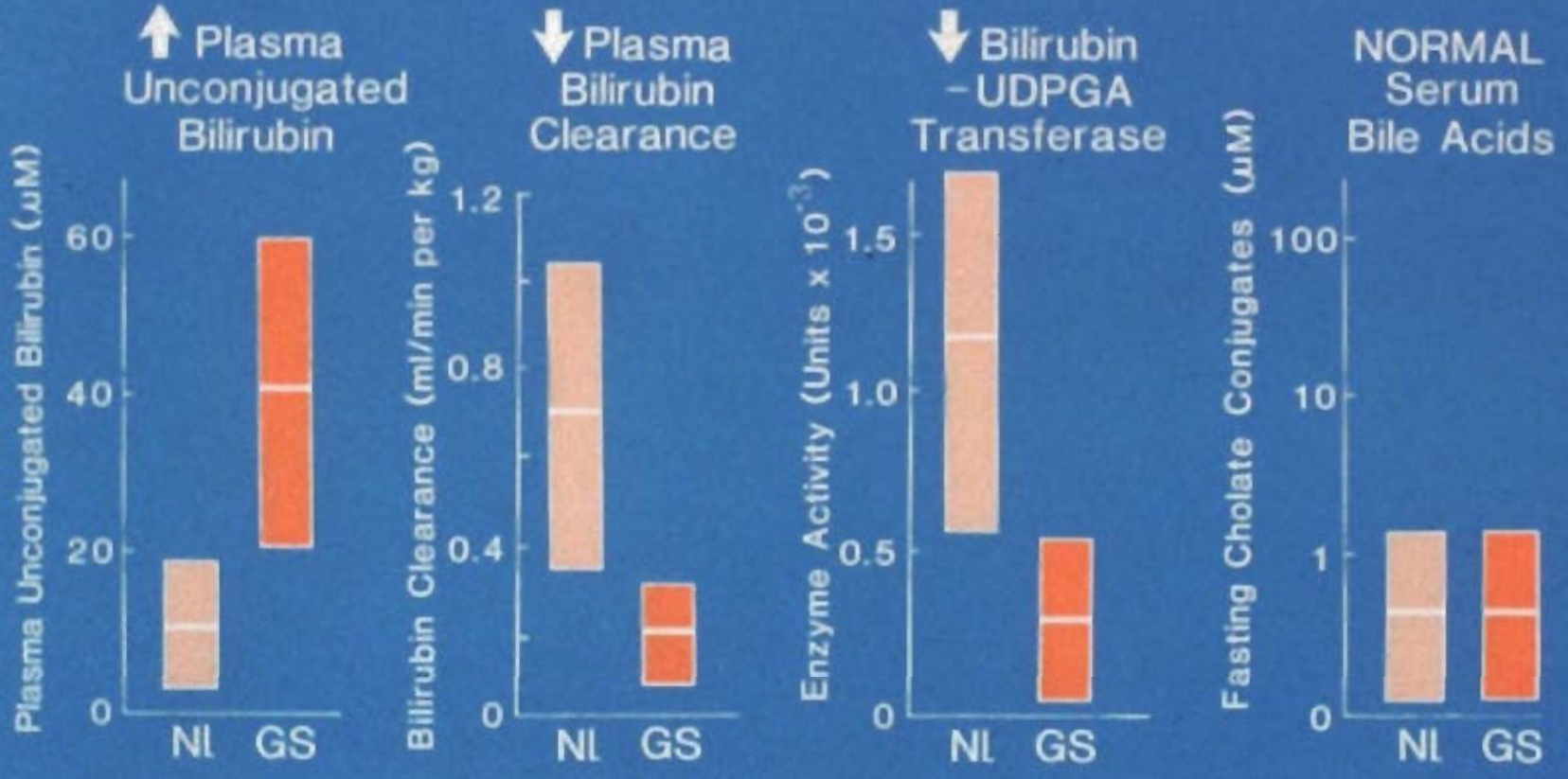
UNCONJUGATED HYPERBILIRUBINEMIA MAY RESULT FROM ABNORMALITIES OF MANY STEPS IN BILIRUBIN METABOLISM



CONJUGATED HYPERBILIRUBINEMIA RESULTS FROM IMPAIRED CANALICULAR SECRETION &/OR BILE FLOW, WITH REGURGITATION OF BILIRUBIN INTO PLASMA



