

Porphyria, metals and rare liver diseases

David Cassiman, MD, PhD

Gastroenterology-Hepatology and Metabolic Center

University Hospitals Leuven

Female, 21 years

Medical history:

- 2012 birth of first child
- 08/2013: abdominal pain → “acute right-sided colitis”
- 2014 birth of second child
- 01/2015: “pyelonephritis” Rx trimethoprim/sulfamethoxazole
- 02/2015: abdominal pain → “esophagitis grade A”

2012-2015: 12 admissions in Emergency dept, 3 gastroscopies, two colonoscopies, 16 abdominal imaging exams (3 CTs), 21 lab workups

→ Referral to liaison psychiatry

Seeks second opinion in university hospital

Admission Leuven

Abdominal pain for 1 week, nausea and vomiting

No inflammation, no peritonitis on physical exam, normal lactate

Repetitive imaging negative but distended colon with constipation

Hyponatremia	123 mmol/L (135-145)
--------------	----------------------

pOsm	256 (low)
------	-----------

UNa	98 (too high)
-----	---------------

UOsm	513 (too high)
------	----------------

Lead, C1 esterase and porphyrins were checked

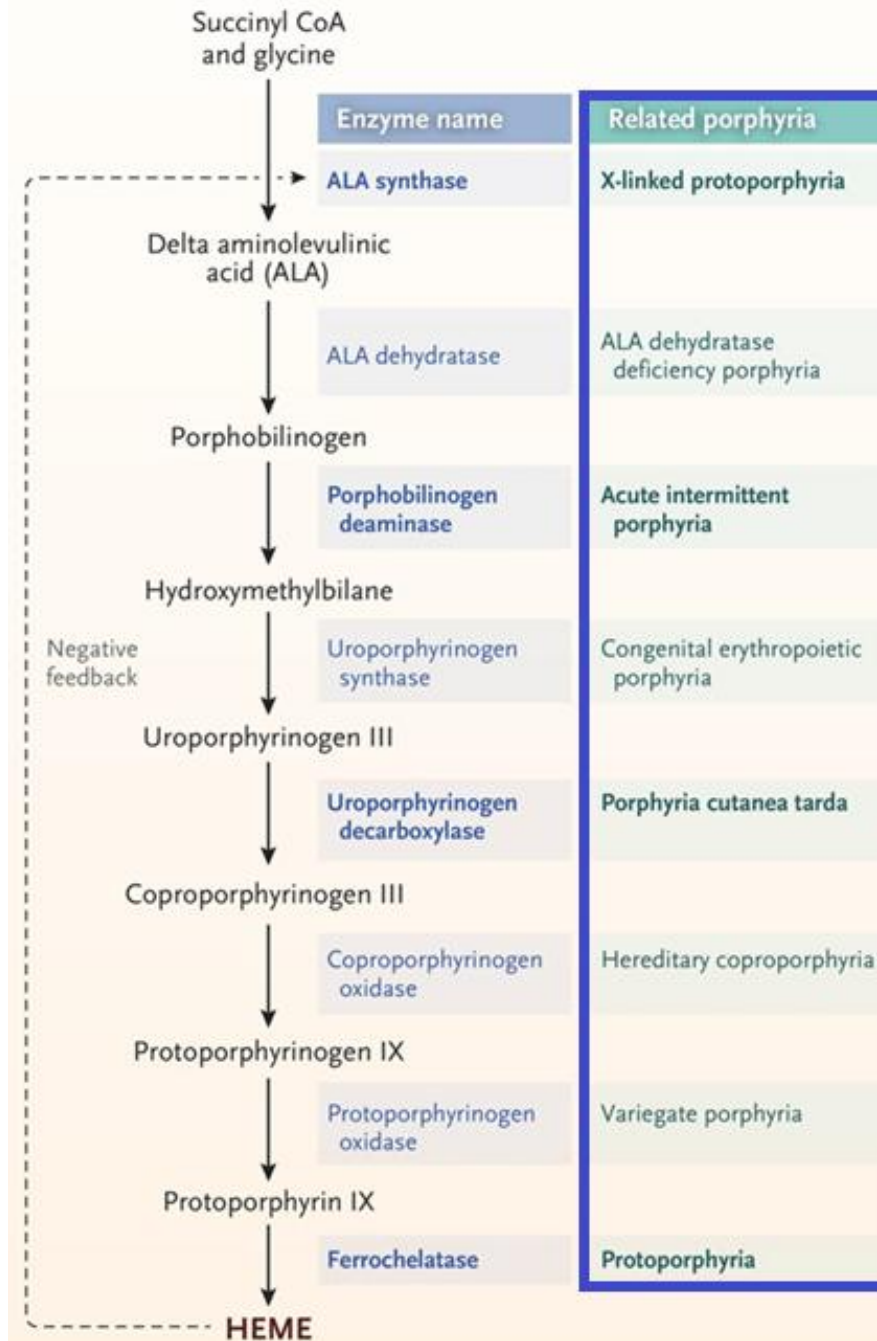
Spot urine

PBG	*	38.4 mg/L	0.0 - 2.0
-----	---	-----------	-----------

Blood

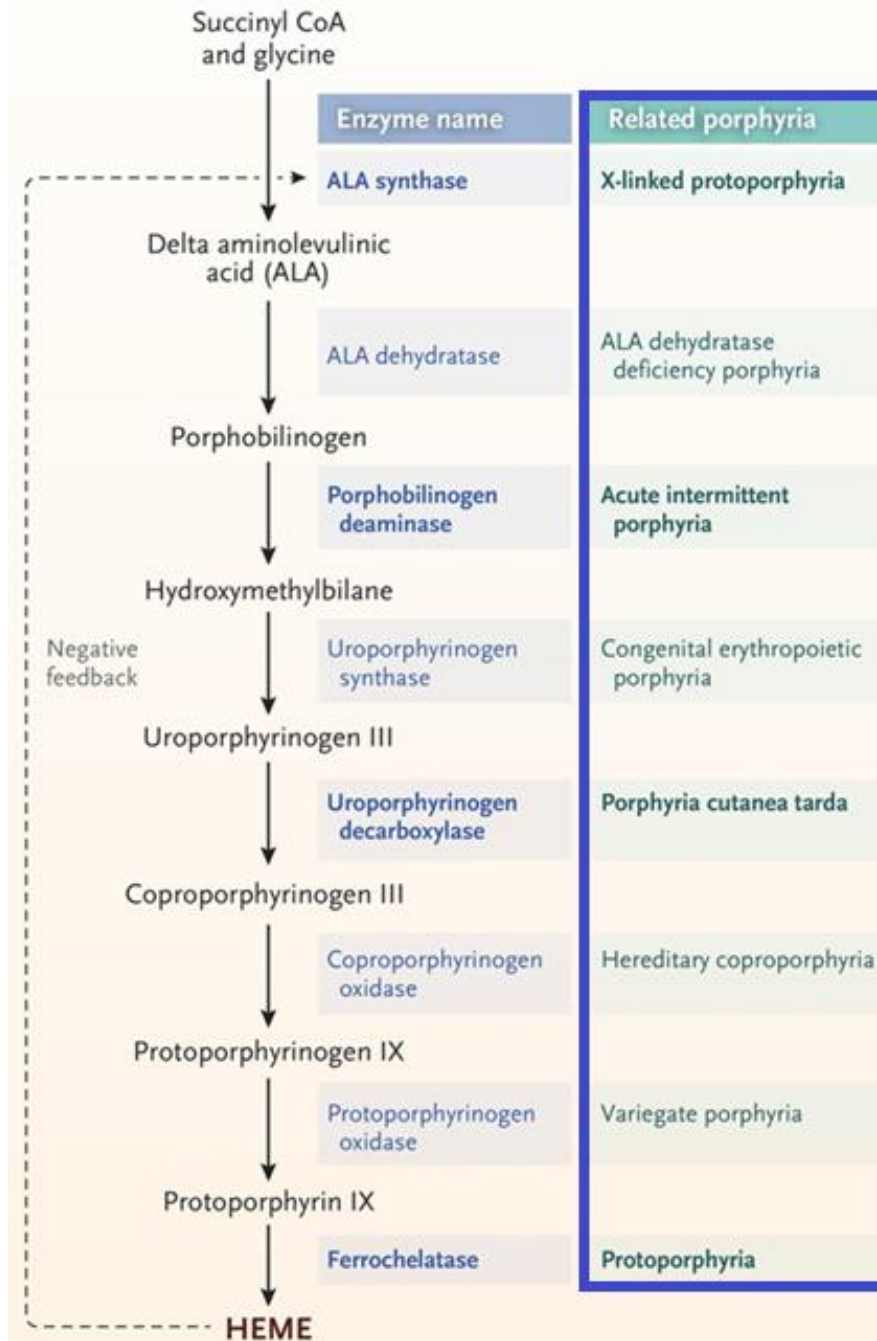
PBG-deaminase	*	5.7 nmol/L RBC.s	6.8 - 14.3
---------------	---	------------------	------------

Heme Synthesis



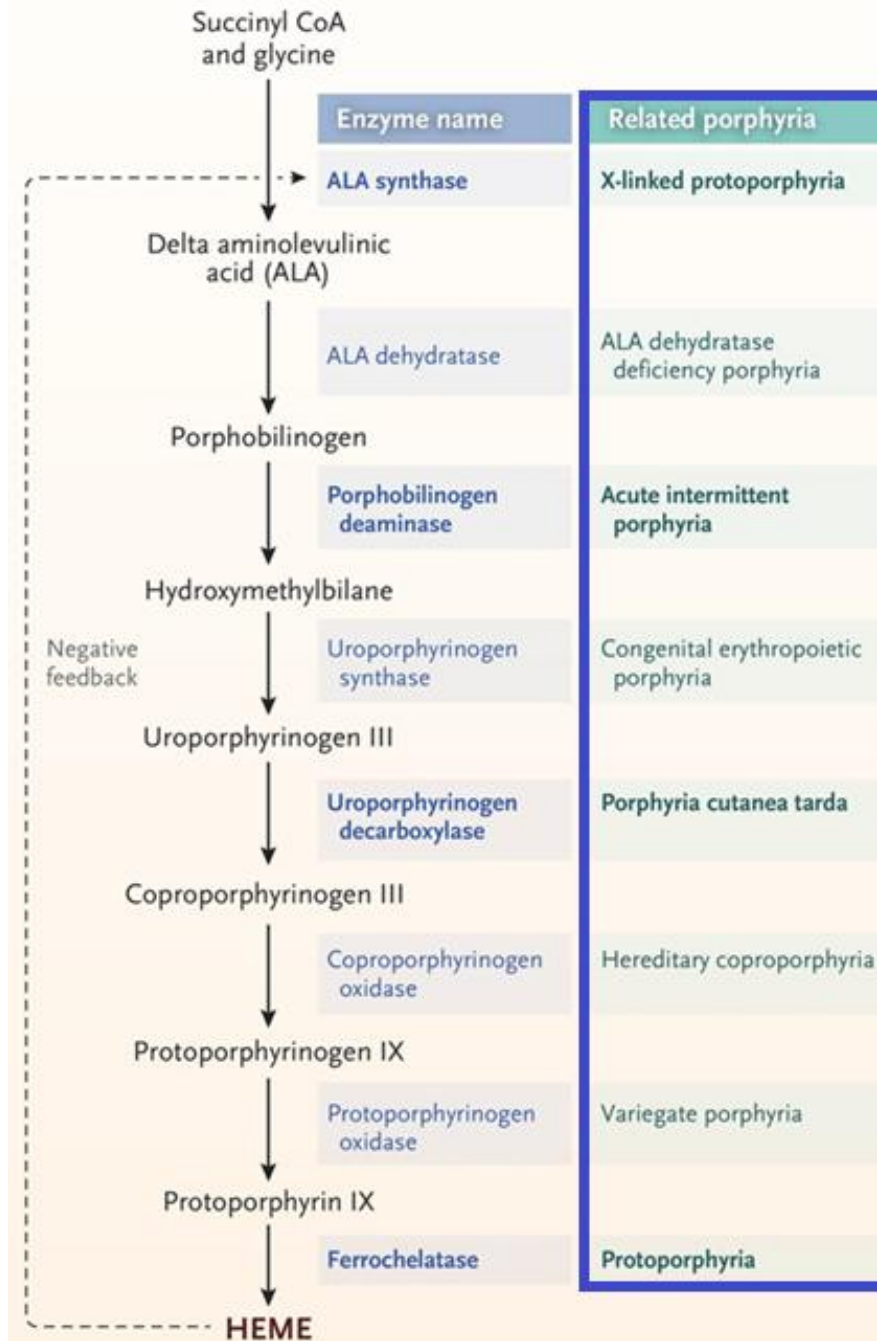
Acute
(hepatic)
porphyrias

Heme Synthesis



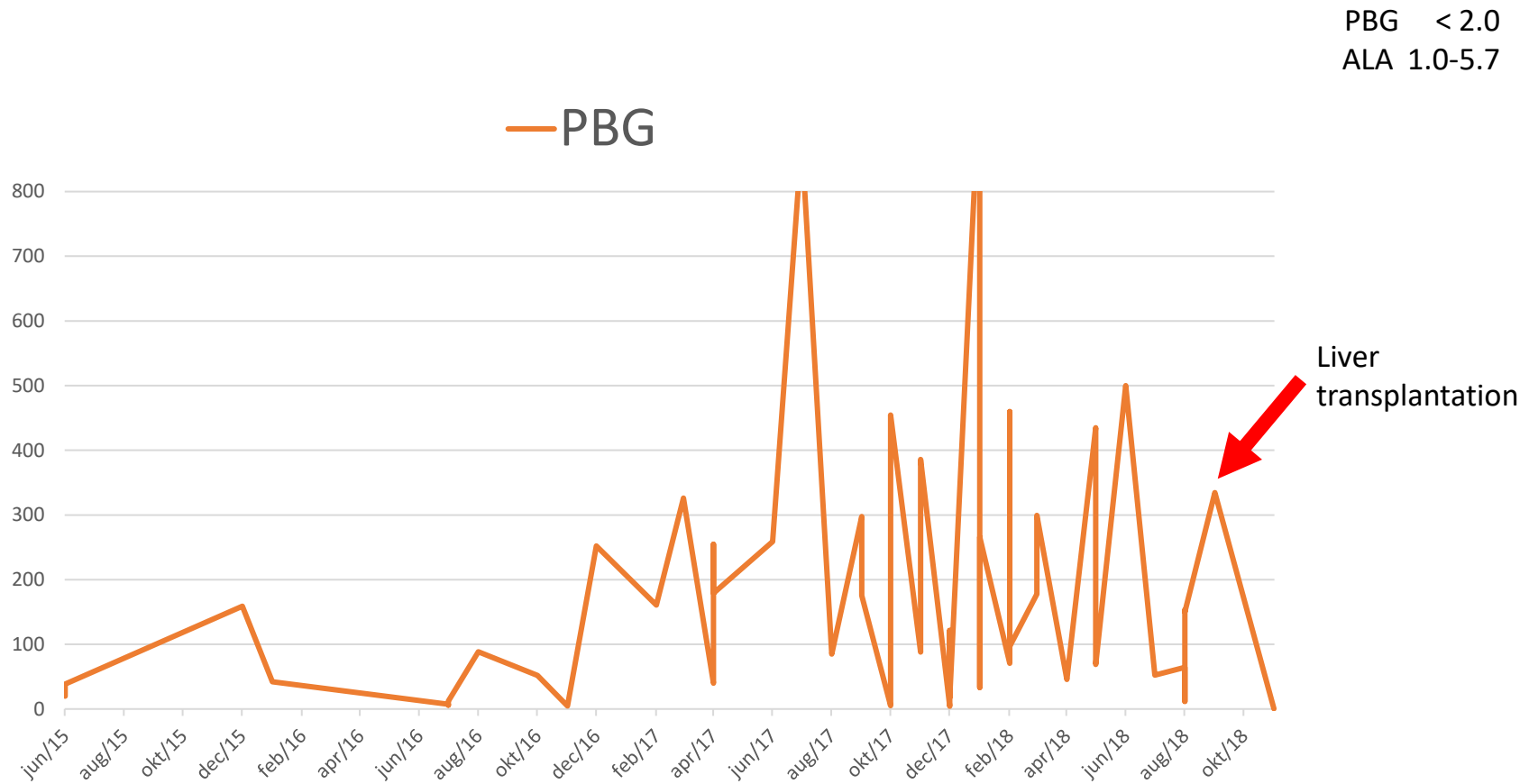
Blistering porphyrias

Heme Synthesis



Burning porphyria

Evolution next 3 years



3 years between diagnosis and LTx

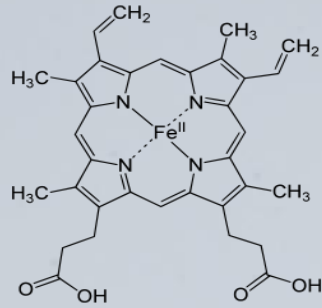
- Crescendo attacks, finally /2wk
- > 80 Hemin vials IV
- Addictive behavior (pethidine)
- Loss of employment and financial problems
- Marital problems, care for children delegated

Journal of Inherited Metabolic Disease (2018) 41:809–817
<https://doi.org/10.1007/s10545-018-0178-z>

ORIGINAL ARTICLE

Medical and financial burden of acute intermittent porphyria

Rochus A. Neeleman¹ • Margreet A. E. M. Wagenmakers¹ • Rita H. Koole-Lesuis¹ • G. Sophie Mijnhout²
J. H. Paul Wilson¹ • Edith C. H. Friesema¹ • Janneke G. Langendonk¹

