Management of jaundice

Cath Harrison
Consultant Neonatologist, SJUH
May 2005

- Introduction
- Physiology
- History
- Testing
- Level to treat
- Why treat
- Treatment options
- Current management

Introduction

- Neonatal jaundice common
- > 50% healthy term infants
- Re-emergence of kernicterus
- AAP guidelines- July 2004

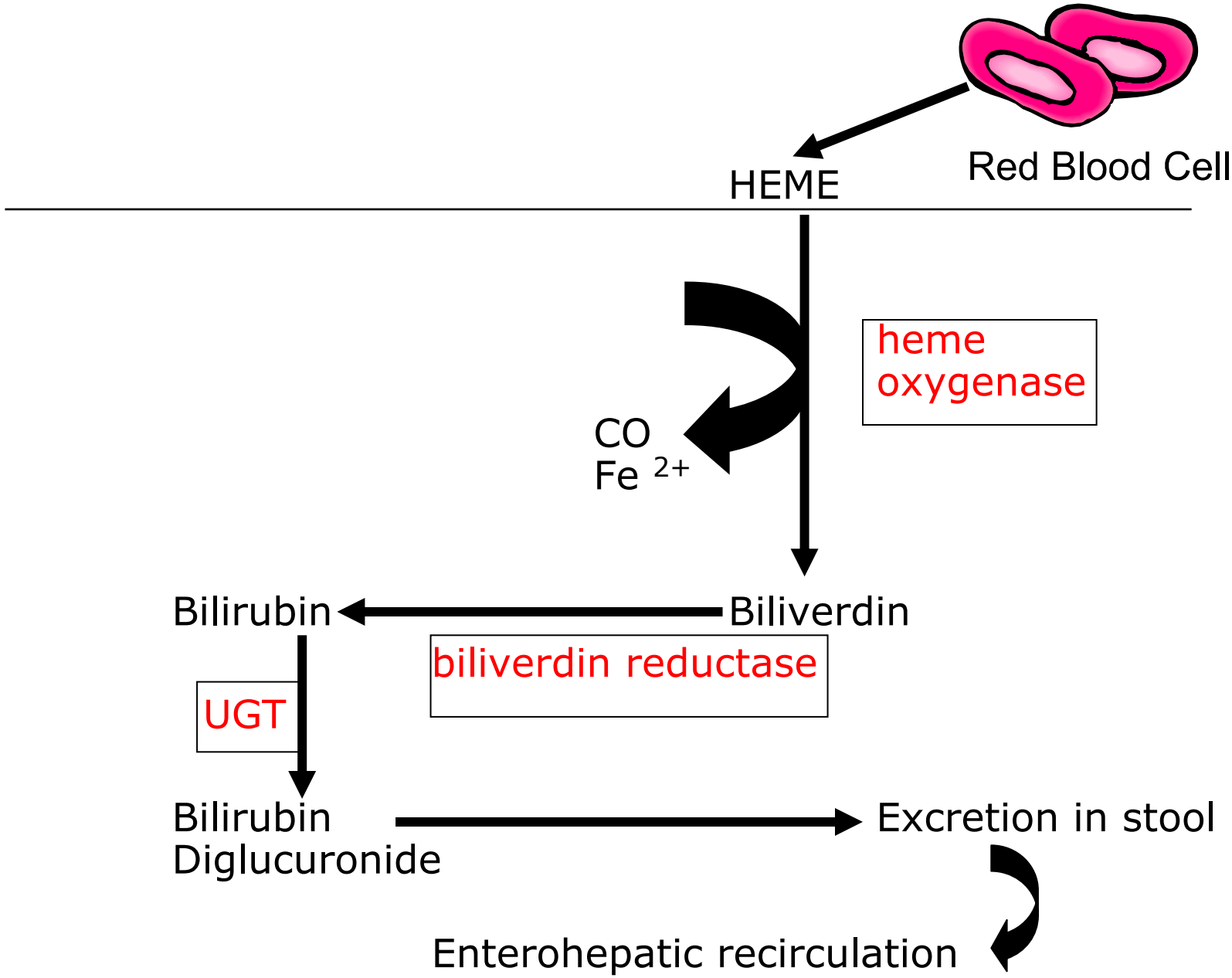
Physiology

- In utero bilirubin handled by placenta and mothers liver
- After birth, neonate must cope with increase in bilirubin production and decreased ability to clear bilirubin
- Course of adjustment uncertain

Why are neonates prone to jaundice?

- Increased bilirubin load
  - Red cell life span shorter & turnover higher
- Increased bilirubin production
  - Racial groups
  - Blood group compatibility
  - Increased enterohepatic circulation of bilirubin

