MALATTIA RARE E DISABILITA'
Roma 3 Dicembre 2008

PROGRESSI DIAGNOSTICI E TERAPEUTICI NELLE MALATTIE METABOLICHE EREDITARIE

Alberto Burlina
U.O.C. Malattie Metaboliche Ereditarie
Azienda Ospedaliera Padova

Rare diseases in disabled children: an epidemiological survey

Arch Dis Child 2008;**93**:115–118. doi:10.1136/adc.2006.104455

P Guillem,[1] C Cans,[2] E Robert-Gnansia,[3] S Aymé,[4] P S Jouk[5]

Table 2 Children with severe MSN_I and an identified rare disease (n = 459)

Rare disease group	N (%)
Neurological diseases	110 (24.1)
Syndromes	34
CNS structural anomalies	76
Syndromes with dysmorphy or malformation and intellectual impairment	56 (12.2)
With chromosomal abnormality	24
Without chromosomal abnormality	32
Severe congenital or genetic vision loss	52 (11.3)
Skeletal diseases	50 (10.9)
Generalised	9
Focalised	41
Severe congenital or genetic deafness	45 (9.8)
Neuromuscular diseases	41 (8.9)
Hereditary metabolic diseases	27 (5.9)
Tumours	24 (5.2)
Embryofetopathies	19 (4.1)
Other rare diseases	35 (7.6)
Systemic disease	5
Dermatological disease	6
Haematological disease	1
Immunodeficiency	1
Collagen and extracellular matrix disease	2
Others	20
Total	459 (100)

CNS, central nervous system.

The incidence of inherited metabolic disorders in the West Midlands, UK

S Sanderson, A Green, M A Preece, H Burton

Arch Dis Child 2006;91:896–899. doi: 10.1136/adc.2005.091637

Table 2 Comparison of the birth prevalence of IMDs in published population-based studies with that in developed countries

	West Midlands (this study)	Italy*	West Midlands ethnicity study	Canada (British Columbia)†
Year published	2005	2002	1998	2000
Primary study period for reported results	1999–2003	1993–97 (data collected from 1985 to 1997)	1981–91	1969–96 (time period varies for each disorder)
Number of patients	396	1935	263	249
Disorder groups				
Amino acid	1 in 5354	1 in 36 389*		1 in 6606
PKU	1 in 12 420	1 in 19 589‡	1 in 14 452 (Pakistani); 1 in 12 611 (white)	1 in 13 290
Carbohydrates	1 in 16 343	1 in 19 532		
Urea cycle	1 in 22 179	1 in 41 506		
Glycogen storage	1 in 14 786	1 in 34 056		1 in 43 160 1 in 69 054
Lysosomal storage	1 in 5175	1 in 8275		1 in 13 112
Mitochondrial	1 in 4929			1 in 31 436
Peroxisomal	1 in 13 500	1 in 71 794		1 in 28 960
Organic acids	1 in 7962	1 in 21 422		1 in 27 082
Total	1 in 784	1 in 3707 (1985–97) 1 in 2758* (1993–97) 1 in 2555 (1993–97)	1 in 2691 1 in 318 (Pakistani); 1 in 3760 (white)	1 in 2500†

*Excluding PKU (phenylketonuria).
†Excludes disorders of collagen, metal, lipids and porphyria.
‡Data from the Italian National Neonatal Screening Survey.[10]

PREVENZIONE

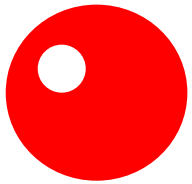
TRATTAMENTO

Screening neonatale

Screening tradizionale

(da piu’ di 30 anni….)