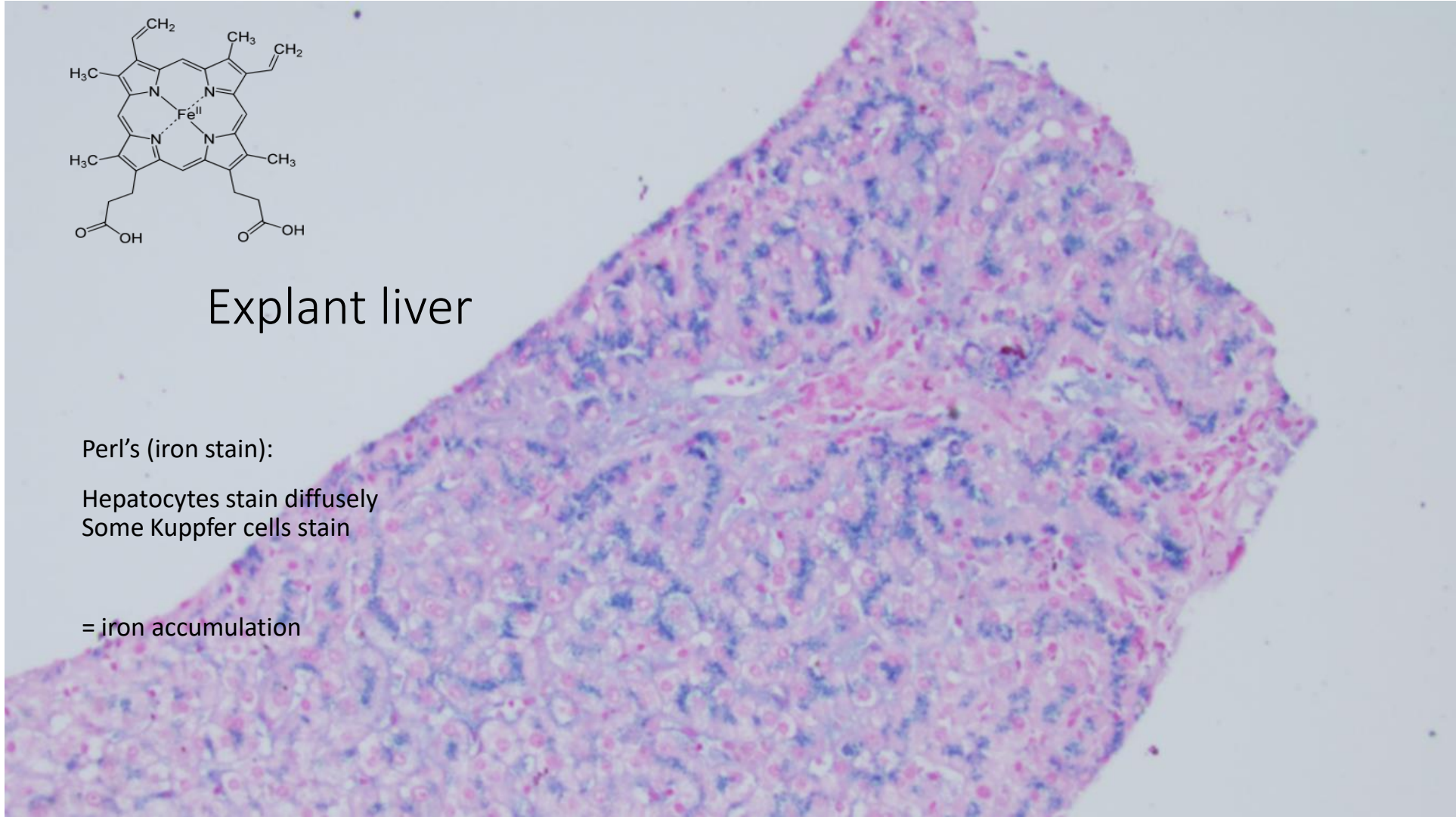


Explant liver

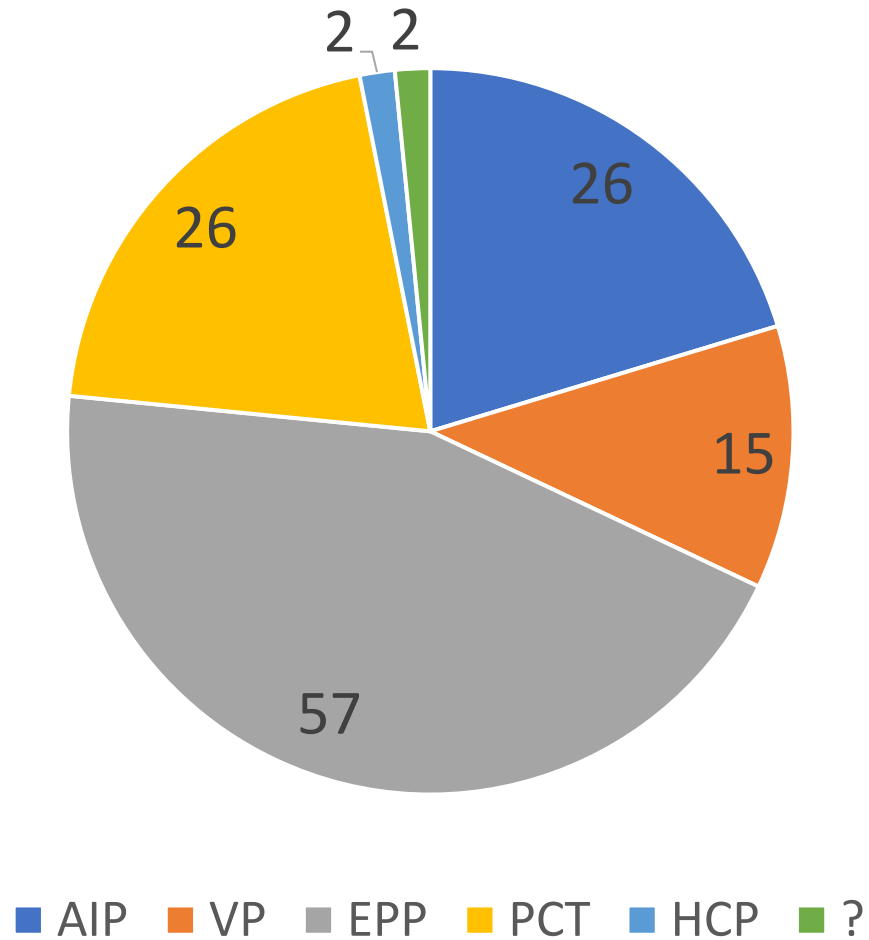
Perl's (iron stain):

Hepatocytes stain diffusely
Some Kupffer cells stain

= iron accumulation



Porphyria patients Leuven

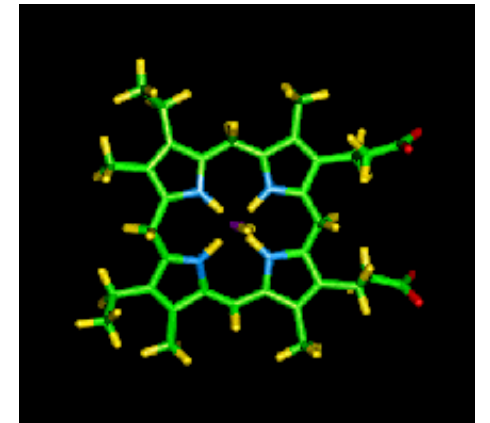
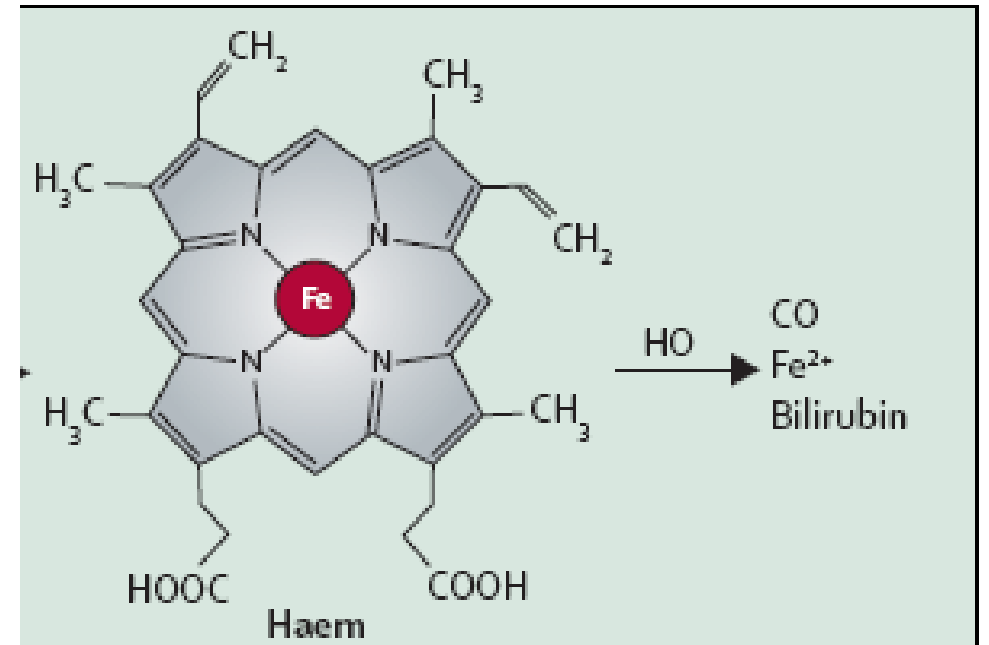


Haem Biochemistry

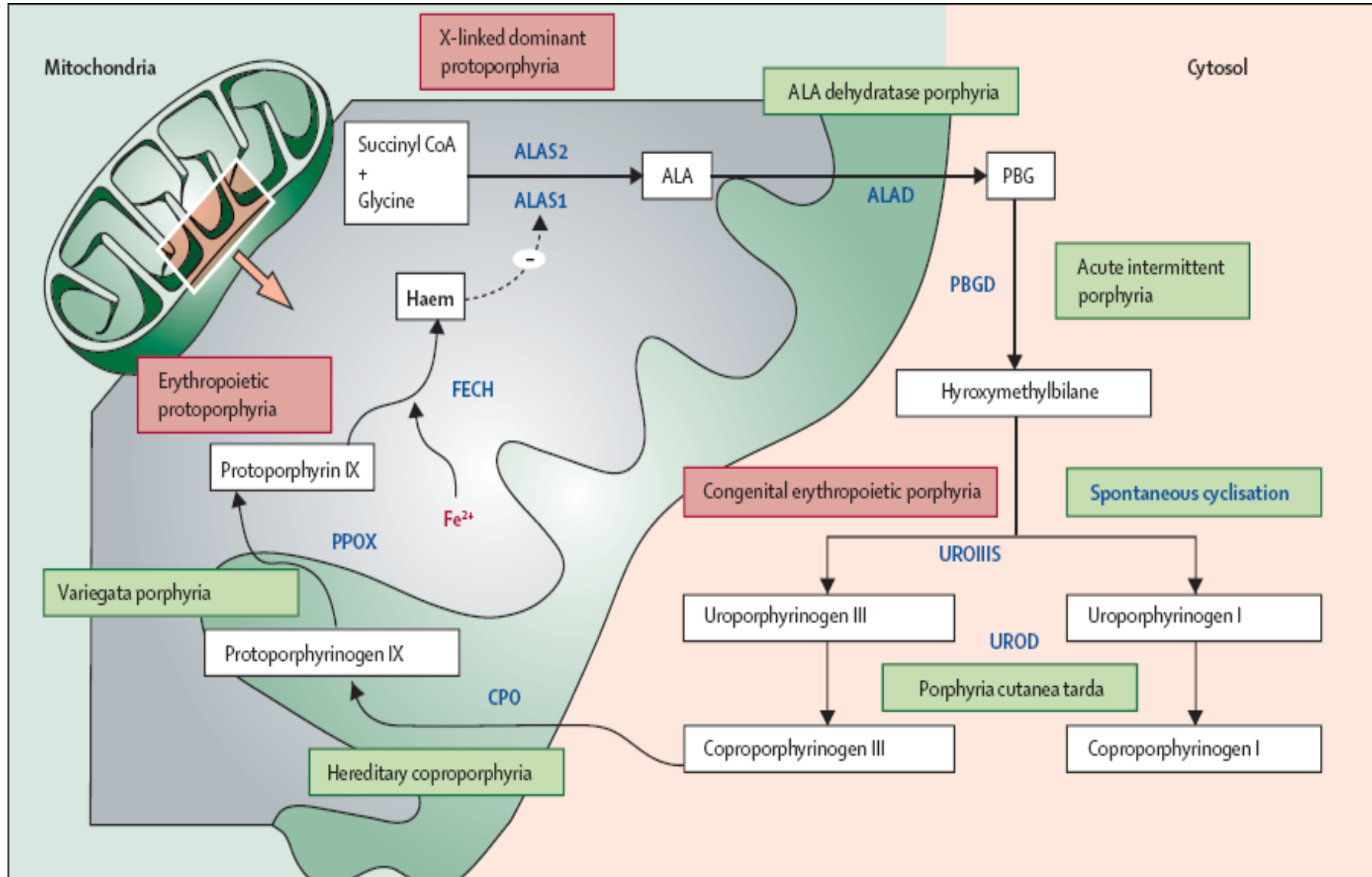
Synthesized in all tissues

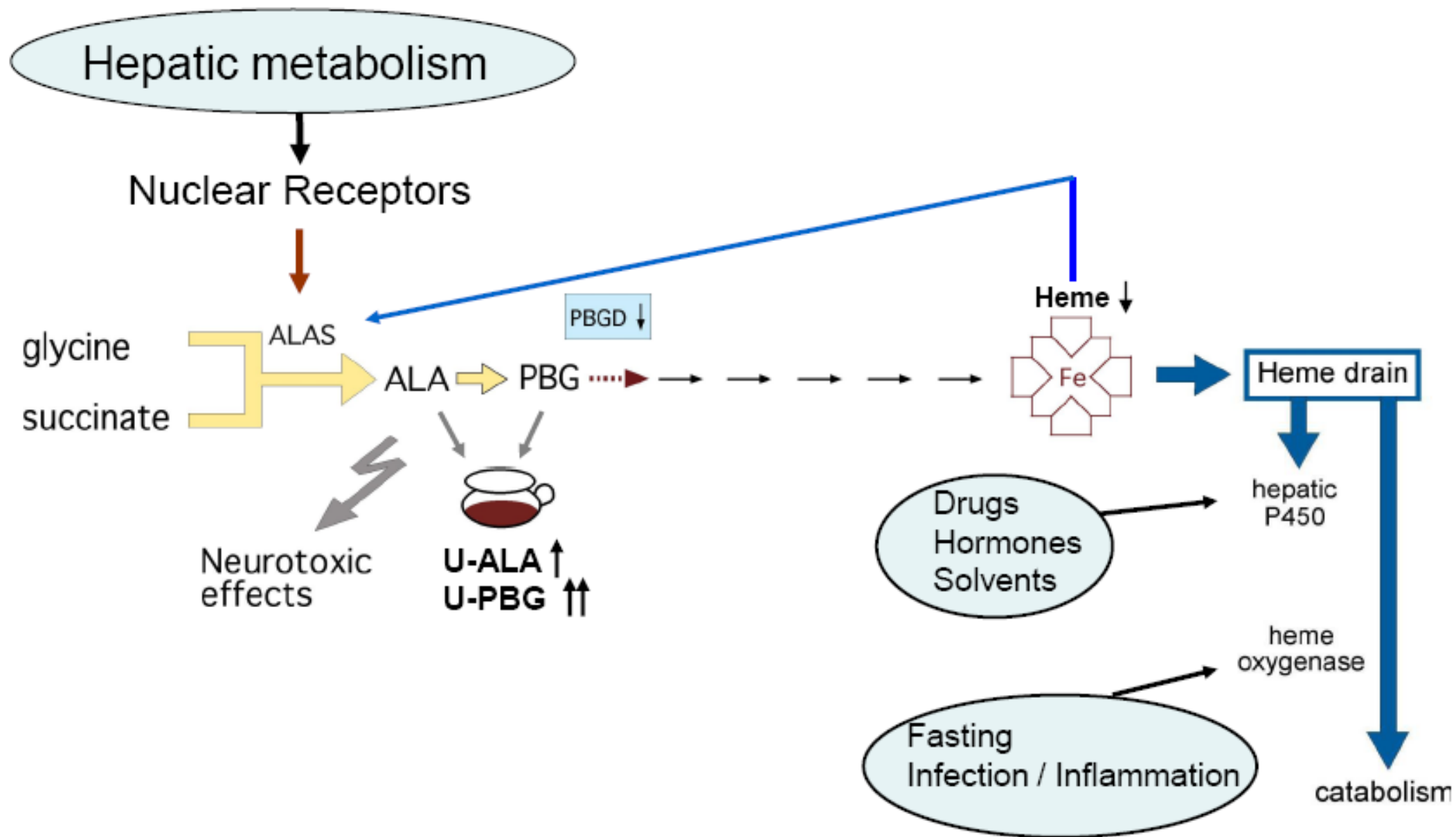
- 80% for hemoglobin (bone marrow)
- 20% for enzymes
- Mainly hepatic (CYP450, catalase, peroxidase,...)

8 enzymes in synthesis pathway



Biosynthesis of heme







Autonomous Nervous System

The Clinical Symptoms of Acute Porphyria



Peripheral Nervous System



Central Nervous System

Clinical presentation acute porphyria

- Females > males (5:1)
- Rarely before puberty or after menopause
- Can be life-threatening when missed

Symptoms/signs

- Abdominal pain (98%), vomiting, constipation
- Hypertension, tachycardia
- Psychiatric symptoms (anxiety, confusion, hallucinations)
- Epilepsy
- Motoric neuropathy: mild → severe (paralysis)
- Hyponatremia (<135) 40%

Treatment AIP

- Supportive (glucose 3L 10%, opiates, anti-emetics)
- ONLY SAFE MEDS www.porphyrria-europe.com
- ? Removal/avoidance of precipitating factor
- **IV hemin**: Normosang1 flask/d, 4 days (cave **thrombosis** → DVC!)
- Start treatment early (<24 uur)
- **Givosiran RNAi 1/month** for recurrent attacks

Prognosis is excellent if diagnosed early



[Home](#) | [New Search](#) | [About](#) | [Epnets](#) | [Help](#)

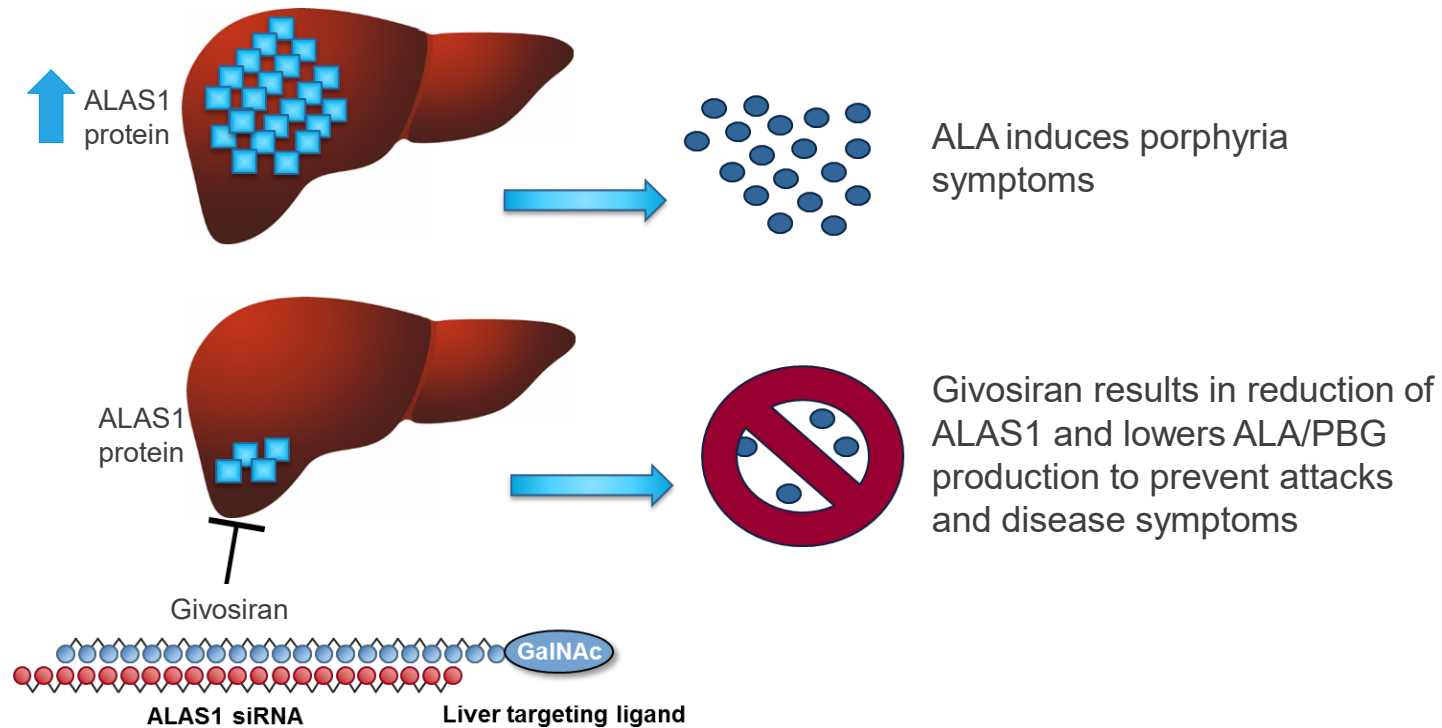
ATC code	Generic name	Trade name	Classification	Type of drug	Info
J01EE01	Sulfamethoxazole and trimethoprim	BACTRIM disp tabs	P	ANTIBACTERIALS FOR SYSTEMIC USE	
Show alternative drugs in category combinations of sulfonamides and trimethoprim, incl. derivatives					

[Home](#) | [New Search](#) | [Contact us](#)

