NVvM, Papendal, 11 dec 2003

Peroxisomal mosaics in patients : modulation of gene expression ?

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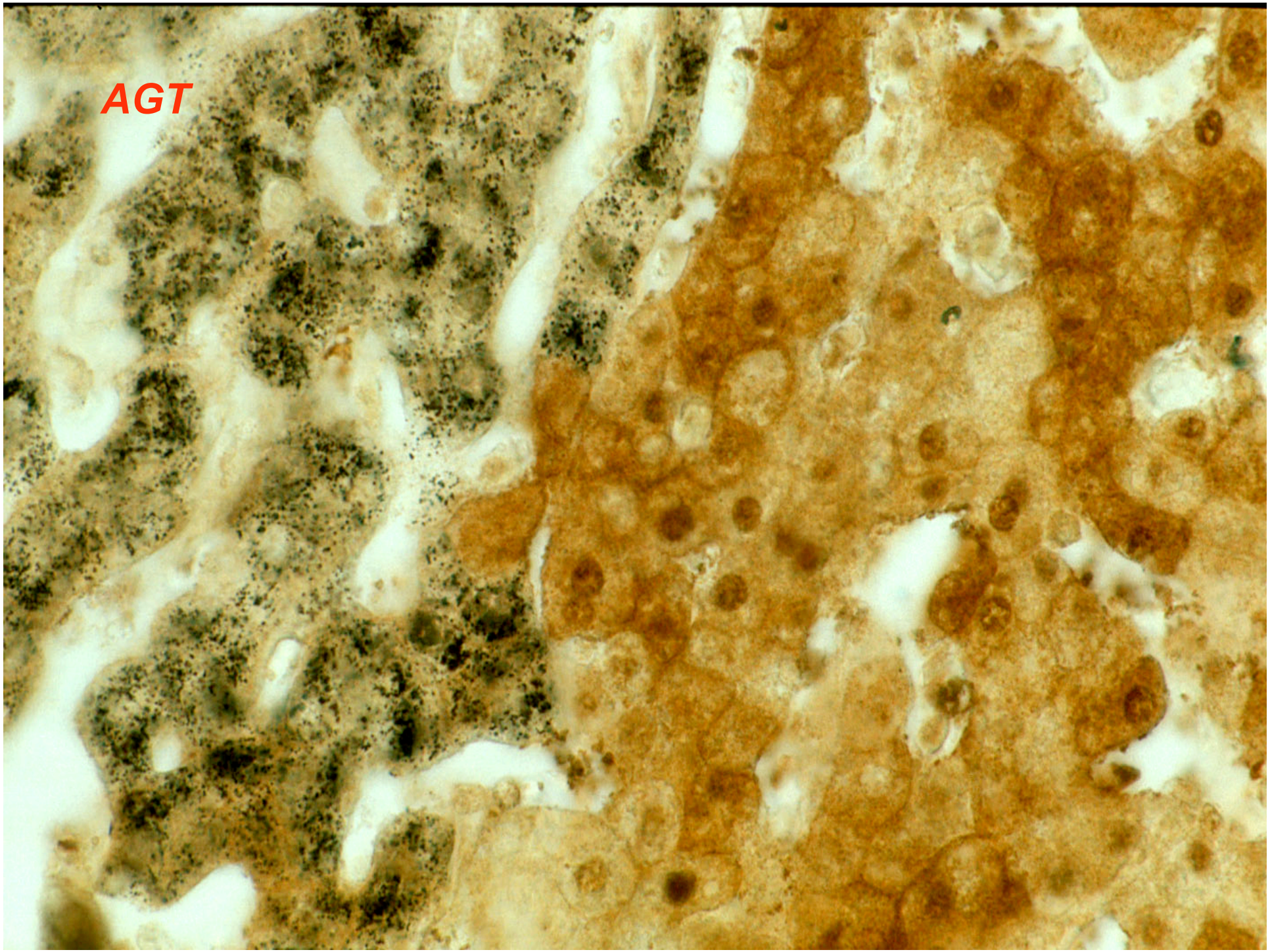
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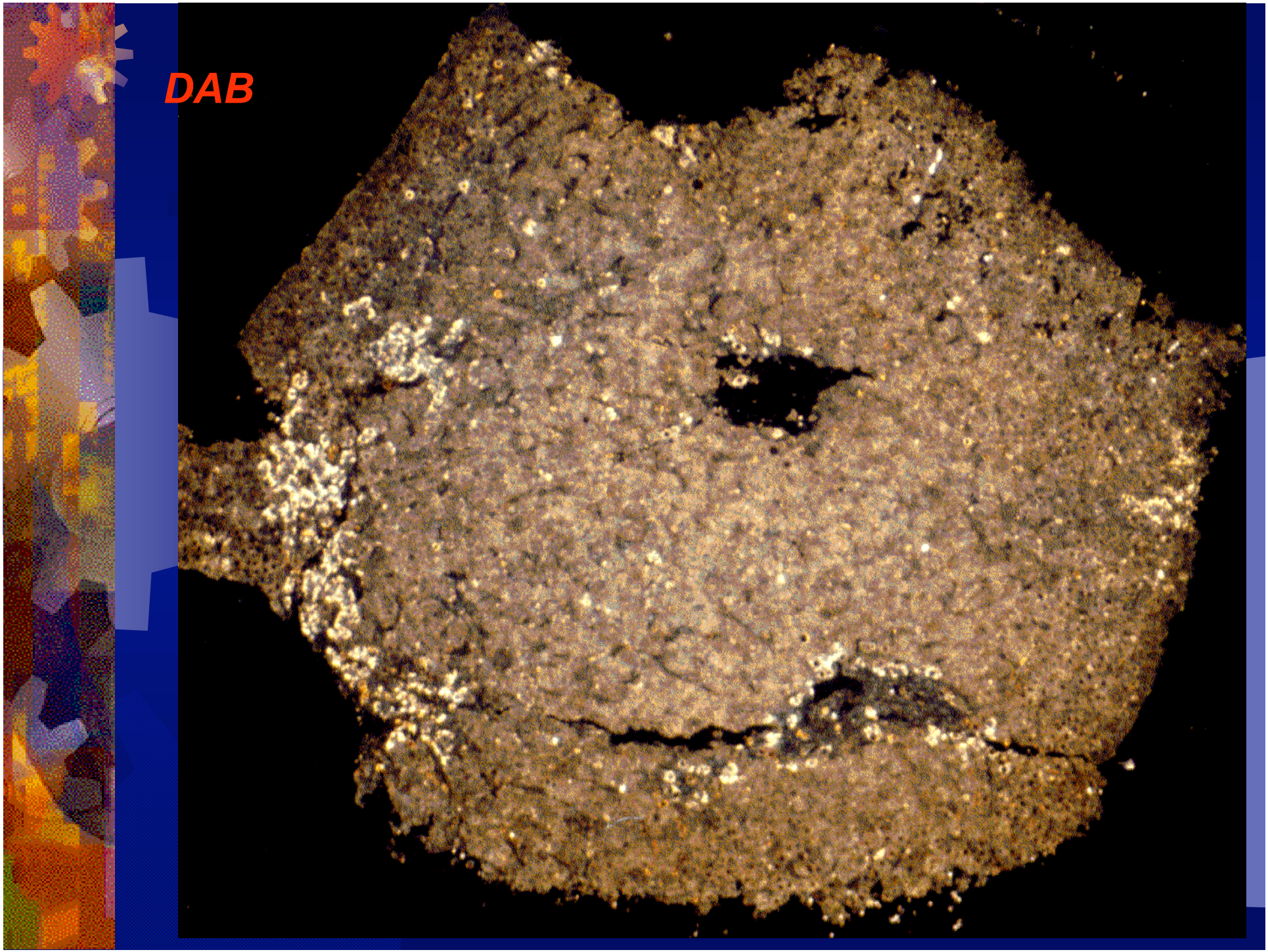
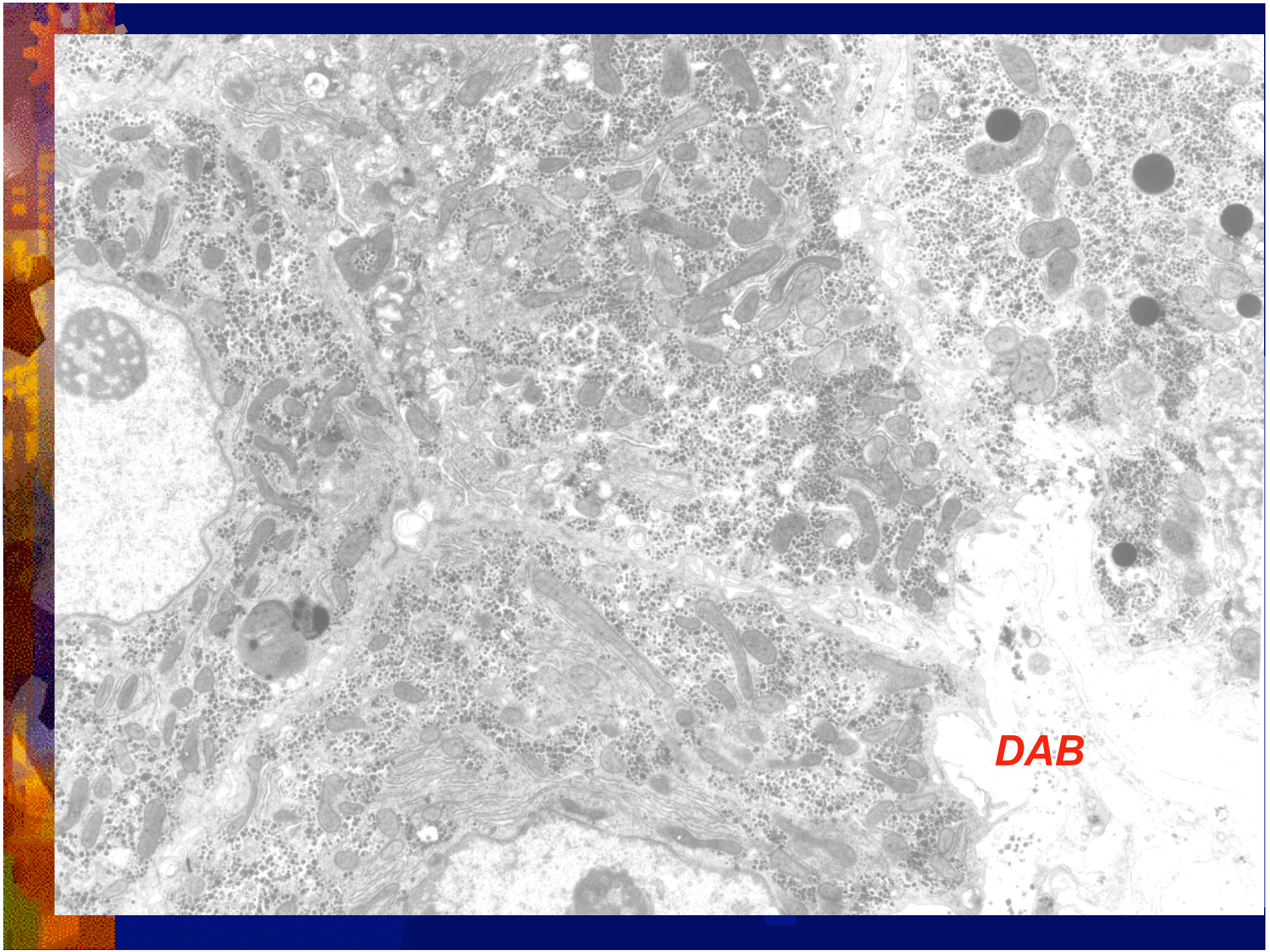