- **Una malattia**
- **Un test**
- **Un metabolita**
- **Cut-off**



PKU

↓

BIA

↓

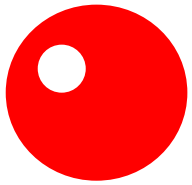
Phe

↓

4 mg/dL

Screening by MS/MS
(Multiplex Testing)

- **Molte malattie**
- **un test**
- **Molti metaboliti**
- **ampio cut-off**



$(MME)_n$

↓

MS/MS

↓

$(AA,AC)_n$

↓

0.1-1,000 µM

Tecnologia: MS/MS

SCREENING NEONATALE MEDIANTE MS/MS

- DIFETTI AMINO ACIDI

Phe, Phe/Tyr = PKU or hyperPhe

Ile and Val, Ile/Ala = MSUD

Arg = Argininemia

Orn = HHH syndrome

Cit: Citrullinemia vs
Argininosuccinic aciduria

Met: homocystinuria

Tyr:Tyrosinemia I, II, III,
transient neonatal, liver disease

- DIFETTI ACIDI ORGANICI e β OSSIDAZIONE ACIDI GRASSI

C6, C8, C10:1 C10 + ratios = MCADC14:1,

C16, 18 +ratio C14:1/C2 = VLCAD free carnitine, free/C16, free/C18 = CPT I

C5-dicarboxylic = GA I

C3-dicarboxylic = malonic

C16, C18:1 , C18; CPT II vs CACT

C14-OH, C16-OH, C18:1-OH, C18-OH;LCHAD vs MTP

C5; IVA vs 2MBCD

C4: SCAD vs IBCD

C3: PPA vs MMA vs cbl (B12)

Costo dello screening

- Strumento (250.000 EURO)
- Manutenzione:2 giorni ogni 6 mesi
- 1 biologo / 2 tecnici/ 2 amministrativi
- 60 campioni ogni 2 ore
- 400 campioni/settimana (automatico)
- gestione automatizzata
- centro operativo 6/7
- Posta prioritaria e giornaliera

COSTO / TEST € 45

MS/MS : ESPERIENZA VENETO (2002 - 2008)

	N casi	Positivi screening
PKU	0	1
MSUD	3	0
ASL	2	0
ASS	2	0
NKH	3	0
3MCC	0	1
MMA	3	1
PA	4	0
MCAD	4	1
VLCAD	4	0
MADD	11	0
LCHAD	4	0
CPT I	1	0
Total cases	41(1/7500)	3 (1/2550)

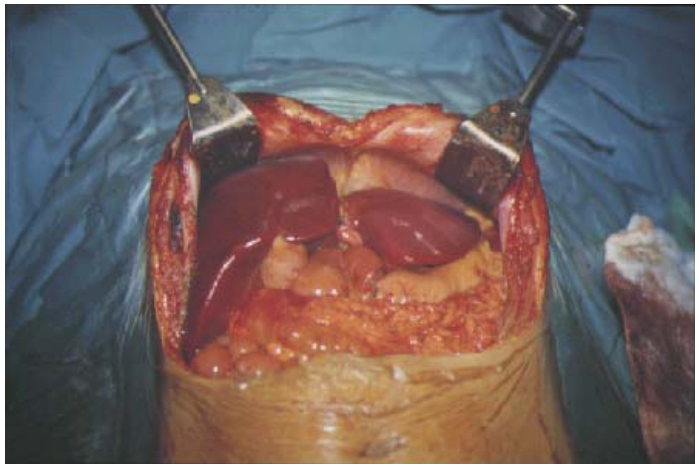
SI
Trentino
Valle
d'Aosta
Friuli
Lombardia
SI
SI
Veneto
Piemonte
Emilia Romagna
SI
SI
Marche
Liguria
Toscana
Umbria
Abruzzo
Molise
SI
Lazio
Puglia
Campania
Sardegna
Basilicata
Calabria
SI
Sicilia
SI

Trattamento

Strategie di trattamento per IEM

- **Ridurre il substrato**
  - Riduzione del substrato mediante restrizione dietetica
  - Riduzione del substrato per inibizione di enzimi lungo la via metabolica
  - Correzione del difetto di produzione
  - Rifornimento dei prodotti depleti
  - Incremento dei substrati
  - Rifornire substrati alternativi
- **Riduzione della tossicità dei metaboliti**
  - Rimozione dei metaboliti tossici
  - Blocco degli effetti dei metaboliti tossici
  - Prevenire la produzione dei metaboliti tossici mediante inibizione enzimatica
- **Stimulazione dell'attività enzimatica residua**
  - Trattamento con co-enzimi
  - Terapia enzimatica sostitutiva
- **Sostituzione enzimatica**
  - Trasferimento di cellule staminali ematopoietiche
  - Trapianto di altri organi
  - Sostituzione farmacologica dell'enzima
  - Terapia genica