Givosiran: Investigational RNAi Therapeutic for AHP

Therapeutic Hypothesis

- Reduction of Liver ALAS1 Protein to Lower ALA and PBG



AHP, Acute Hepatic Porphria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

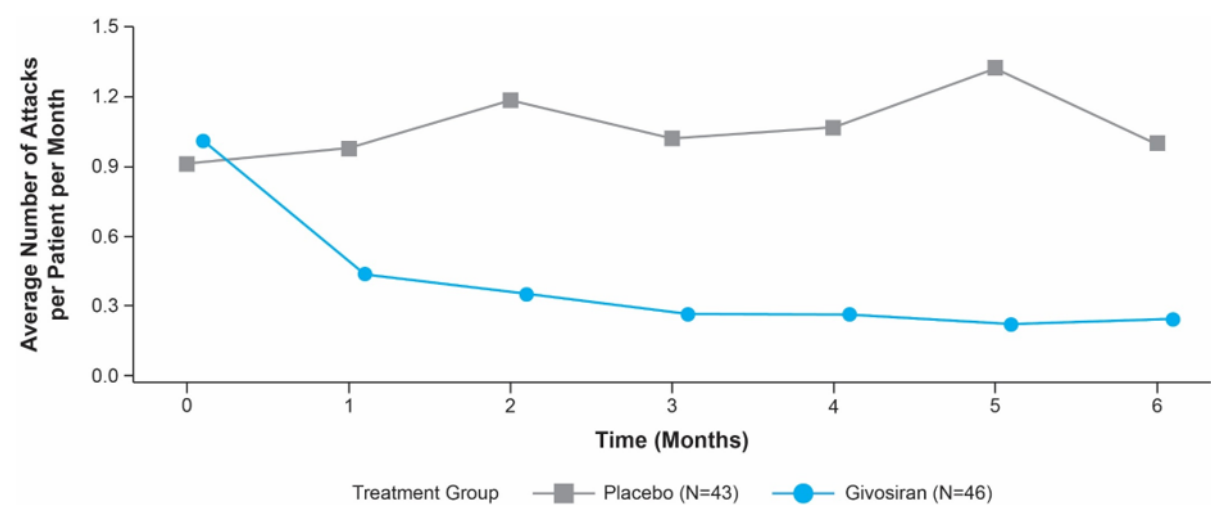
JUNE 11, 2020

VOL. 382 NO. 24

Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

M. Balwani, E. Sardh, P. Ventura, P.A. Peiró, D.C. Rees, U. Stölzel, D.M. Bissell, H.L. Bonkovsky, J. Windyga, K.E. Anderson, C. Parker, S.M. Silver, S.B. Keel, J.-D. Wang, P.E. Stein, P. Harper, D. Vassiliou, B. Wang, J. Phillips, A. Ivanova, J.G. Langendonk, R. Kauppinen, E. Minder, Y. Horie, C. Penz, J. Chen, S. Liu, J.J. Ko, M.T. Sweetser, P. Garg, A. Vaishnaw, J.B. Kim, A.R. Simon, and L. Gouya, for the ENVISION Investigators*

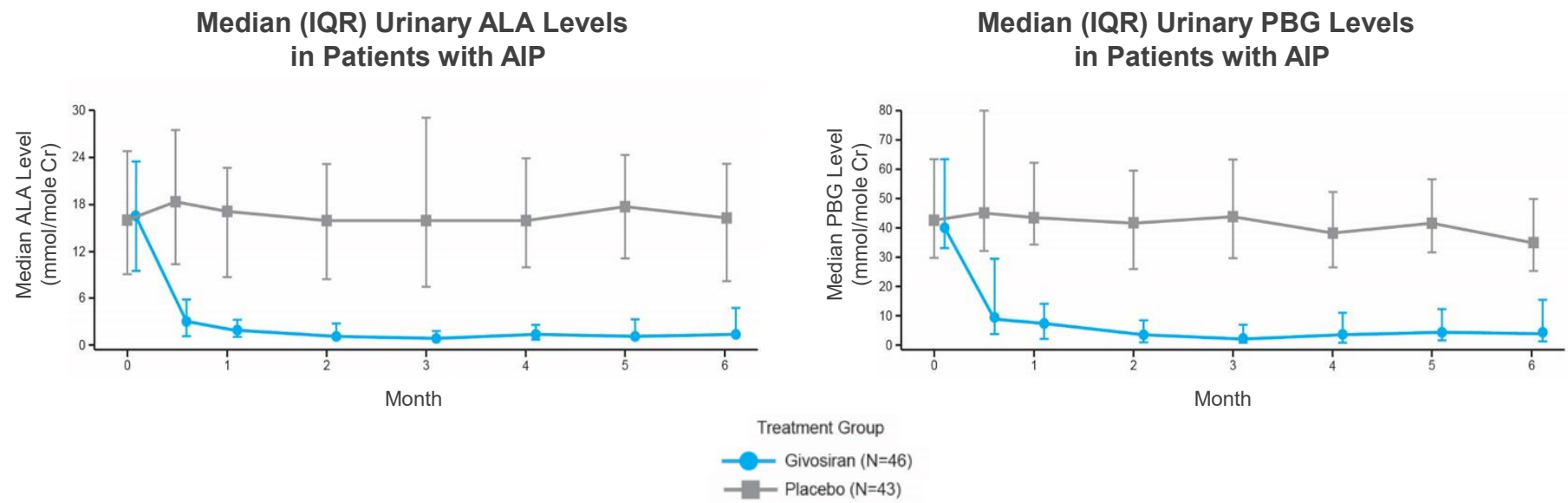
Mean Number of Attacks per Month in Patients with AIP



The decrease in AAR was evident within the first month and was sustained throughout the intervention period

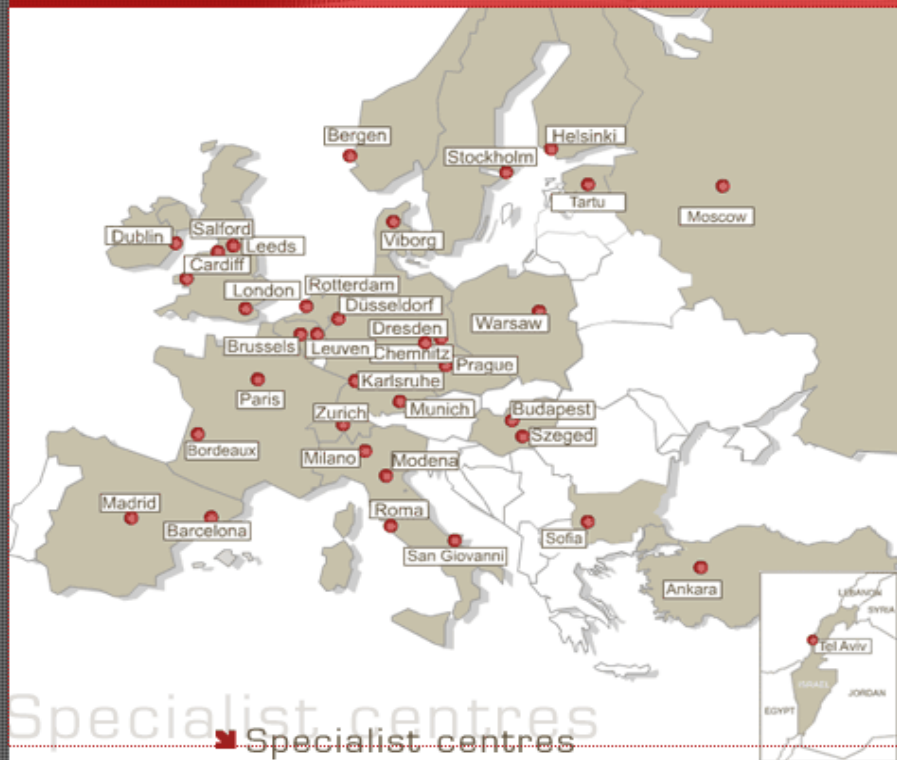
• The estimate at Month 0 represents the period between randomization and 6 months previous. One month = 28 days
Balwani and Sardh et al. *N Engl J Med* 2020;382:2289–301

Urinary ALA and PBG Levels in Patients with AIP



Reductions in levels of urinary ALA and PBG were sustained throughout the intervention period; in the givosiran group, the median percent reduction from baseline at 6 months was 86% for urinary ALA levels and 91% for PBG levels

• Balwani and Sardh et al. *N Engl J Med* 2020;382:2289–301



Specialist centres

For patients and families

English

- Introduction to porphyria
- Acute porphyrias
- Congenital Erythropoietic Porphyria (CEP)
- Erythropoietic Protoporphyria (EPP)
- Porphyria Cutanea Tarda (PCT)

For patients and families

For healthcare professionals

- The Porphyrias
- Laboratory diagnosis
- Investigating the family
- Treatment
- Congresses and events

For healthcare professionals

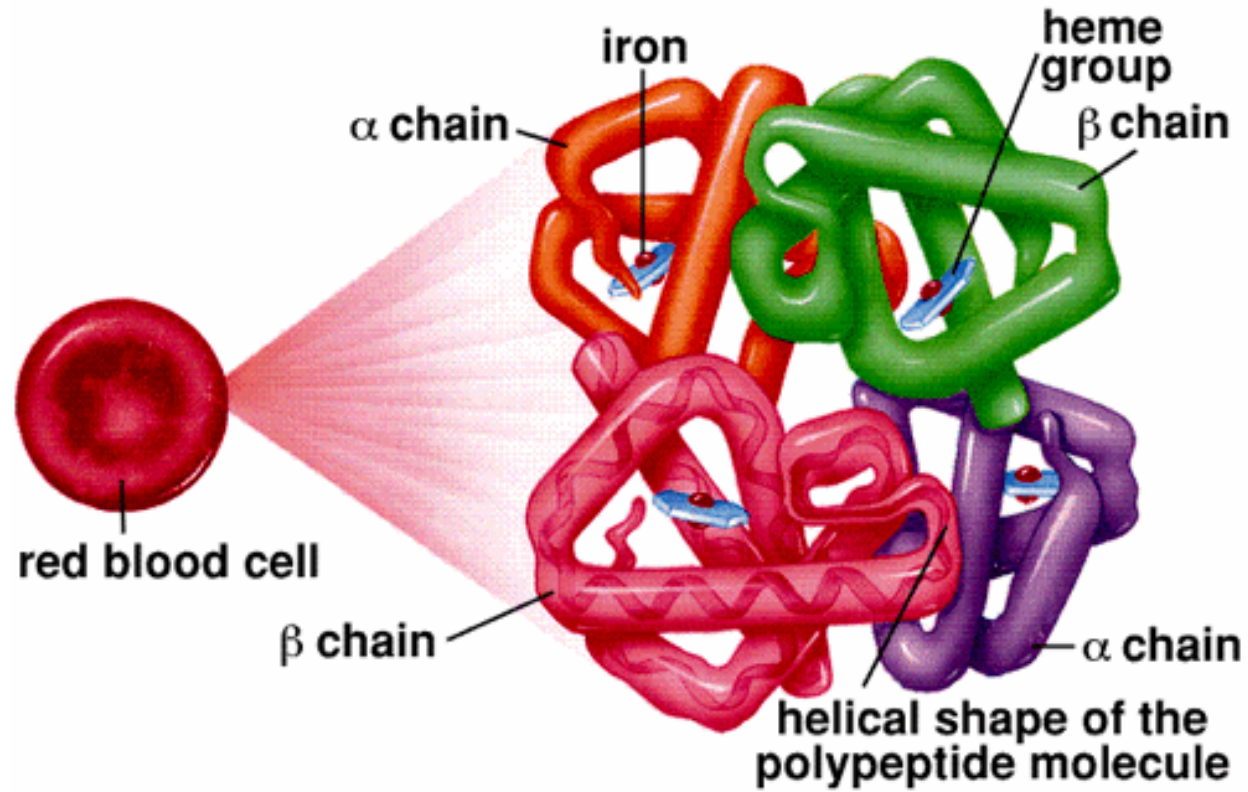
Drugs and acute porphyrias

- Background information
- How to use the information?
- Common prescribing problems
- Selecting a drug
- Pain Management

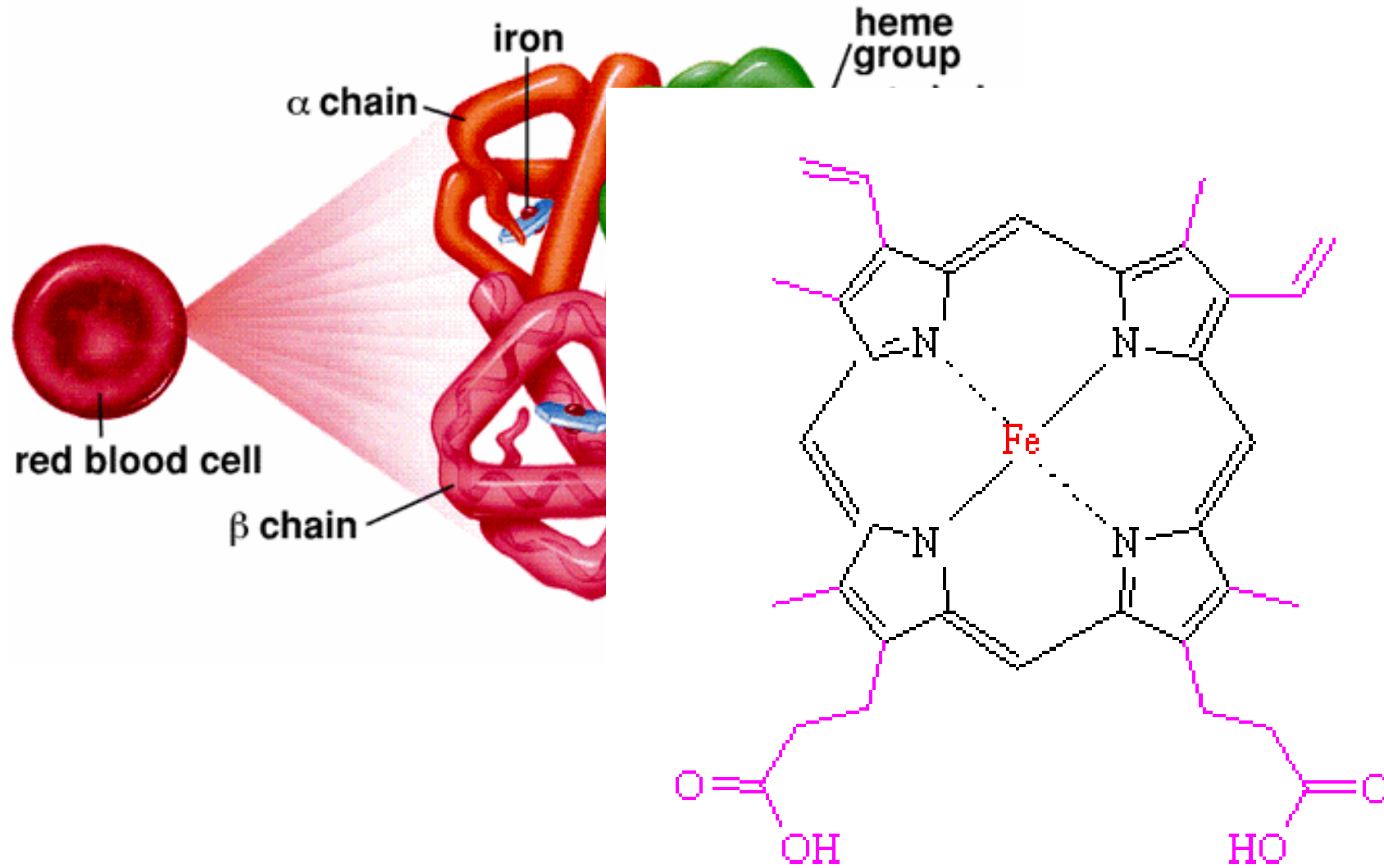
Drugs and porphyria

Iron accumulation

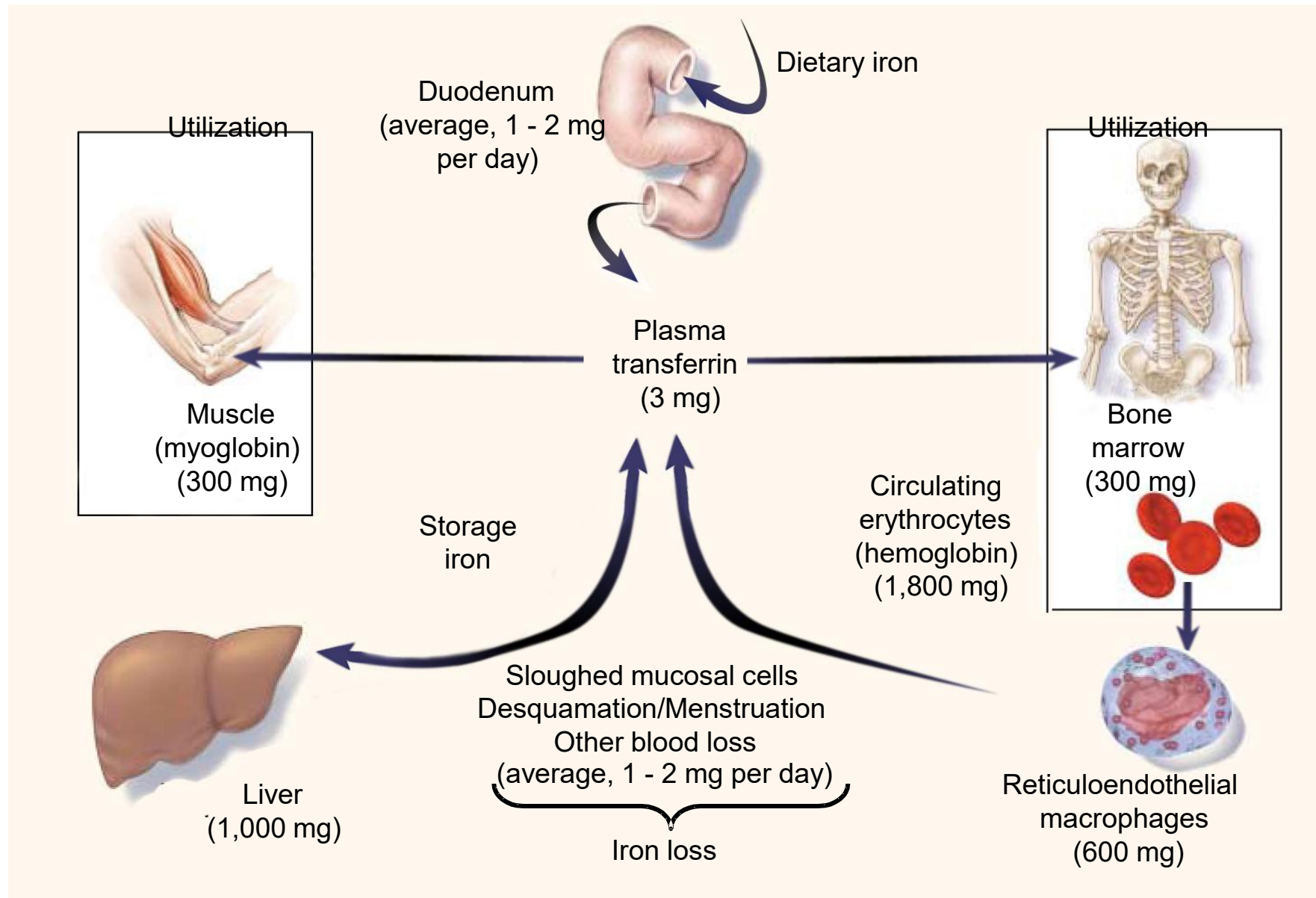
Hemoglobin Molecule



Hemoglobin Molecule

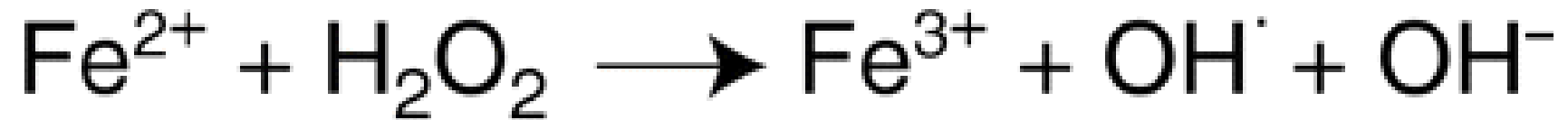


Body Iron Distribution and Storage



Too much iron is bad for you

Fenton chemistry



Too much iron is bad for you

When Tf sat > 75% => 'free plasma iron' ↑

Intracellular iron overload is deleterious (ROS)

Epidemiological association between iron levels and malignancy



Iron parameters: interpretation

1. **IRON** Fasting vs. non-fasting

2. **TRANSFERRIN** = neg. acute phase protein ($TF \downarrow \Rightarrow TFsat \uparrow$)

3. **FERRITIN** = pos. acute phase protein

inflammation $\Rightarrow$ ferritin high

neoplastic disease $\Rightarrow$ ferritin high

DD/ Hepatitis! Alcohol! Metabolic syndrome! (ferritin 500-1200 ng/ml)