GILBERT'S SYNDROME IS A MILD, CHRONIC, UNCONJUGATED HYPERBILIRUBINEMIA, DEFINED BY FOUR FEATURES

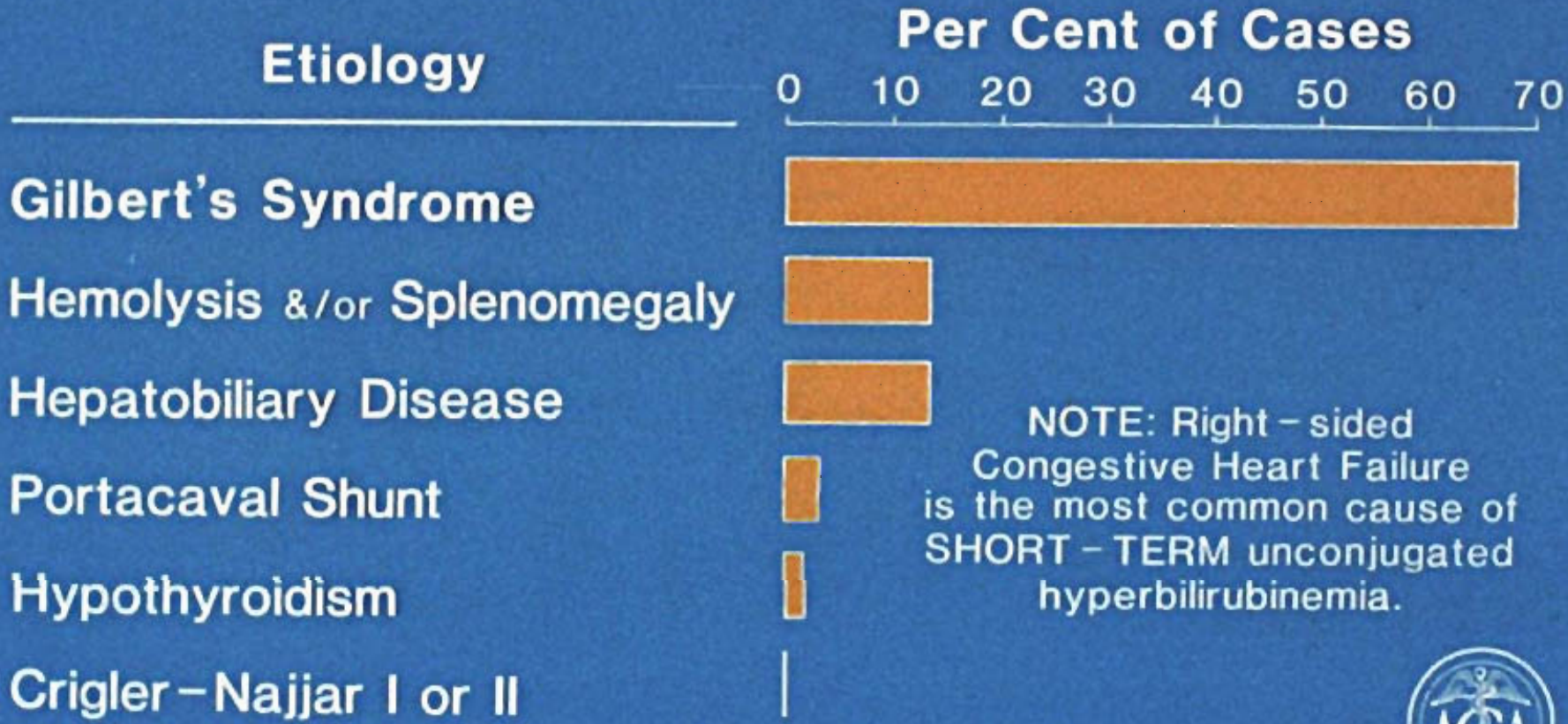


Heterogeneous with regard to: ultrastructure, hemolysis & uptake of other organic anions.

PRINCIPAL DIFFERENTIAL CHARACTERISTICS OF GILBERT'S AND CRIGLER-NAJJAR SYNDROMES

Characteristic	Crigler-Najjar Type I	Crigler-Najjar Type II	Gilbert's
Bilirubin-UDPGA Transferase Activity	Undetectable	<10% of normal	10-50% of normal
Bile Bilirubin Composition	>90% UCB	>90% BMG	>15% BMG
Transport of other organic anions	Normal	Normal	Abnormal in some
Plasma Total Bilirubin (μM)	305-850 (usually >340)	100-770 (usually <340)	<70 in absence of fasting or hemolysis
Incidence	<100 cases	Uncommon	≈7% of population
Inheritance	Autosomal Recessive	? Autosomal Dominant	Autosomal Dominant (variable penetrance)

IN WESTERN NATIONS, GILBERT'S SYNDROME IS THE MOST COMMON CAUSE OF CHRONIC UNCONJUGATED HYPERBILIRUBINEMIA



NOTE: Right-sided Congestive Heart Failure is the most common cause of SHORT-TERM unconjugated hyperbilirubinemia.

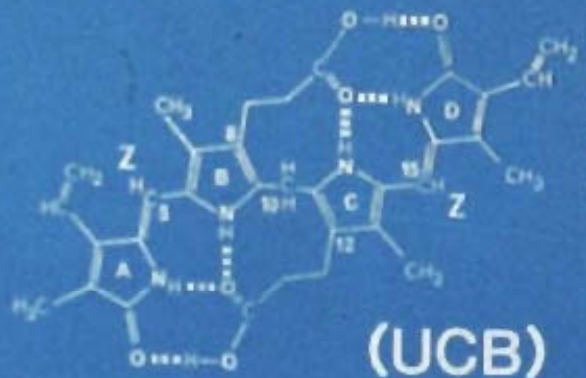
AGA

"PHYSIOLOGICAL" NEONATAL JAUNDICE RESULTS FROM IMMATURITY OF ALL STEPS IN BILIRUBIN METABOLISM

PHOTOISOMERIZATION OF BILIRUBIN IN SKIN PRODUCES POLAR DERIVATIVES THAT CAN BE EXCRETED IN BILE WITHOUT CONJUGATION

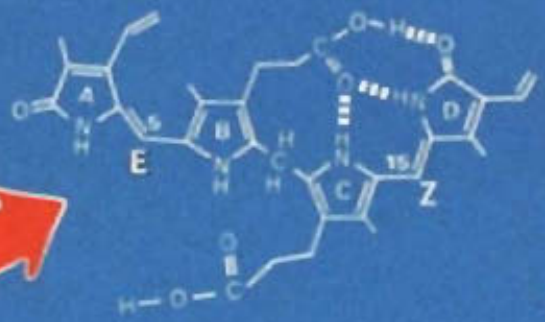
Light

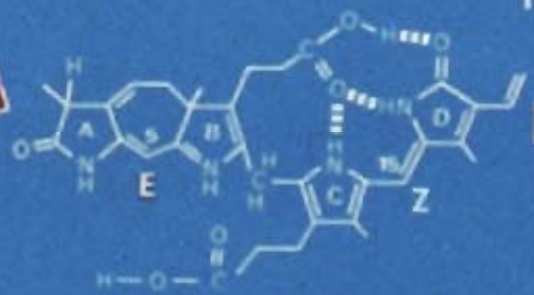
Unconjugated
Bilirubin IXα ,ZZ



(UCB)