ALTERNATIVES TO IN TOTO LIVER TRANSPANTATION



“split liver”

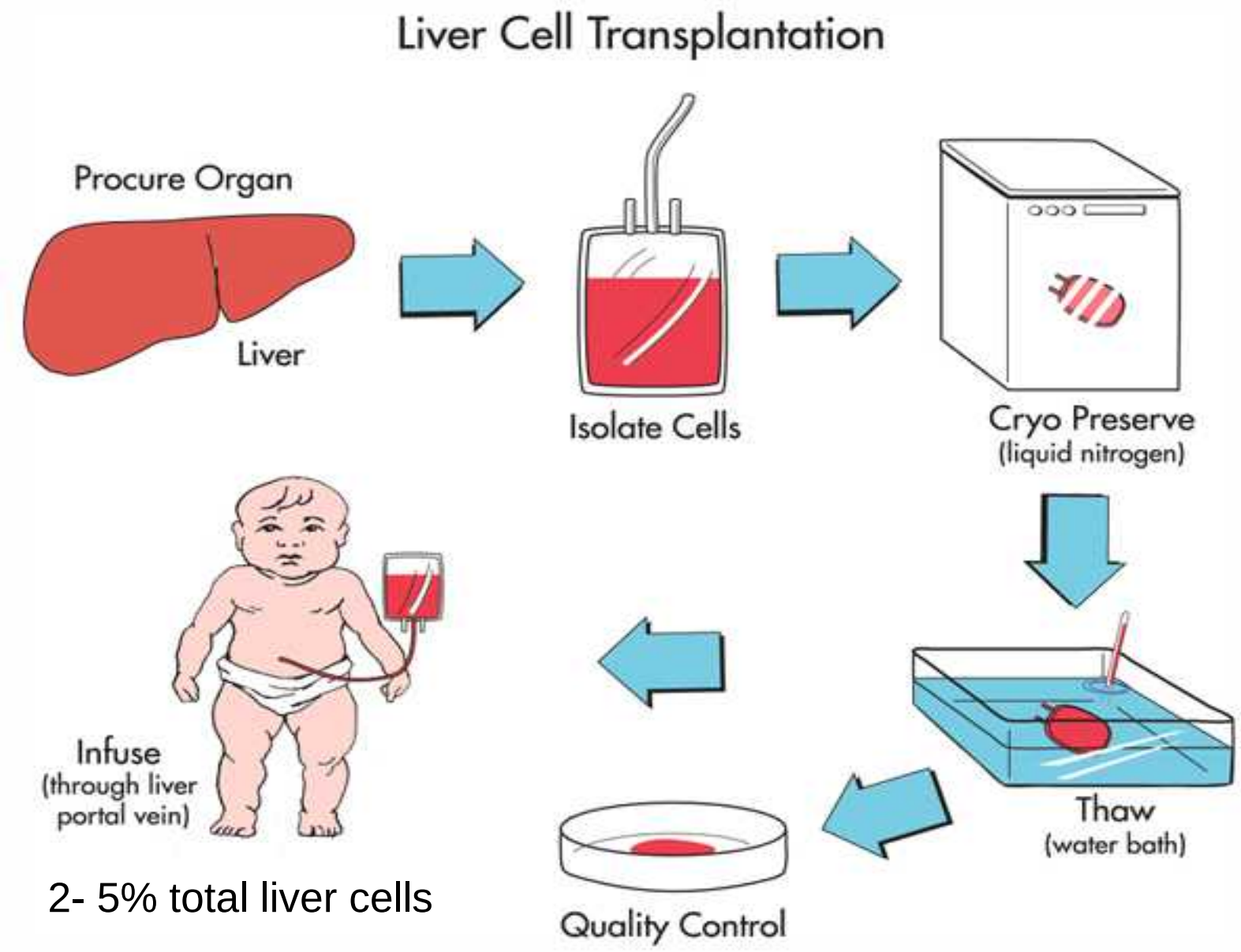
Living donor

