Wilson's disease from a COMP perspective

Kerstin Westermark
Medical Products Agency
Sweden

Wilson´s Disease Center
Uppsala University Hospital

Kerstin Westermark, M.D., Assoc. Prof.

Diagnostics

- MRI (brain)
- PET (dopamine)
- PET (copper)

Patient care

- WD team
- Patient support group
- Long term treatment with Trientine

Genetics

- WD gene mutations (Manifold sequencing)

Psychiatrics

- Mapping psychopatology and neurophysiology

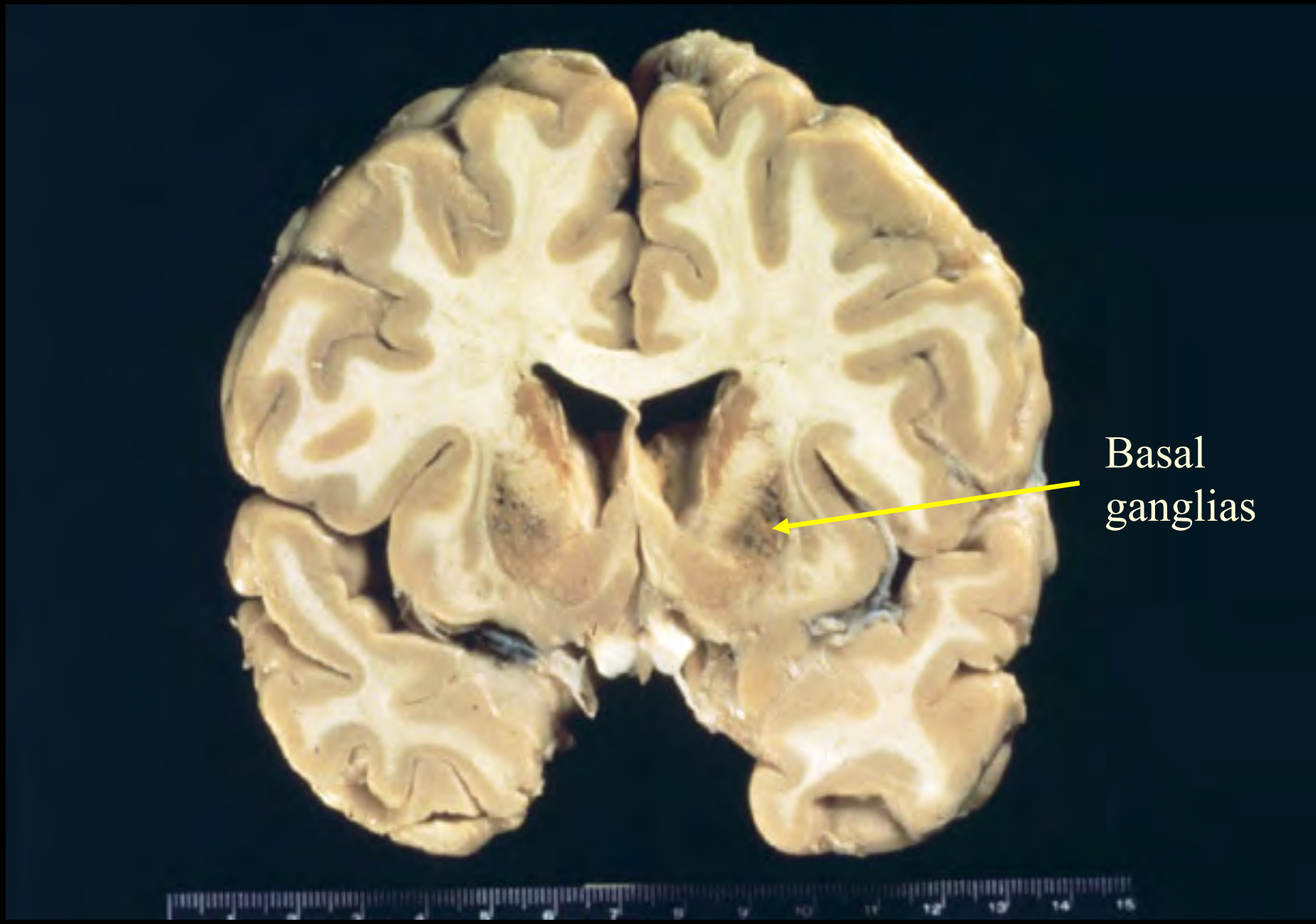
Progressive lenticular degeneration a familial nervous disase associated with cirrhosis of the liver