DAB


DAB

Human peroxisomal disorders

Pxbiogenesis =assembly deficiencies

*Zellweger = CHRs

*Neonatal ALD */ 50 000*

*Infantile Refsum disease

*Mosaics *10/170*

▪***Multiple enzyme deficiencies***

Rhizomelic chondro-dysplasia punctata type 1

Single enzym/protein deficiencies

°X-ALD=ALDprot mut; funct def of VLCacyl-CoA synthase */ 35 000*

°Acyl-CoA oxidase deficiency

°D-bifunctional enzyme defic.

°(Thiolase (straight chain) def.)

°Racemase deficiency

°RCDP 2=DHAPAT defic.

°RCDP3=alkylDHAP synthase def.

°Classical=adult Refsum dis = phytanoylCoA hydroxylase def.

°Mevalonate kinase def.

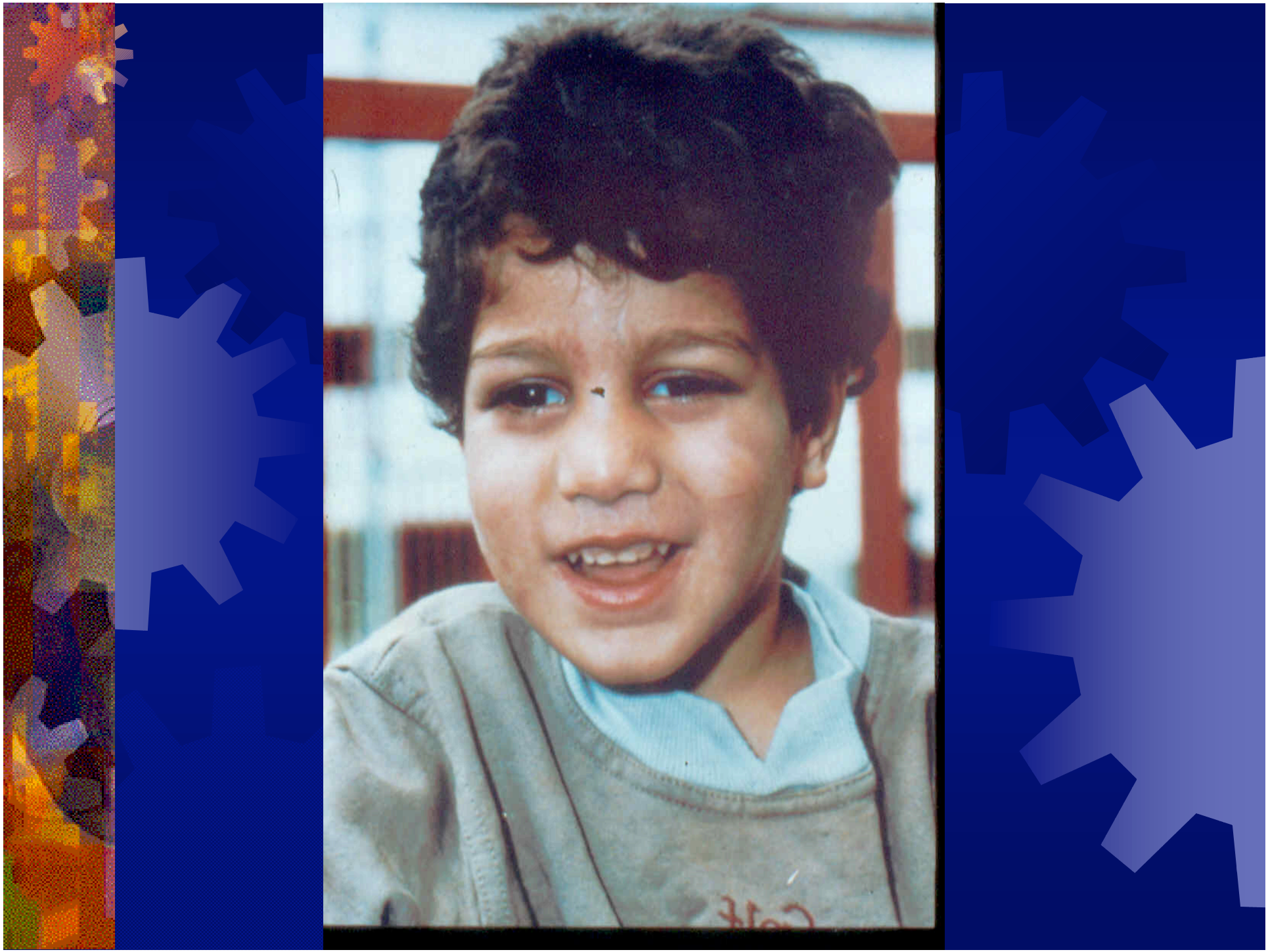
°Isolated hyperpipecolic acidemia

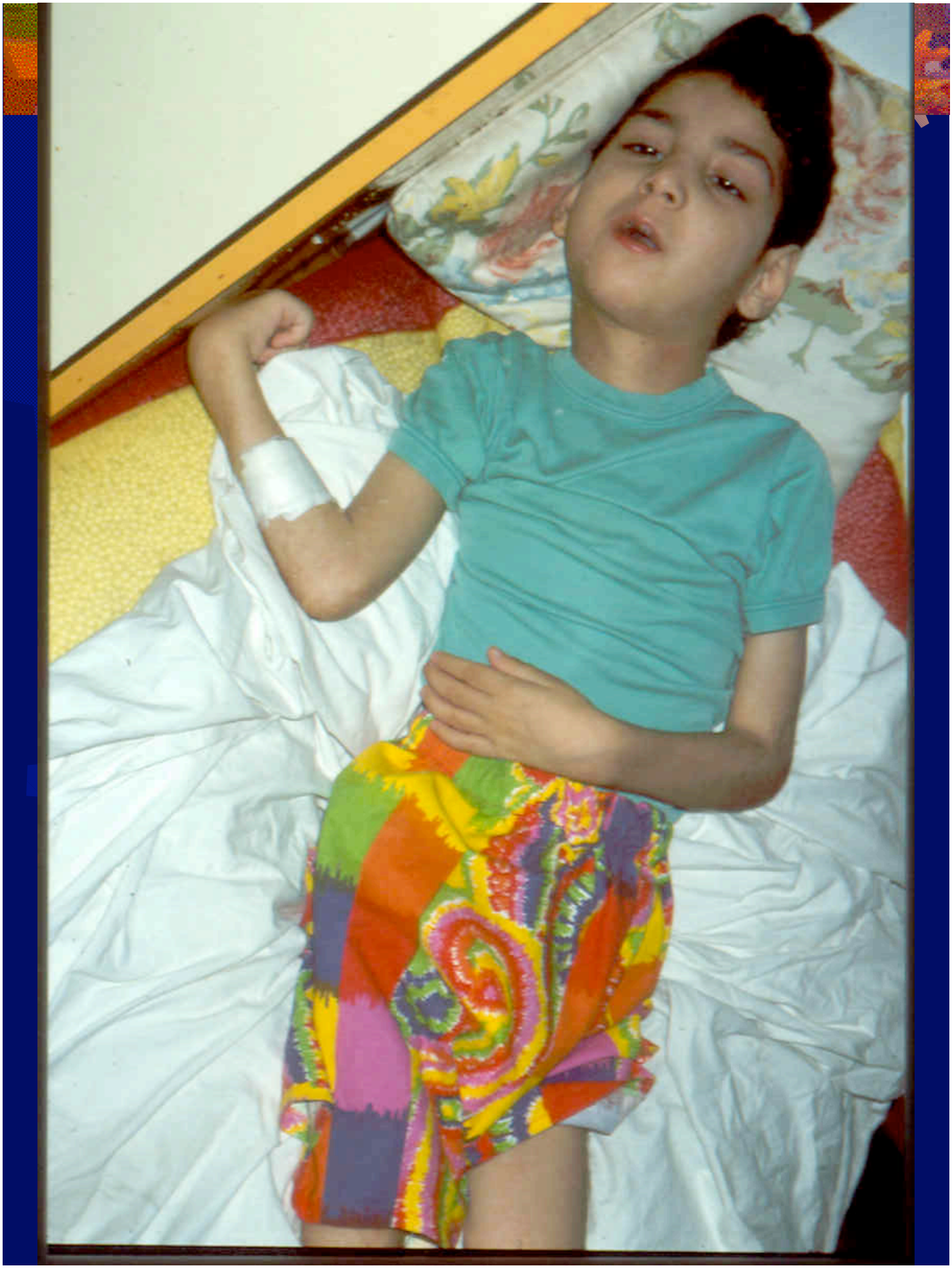
°Primary hyperoxaluria1=AGT def