Auxiliary liver transplantation

Xenotransplantation

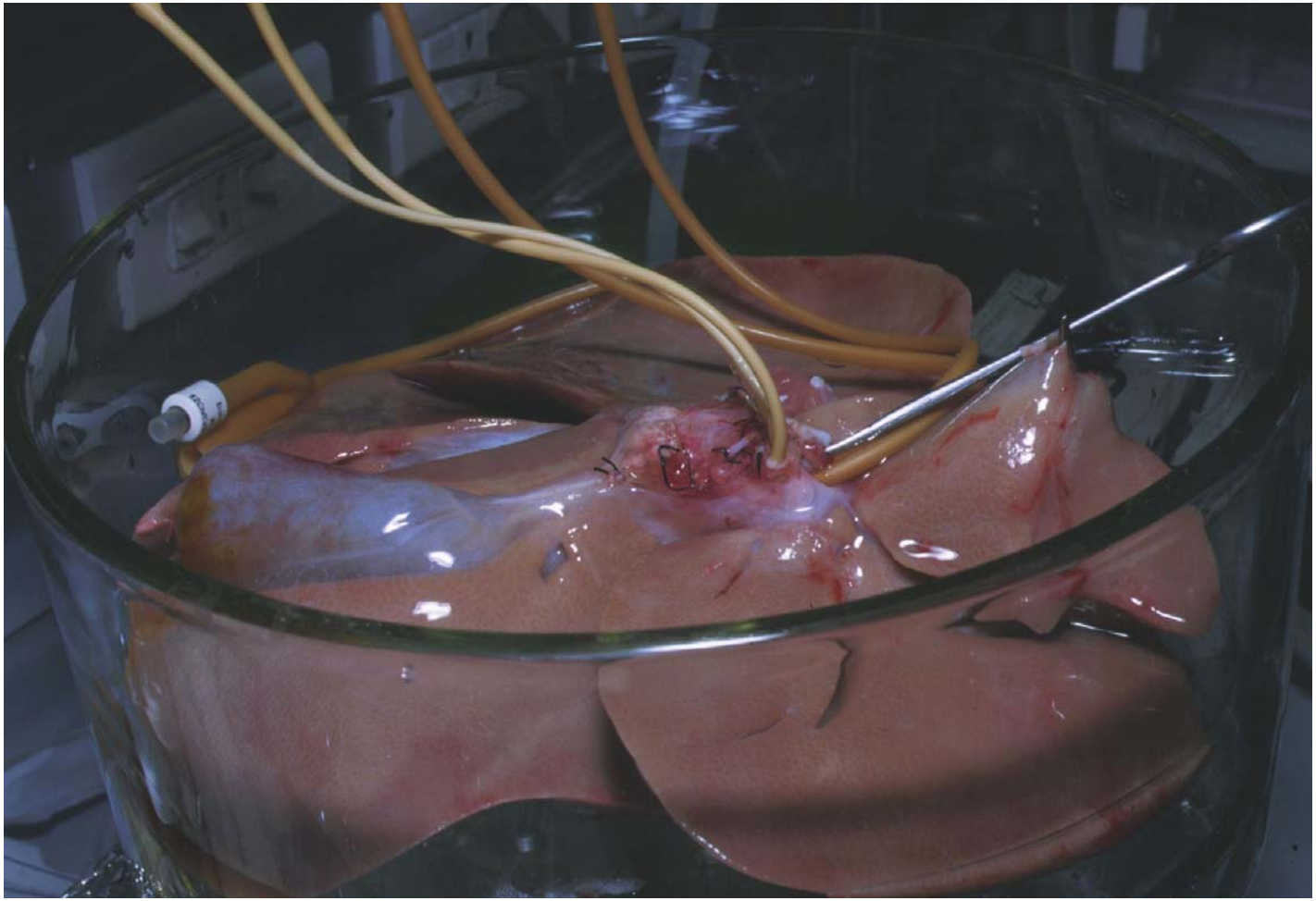
Artificial liver