Photobilirubin I





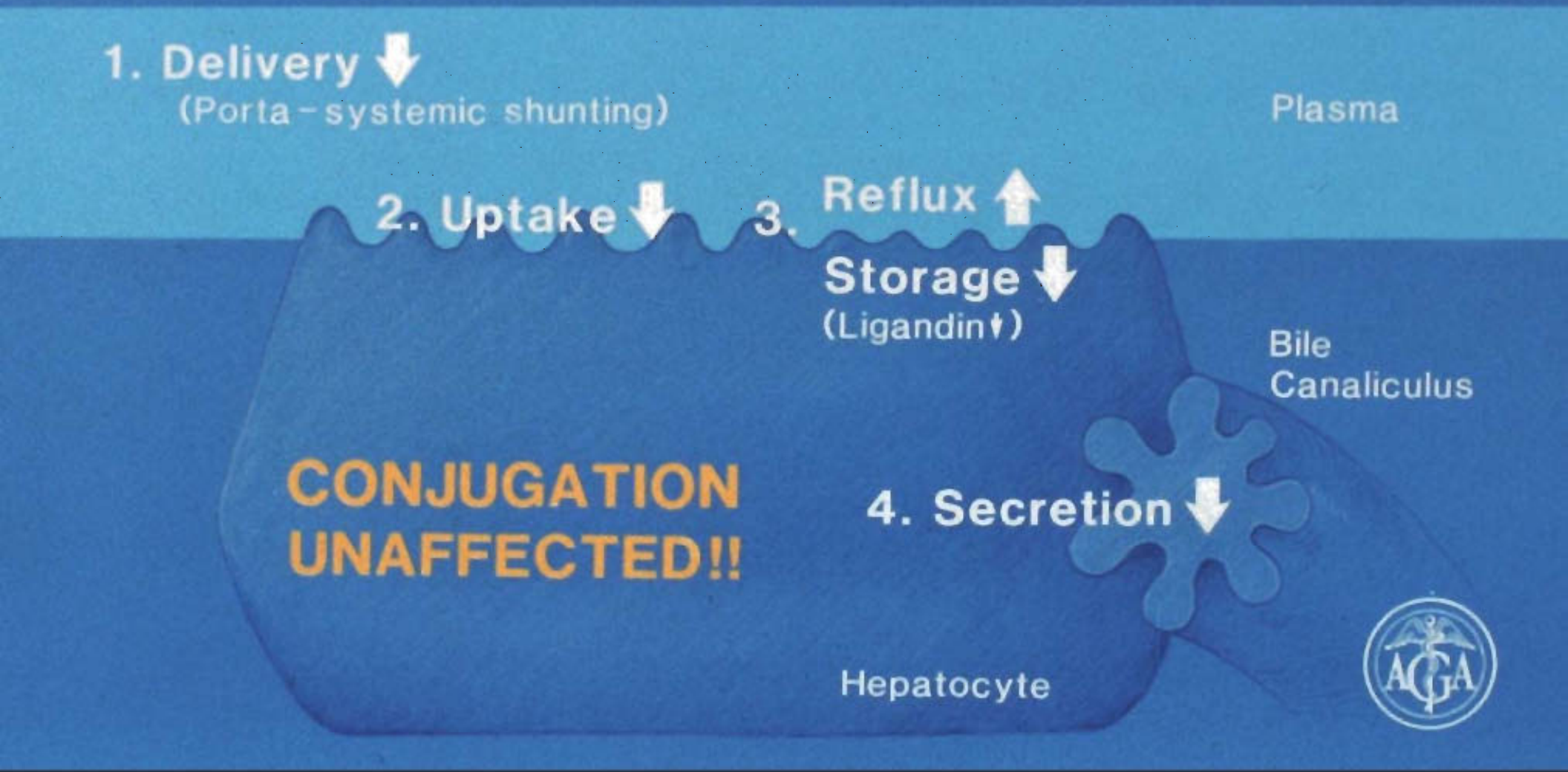
Photobilirubin II

SKIN | PLASMA | LIVER | BILE

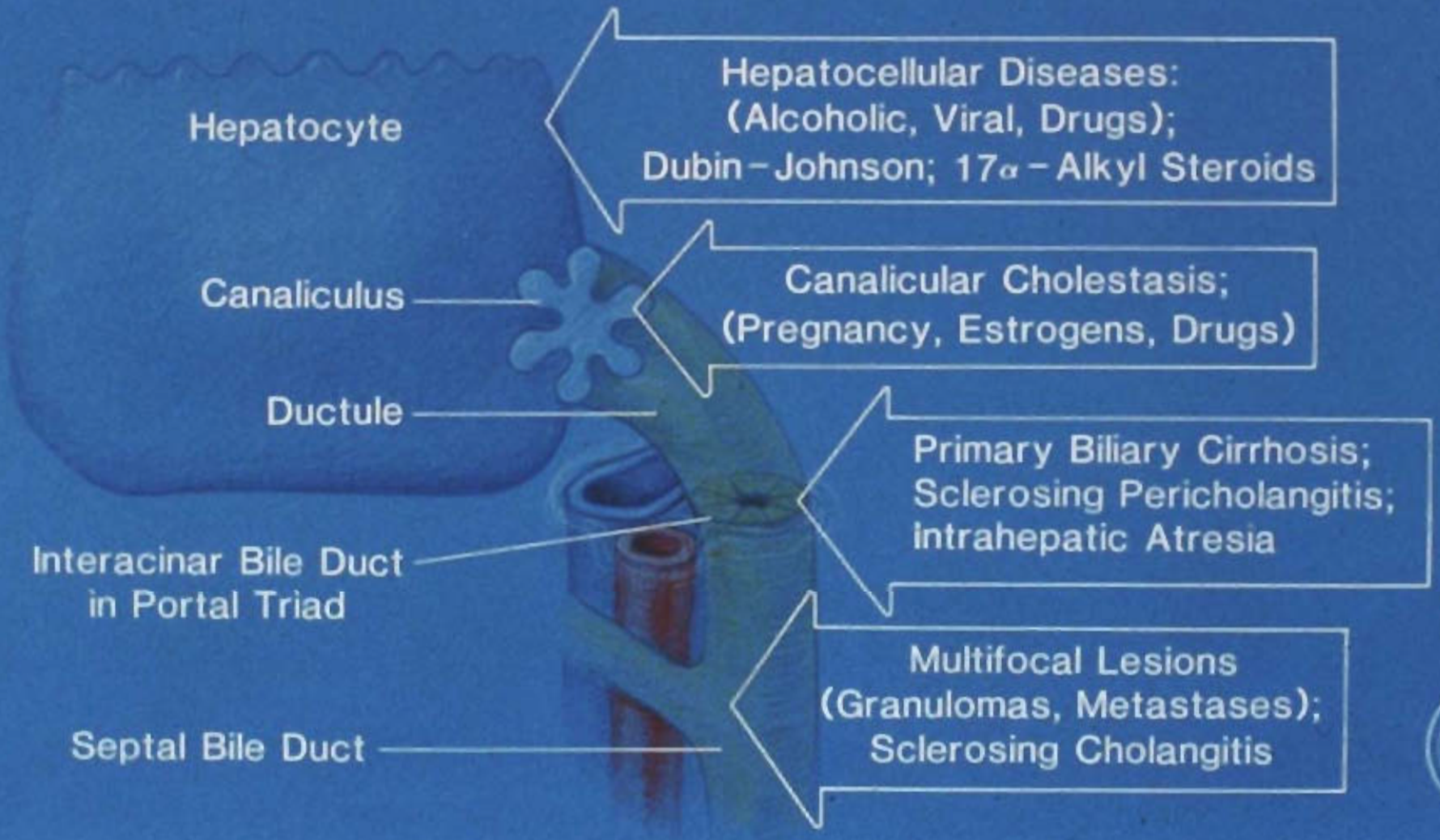