SAK Wilson
Thesis, Univ. of Edinburgh, 1911

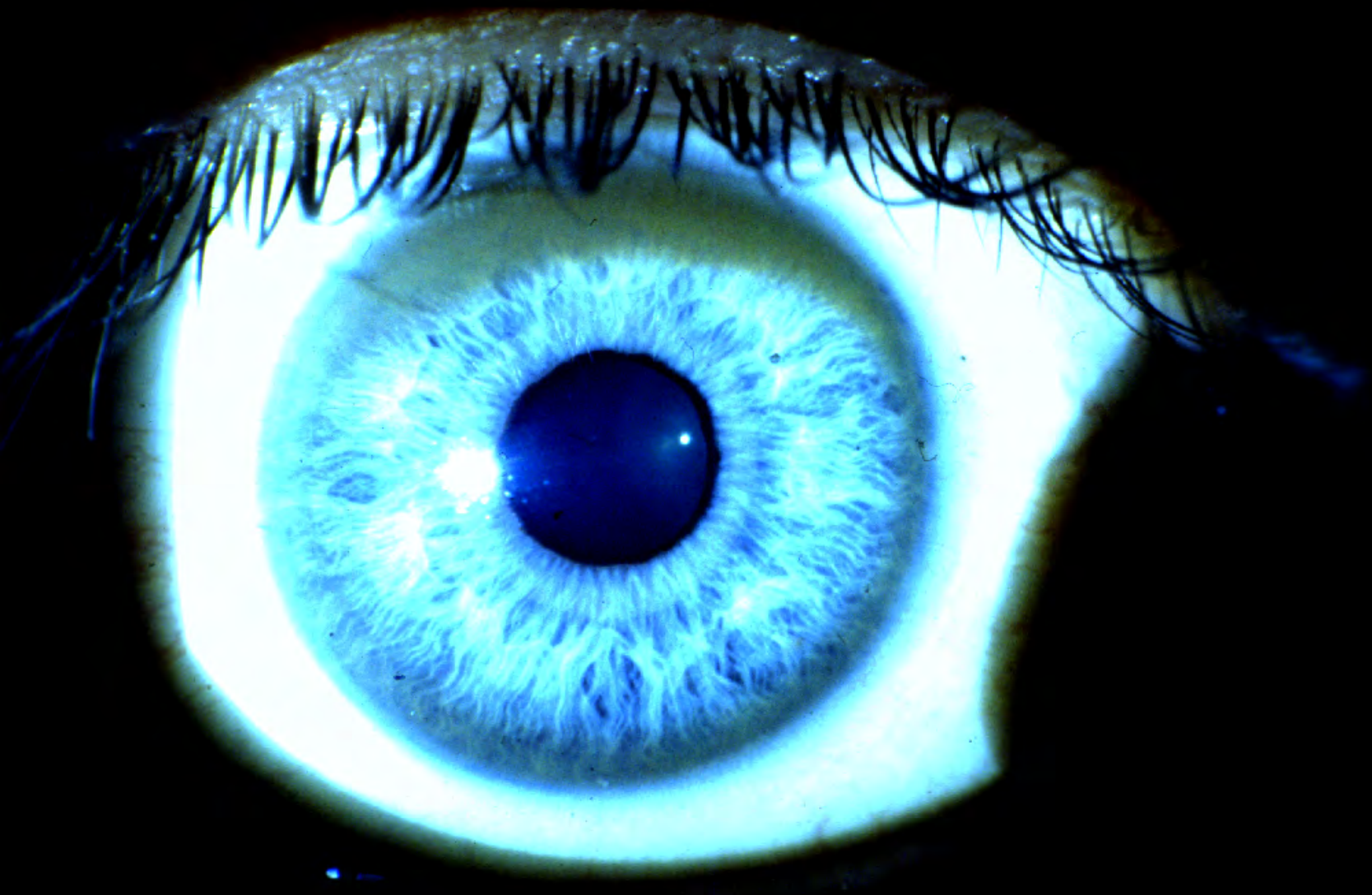
Spasticity

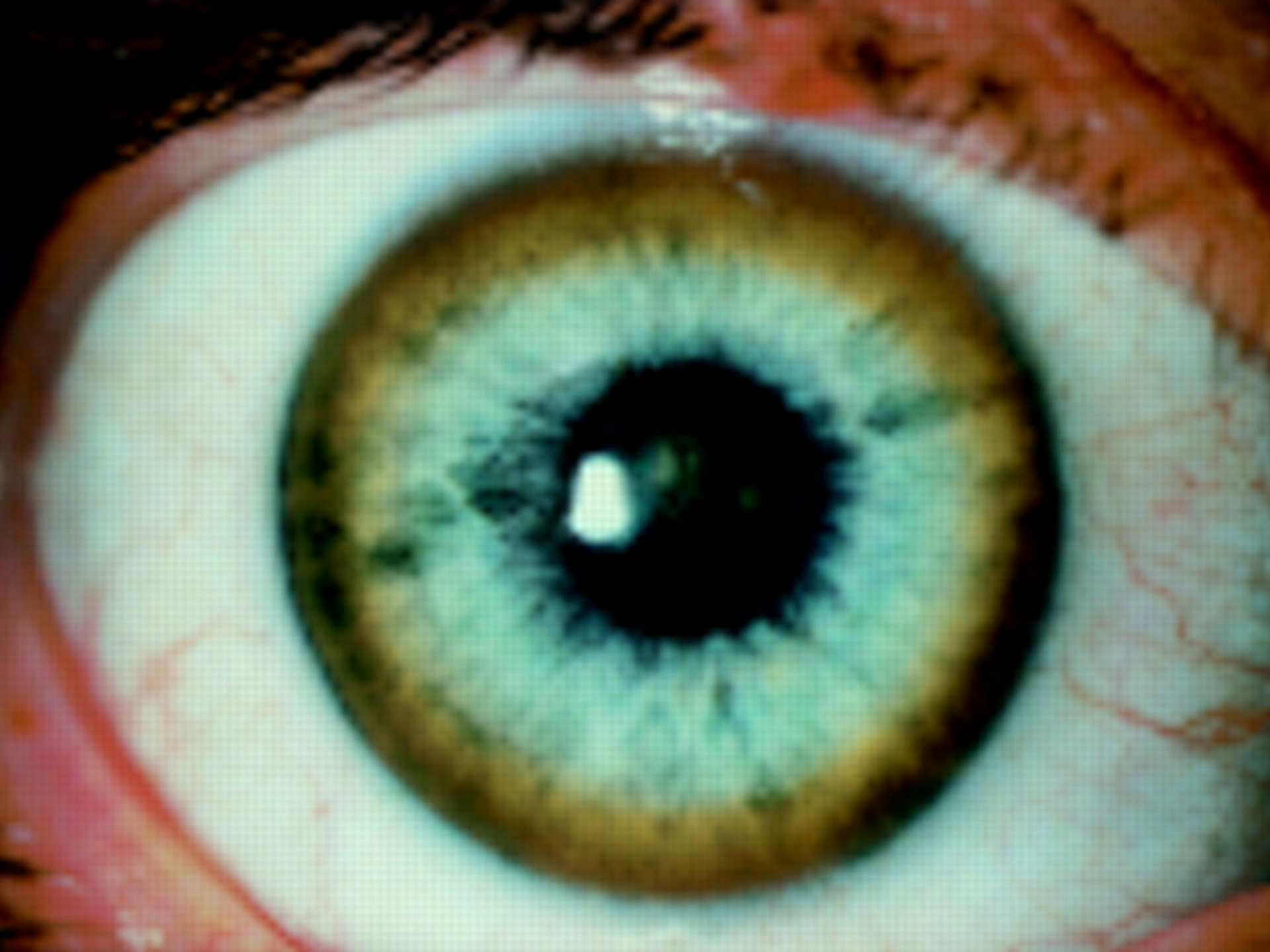
Tremor