HEPATOCYTES TRANSPLANTATION

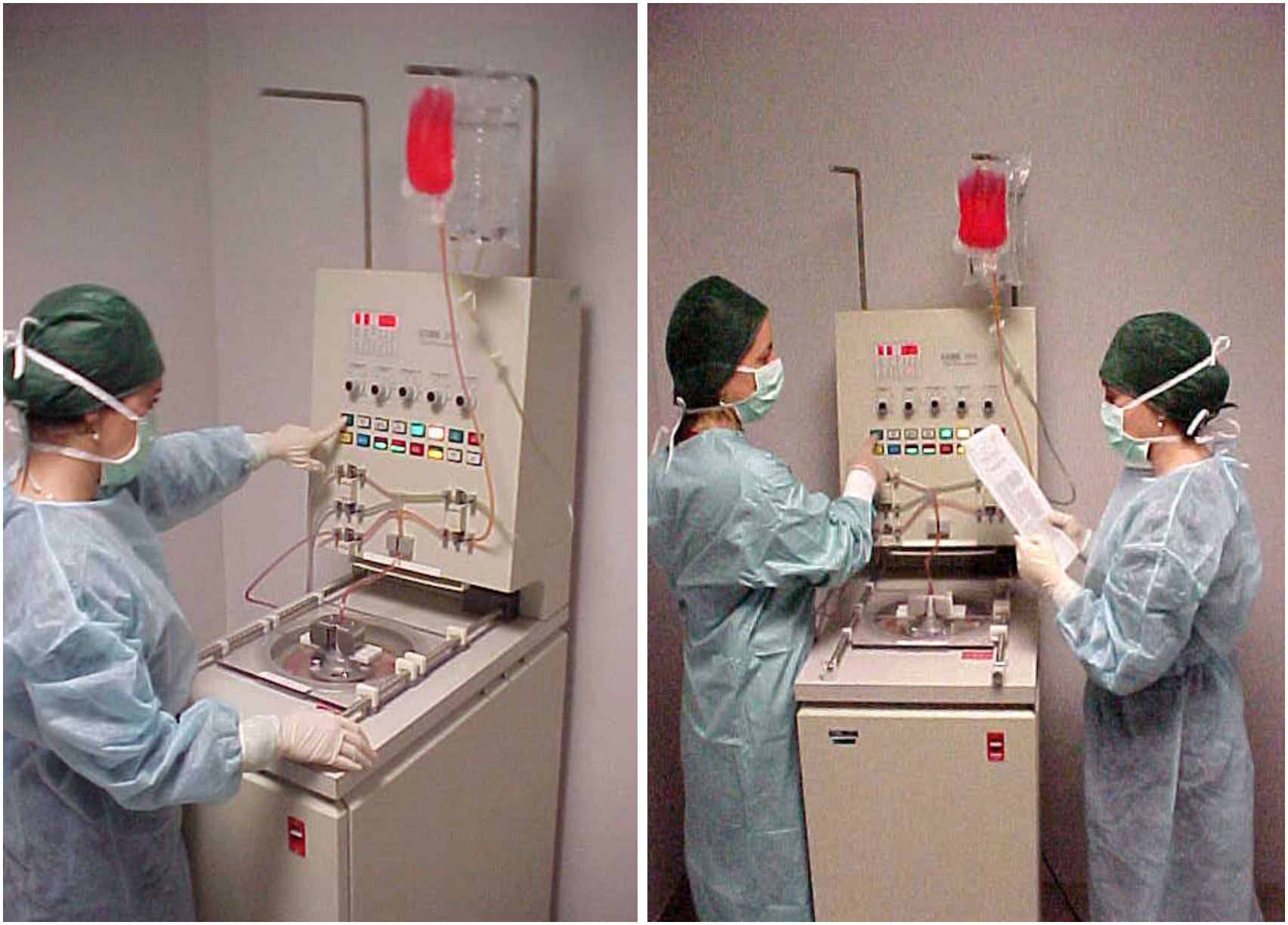


2- 5% total liver cells