Reverts to UCB

Stable: Unchanged

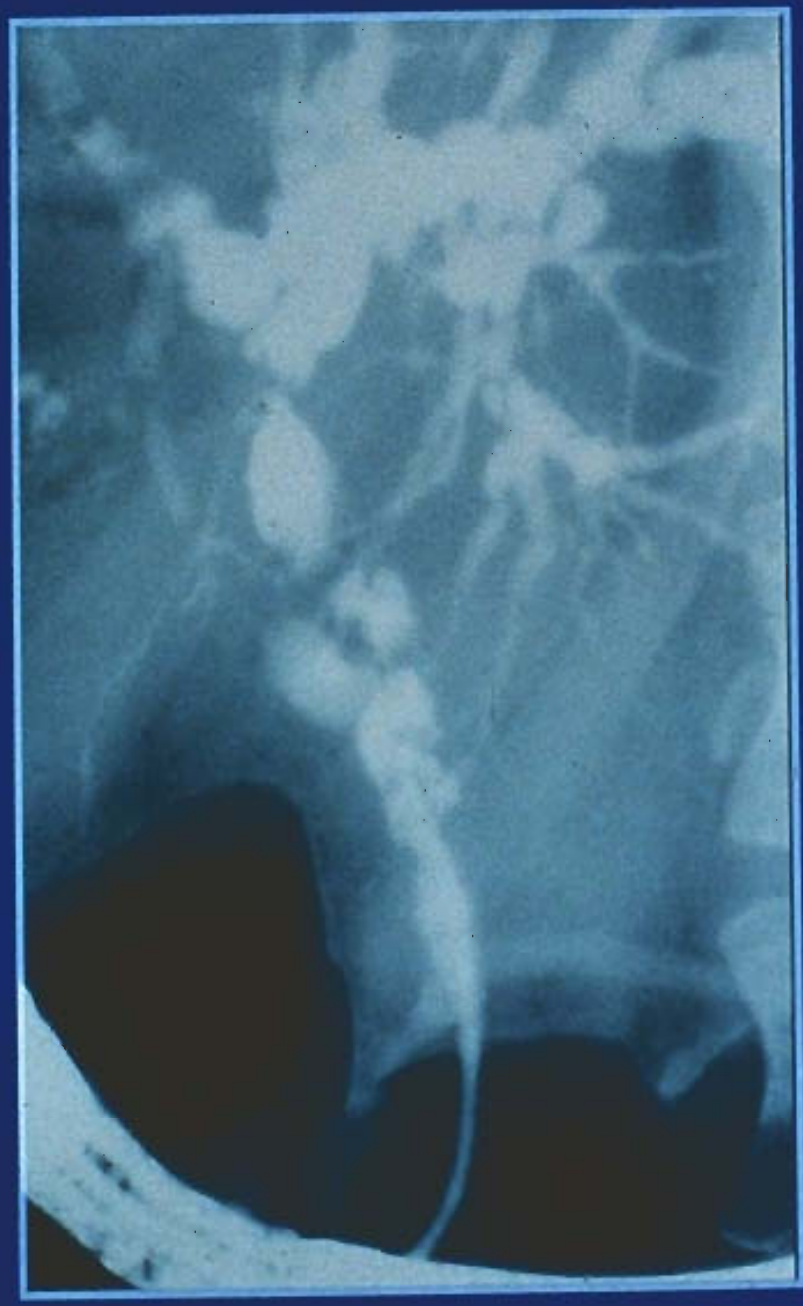
HEPATOCELLULAR DISEASES IMPAIR MANY STEPS IN HEPATOCYTIC TRANSPORT, BUT NOT CONJUGATION