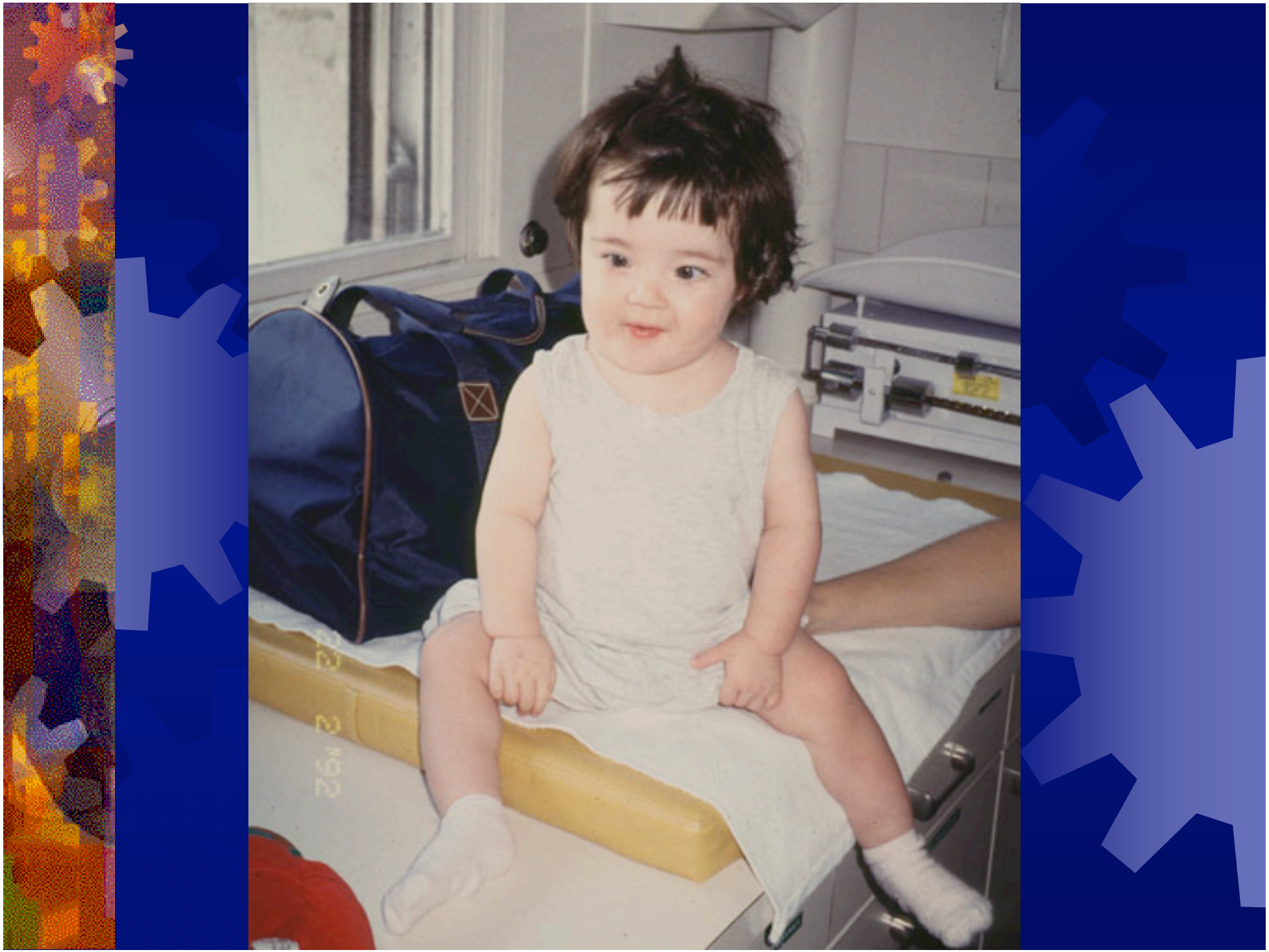
°Mulibrey nanism=TRIM37 defic.

Clinical and biochemical data

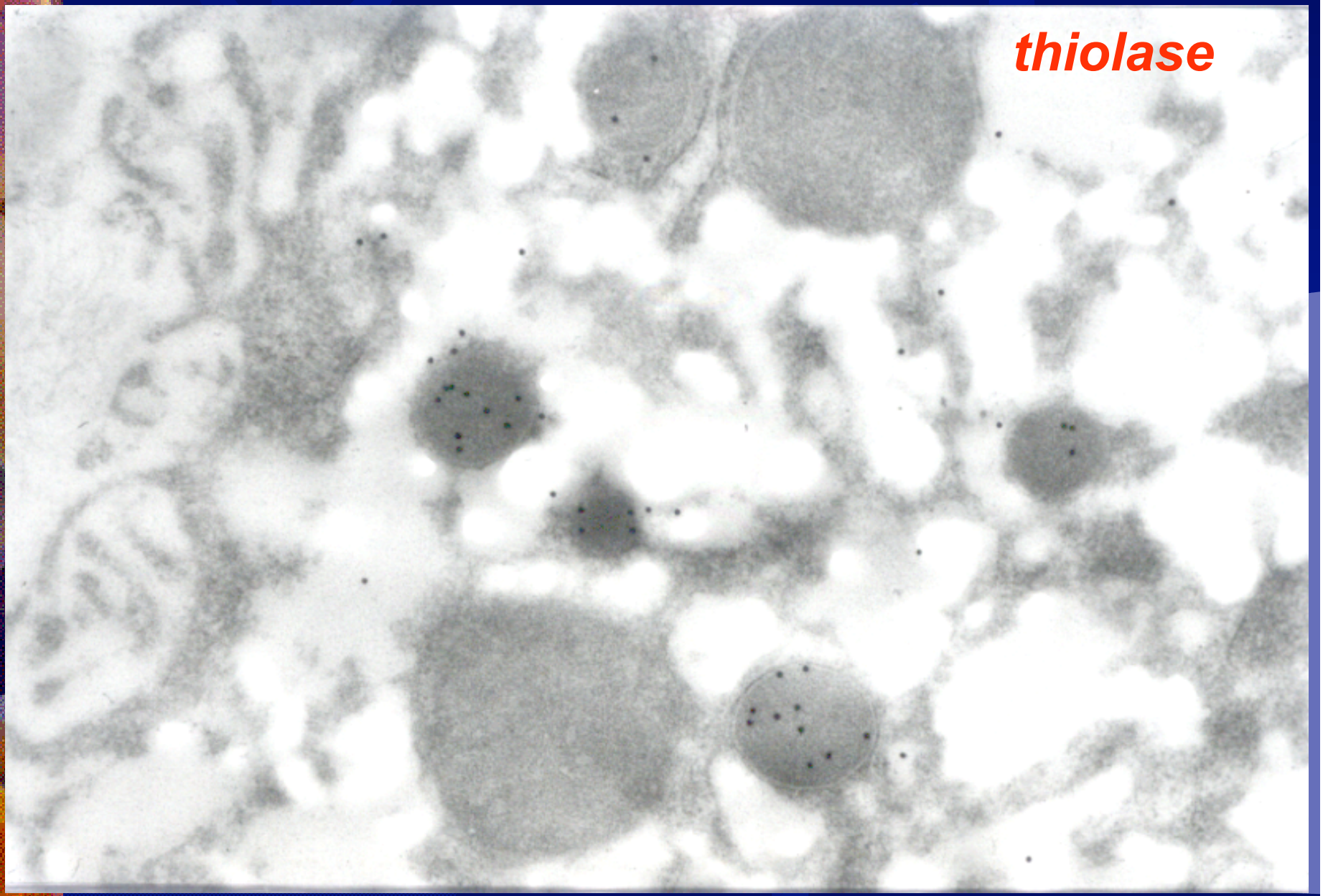
	Pt 1	Pt 2	Pt3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt10
Age	†13y6	†8y7	11y	†15y	† 17y	7y	†13 m	14y	†24 y	43y
VLCFA	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Bile ac	+	+	+	+	+	+		+	+	
Phyt	↑	↑		↑	↑	↑		↑	↑	nor
Plasmal	nor	nor	mild↓	↓		nor	nor	nor	nor	
Neonat	nor			nor		nor		nor	nor	nor
dysmor	no	±	±	no	no	+	±	no	no	no
Evolut	neuro degen, veget	pyr tr eye conta ct	walks, talks	PMR deaf menarc he	school 8y catara ct	syntax vocab	Pneu monia	neuro-degen, eye contac t	12y!	2y: eye, ment al
Cultur. fibrobl	nor	nor	25% 50%	plasm al	nor	20%	nor	nor	mo sai c	mild