Hepatocyte Transplantation

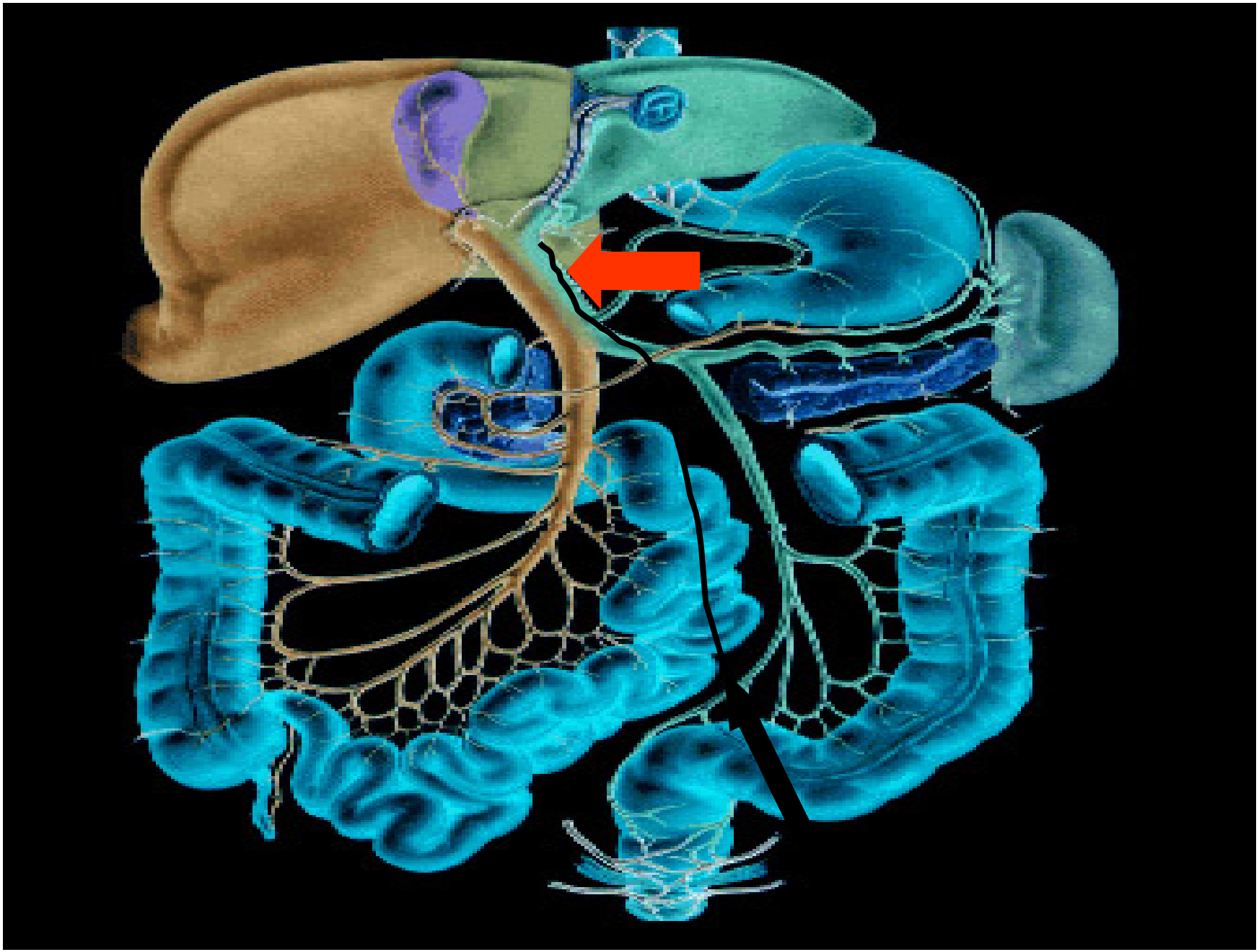


·Isolated cells were filtered (450-250-150um filters)