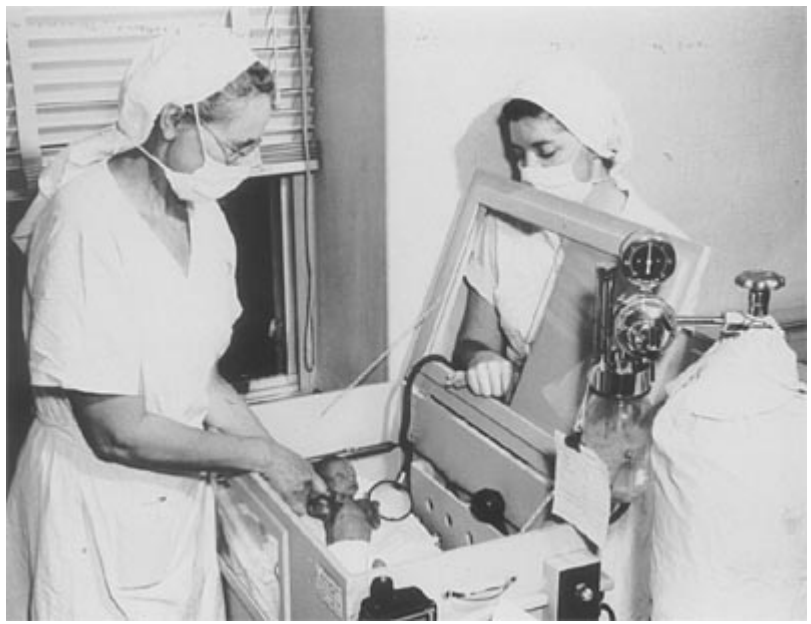
- Feeding
  - Breast milk- competitive inhibitor of UDGT
    - Increases bilirubin reabsorbed from gut
  - Inadequate nutrition
    - Limits newborns capacity to excrete bilirubin in stools
    - Breast Feeds typically established 96 hours after birth
    - Greatest risk for hyperbilirubinemia is 3-5 days
    - Dehydration contribute to onset and progression of jaundice


Red Blood Cell
HEME
heme oxygenase
CO
Fe 2+
Bilirubin
Biliverdin
biliverdin reductase
UGT
Bilirubin Diglucuronide
Excretion in stool
Enterohepatic recirculation

Why is bilirubin dangerous?

- Bilirubin must be bound to carrier protein to be transported
- Free bilirubin-
  - Not bound to albumin
  - Crosses blood brain barrier
  - Neurotoxicity
- Risk of neurotoxicity increases with
  - Decreased binding
  - Decreased albumin

History



18th century

1724

- "true jaundice, and, on the other hand, the icteric tinge which may be observed in infants, immediately after birth……

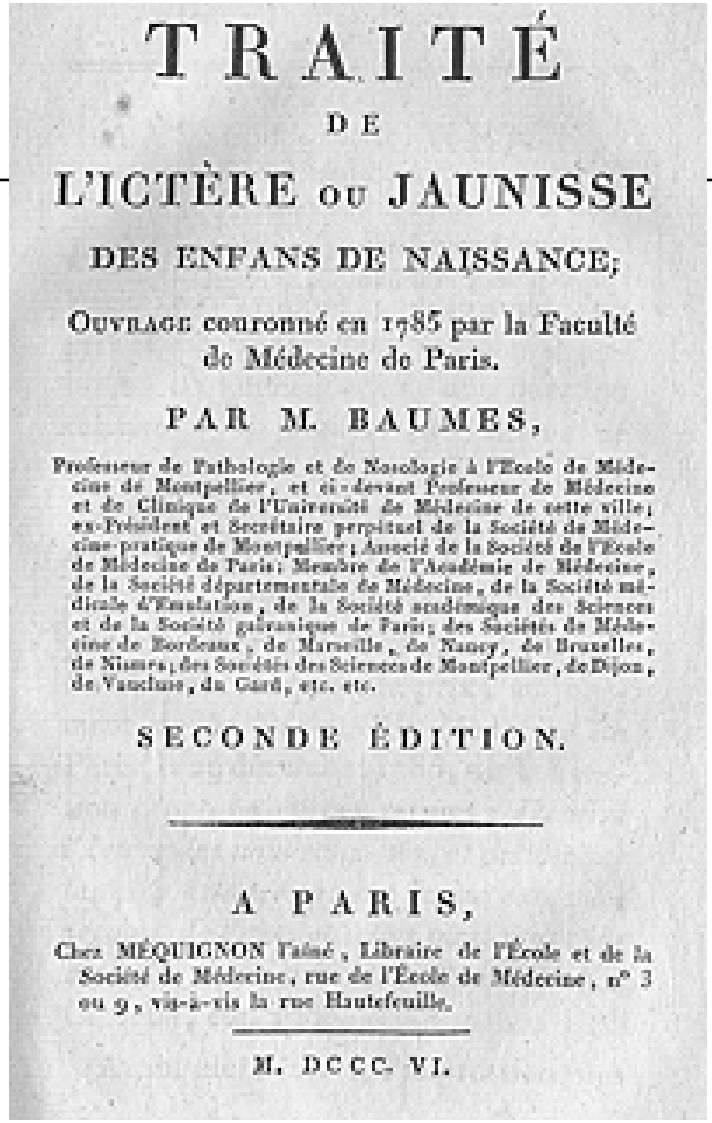
  the latter, is of no account and disappears spontaneously after meconium has been passed"

  Juncker

1737

- "I do not remember many practical authors. . . . who have taken notice of the jaundice in infants; nevertheless, many die of it for want of proper and seasonable helps; and most people are so stupidly ignorant that they imagine because the poor child grows yellow-consequently it must die, and therefore they will not look out for help"

  Bracken - The Midwives Companion



TRAITÉ

DE

L'ICTÈRE ou JAUNISSE

DES ENFANS DE NAISSANCE;

Ouvrage couronné en 1785 par la Faculté de Médecine de Paris.