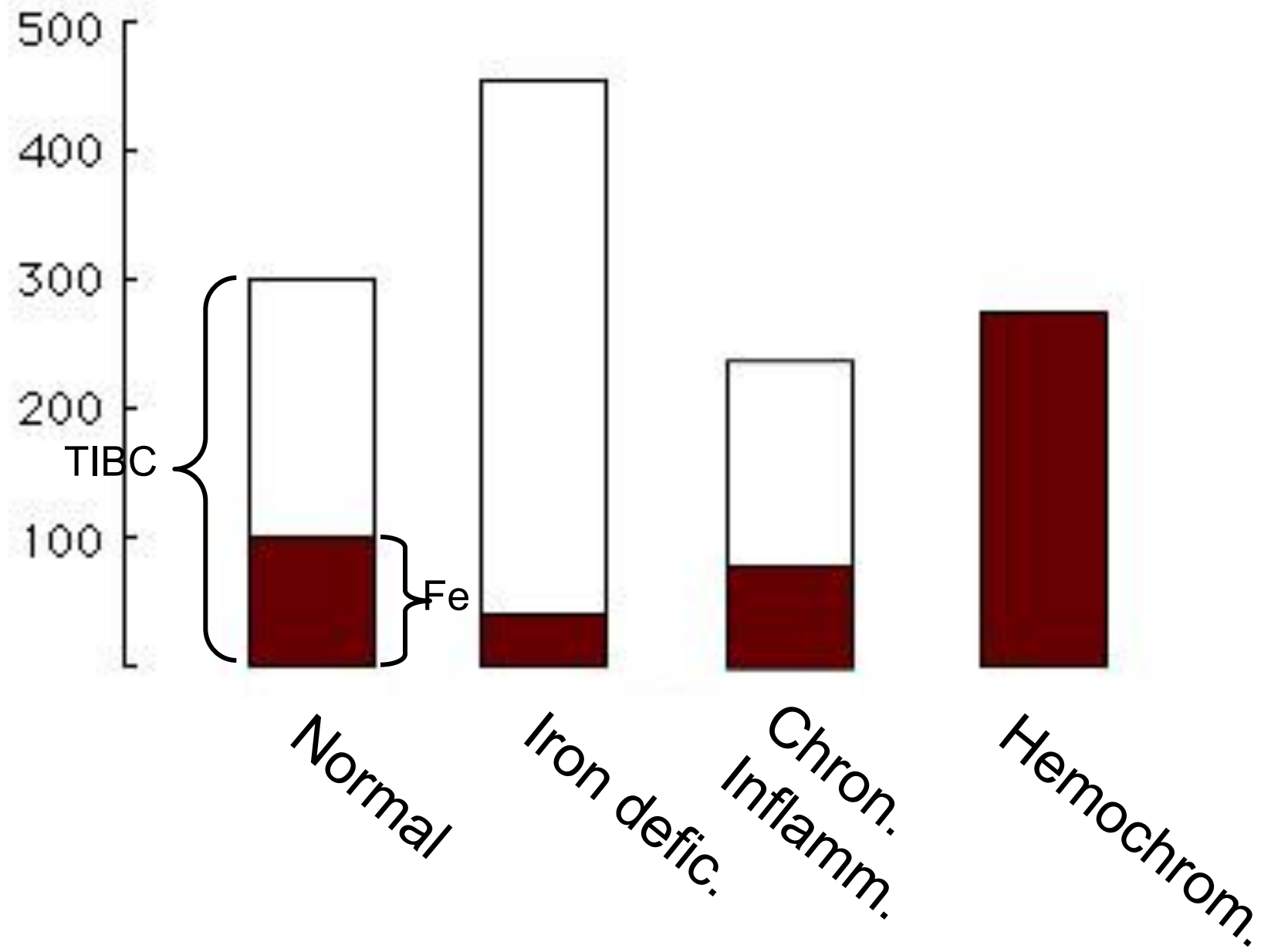
ferritin $\uparrow\uparrow\uparrow$:

Hyperferritinemia-cataract syndrome (L-ferritin)

Macrophage-activation syndrome, HLH

Gaucher and other M Φ storage diseases

Adult Still's disease



Iron accumulation: 1. Acquired

Chronic hemolysis +/- transfusions

Dyserythropoiesis (thalassemia) +/- transfusions

Iatrogenic (IM/IV Fe, transfusions)

Dietary (rare – Bantu siderosis) + AD gene?

Iron accumulation: 2. Genetic

Type I: HFE (C282Y, H63D, S65C)

Type II: juvenile (<30yrs; heart/endocrine)

IIa: hemojuvelin (HJV)

IIb: hepcidin (HAMP)

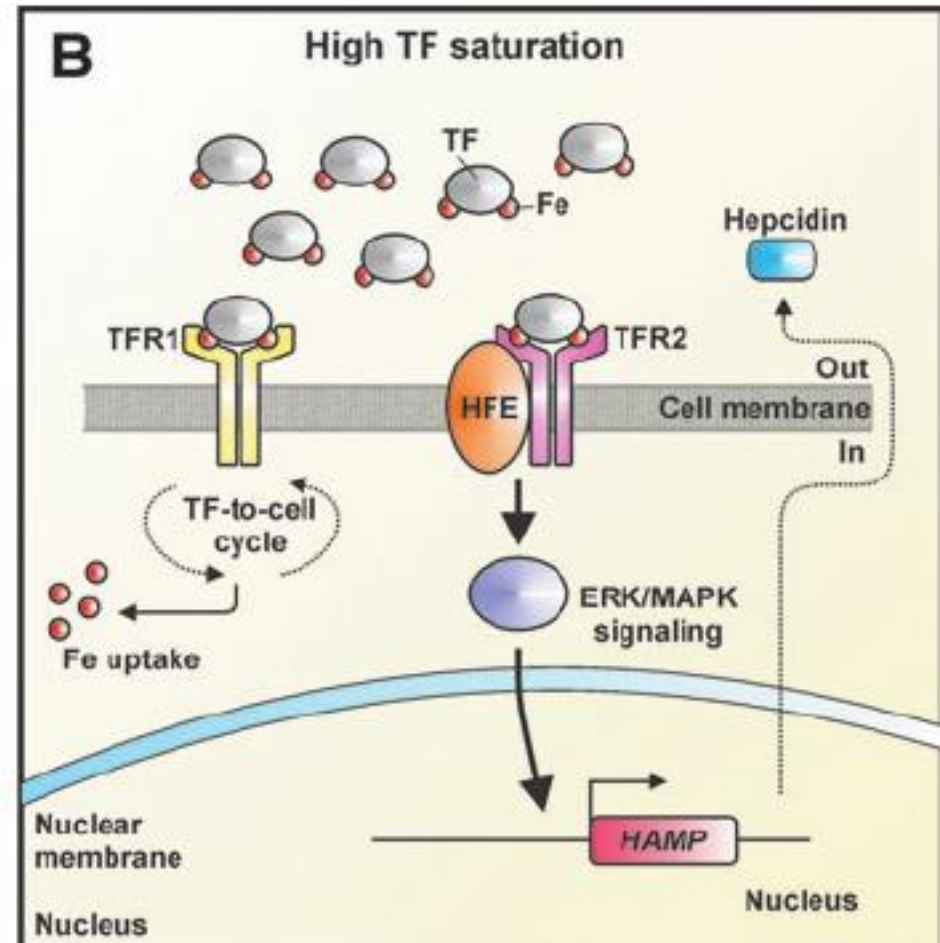
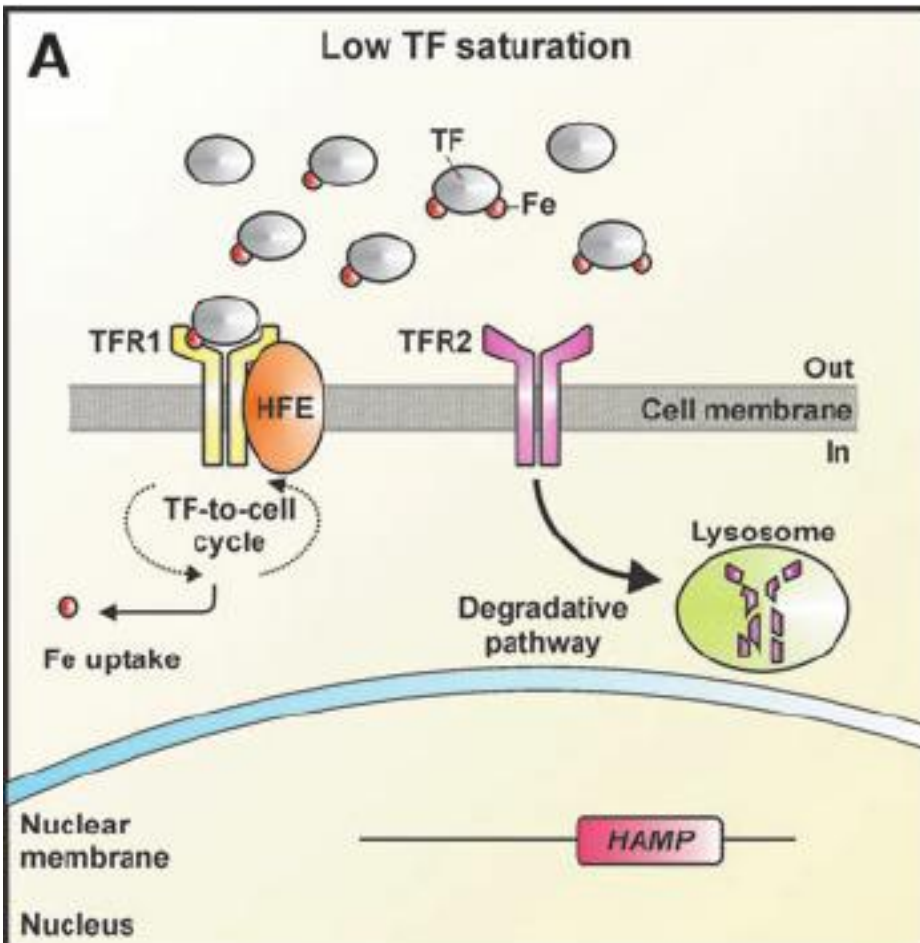
Type III: transferrin 2 receptor

Type IV: ferroportin (AD)

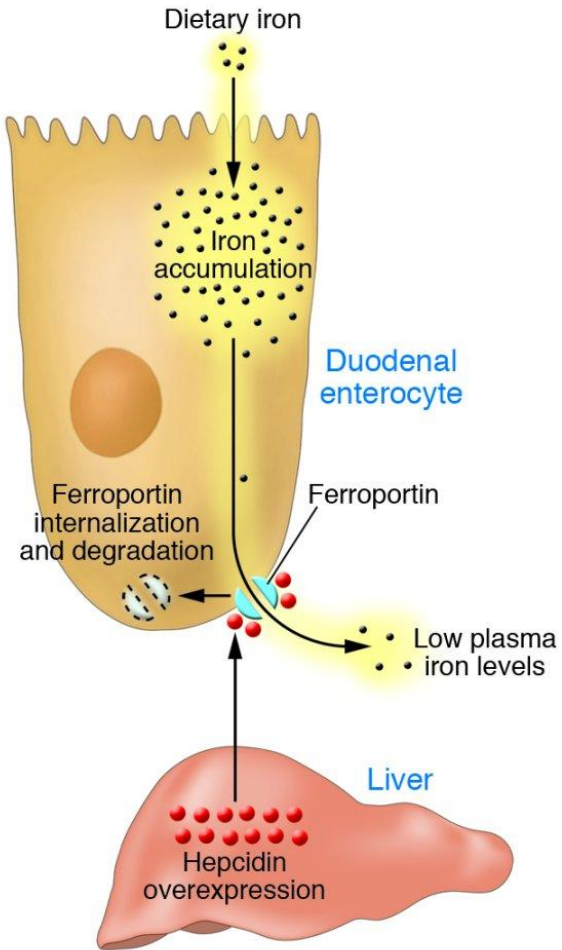
IVa: RE cells

IVb: hepatocytes (gain-of-function)

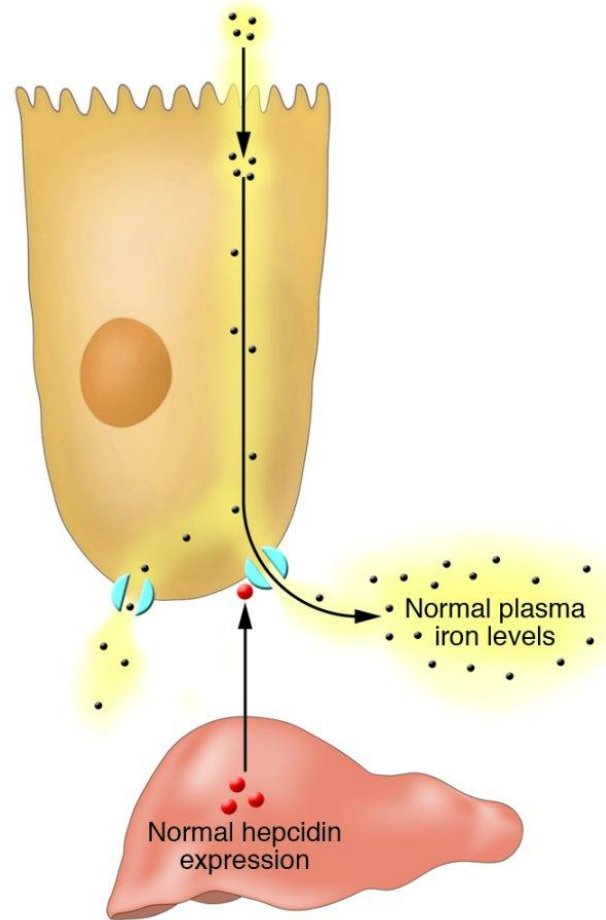
Aceruloplasminemia



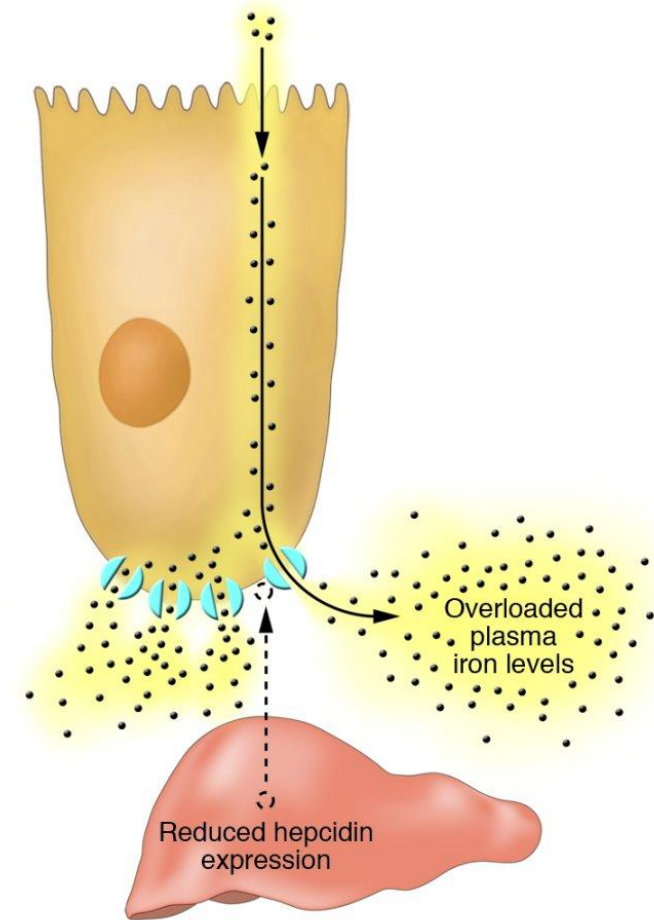
A Anemia of chronic disease



B Normal



C Hemochromatosis (iron overload)



Iron accumulation: 2. Genetic

I: HFE

95%

IIa: HJV

70pts

IIb: HAMP

10pts

III: TfR2

32pts

IV: ferroportin

IVa

112pts

IVb

20pts

Aceruloplasminemia

45pts

HFE-related haemochromatosis

HFE (type I) haemochromatosis

Most common genetic disease in Caucasians

Autosomal recessive

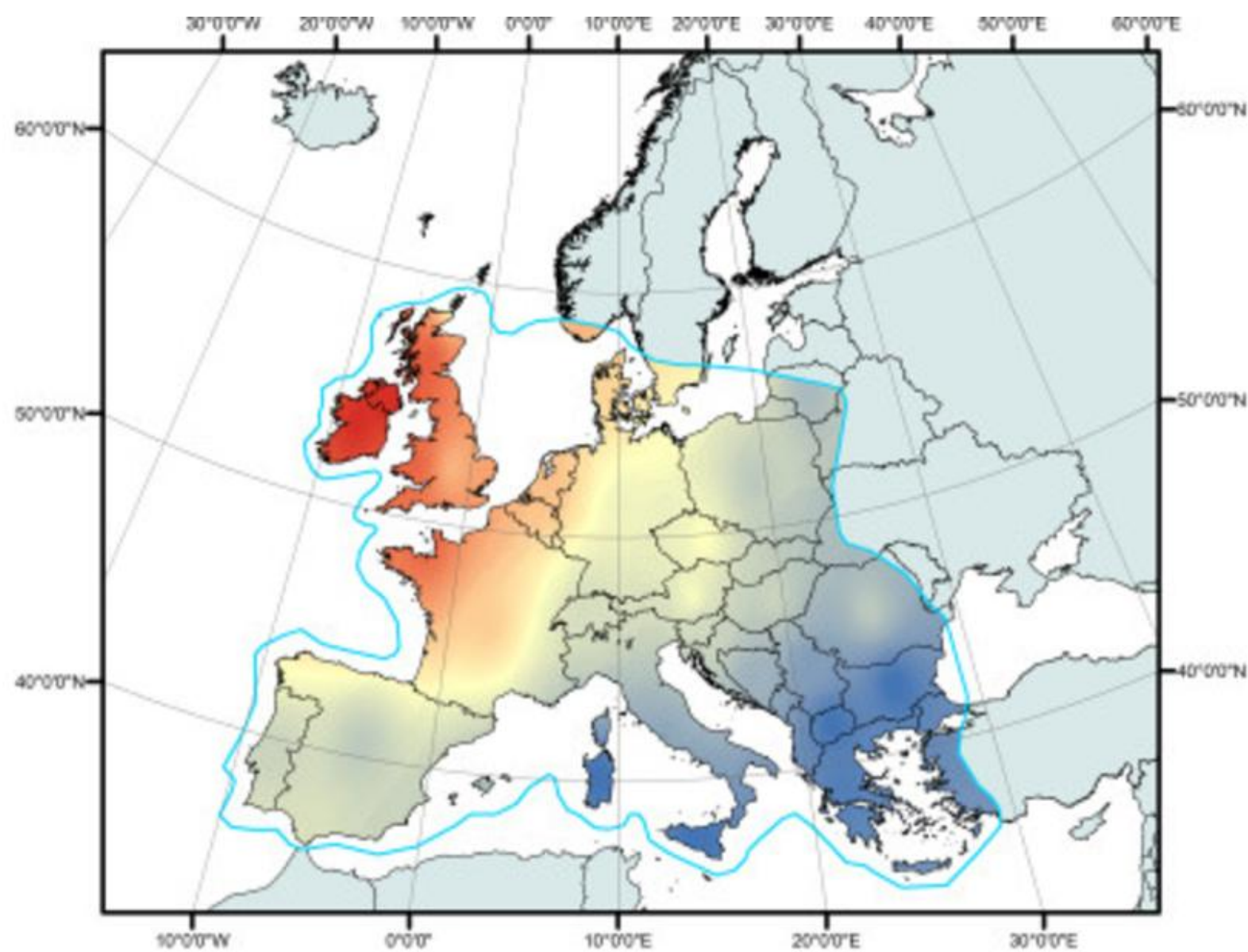
Homozygosity C282Y/C282Y

Compound heterozygosity: C282Y/H63D...

Clinical relevance?

Incidence in Europe: 1 in 200

Carrier frequency 10%



Weighted C282Y Allele Frequency (%)

High : 9.90

Mean : 4.27

Low : 0

Prevalence of C282Y and H63D Mutations in the Hemochromatosis (*HFE*) Gene in the United States

Karen K. Steinberg, PhD

Mary E. Cogswell, DrPH

Joy C. Chang, PhD

Samuel P. Caudill, PhD

Geraldine M. McQuillan, PhD

Barbara A. Bowman, PhD

Laurence M. Grummer-Strawn, DrPH

Eric J. Sampson, PhD

Muin J. Khoury, MD, PhD

Margaret L. Gallagher, PhD

NOW THAT THE HUMAN GENOME has been sequenced, and as scientists elucidate the location and function of all human genes, public health policy-makers face the daunting task of mak-

Context Population-based estimates of the prevalence of disease-associated mutations, such as hemochromatosis (*HFE*) gene mutations, are needed to determine the usefulness of genetic screening.