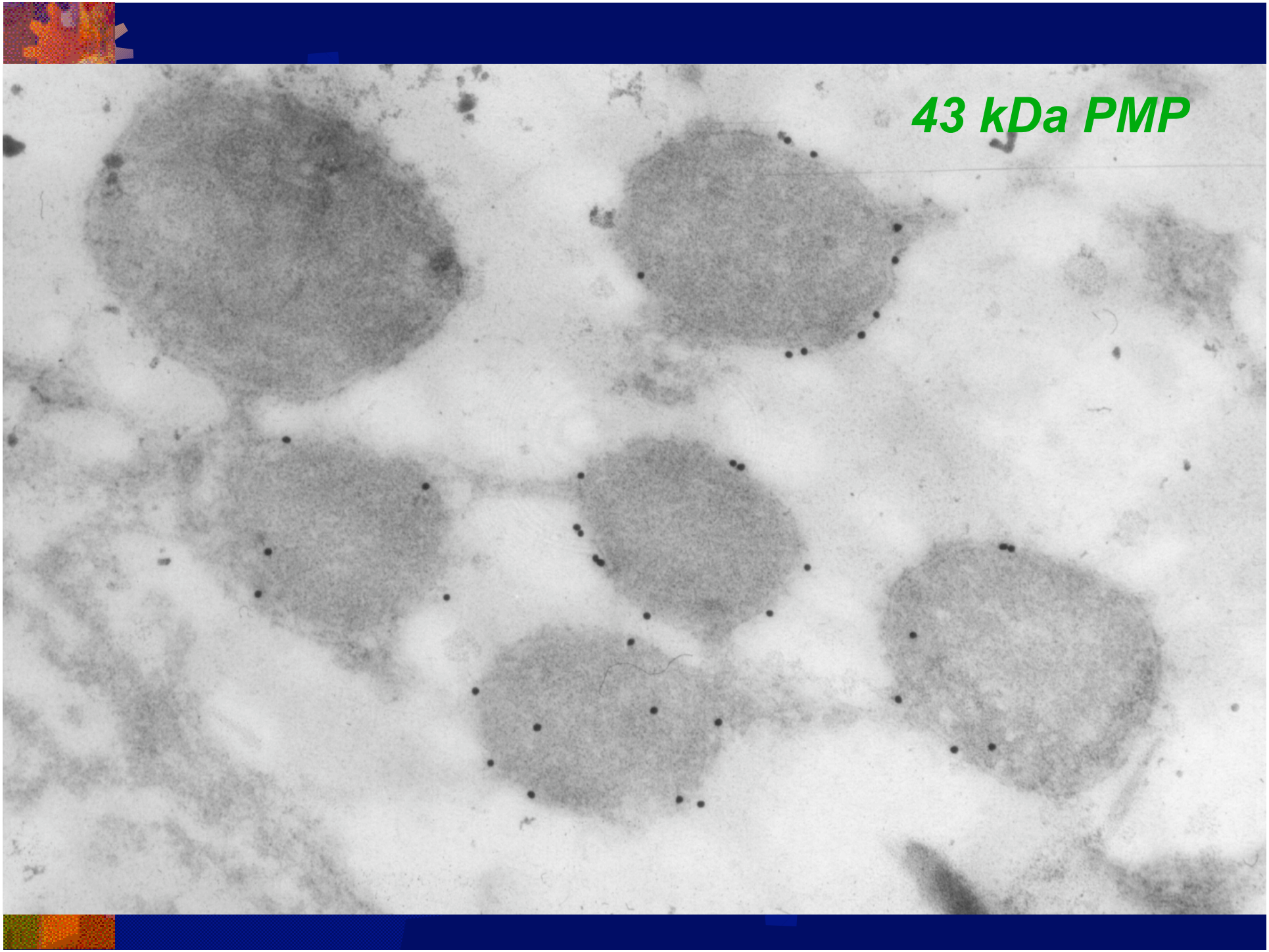







CARNAVAL

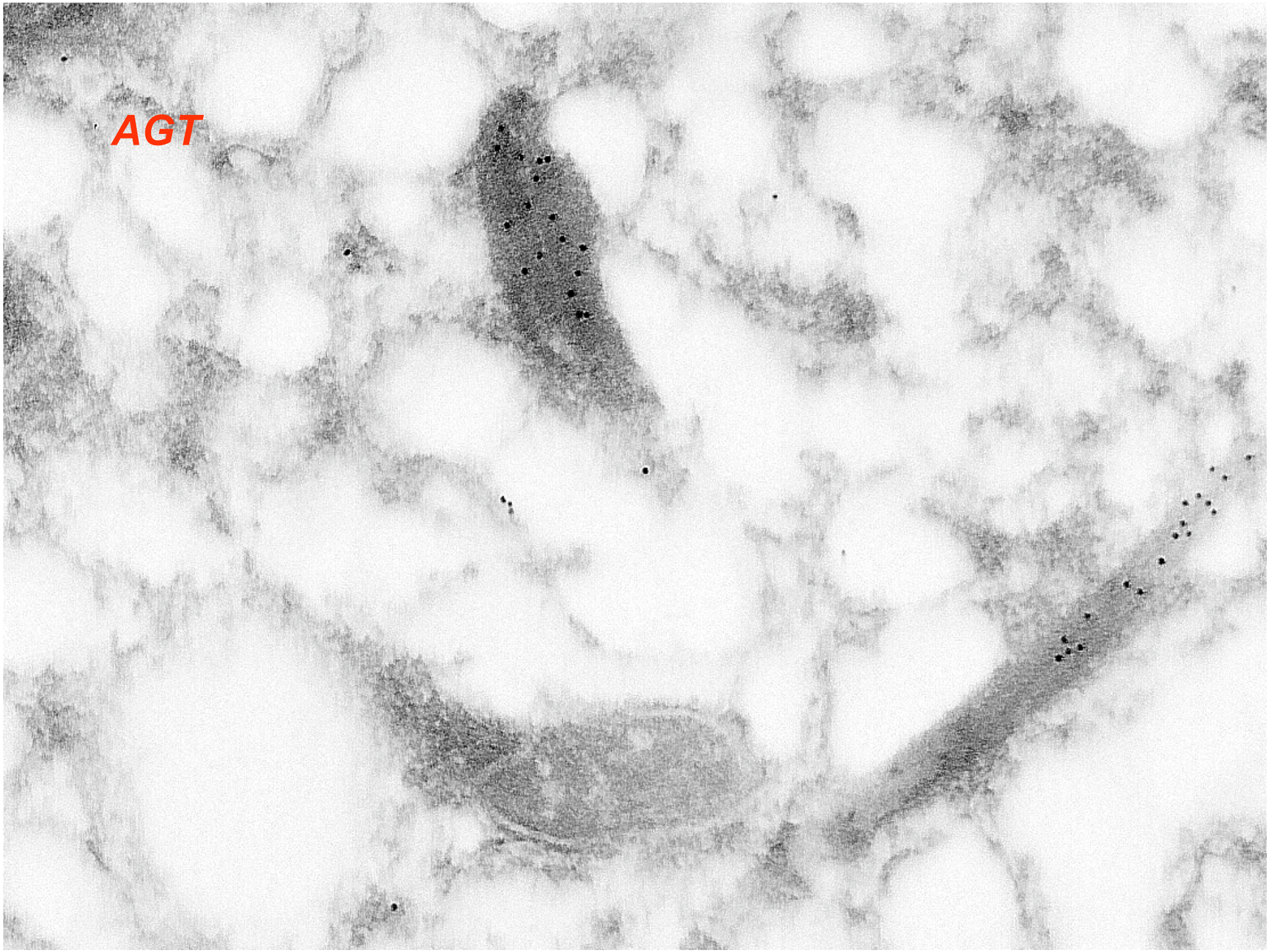

thiolase


43 kDa PMP

MORPHOMETRY OF HEPATIC PEROXISOMES

Measurements in those cells that contain peroxisomes

	PAT 1	PAT 2	PAT 3	PAT 4	CONTROLS
N measured	127	117	108	98	1124
D-CIRCLE (mm)					
mean	0.551	0.436	***0.324***	0.457	0.517 0.433-0.617
corr. mean	0.682	***0.551***	***0.387***	0.554	0.635 0.569-0.717
max	0.945	0.919	***0.510***	0.750	1.027