PAR M. BAUMES,

Professeur de Pathologie et de Nosologie à l'Ecole de Médecine de Montpellier, et ci-devant Professeur de Médecine et de Clinique de l'Université de Médecine de cette ville; ex-Président et Secrétaire perpétuel de la Société de Médecine-pratique de Montpellier; Associé de la Société de l'Ecole de Médecine de Paris; Membre de l'Académie de Médecine, de la Société départementale de Médecine, de la Société médicale d'Emulation, de la Société académique des Sciences et de la Société galvanique de Paris; des Sociétés de Médecine de Bordeaux, de Marseille, de Nancy, de Bruxelles, de Nismes; des Sociétés des Sciences de Montpellier, de Dijon, de Vaucluse, du Gard, etc. etc.

SECONDE ÉDITION.

A PARIS,

Chez MÉQUIGNON l'aîné, Libraire de l'École et de la Société de Médecine, rue de l'École de Médecine, n° 3 ou 9, vis-à-vis la rue Hautefeuille.

M. DCCC. VI.

1905 "…… In some jaundice persists for weeks…….from a deficiency of intestinal juices. The feeding during this period must be carefully watched, and it will usually be found safer to give the increase in food every second or every third day"

John Zahorsky

1908 "Occurrence of icterus neonatorum ...between 15% and nearly all infants"

Shaw and Fetra. The Diseases of Children

1921 Icterus neonatorum- - "yellow colouration of the skin is at first hidden…..can only be seen when blood is pressed out of a portion of skin e.g. tip of the nose…"

Dr August Ritter von Reuss.The diseases of the newborn

Still 1909

- " jaundice…lasting for an unusually long time…may be due to some catarrhal condition consequent upon chilling…..he has just come from an environment where the temperature was 99°or more, now he lies naked, or in the sorry protection of a flimsy shawl, in a room with a temperature of 65° or less, while he awaits the attentions of a nurse who is perhaps none too careful to avoid chill in washing him…."

1930

Icterus is "much less common in private than in hospital patients, suggesting with care and the better condition of the patient at birth, it is less likely to occur"

"on this account, slight chills are regarded by some as the cause"

Donald Paterson. Sick Children Diagnosis and Treatment

Incidence

- > 50% healthy term infants
- Incidence of jaundice varies from one nursery
  - Lab standards, feeding policies, drugs
  - Intensity and duration of illumination in the nursery

Lucey JF Pediatrics. 1969;44(2):155-7

- Prevention of rhesus incompatibility
- Newborn hyperbilirubinemia- commonest readmission diagnosis

Stevenson DK et al. J Perinatol.2004;24(8):521-5.

- Testing
  - 1994-AAP
    - Aim to reduce unnecessary testing and treatment
  - Universal screening

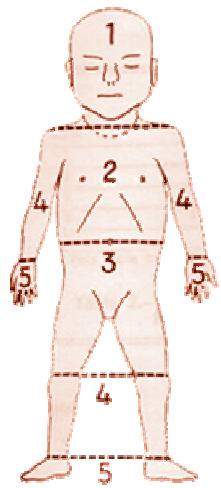
    Bhutani VK, Johnson L, Sivieri EM Pediatrics. 1999;103(1):6-14.
  - Cost *v* benefit

1. Inspection

- Initial diagnosis
- Unreliable
- SBR 119-136 μmol – visible
- Face and trunk, not extremities SBR= 204
  Riskin A, Abend-Weinger M, Bader D. Clin Pediatr (Phila). 2003;42(2):153-8
- Intraobserver agreement about jaundice only marginally better than chance alone!
  Moyer VA, Ahn C, Sneed S. Arch Pediatr Adolesc Med. 2000;154(4):391-4