Objective To estimate the prevalence of the *HFE* mutations C282Y and H63D in the US population.

Design Cross-sectional population-based study of samples in the DNA bank from phase 2 of the Third National Health and Nutrition Examination Survey conducted from 1992 to 1994.

Setting and Participants Genotyped samples of cells from a total of 5171 participants, cross-classified by sex, age, and race/ethnicity in the analysis.

Main Outcome Measures Estimates of the prevalence of C282Y and H63D mutations.

Results The prevalence of C282Y homozygosity is estimated to be 0.26% (95% confidence interval [CI], 0.12%-0.49%); 1.89% (95% CI, 1.48%-2.43%) for H63D homozygosity; and 1.97% (95% CI, 1.54%-2.49%) for compound heterozygosity. The prevalence estimates for C282Y heterozygosity (C282Y/wild type) are 9.54% among non-Hispanic whites, 2.33% among non-Hispanic blacks, and 2.75% among Mexican-Americans. The prevalence estimates of the C282Y mutation in the US population are 5.4% (95% CI, 4.7%-6.2%) and 13.5% (95% CI, 12.5%-14.8%) for the H63D mutation.

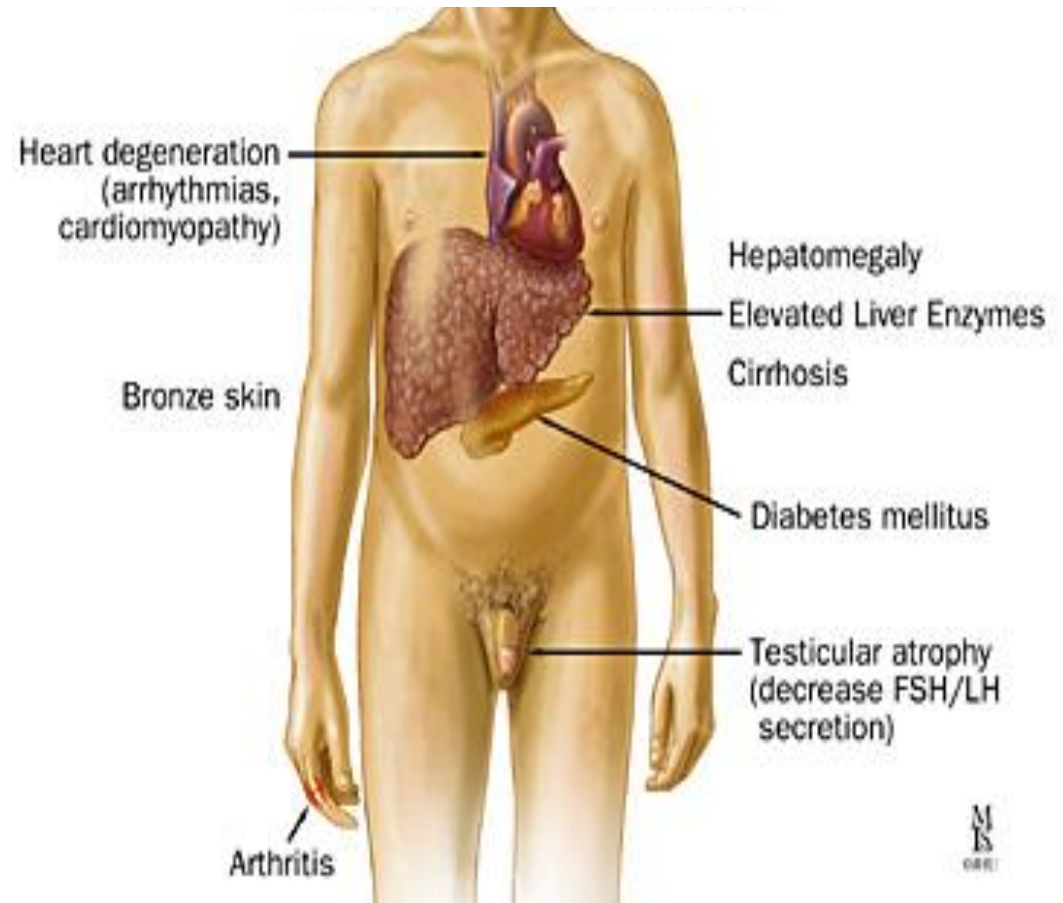
Clinical presentation of hemochromatosis

Absorption 2-4mg/d (nl: 1-2mg/d)

Accumulation 1g/yr

Symptomatic from >20g (~ 40-50y)

Later in women



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JANUARY 17, 2008

VOL. 358 NO. 3

Iron-Overload–Related Disease in *HFE* Hereditary Hemochromatosis

Katrina J. Allen, M.D., Ph.D., Lyle C. Gurrin, Ph.D., Clare C. Constantine, Ph.D., Nicholas J. Osborne, Ph.D.,
Martin B. Delatycki, M.D., Ph.D., Amanda J. Nicoll, M.D., Ph.D., Christine E. McLaren, Ph.D., Melanie Bahlo, Ph.D.,
Amy E. Nisselle, B.Sc., Chris D. Vulpe, M.D., Ph.D., Gregory J. Anderson, Ph.D., Melissa C. Southey, Ph.D.,
Graham G. Giles, Ph.D., Dallas R. English, Ph.D., John L. Hopper, Ph.D., John K. Olynyk, M.D.,
Lawrie W. Powell, M.D., Ph.D., and Dorota M. Gertig, M.D., D.Sc.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JANUARY 17, 2008

VOL. 358 NO. 3

Iron-Overload–Related Disease in *HFE* Hereditary Hemochromatosis

RESULTS

Ka
Martin
Ar The proportion of C282Y homozygotes with documented iron-overload–related disease was 28.4% (95% confidence interval [CI], 18.8 to 40.2) for men and 1.2% (95% CI, 0.03 to 6.5) for women. Only one non-C282Y homozygote (a compound heterozygote) had documented iron-overload–related disease. Male C282Y homozygotes with a serum ferritin level of 1000 μg per liter or more were more likely to report fatigue, use of arthritis medicine, and a history of liver disease than were men who had the wild-type gene. .D.,
, Ph.D.,
.D.,

CONCLUSIONS

In persons who are homozygous for the C282Y mutation, iron-overload–related disease developed in a substantial proportion of men but in a small proportion of women.

Penetrance is LOW (1 to 30%?)

↓↓ Growth, menstrual losses, pregnancy, diet, blood loss, PPI

↑↑ Alcohol, viral hepatitis, fatty livers

Genetic modifiers (e.g. transferrin variant, BMP2)

Proton Pump Inhibitors Decrease Phlebotomy Need in HFE Hemochromatosis: Double-Blind Randomized Placebo-Controlled Trial



Annick Vanclooster,¹ Cees van Deursen,^{2,4} Reggy Jaspers,³ David Cassiman,¹ and Ger Koek^{4,5,6}

ARTICLE

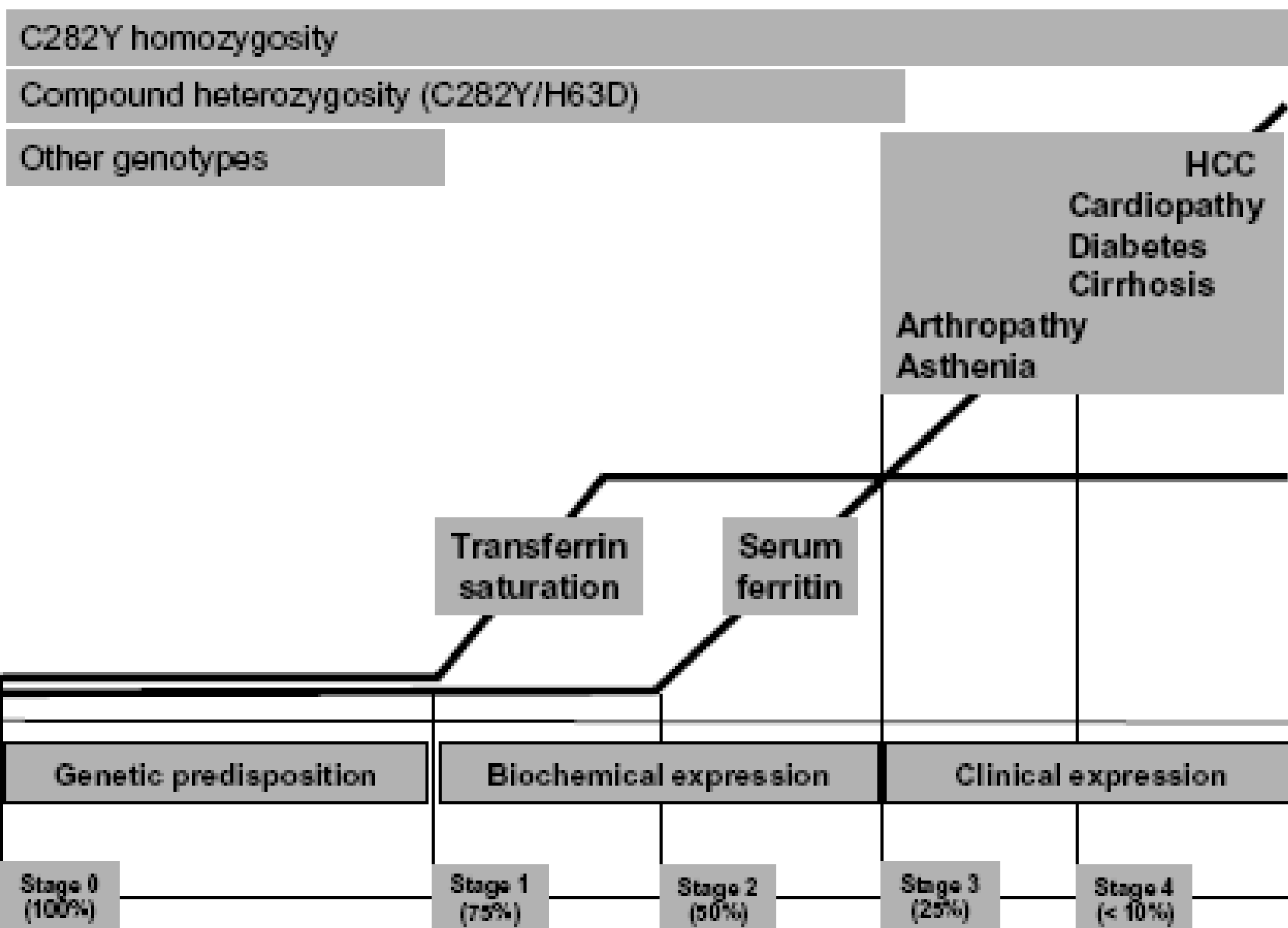
Received 1 May 2014 | Accepted 6 Aug 2014 | Published 29 Oct 2014 | Updated 30 Mar 2014

DOI: 10.1038/ncomms5926

Novel loci affecting iron homeostasis and their effects in individuals at risk for hemochromatosis

Beben Benyamin^{1,2}, Tonu Esko^{3,4}, Janina S. Ried⁵, Aparna Radhakrishnan⁶, Sita H. Vermeulen^{7,8}, Michela Traglia^{9,10}, Martin Gögele¹¹, Denise Anderson¹², Linda Broer^{13,14}, Clara Podmore¹⁵, Jiañan Luan¹⁵, Zoltan Kutalik^{16,17}, Serena Sanna¹⁸, Peter van der Meer¹⁹, Toshiko Tanaka²⁰, Fudi Wang²¹, Harm-Jan Westra²², Lude Franke²², Evelin Mihailov^{3,23}, Lili Milani³, Jonas Hålldin³, Juliane Winkelmann^{24,25,26,27}, Thomas Meitinger^{26,28}, Joachim Thiery^{29,30}, Annette Peters^{31,32}, Melanie Waldenberger^{31,32}, Augusto Rendon^{6,33,34}, Jennifer Jolley^{6,33}, Jennifer Sambrook^{6,33}, Lambertus A. Kiemeny^{7,35}, Fred C. Sweep³⁶, Cinzia F. Sala³⁷, Christine Schwienbacher¹¹, Irene Pichler¹¹, Jennie Hui^{38,39}, Ayse Demirkan^{13,40}, Aaron Isaacs^{13,41}, Najaf Amin¹³, Maristella Steri¹⁸, Gérard Waeber⁴², Niek Verweij¹⁹, Joseph E. Powell^{1,43}, Dale R. Nyholt², Andrew C. Heath⁴⁴, Pamela A.F. Madden⁴⁴, Peter M. Visscher^{1,43}, Margaret J. Wright², Grant W. Montgomery², Nicholas G. Martin², Dena Hernandez⁴⁵, Stefania Bandinelli⁴⁶, Pim van der Harst^{19,47,48}, Manuela Uda¹⁸, Peter Vollenweider⁴², Robert A. Scott¹⁵, Claudia Langenberg¹⁵, Nicholas J. Wareham¹⁵, InterAct Consortium[†], Cornelia van Duijn^{13,41,49}, John Beilby^{38,39}, Peter P. Pramstaller^{11,50}, Andrew A. Hicks¹¹, Willem H. Ouwehand^{6,33}, Konrad Oexle²⁸, Christian Gieger^{5,31,32}, Andres Metspalu³, Clara Camaschella^{9,51}, Daniela Toniolo⁹, Dorine W. Swinkels³⁶ & John B. Whitfield²

Variation in body iron is associated with or causes diseases, including anaemia and iron overload. Here, we analyse genetic association data on biochemical markers of iron status from 11 European-population studies, with replication in eight additional cohorts (total up to 48,972 subjects). We find 11 genome-wide-significant ($P < 5 \times 10^{-8}$) loci, some including known iron-related genes (*HFE*, *SLC40A1*, *TF*, *TFR2*, *TFRC*, *TMPRSS6*) and others novel (*ABO*, *ARNTL*, *FADS2*, *NAT2*, *TEX14*). SNPs at *ARNTL*, *TF*, and *TFR2* affect iron markers in *HFE* C282Y homozygotes at risk for hemochromatosis. There is substantial overlap between our iron loci and loci affecting erythrocyte and lipid phenotypes. These results will facilitate investigation of the roles of iron in disease.



Diagnosis

1. High serum iron (low sens/spec)
2. Transferrin saturation > 45 %
3. High ferritin

Exclude 'false positive' increased ferritin

Exclude acquired forms of iron accumulation (anemia!)

Mutation-analysis HFE gene (4-6 wks)

Liver biopsy? MRI with density measurement liver/spleen?

Role of abdominal MRI

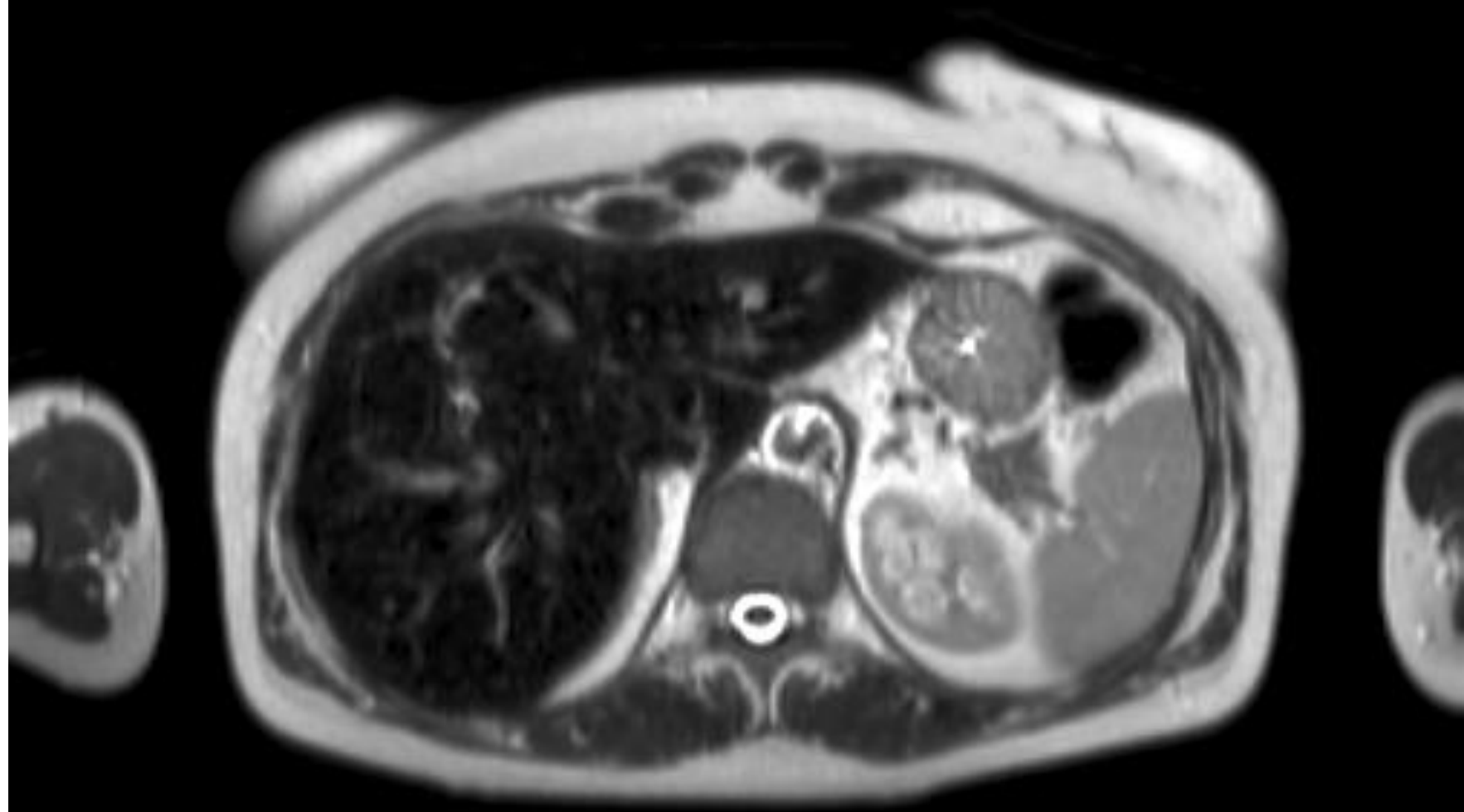
T2 (water=white): more black than paravertebral muscle = iron accumulation

Only liver is more black

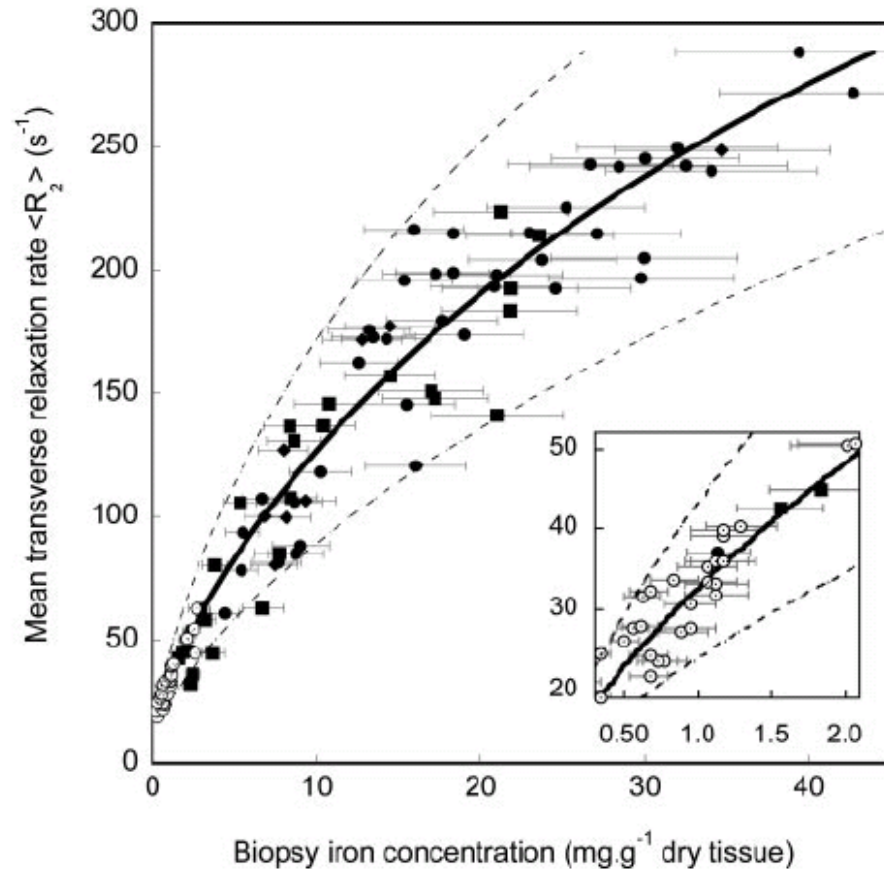
➔ Hepatocytic iron accumulation (1, 2, 3, 4b)

Liver AND spleen are more black

➔ Iron accumulation in RE cells (4a, secondary)



Relaxometry: R2 effect



50-75 Hz : 3.2 mg Fe/gram liver = mild iron accumulation.