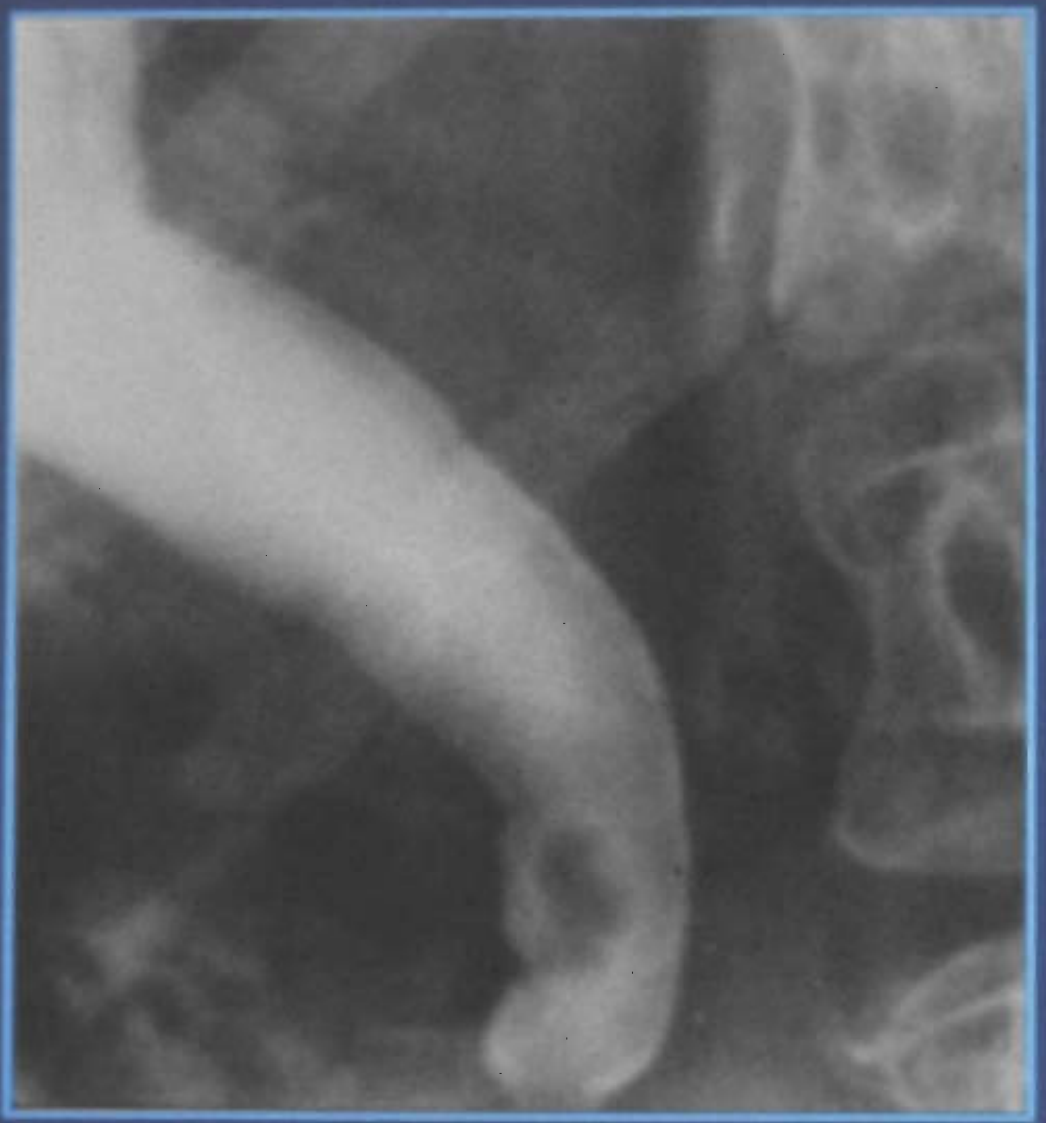
SITES OF INTRAHEPATIC BLOCK IN CONJUGATED HYPERBILIRUBINEMIAS



SCLEROSING CHOLANGITIS

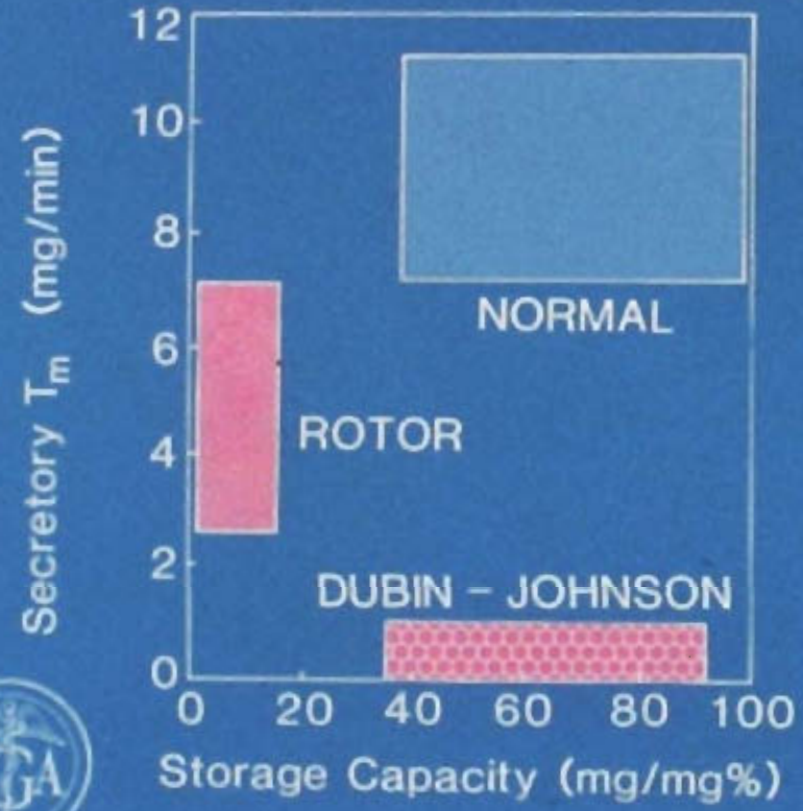


COMMON DUCT STONE



DUBIN-JOHNSON AND ROTOR'S SYNDROMES ARE DIFFERENT HEREDITARY DEFECTS IN HEPATIC ORGANIC ANION TRANSPORT

BSP: Transport Maximum (T_m) & Relative Storage Capacity