Kramer's rule

- jaundice starts on the head
- extends towards the feet as the level rises

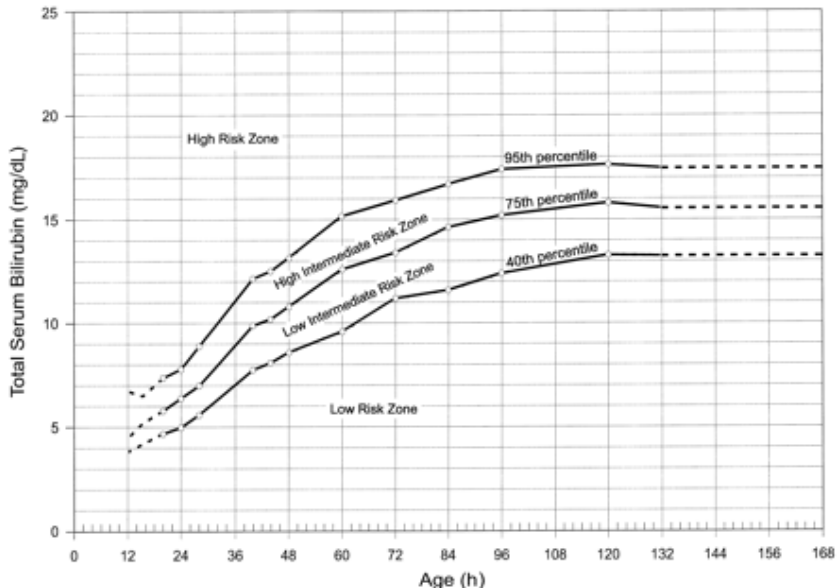


Zone	1	2	3	4	5
SBR umol/L	100	150	200	250	>250

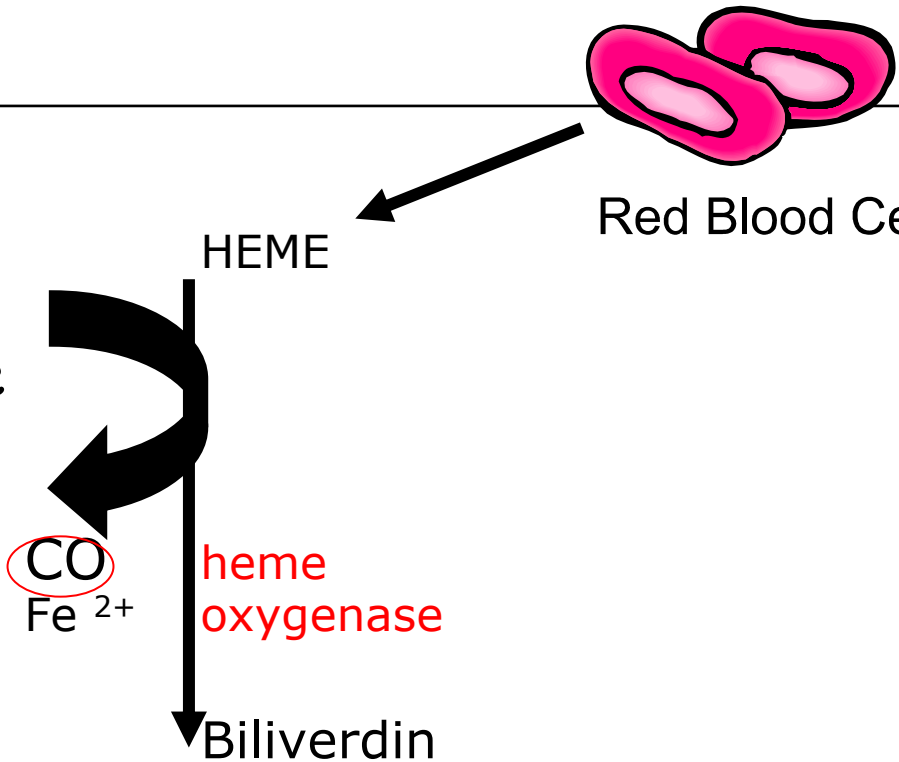
Kramer LI. Amer J Dis Child. 1969; 118: 454-458

2. Transcutaneous bilirubinometers

- Acceptable correlation between TcB and SBR
- Variable accuracy
  - Skin pigmentation
  - SBR > 257
  - < 35/40
- Easy, non-invasive, repeatable
- Predischarge screening tool SBR> 95th C



3. End tidal Carbon Monoxide



Direct measurement of rate of heme catabolism and rate of bilirubin production

Correct for ambient carbon monoxide

4. Serum bilirubin

- SBR = bilirubin produced – bilirubin eliminated
- Severe haemolysis not essential for imbalance to occur
- Mainstay of management of neonatal jaundice
- Need high precision, reproducibilty, accuracy
- Large inter-laboratory variability

Vreman HJ et al Clin Chem. 1996;42(6 Pt 1):869-73

5. Bilirubin:albumin ratio

- correlates to unbound bilirubin
  - ability of bilirubin to bind
  - amount of albumin

- if bilirubin load exceeds binding capacity→free bilirubin

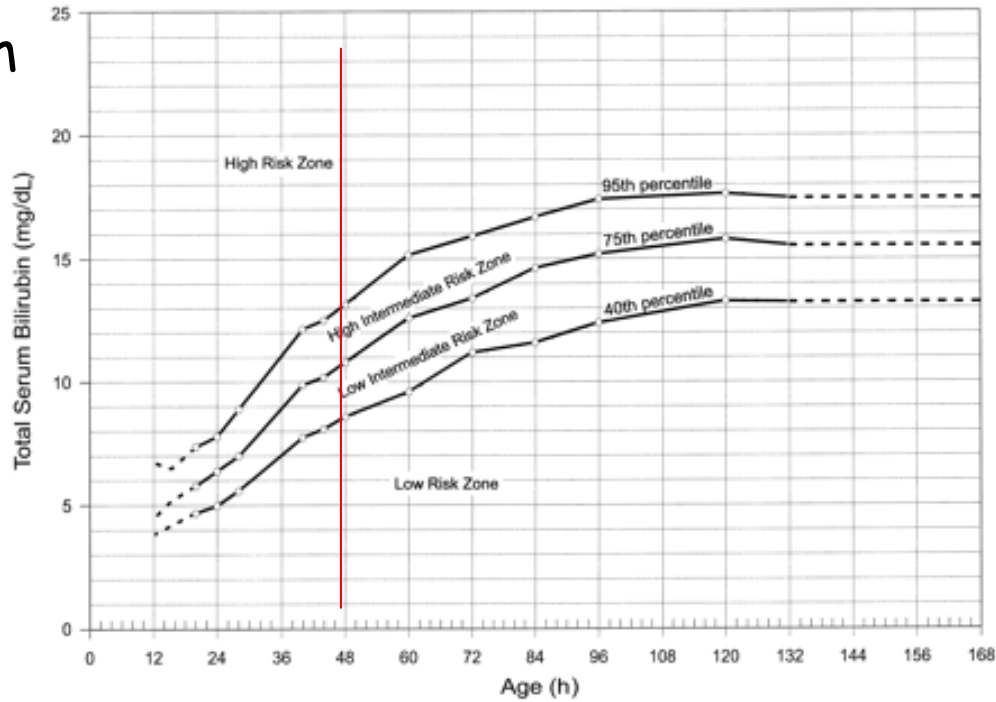
- SBR (mg/dl) : Serum albumin (g/dl)
- Ratio > 0.63 may be associated with ABR changes