76-125 Hz : 7 mg Fe/gram liver = moderate

> 125 Hz : more than 15 mg Fe/gram liver = severe

Biopsy?

< 40yr

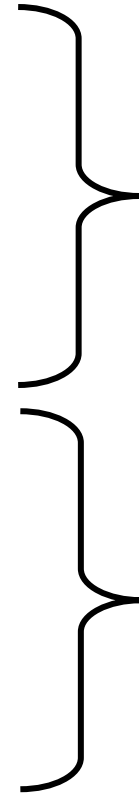
Ferritin < 1000

Normal AST/ALT

> 40yr

Ferritin > 1000

Abnormal AST/ALT



NO biopsy

biopsy

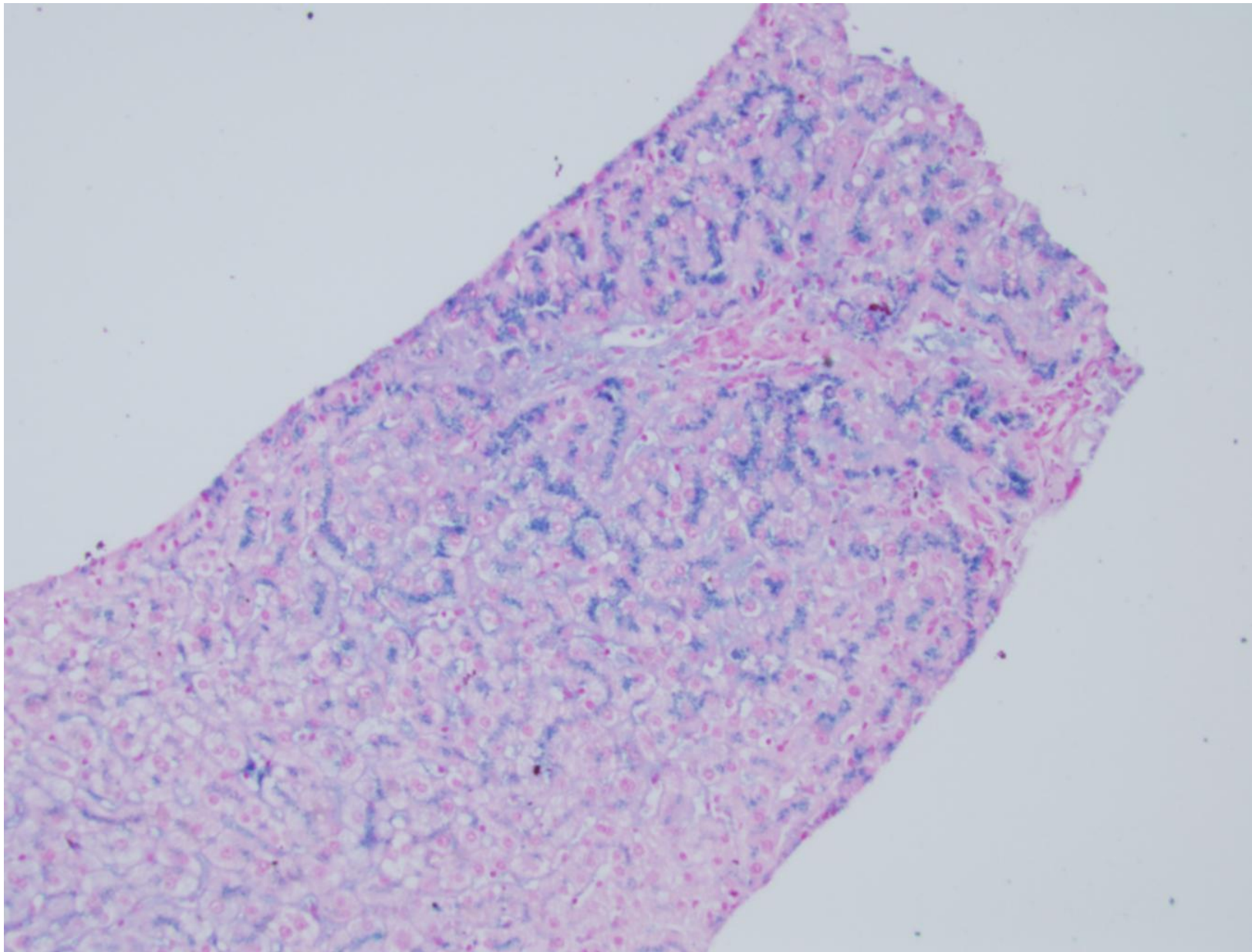
AASLD Guidelines 2011

Relevance of biopsy?

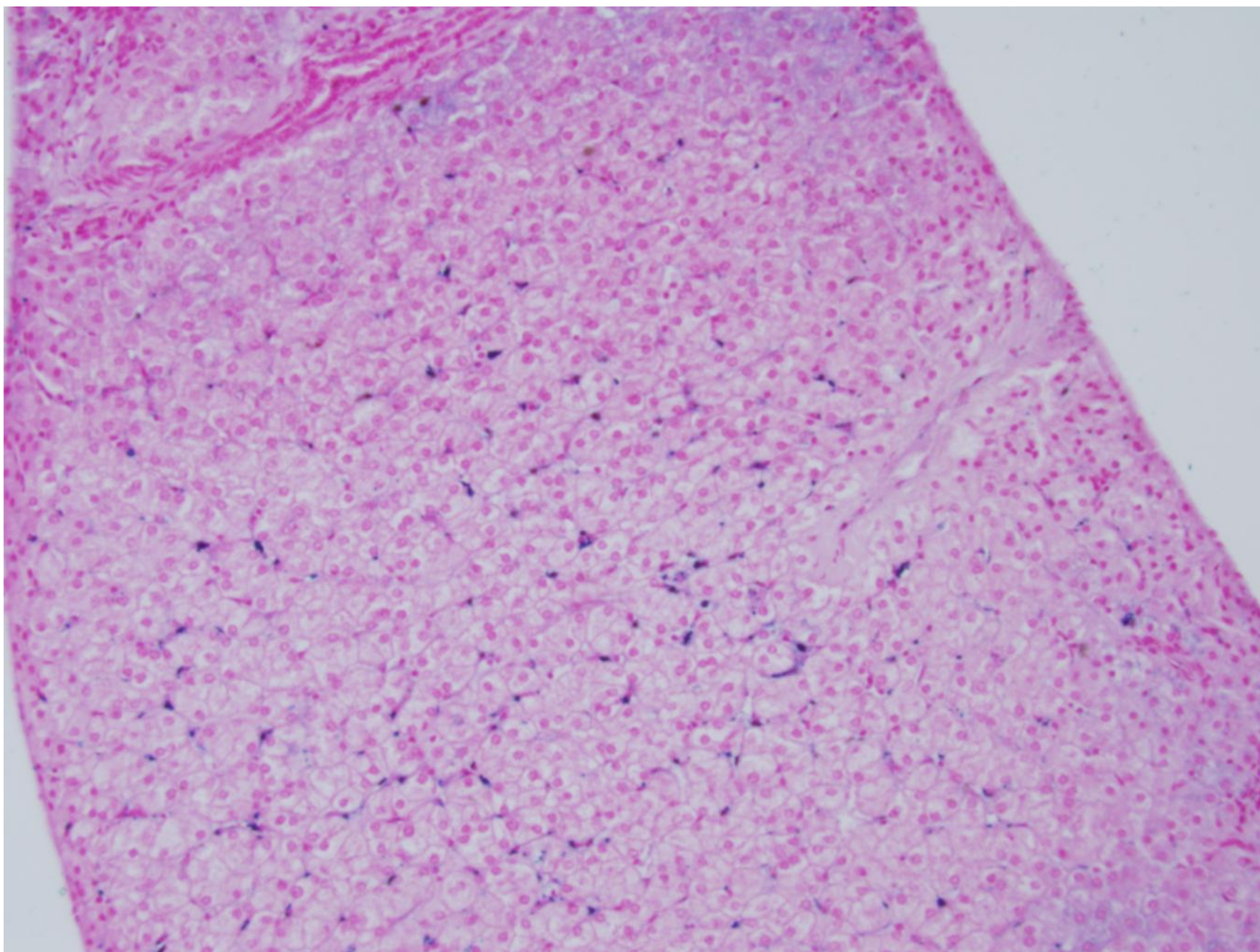
1. Confirm iron accumulation (Perls' stain)
2. Pattern iron accumulation:

 Hepatocytes: HFE, HJV, HAMP, Tf2, ferroportin B

 Kupffer cells: secondary, ferroportin A
3. Staging fibrosis/cirrhosis



HFE: hepatocytic iron, gradient periportally → pericentrally



Ferroportin: accumulation in Kupffer cells

Relevance of biopsy?

1. Confirm iron accumulation

2. Pattern iron accumulation:

Hepatocytes

Kupffer cells

} MRI (R2)

3. Staging fibrosis/cirrhosis → Fibroscan

Therapy

Phlebotomies: start at 500 ml weekly

Regeneration of RBC in marrow

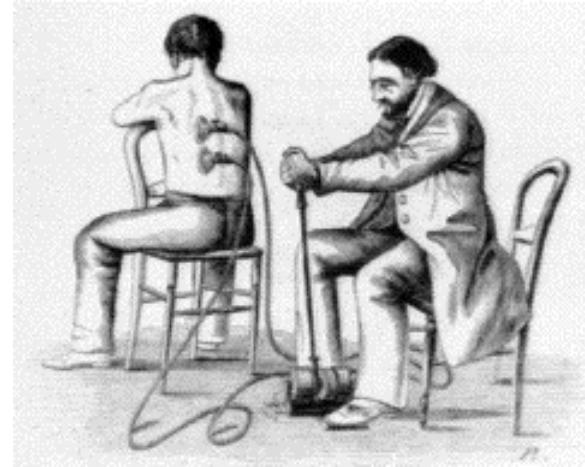
=> Iron usage/depletion from stores

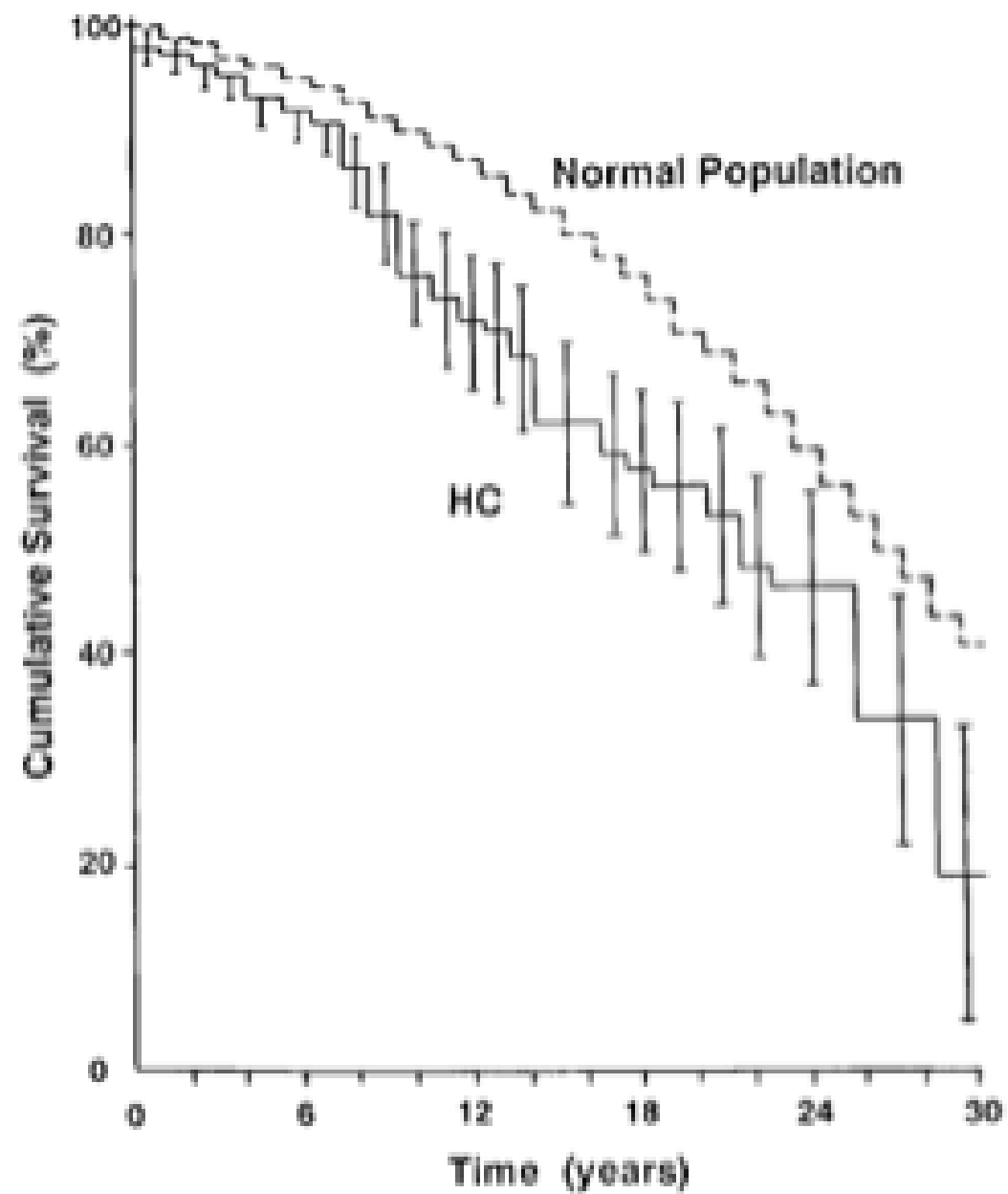
Till reduction of ferritin < 100 ng/ml (and transferrin sat. ↓)

Chronic phase: 1-10 phlebotomies yearly

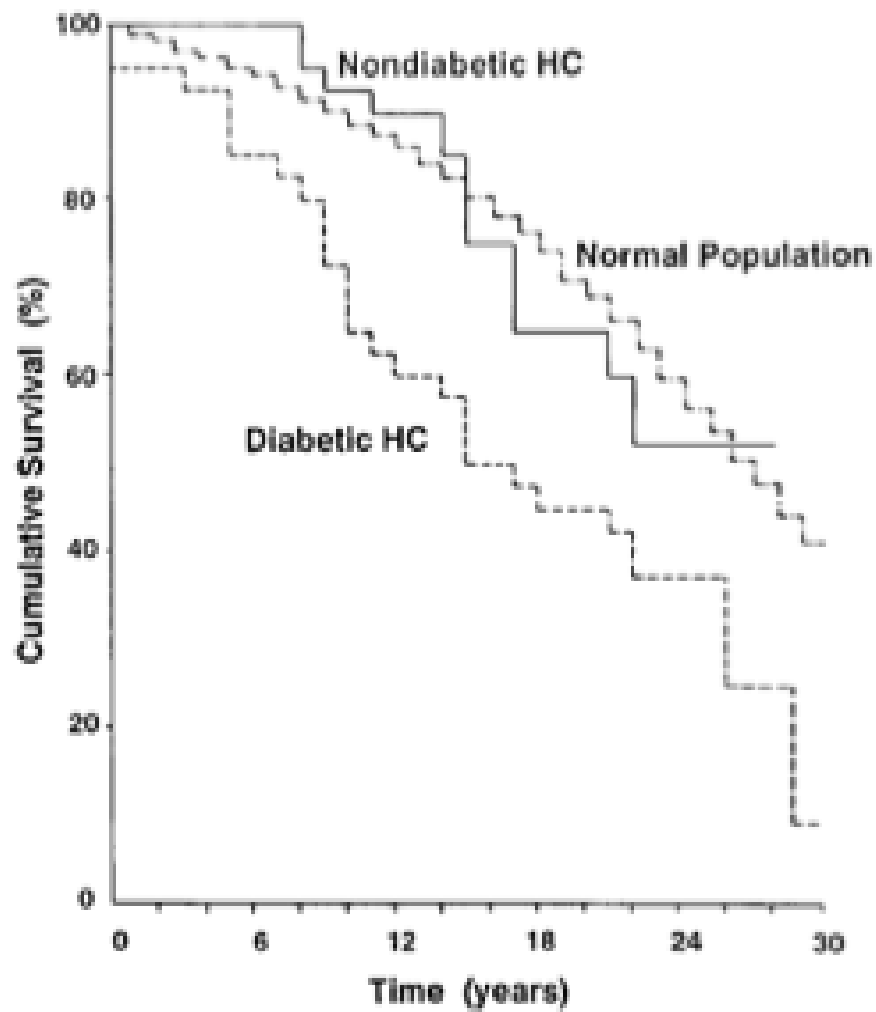
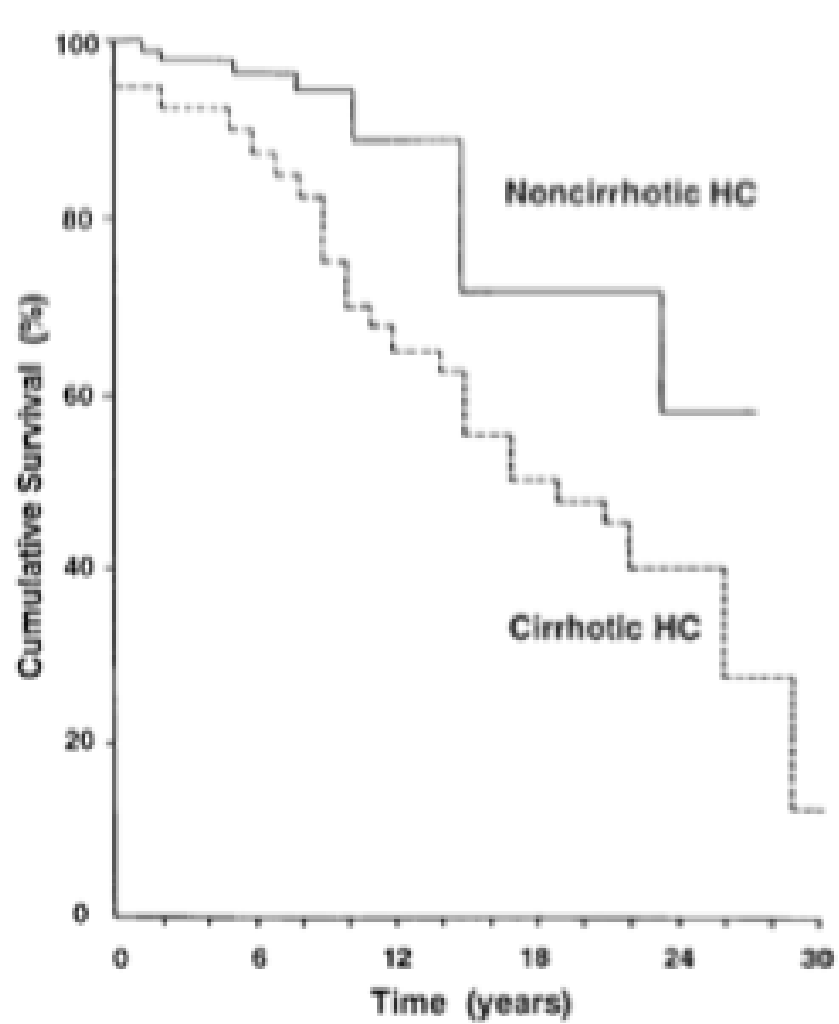
Reversible: AST/ALT↑, pigmentation, diabetes

Irreversible?: cirrhosis, impotence, arthritis





Niederau C. et al. Gastroenterology 1996



Follow-up

Examinations:

Liver ultrasound, in case of cirrhosis every 6mo (**HCC!**)

Fasting glucose, HbA1c, OGTT

Fibroscans

BMC

Other:

FAMILY SCREENING! (+18)

Liver disease => vaccinate for HAV, HBV

Cirrhosis => flu vaccine yearly, pneumococci

RESEARCH ARTICLE

Open Access



Key-interventions derived from three evidence based guidelines for management and follow-up of patients with HFE haemochromatosis

Annick Vanclooster^{1*}, Hub Wollersheim², Kris Vanhaecht³, Dorine Swinkels⁴, Bert Aertgeerts⁵, David Cassiman¹ and on behalf of the Haemochromatosis working group

Algorithm: Increased ferritin

History and physical examination:

1. arguments for inflammation? malignancy?
2. **BMI**? Metabolic syndrome?
3. Iron substitution IM/IV?
4. Family history!
5. Gender
6. **Alcohol** intake

Lab:

Other iron parameters and evolution

Liver tests

Anemia? MCV? Reticulocytosis? Hemolysis?