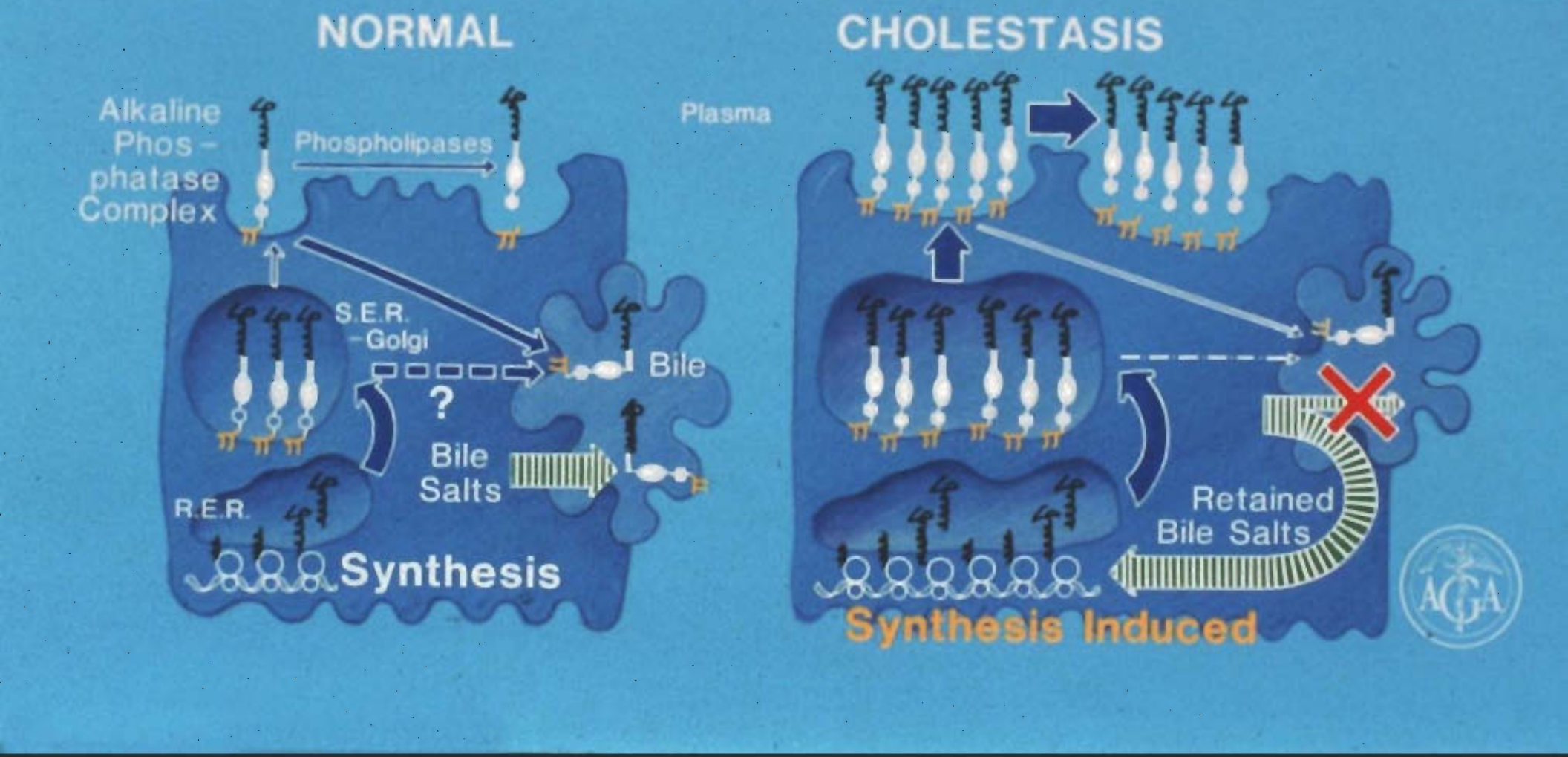
OTHER FEATURES:	DUBIN-JOHNSON	ROTOR
Defect in Organic Anion Transport:	Canalicular Secretion	Pre-canalicular
^{99m}Tc-HIDA:	Biliary tree not opacified	Liver also not opacified
Conjugated Bile Salt Transport:	Normal	Normal
Liver Pigment:	Brown/Black	None
Inheritance:	Autosomal Recessive	Autosomal Recessive