What level to treat

- **1952**
  - kernicterus
    - 50% babies SBR > 31
    - 18% SBR 16-30
  - recommended SBR kept < 20
- **1959**
  - 54 term babies, no isoimmunization, SBR> 20
  - No exchanges. All normal at follow up
- **1972**
  - " at present would not treat any full term infant with exchange transfusion regardless of degree of hyperbilrubinaemia….after excess hemolysis excluded….risk of exchange far greater than kernicterus…"
- **1983**
  - Vigintiphobia

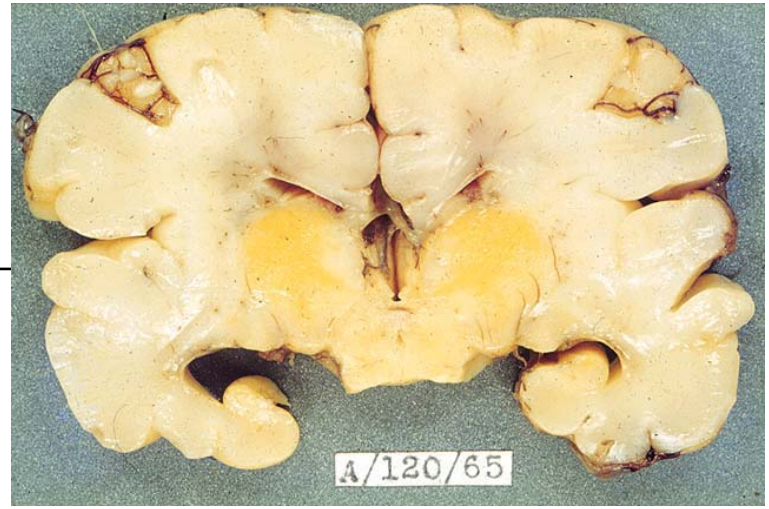
Bhutani nomogram
hour specific SBR values

- hour specific SBR values
- 2840 near-term and term babies
- no obvious evidence of haemolytic disease
- at discharge or 48 hours, SBR has not yet reached its peak
- allows prediction of risk of hyperbilirubinaemia



Bhutani VK, Johnson L, Sivieri EM Pediatrics. 1999;103(1):6-14

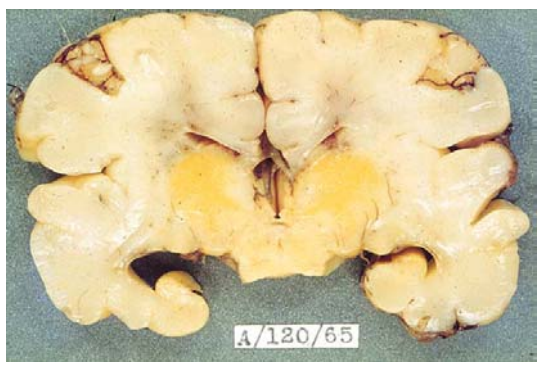
Why treat ?



- kernicterus
  - Yellow kern = nuclear region
  - pathological diagnosis
  - interchangeable with acute or chronic bilirubin encephalopathy
- AAP 2004
  - acute- toxicity in first week of life
  - kernicterus- chronic and permanent sequelae

Kernicterus

- Frequency declined- prevention of rhesus disease
- 1971-1991
  - no published reports in healthy full term babies
  - less aggressive approach to jaundice and notion that kernicterus would not occur in previously healthy babies
- since then….re-emergence of problem



- 1970- length of stay 3.9 days

  Curtin SC, Kozak LJ. Birth. 1998;25(4):259-62

- Today- shorter stay, cost, public pressure for natural childbirth

- early discharge before bilirubin peak ?

- Earlier discharge - responsibility for observing babies in high-risk period shifted

Incidence

- Pilot kernicterus registry USA
  - 1992-2001 80 infants
  - all discharged pre 72 hours
  - 75% readmitted in first week
  - 95% breast fed
  - severe kernicterus sequelae in 80%

- BPSU
  - unconjugated hyperbilirubinemia SBR > 510μmol/l
  - 1st year of study- 38 infants met criteria
  - 6 cases of bilirubin encephalopathy

What can hyperbilirubinaemia do?

- Study 30,000 full term infants
  - If SBR kept < 20 (340)- no adverse effects on IQ, neuro examination or hearing

Newman TB, Maisels MJ Clin Perinatol. 1990;17(2):331-58

- Moderate HB (205-340 in term babies)
  - behavioural and learning difficulties
  - dose – response relationship