Radiology:

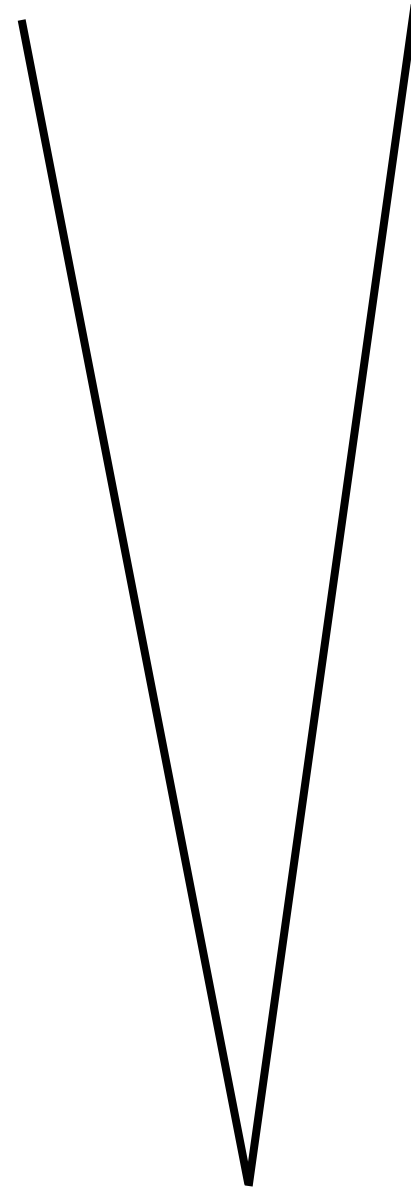
Abdominal US

MRI R2 relaxometry

Fibroscan, HbA1c

(Biopsy)

(Mutation analysis)



Young lady, 23y

Alk Phos	215 U/L	<= 240
AST	59 U/L	<= 32
ALT	77 U/L	<= 31
Gamma GT	56 U/L	<= 35
Iron	356 µg/dL	50 – 170
Transferrin	2.82 g/L	2.00 - 3.60
Transferrin sat	90 %	16 - 45
Ferritin	5465 µg/L	13 - 150

Liver biopsy:

Very pronounced accumulation of iron pigment in hepatocytes, with redistribution to macrophages.

Iron in liver biopsy:

58 mg/g dry weight ($<2\text{mg/g}$)

Hepatic iron index $46.5 \leq 1.0$

No endocrine abnormalities, normal heart US

Genetics:

HFE neg

Genetics:

HFE neg

Ferroportin neg

Genetics:

HFE neg

Ferroportin neg

Hepcidin (HAMP) neg

Genetics:

HFE neg

Ferroportin neg

Hepcidin (HAMP) neg

Hemojuvelin positive

Wilson disease

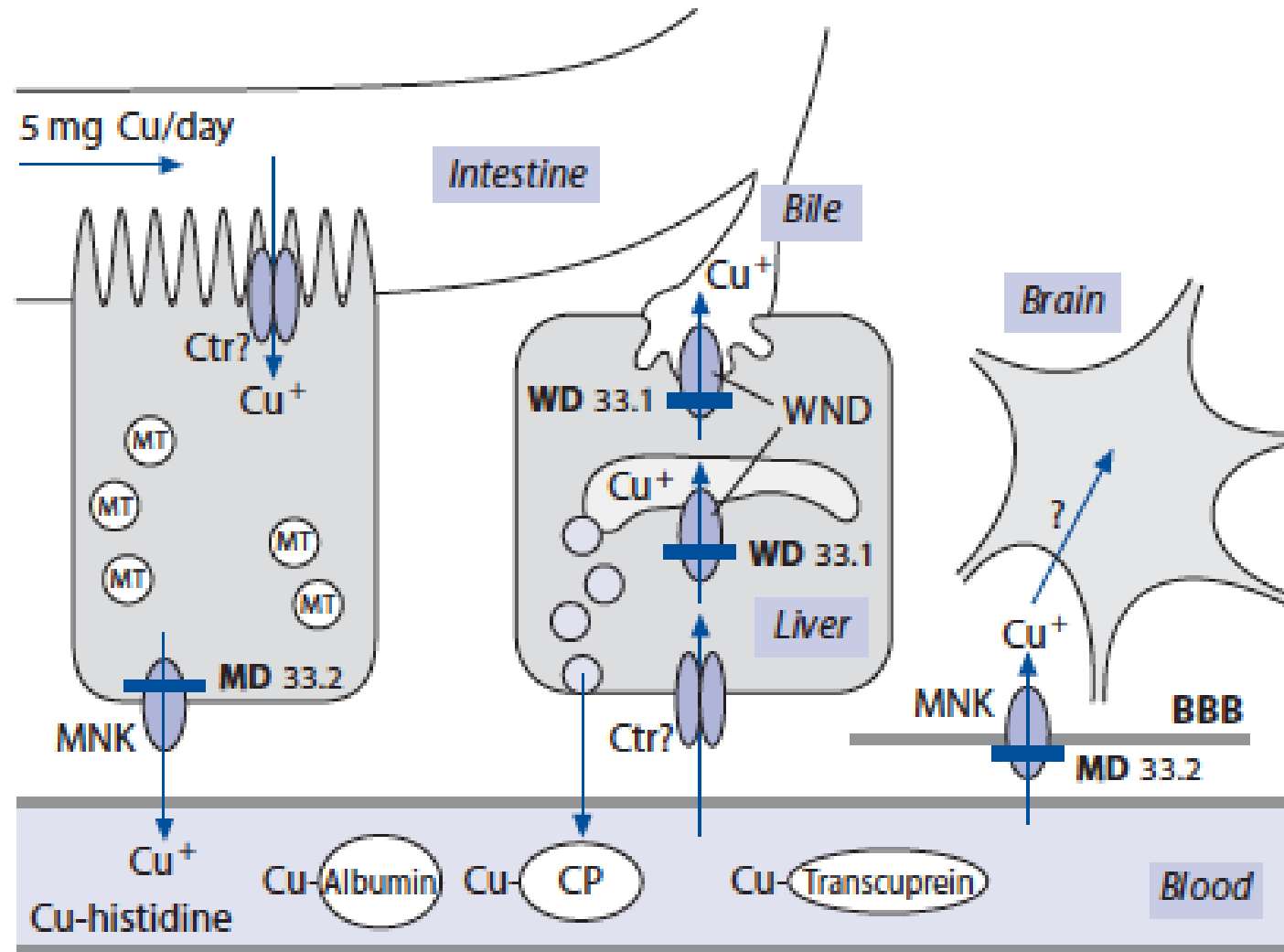
DISEASES AFFECTING LIVER AND BRAIN

- **Wilson**
- Mitochondrial diseases (mtDNA depletion)
- Urea cycle defects (hyperammonemia)
- Hypermanganesemia with dystonia, polycythemia (Mn transporter)
- Glycogen branching enzyme (GSD IV)
- LSDs: Gaucher type II and III, NPC, ...
- Ciliopathy syndromes
- CDG
- Peroxisomal
- Other

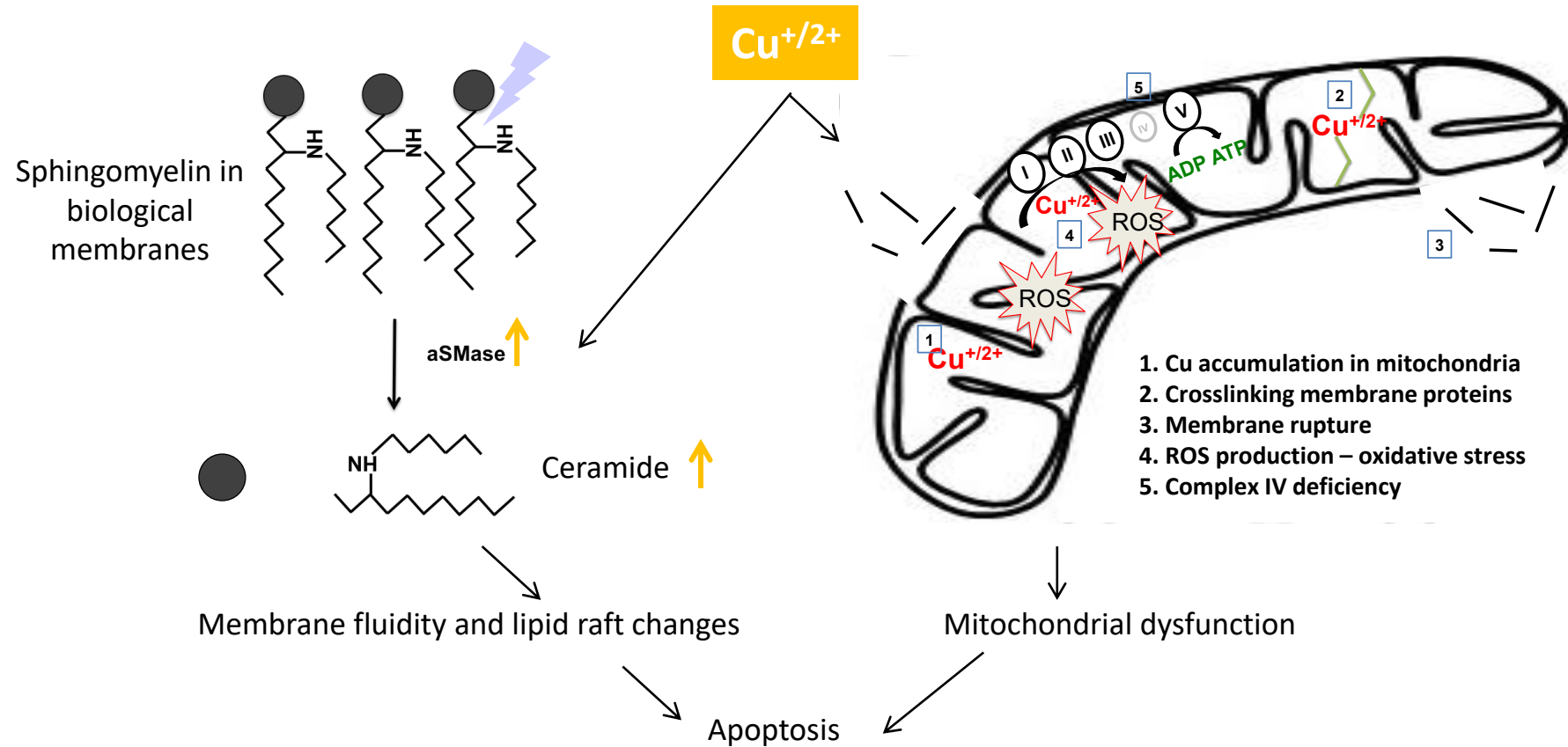
WILSON DISEASE

- Autosomal-recessive intracellular copper accumulation in liver, brain, bone, kidney and cornea
- Incidence: 1/30.000 to 1/100.000
- ATP7b gene, a copper-transporting ATPase
- >250 mutations known (in 1% no mutations found)

WILSON DISEASE



PATHOPHYSIOLOGY OF COPPER TOXICITY

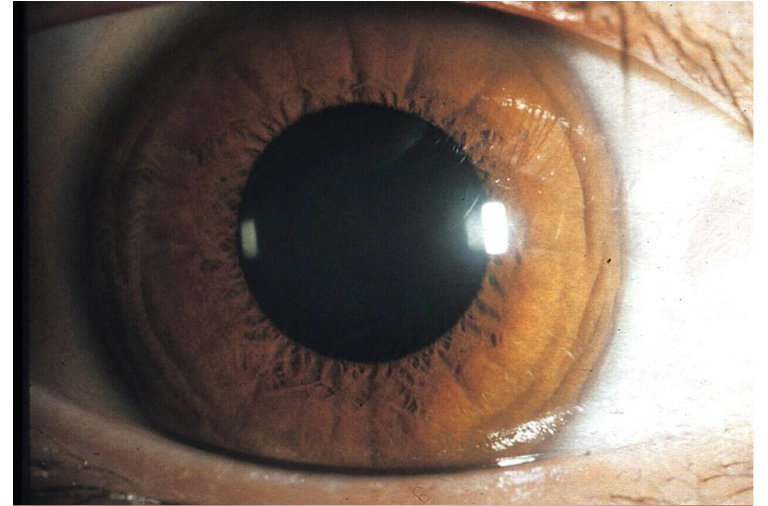


WHEN TO THINK OF WILSON?

- All chronic liver disease patients negative for HBV, HCV, alcohol, HH, auto-immune hepatitis
- Especially with Parkinson-like movement disorder (tremor, dysarthria, dysphagia, incoordination, dystonia)
- Or with psychiatric complaints: depression, personality change, dementia
- Acute liver failure
- Coombs-negative hemolysis
- Kidney: tubulopathy (glucosuria, amino-aciduria, phosphaturia)

HOW TO DIAGNOSE WILSON?

- Decreased ceruloplasmin and/or copper in blood
- Increased urinary copper (D-penicillamine challenge = for kids)
- Kayser-Fleischer ring
- Increased liver copper (>250 mg/g)
- Watch out: hepatitis, ALF, cholestasis
→ FALSE negative/positive
- ATP7b genetics: 2 mutations in trans



COMPLICATIONS: MALIGNANCIES

ORIGINAL ARTICLE

Hepatobiliary malignancies in Wilson disease

Jan Pfeiffenberger^{1,2}, Carolin Mogler^{2,3}, Daniel N. Gotthardt^{1,2}, Henning Schulze-Bergkamen^{2,4}, Thomasz Litwin⁵, Ulrike Reuner⁶, Harald Hefter⁷, Dominik Huster⁸, Peter Schemmer^{2,9}, Anna Członkowska^{5,10}, Peter Schirmacher^{2,3}, Wolfgang Stremmel^{1,2}, David Cassiman¹¹ and Karl Heinz Weiss^{1,2}

Table 2. Wilson's disease cohorts of participating centres

Centre	Warsaw	Heidelberg	Duesseldorf	Dresden	Leuven	Total
Total number of WD patients	753	327	49	32	25	1186
Female [n] (%)	363 (48%)	198 (61%)	29 (59%)	17 (53%)	11 (44%)	618 (52%)
Patients with hepatic symptoms at diagnosis [n] (%)	446 (59%)	229 (70%)	12 (25%)	12 (38%)	17 (68%)	716 (60%)
Patients with neurological symptoms at diagnosis [n] (%)	400 (53%)	96 (29%)	16 (33%)	17 (53%)	6 (24%)	535 (45%)
Total patient years under surveillance since diagnosis of WD (y)	12 941	6392.41	1844.90	1013.08	391	22 582.39
Total patient years since birth (y)	32 442	12 880.49	2120.78	1611.84	1260	50 315.11
Number of HCC cases	2 (pat. 6; 7)	2 (pat. 4; 9)	1 (pat. 5)	1 (pat. 8)	2 (pat. 11; 12)	8
Number of ICC cases	–	4 (pat 1; 2; 3; 10)	–	–	2 (pat. 13; 14)	6

Other study with N=130 in The Netherlands

“No increased risk of HCC in cirrhosis due to Wilson disease”

van Meer S et al. JGH 2015;30:535-9

COMPLICATIONS: OSTEOPENIA AND OSTEOPOROSIS

J Inherit Metab Dis
DOI 10.1007/s10545-015-9815-y

ORIGINAL ARTICLE

Bone demineralisation in a large cohort of Wilson disease patients

Karl Heinz Weiss • Mart Van de Moortele • Daniel Nils Gotthardt •
Jan Pfeiffenberger • Jessica Seeßle • Elena Ullrich • Evelien Gielen •
Herman Borghs • Els Adriaens • Wolfgang Stremmel •
Wouter Meersseman • Steven Boonen • David Cassiman

Table 2 Prevalence of osteopenia and osteoporosis in WD patients and matched controls

Diagnosis	Control	WD
Normal (T-score >-1), <i>n</i> (%)	81 (54.7)	61 (41.2) ^A
Osteopenia (T-score >-2.5 and ≤ -1), <i>n</i> (%)	61 (41.2)	74 (50.0)
Osteoporosis (T-score ≤ -2.5), <i>n</i> (%)	6 (4.1)	13 (8.8)

Significant difference in prevalence between the control and WD population ($\chi^2=6.65$, $df=2$, $p=0.036$), ^A WD patients with normal condition were under represented (less then expected, standardise residual= $-2.33 < -1.96$)

N=148

Female Wilson patient, born 1977

- 1996 (19 years old): presents with subacute liver failure, diagnosed with Wilson disease. Rx D-penicillamine 2x500mg/d
- 1997: “intolerance” to D-Pen, switch to zinc sulphate 3x150mg
- 2000: gastric ulcer bleeding – presence of esophageal varices
- 2000 – 2007: normal transaminases, despite taking only 2/3 of Zn dose
- 2008: liver biopsy (< raised transaminases): F0-F1 fibrosis, 40% macrovesicular steatosis
- 2010: Fibroscan 14.1 kPa (cirrhosis)
- 2010-2015: Lost to follow-up
- 2015: encephalopathy, jaundice, INR increasing: urgent liver Tx

Treatment of Wilson Disease

TREATMENT

Chelation:

1. Penicillamine
2. Trientine
3. TMB: tetrathiomolybdate

Cu uptake inhibition: Zinc

ALF/end-stage liver disease/HCC → liver transplantation

No trials to prove superiority or inferiority, until recently

TREATMENT WITH D-PENICILLAMINE/ CHELATION

Wilson's disease: long-term follow-up of a cohort of 24 patients treated with D-penicillamine

Klaartje F. Lowette^a, Koen Desmet^d, Peter Witters^b, Wim Laleman^c, Chris Verslype^c, Frederik Nevens^c, Johan Fevery^c and David M. Cassiman^c

Background and study aims Detailed data on long-term effectiveness of various drug therapies in Wilson's disease (WD) are lacking. Therefore, we retrospectively reviewed our patient cohort treated with D-penicillamine.

Patients and methods This study reports on the clinical presentation, the diagnostic evaluation, and the disease course in 24 WD patients treated long-term (15 ± 12 years, between 1969 and 2009) with D-penicillamine.

Results The overall survival in our cohort was 91.6%. Twenty-two of 24 patients had liver disease at presentation, 17 of 24 patients (71%) had cirrhosis, 11 of whom had complications of cirrhosis. Six of 11 of these patients showed hepatological improvement (five of six) or stabilization (one of six), three of 11 were transplanted, one of 11 died, one of 11 discontinued follow-up. In the six of 17 cirrhotic patients without complications, improvement (four of six) or stabilization (two of six) occurred. Of all other patients (seven of 24), five of seven showed improvement (three of five) or stabilization (two of five), hepatological deterioration occurred only in one patient due to poor therapy compliance and one of seven discontinued follow-up. Neuropsychiatric symptoms were

present in 13 of 24 at presentation and resolved in one of 13, decreased in seven of 13, stabilized in four of 13 and worsened in one of 13 patients (due to poor compliance). In general, we observed a favorable hepatological and neurological evolution with D-penicillamine.