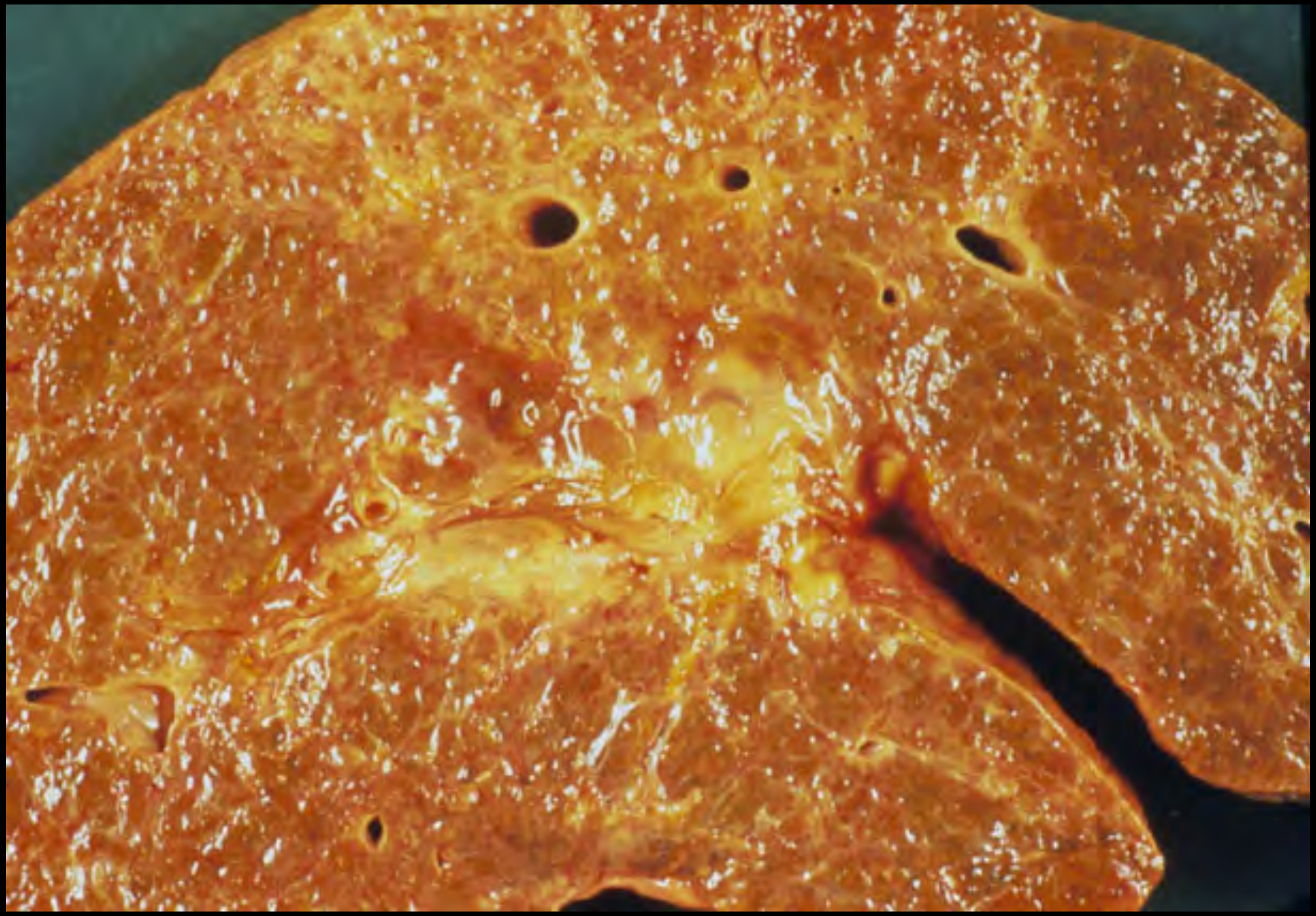
Contractures


Basal
ganglias

Kayser-Fleischer ring







”As the doctor says of a wasting disease, to start with it is easy to cure but difficult to diagnose; after a time, unless it has been diagnosed and treated at the outset, it becomes easy to diagnose but difficult to cure .”