VOLUME PARAMETERS					
Numerical density Nv					
	0.132	0.146	***0.247***	***0.220***	0.101 0.045-0.157
Volume density Vv (%)					
	1.79	1.03	0.55	***1.560***	1.03 0.482-1.551
Surface density Sv					
	0.167	0.117	0.086	***0.180***	0.108 0.052-0.164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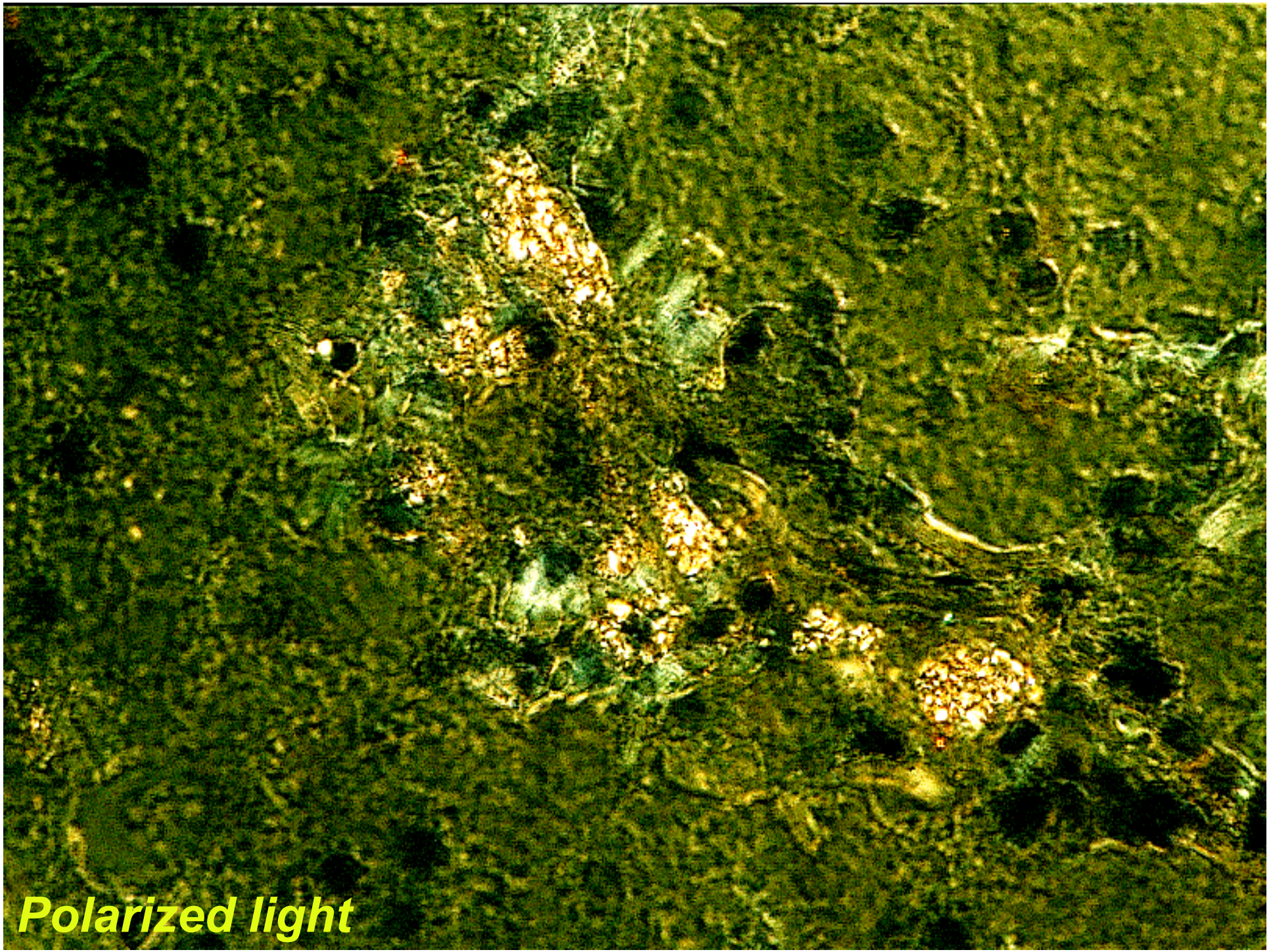
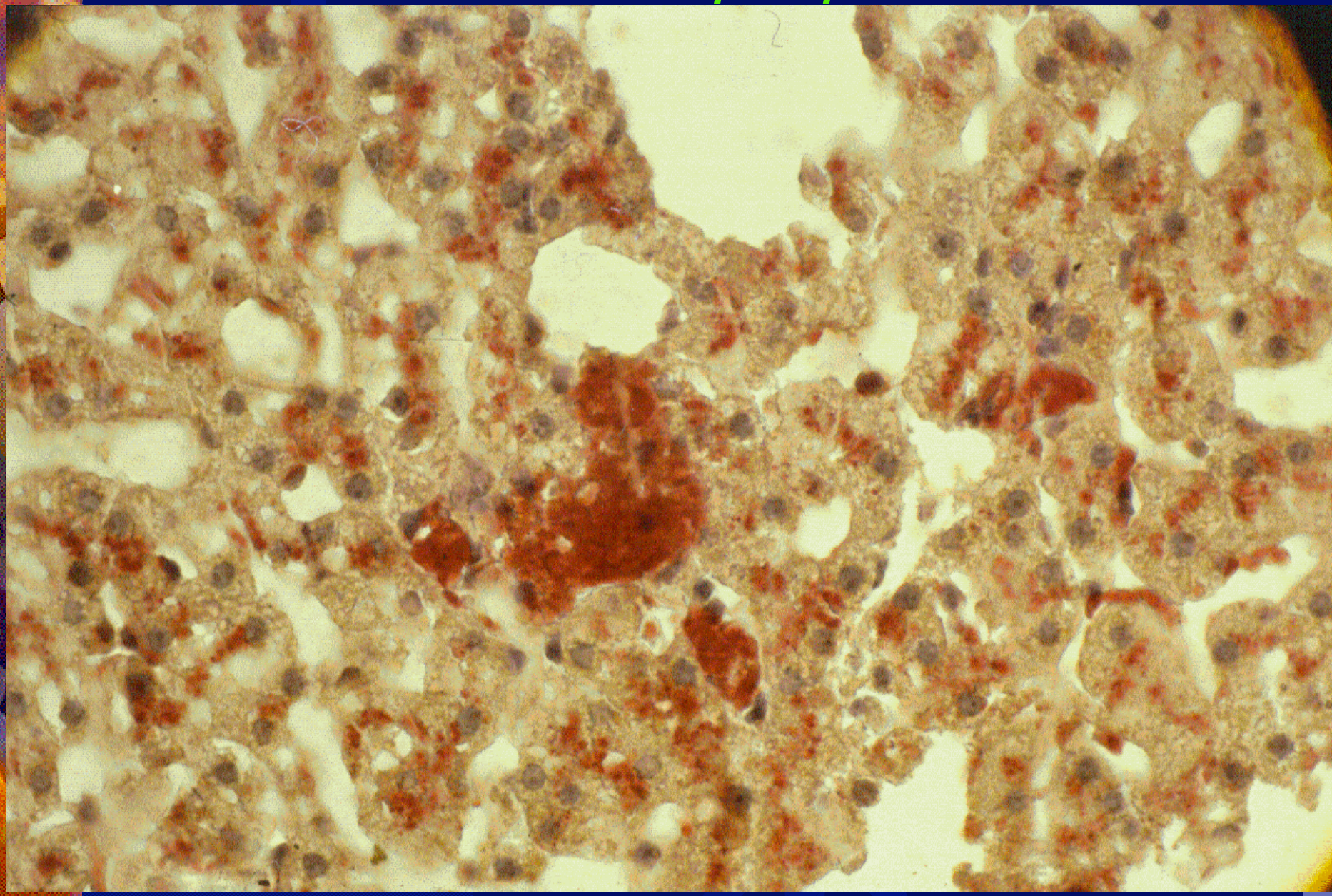
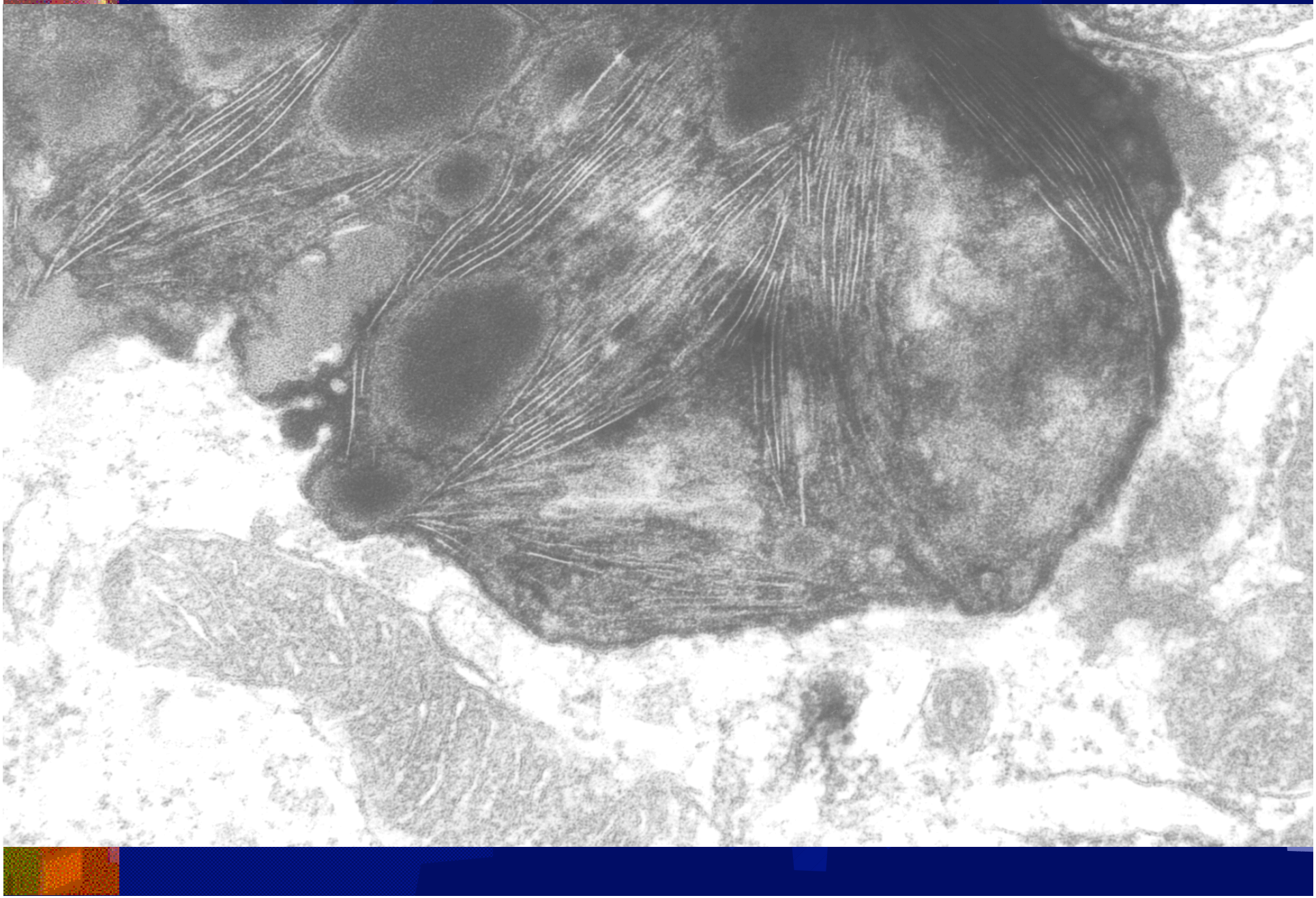
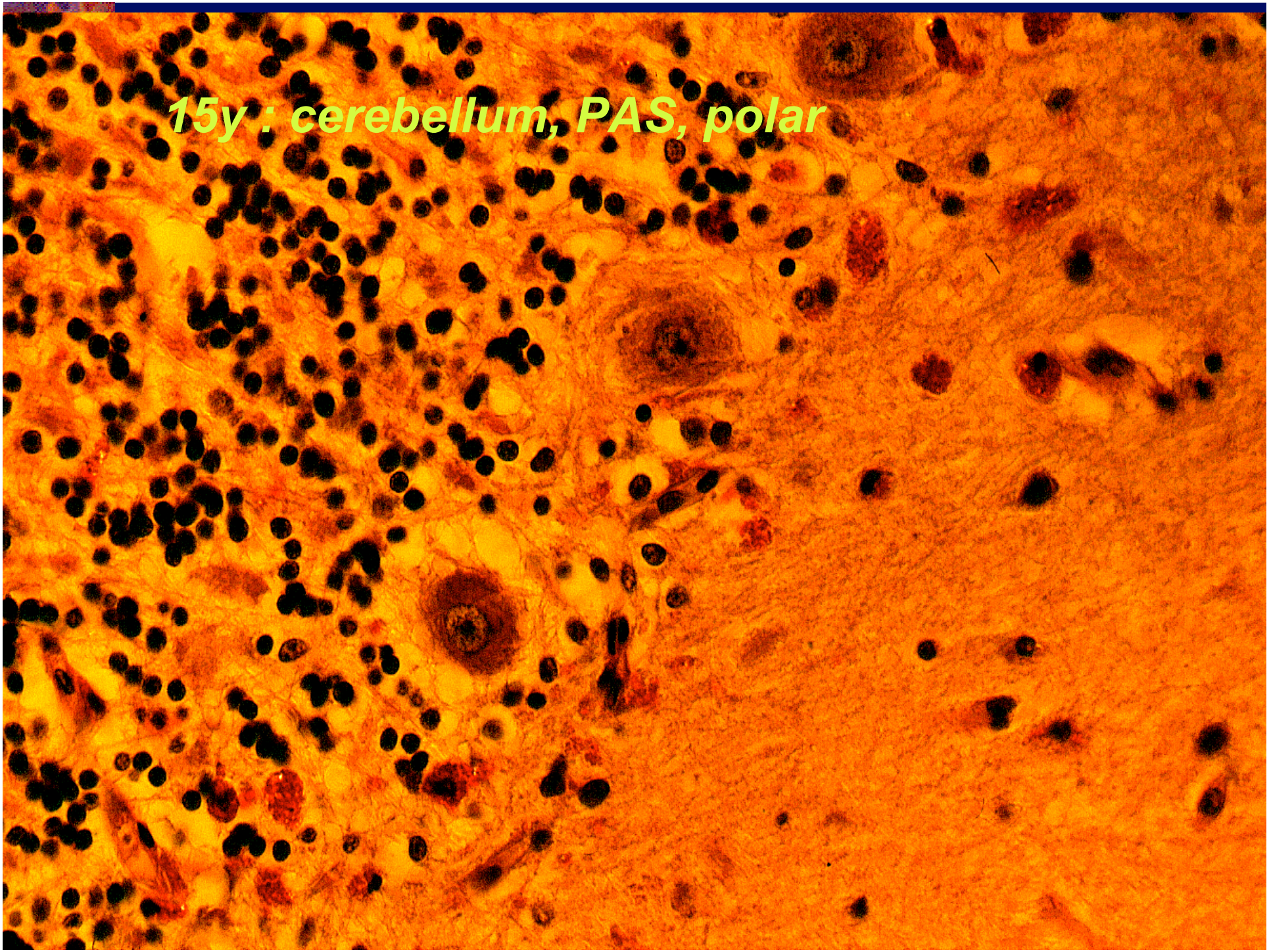