Conclusion Despite the presence of liver disease or neuropsychiatric symptoms at baseline in all but one of the patients, we report beneficial results on liver and neurological disease after very long-term treatment with D-penicillamine, thereby adding to its reputation as 'first-line' therapy in WD. *Eur J Gastroenterol Hepatol* 22:564–571 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2010, 22:564–571

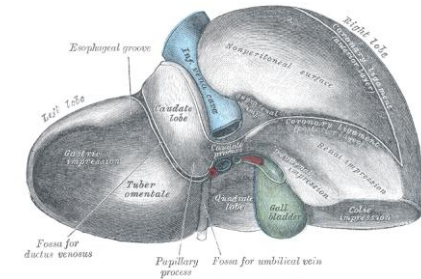
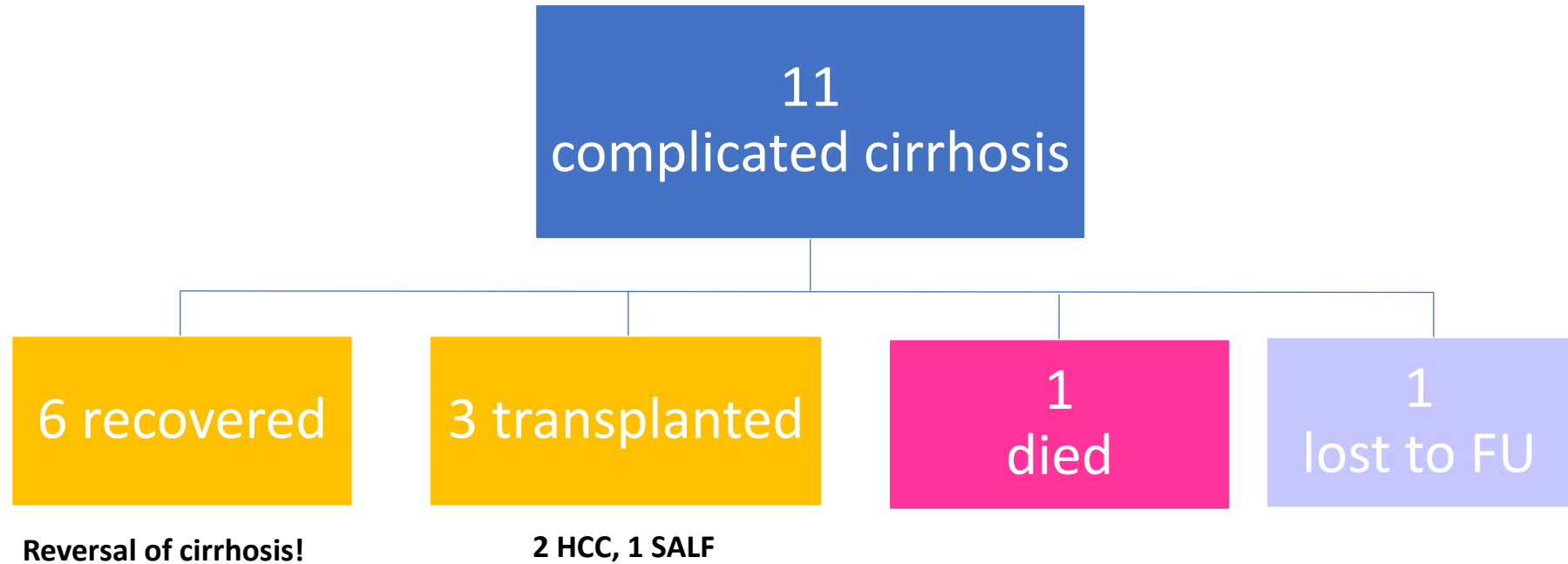
Keywords: D-penicillamine, outcome, Wilson's disease

Departments of ^aInternal Medicine, ^bPediatrics, ^cHepatology and ^dCentral Laboratory, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium

Correspondence to Dr Klaartje Lowette, MD, Department of Internal Medicine, University Hospital Gasthuisberg, University of Leuven, Broekstraat 7, Borgloon BE- 3840, Belgium
Tel: +32 12 741920; fax: +32 12 743948; e-mail: klaartje_lowette@yahoo.com

Received 16 August 2009 Accepted 11 November 2009

OUTCOME



TREATMENT WITH ZINC MONOTHERAPY

GASTROENTEROLOGY 2011;140:1189–1198

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease

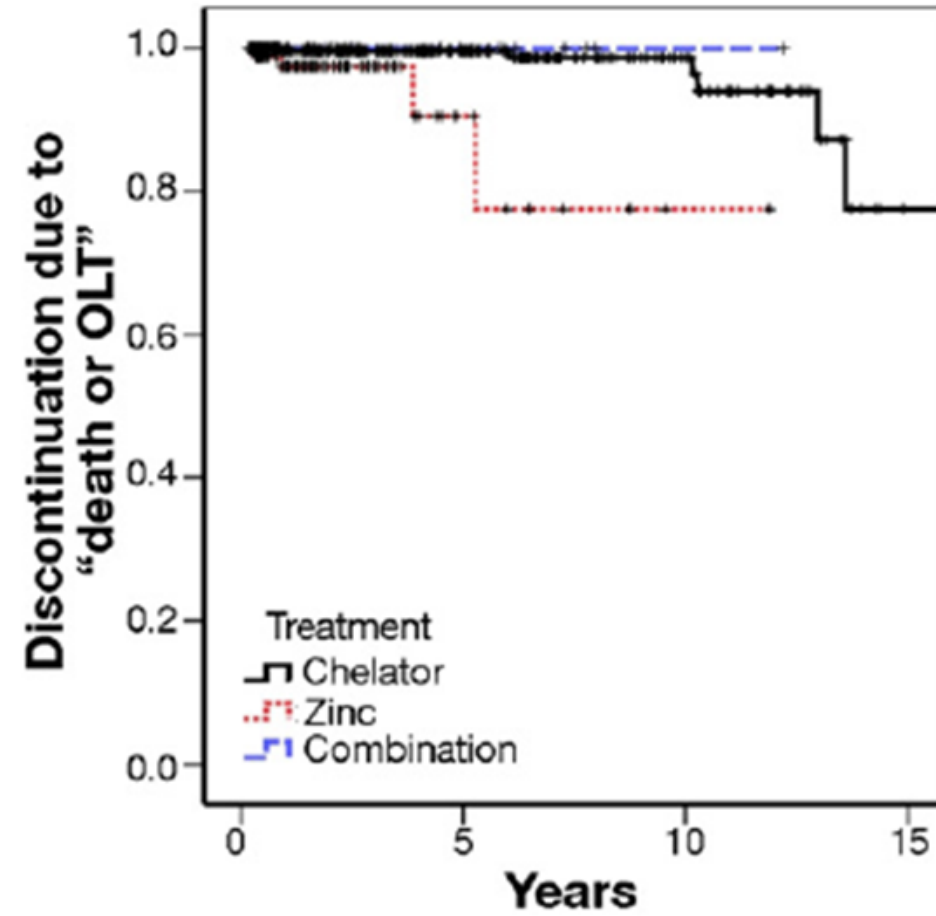
KARL HEINZ WEISS,* DANIEL NILS GOTTHARDT,* DANIELA KLEMM,* UTA MERLE,* DANIELA FERENCI-FOERSTER,[‡] MARK SCHAEFER,* PETER FERENCI,[‡] and WOLFGANG STREMMEL*

**Department of Gastroenterology, University Hospital Heidelberg, Heidelberg, Germany; and [‡]Department of Gastroenterology, University Hospital Vienna, Vienna, Austria*

n = 288

Heidelberg and Vienna

OUTCOME



Chelator vs. zinc	Chelator vs. combination	Zinc vs. combination
$P<.001$	$P=.696$	$P=.140$

LIVER TRANSPLANTATION

Clin Transplant 2013; 27: 914–922 DOI: 10.1111/ctr.12259

© 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Clinical Transplantation

Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease

Weiss KH, Schäfer M, Gotthardt DN, Angerer A, Mogler C, Schirmacher P, Schemmer P, Stremmel W, Sauer P. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease.

Karl Heinz Weiss^{a*}, Mark Schäfer^{a*}, Daniel Nils Gotthardt^a, Alexandra Angerer^a, Carolin Mogler^b, Peter Schirmacher^b,

Conclusion: Survival after OLT for Wilson disease with end-stage liver disease is excellent. Overall, neuropsychiatric symptoms improved after transplantation, substantiating arguments for widening of the indication for liver transplantation in symptomatic neurologic Wilson disease patients with stable liver function.

CHELATION THERAPY SIDE EFFECTS

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:1028–1035

Efficacy and Safety of Oral Chelators in Treatment of Patients With Wilson Disease

KARL HEINZ WEISS,* FLORENTINE THURIK,‡ DANIEL NILS GOTTHARDT,* MARK SCHÄFER,* ULRIKE TEUFEL,§ FRANZISKA WIEGAND,* UTA MERLE,* DANIELA FERENCI-FOERSTER,|| ANDREAS MAIERON,¶ RUDOLF STAUBER,# HEINZ ZOLLER,** HARTMUT H. SCHMIDT,‡‡ ULRIKE REUNER,§§ HARALD HEFTER,||| JEAN MARC TROCELLO,¶¶ RODERICK H. J. HOUWEN,‡ PETER FERENCI,|| and WOLFGANG STREMMEL,* for the EUROWILSON Consortium

- ±20% serious adverse effects (proteinuria, skin rash, hematotoxicity)
- Discontinuation due to adverse effects in 29% for D- penicillamine and 7% for Trientine
- Neurological worsening in 5-20% of patients



omg!

25-30% of WD patients are non-compliant

Low adherence leads to progressive worsening of the clinical condition, and interruption of treatment can lead to a fulminant worsening of the disease and even death

CHELATE

First randomised prospective trial evaluating any trientine vs. DPA

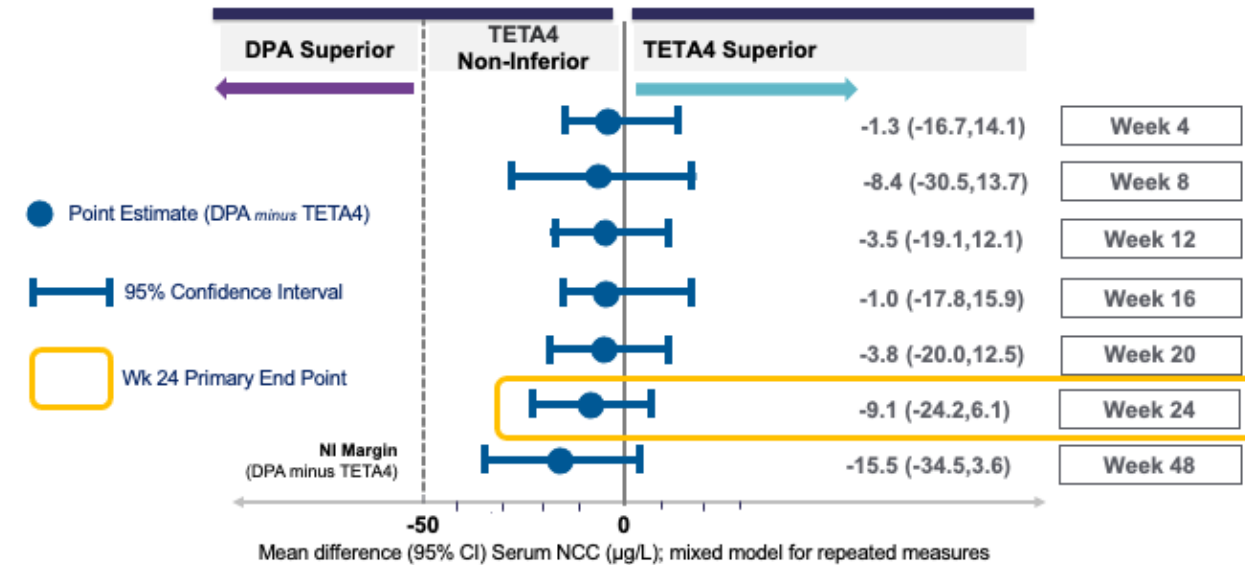
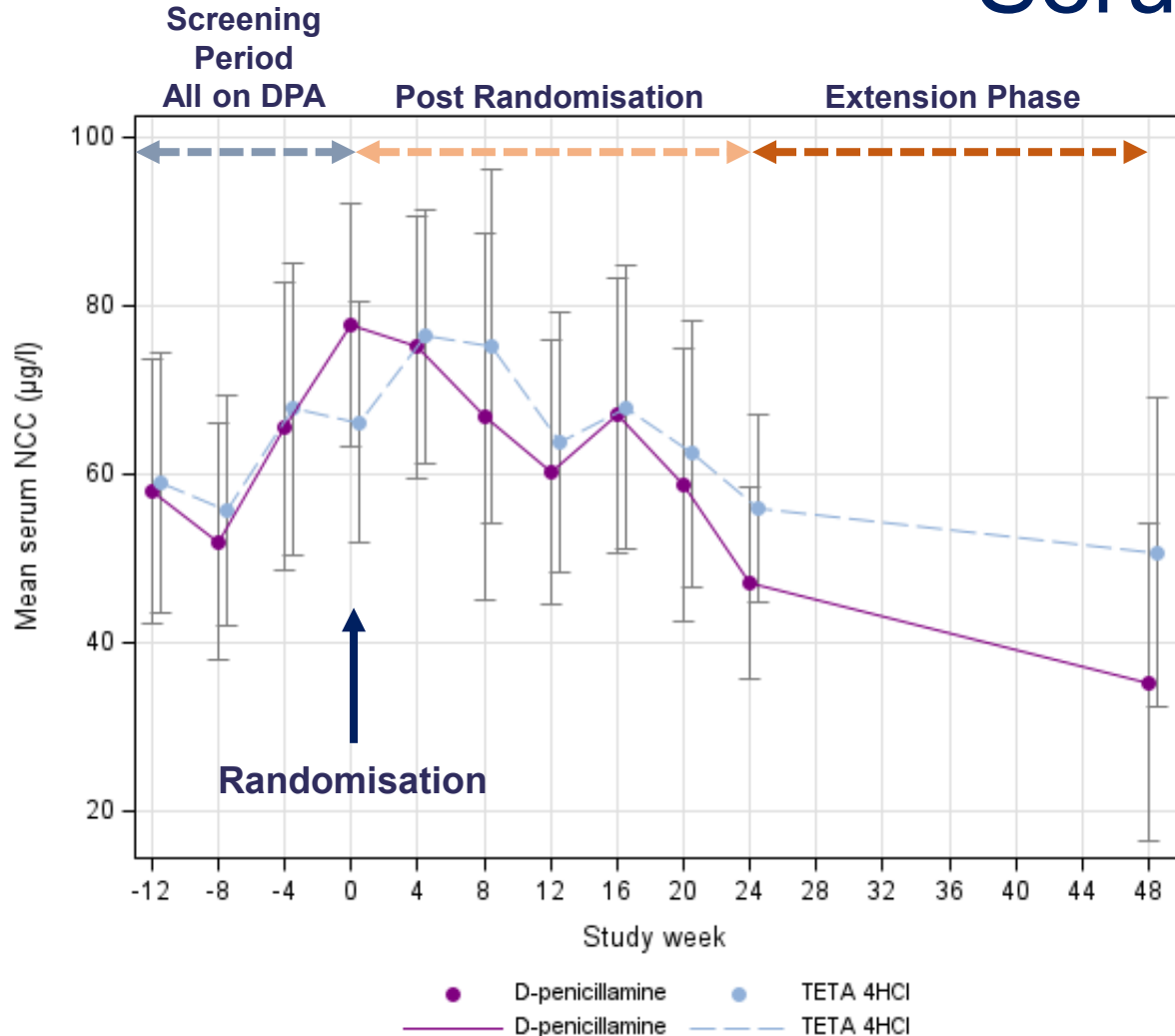
Aim

- To evaluate the efficacy and safety of 4-HCl-Trientine to treat clinically stable adult Wilson Disease patients

Hypothesis

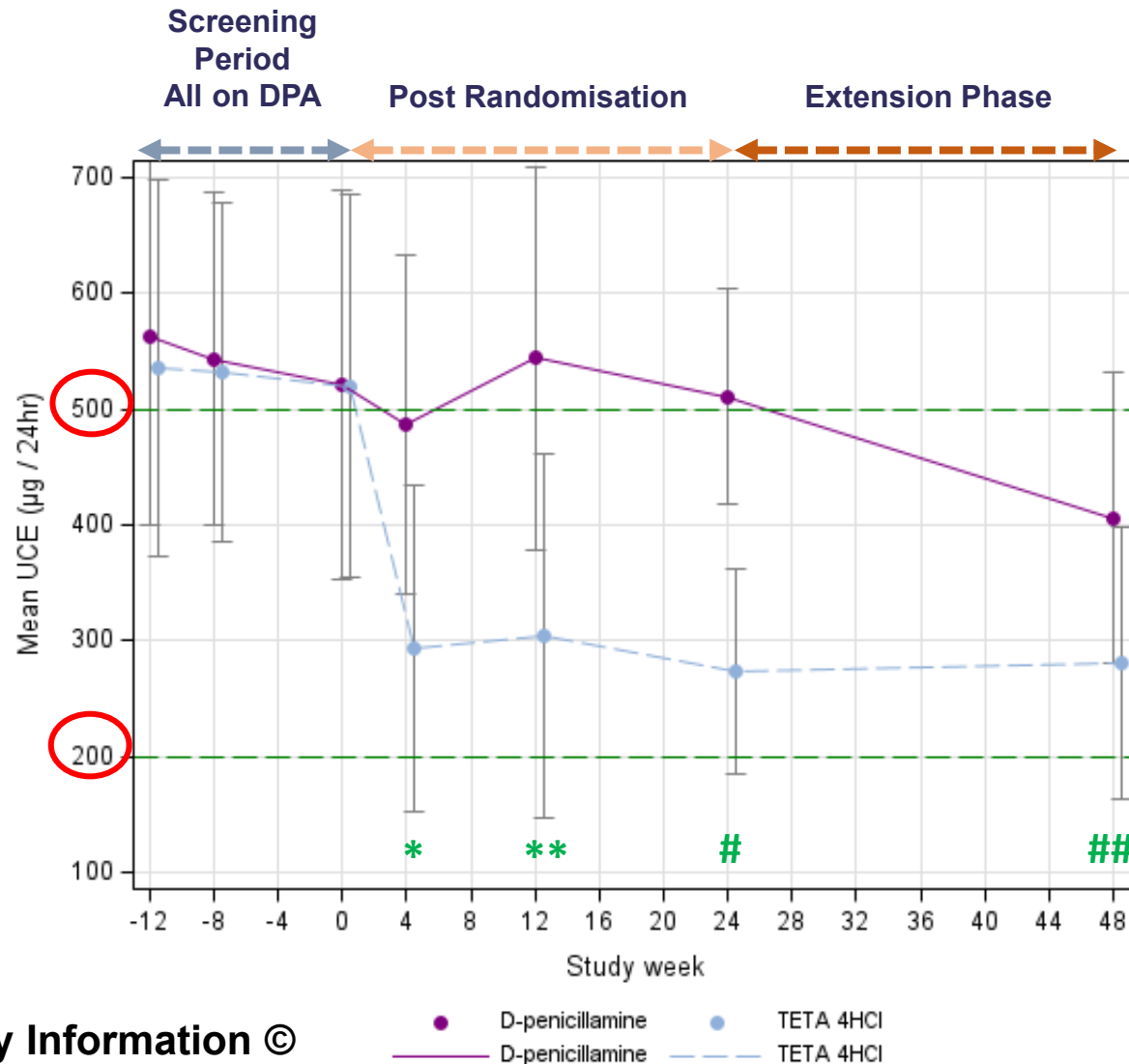
- Compared with continuation of DPA, treatment with 4-HCl-Trientine will be well tolerated and **non inferior** to DPA at 24-weeks post randomisation in terms of efficacy, as measured by serum NCC

Primary Efficacy Measure: Serum NCC



4-HCl-Trientine is non-inferior to DPA
at 24 and 48 wks

Secondary Efficacy Measure: 24 hr Urinary Copper Excretion (UCE)



Recommended UCE Target
Range 200-500 mcg/24 hr

P- values

*	0.015
**	0.008
#	0.0005
##	0.047