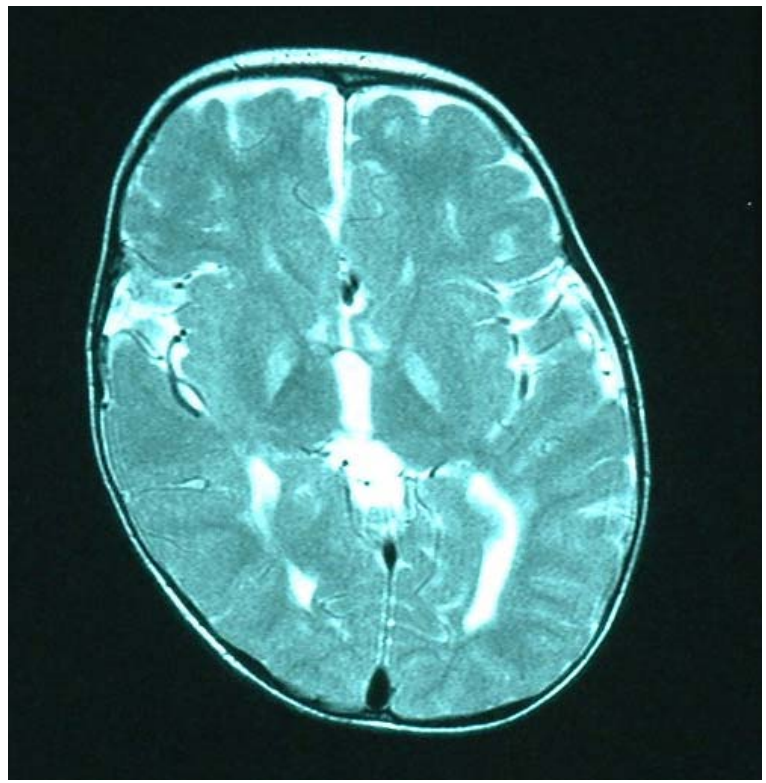
Soorani-Lunsing I, Woltil HA, Hadders-Algra M Pediatr Res. 2001;50(6):701-5

Clinical signs of severe hyperbilirubinaemia

- acute
  - hypertonia- extensor muscles
  - opisthotonus
  - poor feeding
  - high pitched cry
- chronic
  - extrapyramidal movement disorders
  - gaze abnormalities
  - sensorineural hearing loss
  - intellectual deficit

Volpe JJ. Neurology of the newborn

- neuropathic features of bilirubin induced brain injury/kernicterus well known
- limited understanding of neuronal injury and cell death
- chronologic evolution of injury and predictive value to long term disability poorly defined
- MRI patterns recognized



Treatment

- **1908**- "medical intervention in cases of icterus neonatorum is in no sense indicated…."
- **1909**- "icterus neonatorum is usually so evanescent a phenomenom that it calls for no treatment beyond- and I fancy this may be of importance- keeping the baby warm"
- " if the jaundice has not disappeared by the end of the second week, give grey powder. Hyd. Cum.creta gr 1/4, sod.bicarb.gr.j 3 x day…"

Blood exchange transfusion

- Hart - **1925**
  - first exchange transfusion -erythroblastosis fetalis
  - successful, but ignored for next 20 years
- Wiener, Wexler and Gamrin - **1944**
  - failed
- Wallerstein - **1946**
  - 3 successful exchange transfusions- erythroblastosis fetalis.
  - saggital sinus for blood withdrawal and peripheral vein for infusion

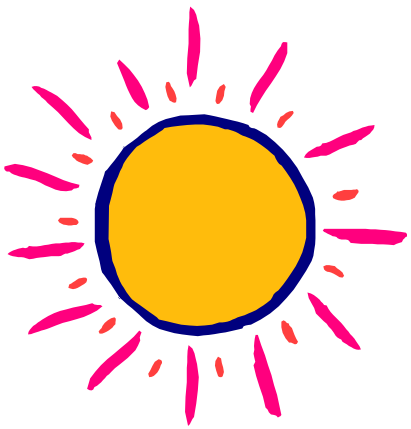
- Definitive technique described by Diamond in **1947**
  - introduced umbilical vein use for exchange transfusion

Diamond LK, Allen FH Jr,Thomas WO Jr NEJM 1951 11;244(2):39-49

- mainstay of treatment **1970s**
- mortality 0-7%
- morbidity
  - blood products
  - metabolic derangement
  - cardiorespiratory
  - catheter complications

- Study 1997
  - No mortality in healthy infants
  - 20% died in sick infant group
  - 14% permanent sequelae
- As Exchange Transfusion becomes less frequently carried out
  - ? Risk of higher morbidity and mortality