Polarized light

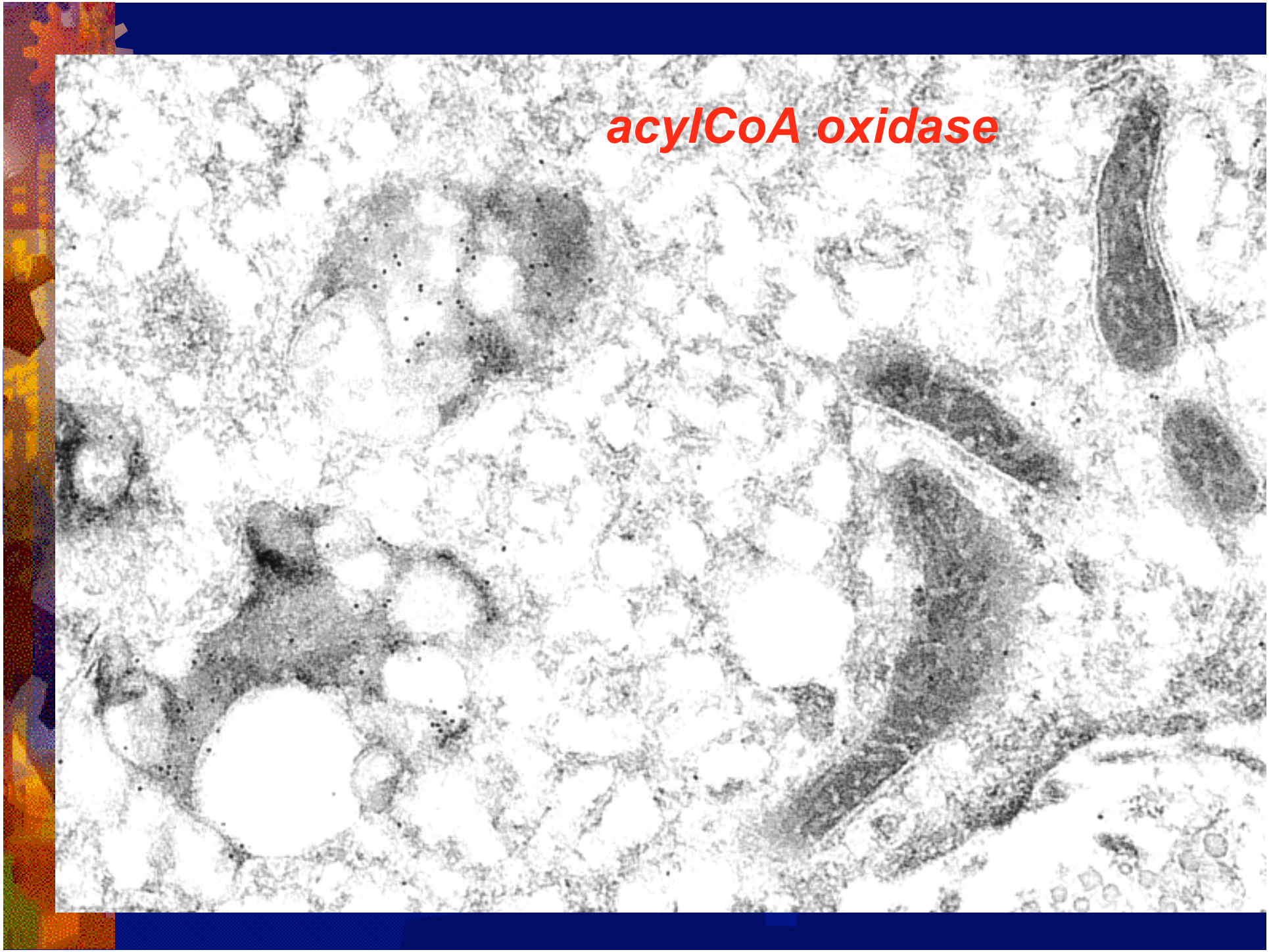
Acid phosphatase

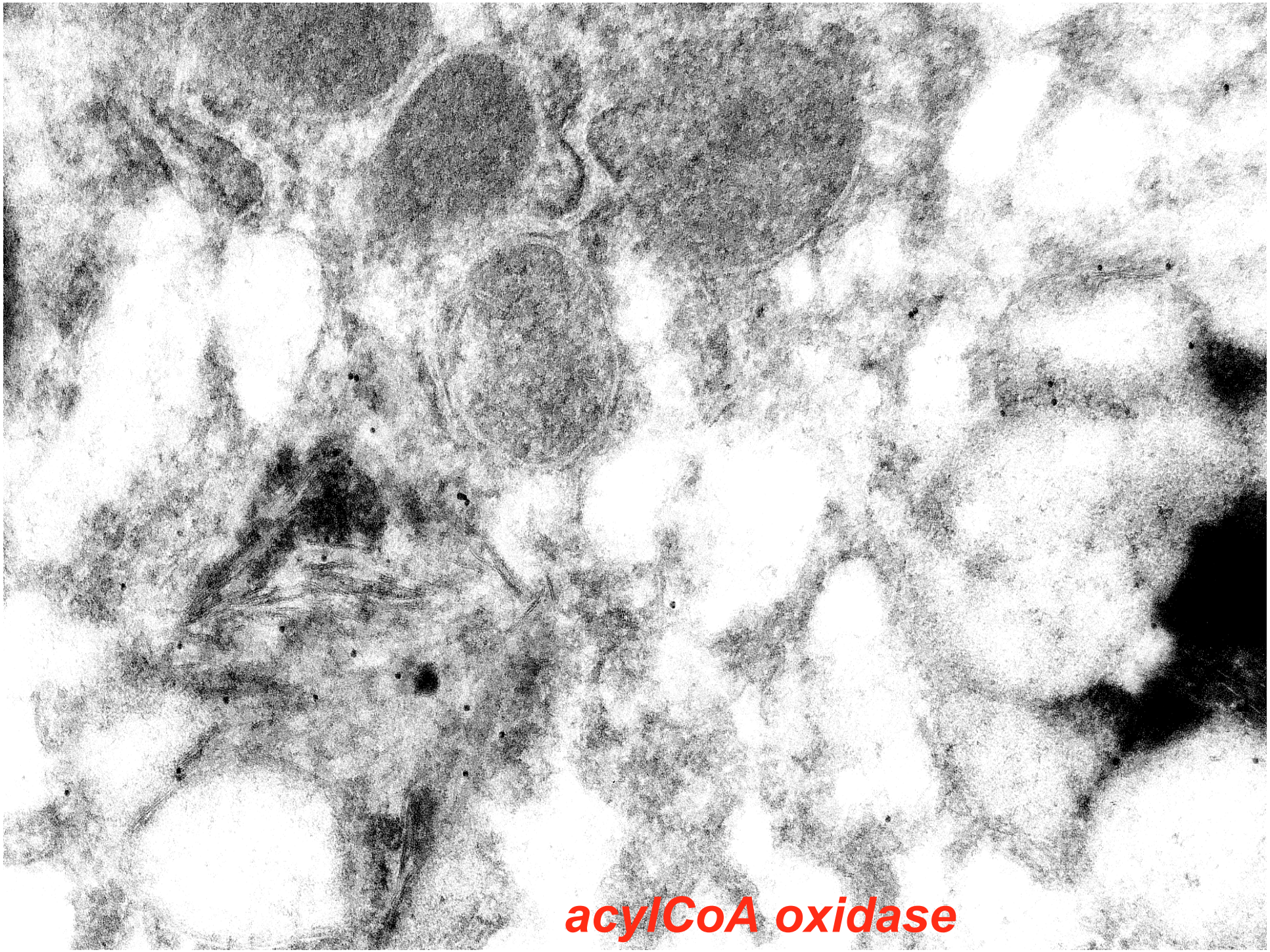


Acid phosphatase (cerium)