Niccolo Machiavelli, The Prince, 1514 (transl. George Bull)

The Penicillamine Story
(From: J M Walshe, Movement Disorders,
Vol. 18, No. 8, 2003)

Early 1950s Univ. College Hosp. London :

JM Walshe, using paper chromatography, observed a new compound in the urine of a patient treated with penicilline - penicillamine.

Penicillamine reacted with ferric chloride: blue colour, presence of an SH-group

Chelating properties?

Boston City Hosp., 1955: JM Walshe

- Denny-Brown/Uzman working on patients with WD
- Treatment with British antilewisite (BAL) i.m. – painful, toxic, tachyphylaxis
- Patient Joe G failing on BAL treatment
- JM Walshe – Penicillamine – copper removing?
- 2 g from prof. Sheehan working on chemical synthesis of penicillin at MIT

Penicillamine ”toxicity testing”

- No published data on toxicity in man/little in animals
- JMW observation: Anyone treated with penicilline (including JMW) excreted penicillamine in the urine – apparently without ill effect
- 1st study in man: JMW took 1 g of penicillamine - a crystalline powder smelling sulphur
- - JMW being well and alive next morning…

”Clinical Trial” – no ECs, No FDA…

…gave the 2nd g to patient Joe G

Result: Satisfactory copper excretion

- Conclusion: Further studies with penicillamine justified
- More penicillamine needed – MSD provided several grams - but MSD penicillamine failed to induce cupriuresis…
- JMW test: No blue colour with ferric chloride (tap water) - long storage – autooxidisation – no SH-radical - no copper chelation

Penicillamine production story

- Mann's Fine Chemicals, New York produced 50 g of penicillamine
- JMW brought this to his father, Sir Francis Walshe, prof. in Neurology in London

  3 patients with WD were treated:

  All responded well - No 1 and 2 were put back on BAL

Penicillamine story, cont.

Patient No 3, Shirley

- severely parkinsonian, failed to improve on BAL - prime case for a trial of a new therapy

  (no ECs, No drug safety committees)
- JMW prepared penicillamine, packed into capsules, gave to Shirley - 450 mg/d.

Shirley improved but not until after 1 year of treatment (low dose)

- Married
- Three children
- 47 years of penicillamine treatment – 1.5 kg in all

Walshe JM, Penicillamine, a new oral therapy for Wilson's disease. Am J Med 1956;21:487-95

Penicillamine Story, cont.

Production problems

Solution:

The Distillers Company Biochemicals –

main manufacturers of penicilline by fermentation - produced penicillamine


FIRE

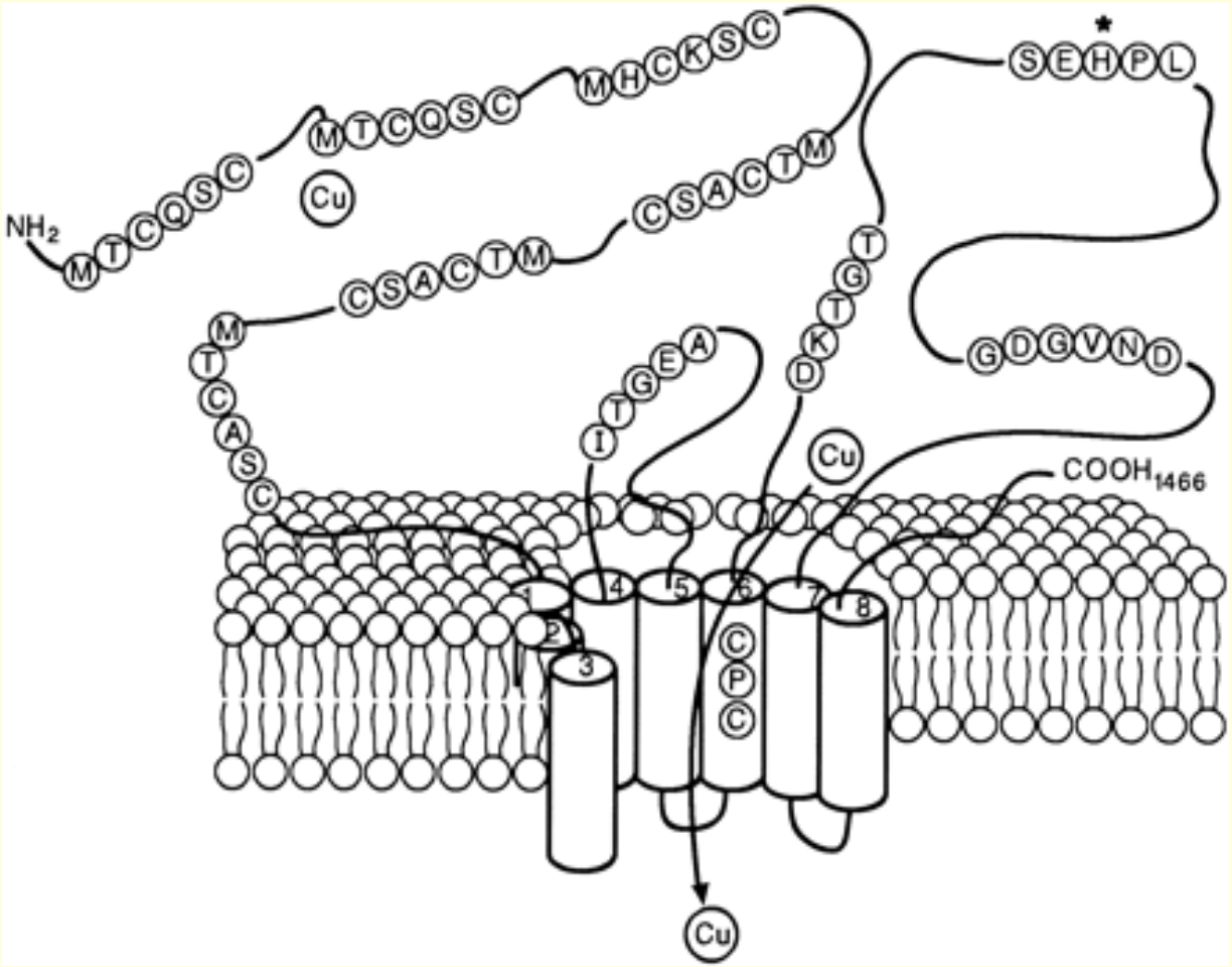
Wilson *disease* history

1993

WD gene cloned by three independent groups:

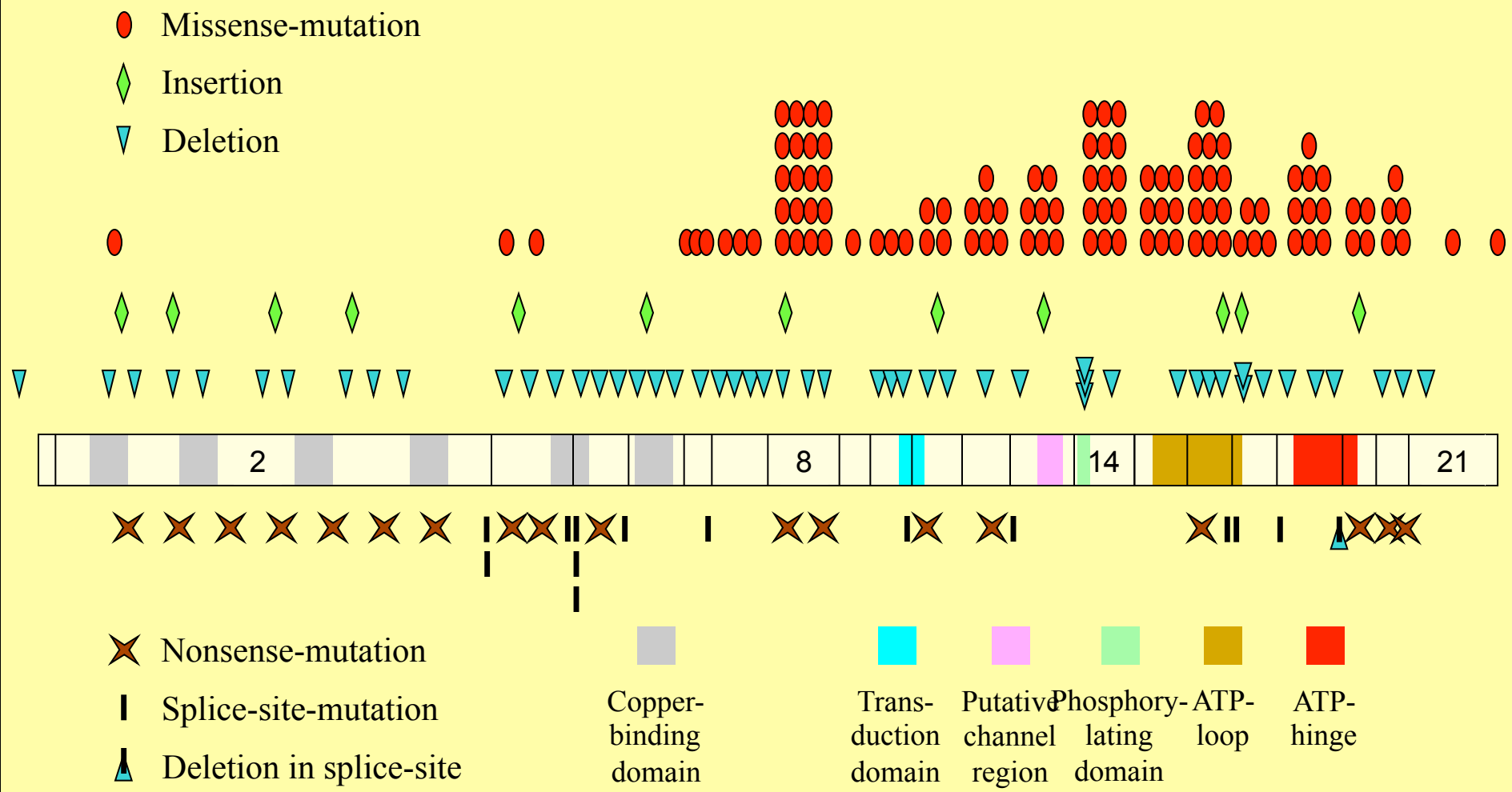
Bull et al, Tanzi et al and Yamaguchi et al

The Wilson's disease gene encodes a copper transporting ATPase which is expressed in hepatocytes - maintains copper homeostasis – excretion of excess copper into the bile



Semin Liver Dis 2000;**20**:353-64

All registered mutations in *ATP7B* 14/02/02



www.uofa-medical-genetics.org/wilson/index.html

The COMP perspective

All treatments presently used have been developed in academic institutions

1954 Peters, Oxford (BAL)

1956 Walshe, Boston (penicillamine)

1961 Schouwink, Arnhem (zinc sulphate)

1969 Walshe, Cambridge (triethylene tetramine - Trientine),

1984 Walshe, Cambridge, (tetrathiomolybdate)

1983 Brewer, Ann Arbor, (zinc acetate)

Conclusions – Drugs for Wilson's disease:

- thanks to academic scientists
- thanks to serendipity

  - and lately
- thanks to the Orphan Drug legislation, EU Directive 2001/04
- treatment for Wilson's disease has become generally available to patients within the EU

Conclusions
Present and Future treatments:

In the future: Gene therapy, cell therapy…based on current molecular knowledge

At present: Liver transplantation in liver failure

At present: Zinc acetate authorised in the US (Galzin) and EU (Wilzin – *Orphan Drug*)

Trientine in the US and in the UK/EU (*Orphan Drug Designation)*

Tetrathiomolybdate used experimentally in the US and EU

Penicillamine – still the main drug for Wilson's disease – after 50 years on the market!

John M. Walshe