- Light treatment
  - **1958** Cremer et al, Lancet
  - Sunlight



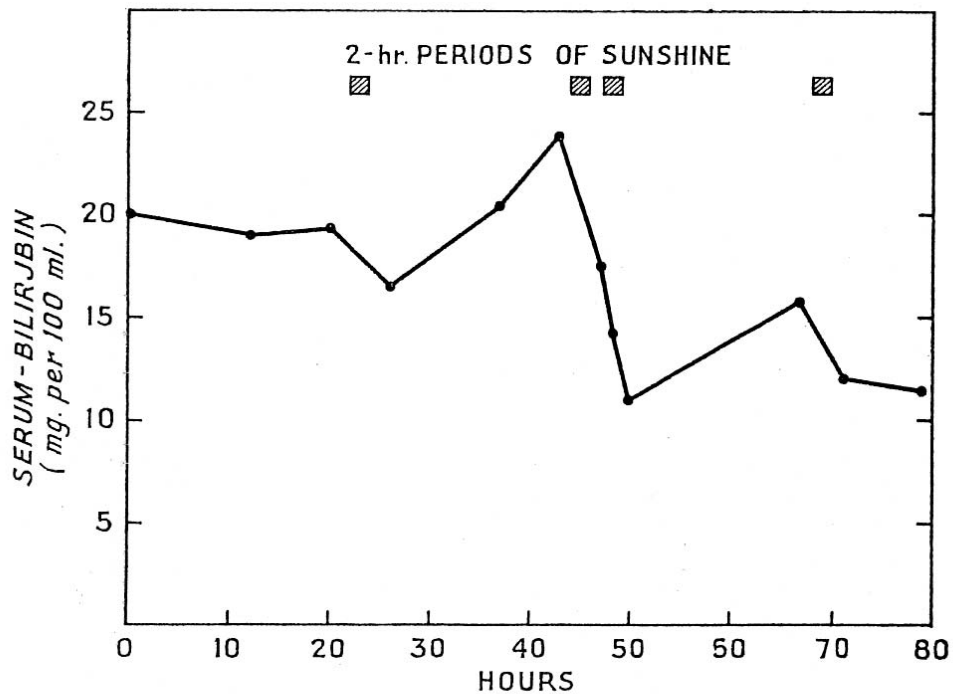
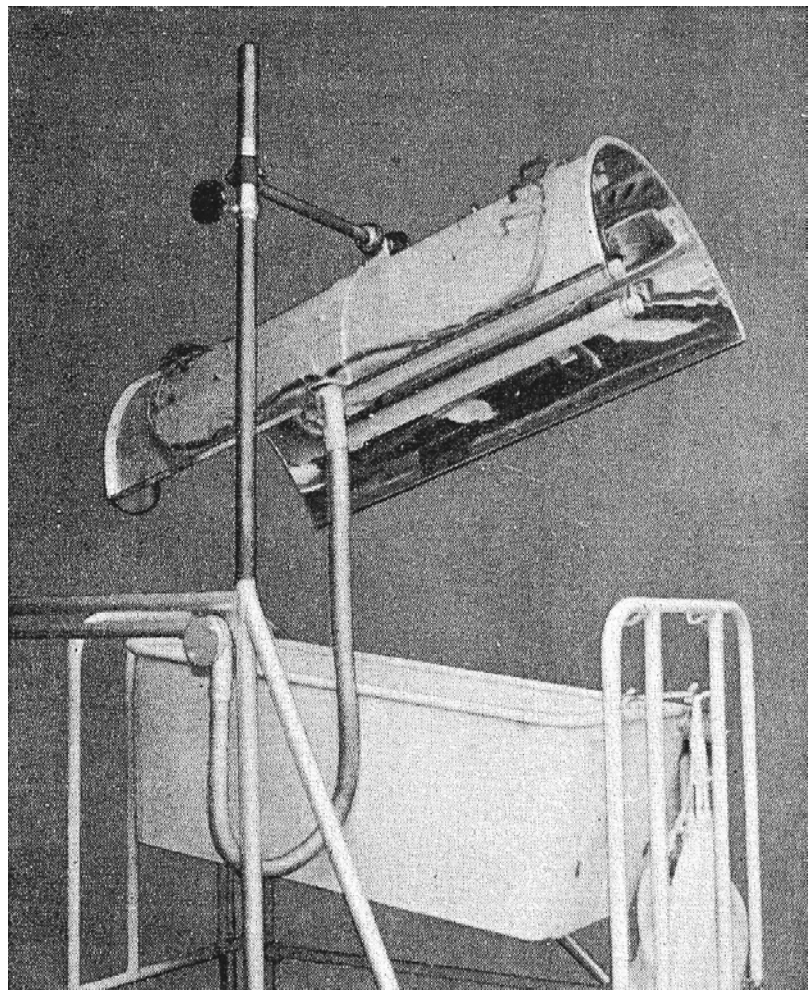


Fig. 5—Sunshine treatment of an icteric infant with jaundice of prematurity (case 6)

- Artificial light- same result
- Found better drops in bilirubin with intermittent PTX
- Specimens left in daylight lose up to 30% bilirubin in 1 hour
  - Sample transportation issue



Cremer RJ, Perryman PW, Richards DH. Lancet 1958;1(7030):1094-7.

- How does it work?
  - Photochemical reactions occur
  - Formation of E-isomers and lumirubin- water soluble
- Efficacy
  - Light intensity wavelength
  - Body surface exposed
  - Dose delivered
    - Power of light
    - Distance from baby

- Intermittent v continuous
  - Conflicting results
  - Theoretically no plausible rationale for intermittent PTX
- Bronze baby
  - Cholestatic jaundice
  - May be related to accumulation of porphyrins
  - Presence of direct hyperbilirubinaemia not C/I
- Contra-indication
  - Congenital porphyria / FH - severe photosensitivity and blistering

Side effects?

- DNA modifying properties

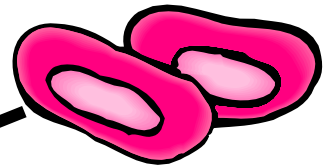
  SpeckWT, Rosenkranz HS. Environ Mutagen. 1979;1(4):321-36.