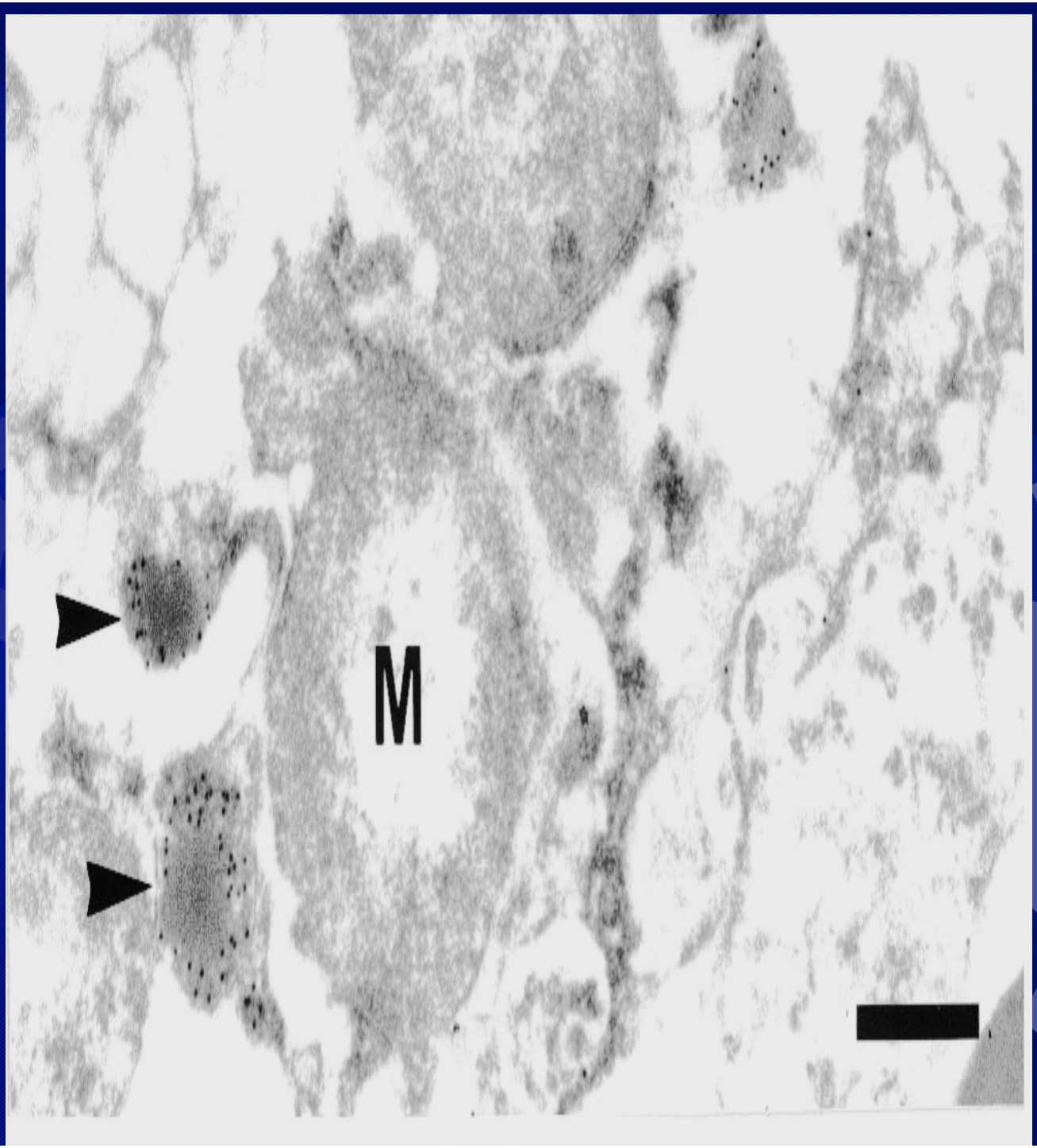


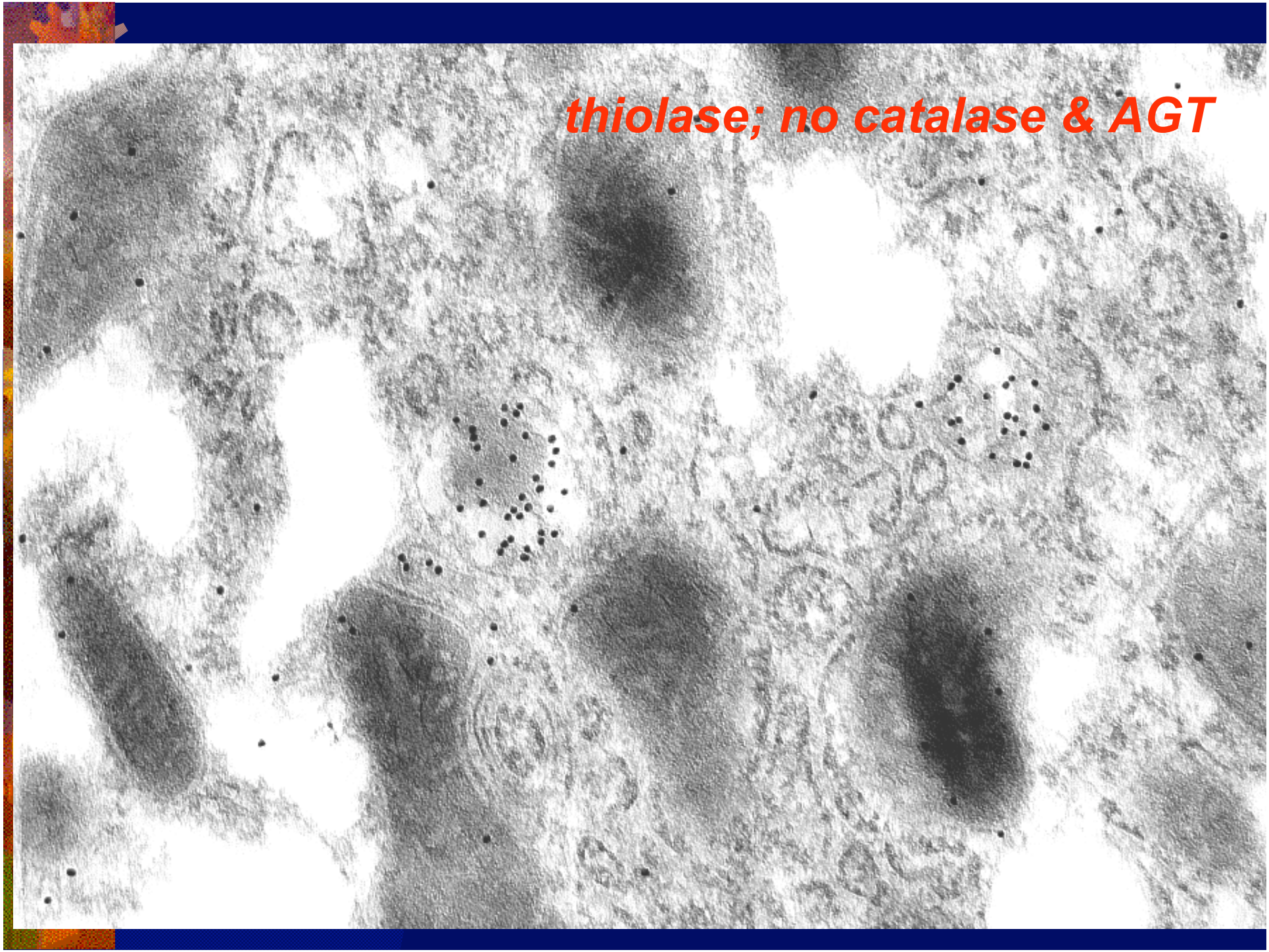

15y : cerebellum, PAS, polar


acylCoA oxidase


acylCoA oxidase

AGT




thiolase; no catalase & AGT

How can peroxisome mosaics be explained ?

a) genome is different:

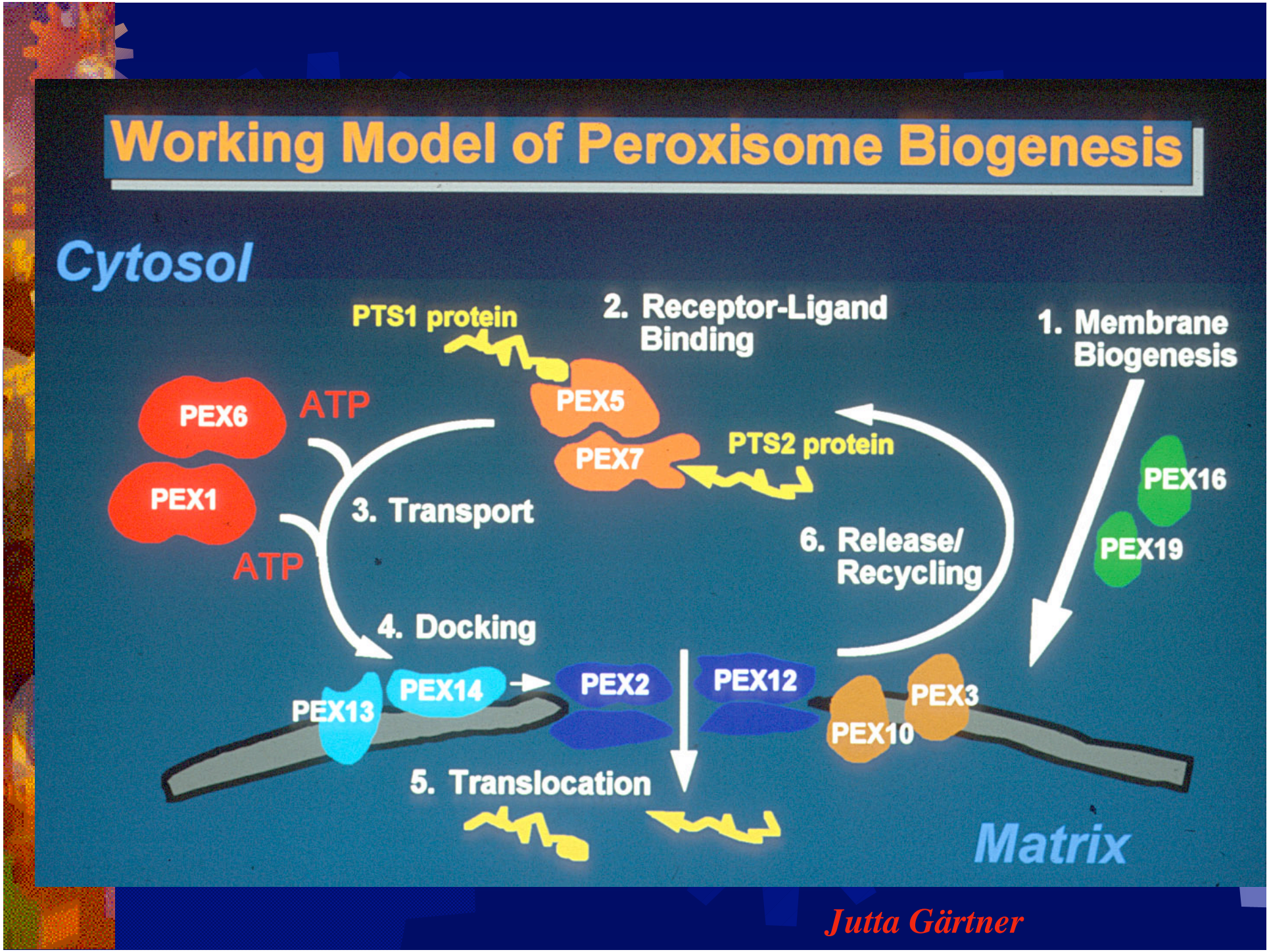
somatic mutation? but consanguinous parents, 2 brothers.

⇒ DNA analysis of + and - areas (LCM).

b) same mutations but differentially expressed:

Human peroxisome biogenesis genes

Phenotype	ComplGr	Gene	Protein
ZS,NALD,IRD	CG1	*PEX 1*	AAA ATPase
ZS	CG10	*PEX 2*	RING, PMP35
ZS	CG12	*PEX 3*	PMP
ZS,NALD	CG2	*PEX 5*	PTS1 receptor
ZS,NALD	CG4 & 6	*PEX 6*	AAA ATPase
RCDP 1	CG11	*PEX 7*	PTS2 receptor
ZS,NALD	CG7	*PEX 10*	RING, PMP
ZS,NALD,IRD	CG3	*PEX 12*	RING, PMP
NALD	CG13	*PEX 13*	SH3,PMP
ZS	CG9	*PEX 16*	PMP
ZS	CG14	*PEX 19*	PMP receptor
NALD	CG8	*PEX 26*	PMP34



Jutta Gärtner

Pexprotein interrelationships & modulation :

Pex6p(mut) is compensated by overexpession of Pex1p (Geisbrecht et al, 1998)