CONJUGATED HYPERBILIRUBINEMIA CAN BE CLASSIFIED INTO TWO MAJOR SYNDROMES

Features	Hepatocellular	Cholestatic*
Itching	Uncommon	75%, often severe
Serum Levels:		
Bile Salts	↑ or ↑↑	↑↑ or ↑↑↑
Alkaline Phosphatase	↑ or ↑↑ (< 3X normal)	↑↑ or ↑↑↑ (> 3X normal)
Cholesterol	↓	↑ or ↑↑
Transaminases	↑ to ↑↑↑	Normal or ↑
Histology	Hepatocyte necrosis and inflammation	Canalicular dilatation and bile-plugging

*NONE OF THESE FEATURES DISTINGUISHES INTRA- FROM EXTRA-HEPATIC CHOLESTASIS

INCREASED PLASMA ALKALINE PHOSPHATASE IN CHOLESTASIS IS DUE TO DECREASED BILIARY SECRETION AND INDUCTION OF HEPATIC SYNTHESIS BY RETAINED BILE SALTS



CHOLESTASIS HAS THREE DEFINITIONS

PATHOPHYSIOLOGICAL:

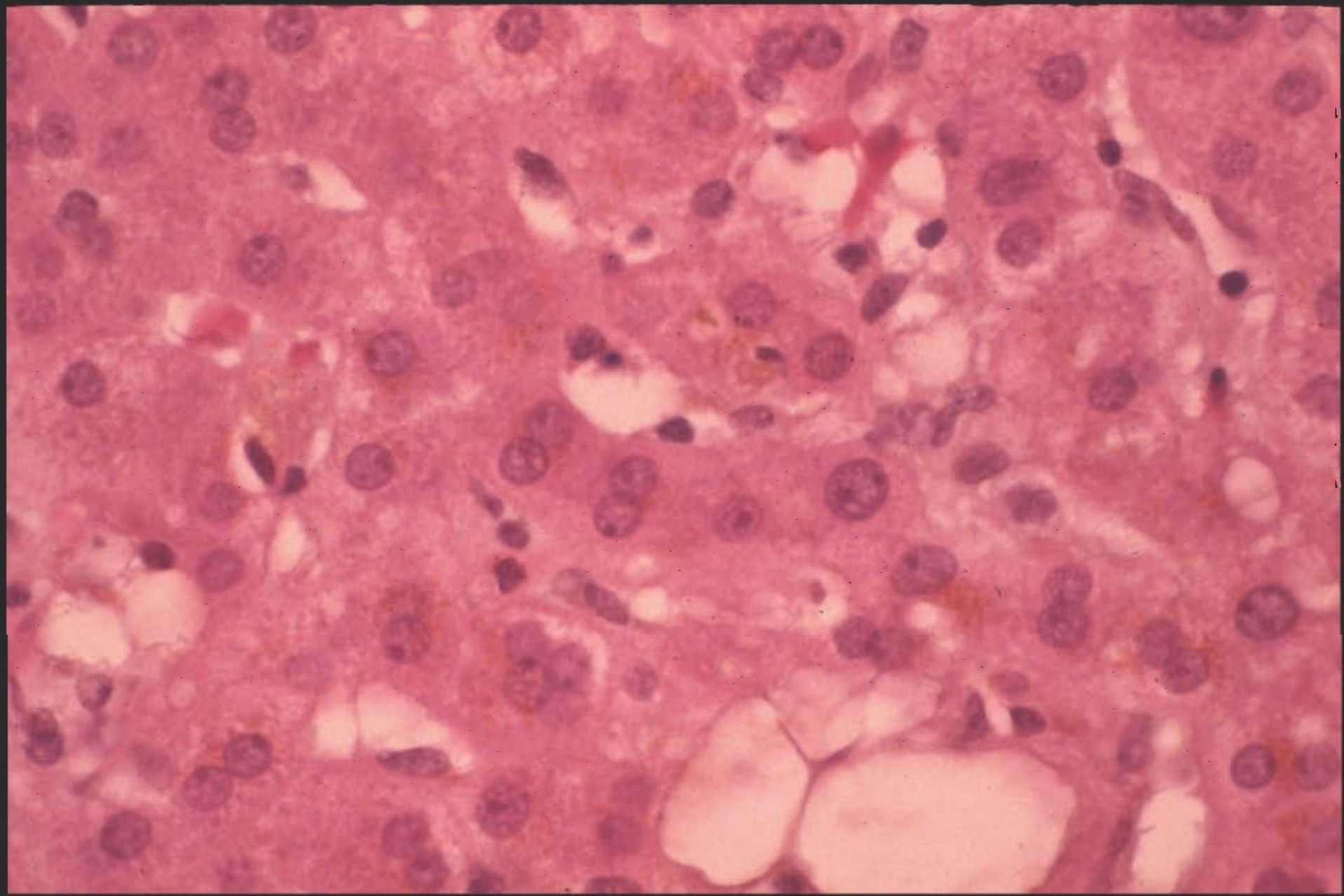
Impaired bile secretion and/or flow.
Regurgitation into plasma of bile components.