- Cerebral blood flow
  - Peak systolic blood flow increased with overhead PTX cf bilibeds.
  - Small number trial n=30

    Hammerman C, Kaplan M Biol Neonate 2004

- Loose stools, dehydration, skin rashes

TREATMENT OPTIONS



Red Blood Cell

HEME

HO INHIBITORS

heme oxygenase

CO

Fe^{2+}

Bilirubin

Biliverdin

biliverdin reductase

INCREASE CONJUGATION

UGT

BILIVERDIN REDUCTASE INHIBITORS

Bilirubin Diglucuronide

Excretion in stool

Enterohepatic recirculation

DECREASE ENTEROHEPATIC RECIRCULATION

Inhibition of heme degradation

1. **Metalloporphyrins**

   - Heme oxygenase rate limiting step in bilirubin production
   - Inhibitors of HO
   - Inhibit bilirubin production
   - Also affect lipid peroxidation

Tin

- Non-biocompatible metal
- Very high potency
- Photosensitization, induce mRNA
- Neonatal trials
  - PTX decreased by 76%
  - i.m. injection
  - No long term effects at 18/12

Stevenson DK et al.J Perinatol. 2004;24(8):521-5

Reddy P et al J Perinatol. 2003;23(6):507-8

Valaes T et al, Pediatrics. 1994;93(1):1-11

- Zinc
  - Biocompatible metal
  - Orally absorbable
  - Chimps only

    Stevenson DK, Wong RJ, Vreman HJ, McDonagh AF, Maisels MJ, Lightner DA. J Perinatol. 2004;24(8):521-5.

    Chromium
  - Biocompatible metal
  - No phototoxicity
  - Orally absorbable

- Ideal treatment combo
  - Narrow spectrum blue light 450-480nm + metalloporphyrin

2. D penicillamine

- Europe but not USA
- Chelating agent
- Does not displace bilirubin from albumin

  - Historical trial for ABO incompatibility
    ↓ exchange transfusions- not stat significant

    Side effects
    - Adults- fatal with aplastic anaemia, thrombocytopenia, myasthenia

    - Potential effects- ↓ Ca^{2+} influx, ↓ myocardial contractility

- 3.Peptide inhibitors of Heme Oxygenase
  - Immunosuppressive
  - No human studies
  - Mice- upregulation of HO mRNA

Inhibiting biliverdin reductase

- Potentially useful
- Enzyme that converts biliverdin to bilirubin
- Biliverdin
  - Water soluble
  - Excretable
- No studies yet
- Side effect – green babies!

Increase bilirubin conjugation

- 1. Phenobarbitol
- Enhances UPGT, improves conjugation
- Given last weeks of pregnancy
  - ↓incidence of severe jaundice
  - Need for exchange ↓by factor of 6
- Side effects
  - sleepiness, stupor, breathing ↓

- 2. Clofibrate
- Antilipidaemic agent
- Reduces VLDL and cholesterol
- ↑ bilirubin conjugation and excretion
  - Lower SBR, shorter duration of jaundice
  - ↓ use of PTX
- Side effects
  - Nausea (adults), muscle cramps, pruritis, leukopenia
  - Neonatal study- no side effects but no long term follow up

3. Herbal remedies

" *where there's tea, there's hope"* Sir Arthur Pinero 1855

- Artemesia (yin-chen), Huang-lin (coptis chinesis)
- Hepatoprotective
- ? Antioxidant effect
- Constitutive androstane receptor related
  - Bilirubin clearance
  - Herbal teas in mice→accelerated clearance of bilirubin, need CAR to do so

Lazar MA J Clin Invest. 2004;113(1):23-5.
Huang W, Zhang J, Moore DD J Clin Invest.2004;113(1):137-43

Decrease enterohepatic recirculation of bilirubin

Oral feeding

Early feeds

Fluid supplementation will not prevent ↑ SBR

Oral charcoal

Reduces SBR

Agar

Can bind to bilirubin in GI tract

↓ duration of PTX

Yetman RJ et al J Pediatr. 1998;133(5):705-7

Davis DR, Yeary RA. Dev Pharmacol Ther1987;10(1):12-20

Others

Albumin

- ↑ bilirubin binding
- prevents free bilirubin entry into brain
- Pre – exchange
  - Conflicting results re efficacy

Bilirubin oxidase

- Oxidation of bilirubin → water soluble and excretable
- Side effects- enzyme derived from fungus, allergic reactions possible

Kimura M, Matsumura Y, Miyauchi Y, Maeda H. Proc Soc Exp Biol Med. 1988;188(3):364-9

AAP guidelines 2004 (>35/40)

- Prevention
- PTX
  - Direct/conjugated should not be subtracted from total bilirubin
- Haemolysis
  - I.V. gammaglobulin 0.5-1g/kg over 2 hours
- Albumin
  - If serum albumin < 30
- Exchange
  - In any infant with signs of encephalopathy even if SBR falling

- Parent info
  - Written and verbal

- Follow-up
  - by health care professional

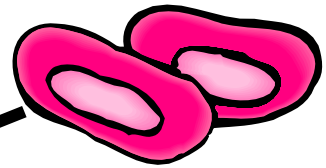
Infants discharged	should be seen by age
< 24 hours	72 hours
24 - 48 hours	96 hours
48 - 72 hours	120 hours

Earlier or more frequent follow-up if risk factors.

SUMMARY

TREATMENT OPTIONS

1.PHOTOTHERAPY
2.EXCHANGE TRANSFUSIONS



Red Blood Cell

HEME

3.HO INHIBITORS

heme oxygenase

CO
Fe^{2+}

Biliverdin

biliverdin reductase

4. BILIVERDIN REDUCTASE INHIBITORS

Bilirubin

5. INCREASE CONJUGATION

UGT

Bilirubin Diglucuronide

Excretion in stool

Enterohepatic recirculation

6. DECREASE ENTEROHEPATIC RECIRCULATION

Summary

- Kernicterus still rare
- Need to be more aware
- Remember high risk babies
- More frequent follow up
- Future research-
  - Tin MP
  - ETCO