interacts with Pex26p (Matsumoto et al, 2003)

is temperature sensitive (Imamura et al, 2000)

Pex2p(mut) is compensated by overexpression of PMP70 (Gärtner et al, 1998);

is temperature sensitive (akiyama et al, 2002)

Function of mutated gene product Pex6p can be modulated by the amount≈activity of Pexp1 and Pex26p and temperature; and of mut Pex2p by the amount≈activity of PMP70 and temperature.

Since (most) protein concentrations normally vary between hepatocytes, for ex albumin,

Hypothesis to explain mosaic:

Normal peroxisome biogenesis is restored in cells where compensatory proteins are high (pex1p, Pex26p, PMP70); and when temperature is low.

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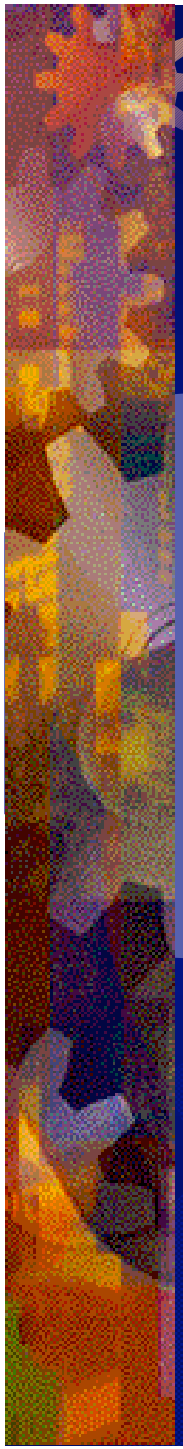
Nieves Saracibar & Begoña A. Pueyo, Vitoria
Jean-Marie Saudubray, Paris



Refs:

***Marianne Depreter et al: Human peroxisomal disorders, 2003,* Microsc Res Techn 61: 203-223**

***"Peroxisomal disorders and regulation of genes", eds Roels, Baes, DeBie,* 416 pp., Kluwer Acad Publ, in press.**