CLINICAL:

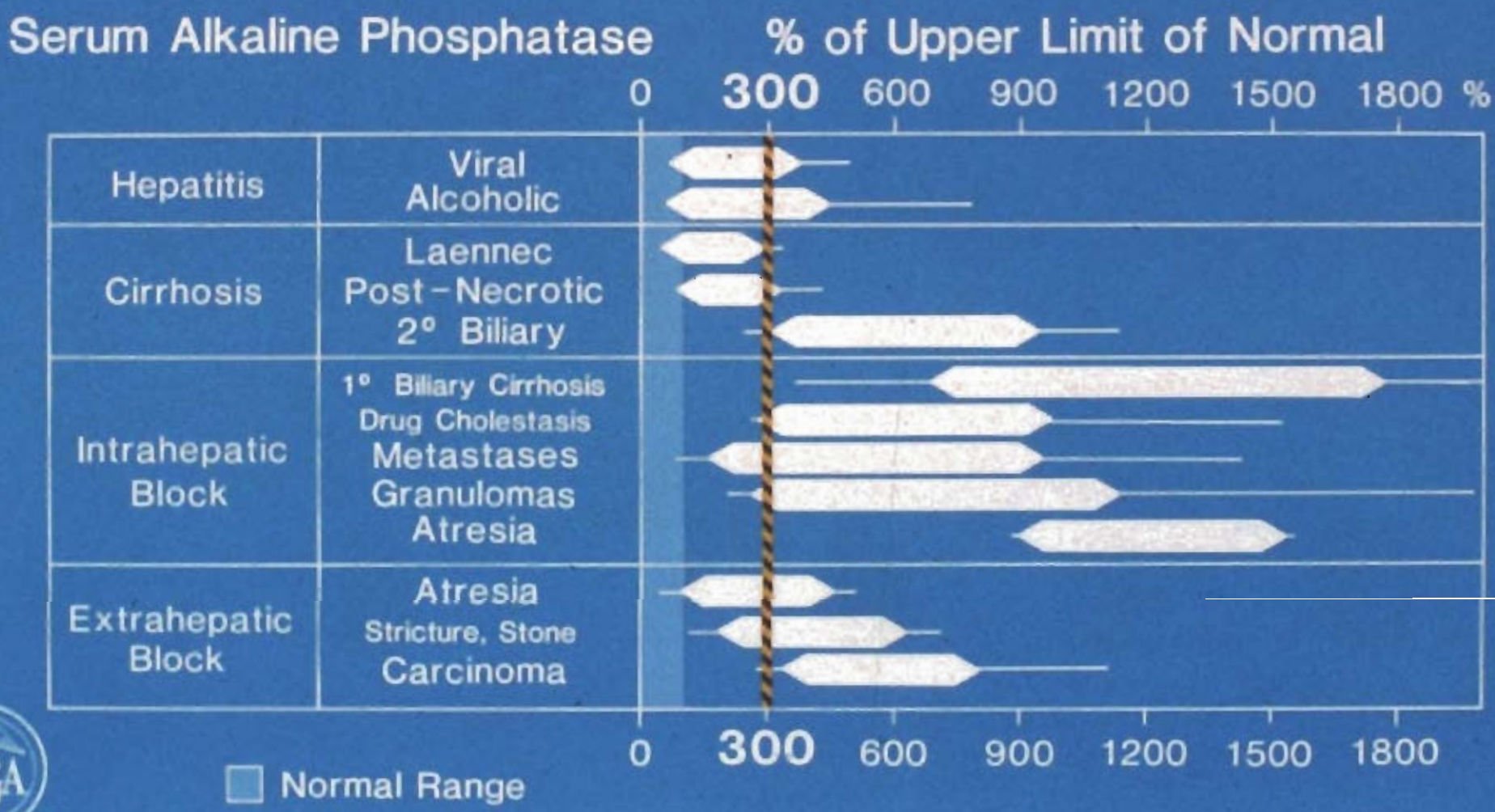
>3X elevation of serum alkaline phosphatase, increased serum cholesterol, and pruritus.

PATHOLOGICAL:

Blunting and loss of canalicular microvilli.
Canalicular dilatation and bile plugs.
Bile lakes with biliary obstruction.



SERUM ALKALINE PHOSPHATASE LEVELS DISTINGUISH HEPATOCELLULAR DISEASES FROM CHOLESTASIS



SUBSTANCES RETAINED DUE TO IMPAIRED HEPATIC FUNCTION PRODUCE VARIED CLINICAL MANIFESTATIONS

Endogenous Substances Retained	Manifestations Due To: Retention in Tissues	Deficiency in Intestinal Lumen
Bilirubin	Jaundice, Bilirubinuria, Kernicterus	Acholic stools
Bile Salts	? Increased damage to hepatocytes	Steatorrhea, Fat soluble vitamin deficiency
Phospholipids & Cholesterol	Hyperlipidemia, Xanthomas, Lipoprotein-X in plasma	--
Ammonia	Encephalopathy	--