Centrifuged Cobe 2991 cell processor

Purified hepatocytes in ringer lacate with 1% serum albumin



CASE I : GSD type IA

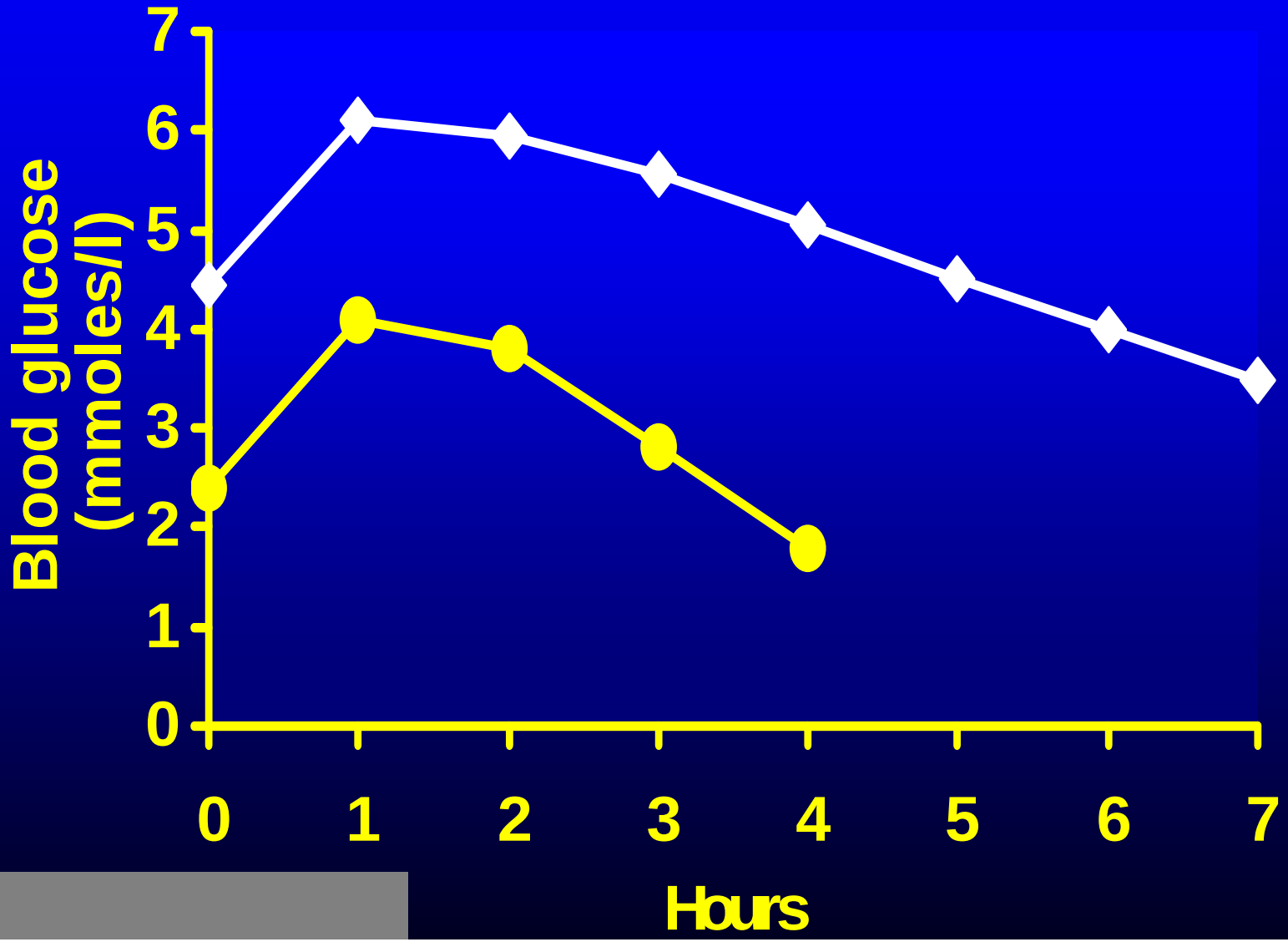
- 47-year-old woman with GSDIa (body weight 49 kg, height 150 cm)
- At age 3 years hepatomegaly, hypoglycemia and lactic acidosis.
- Undetectable glucose-6-phosphatase activity in liver biopsy.
- Normal creatinine and liver function tests
- Multiple hepatic adenomas on ultrasound, CT scan and NMR.
- Depressive neurosis, poor compliance with dietary treatment

Patient characteristics - II

- **Uncooked corn starch meals every 3 hours to maintain glycemia>3.5 mmol/l**
- **Depressive neurosis, poor compliance with dietary treatment**
- **Reluctant to OLT**
- **Informed consent to hepatocyte transplantation after permission by the Ethics Committee**

MM1

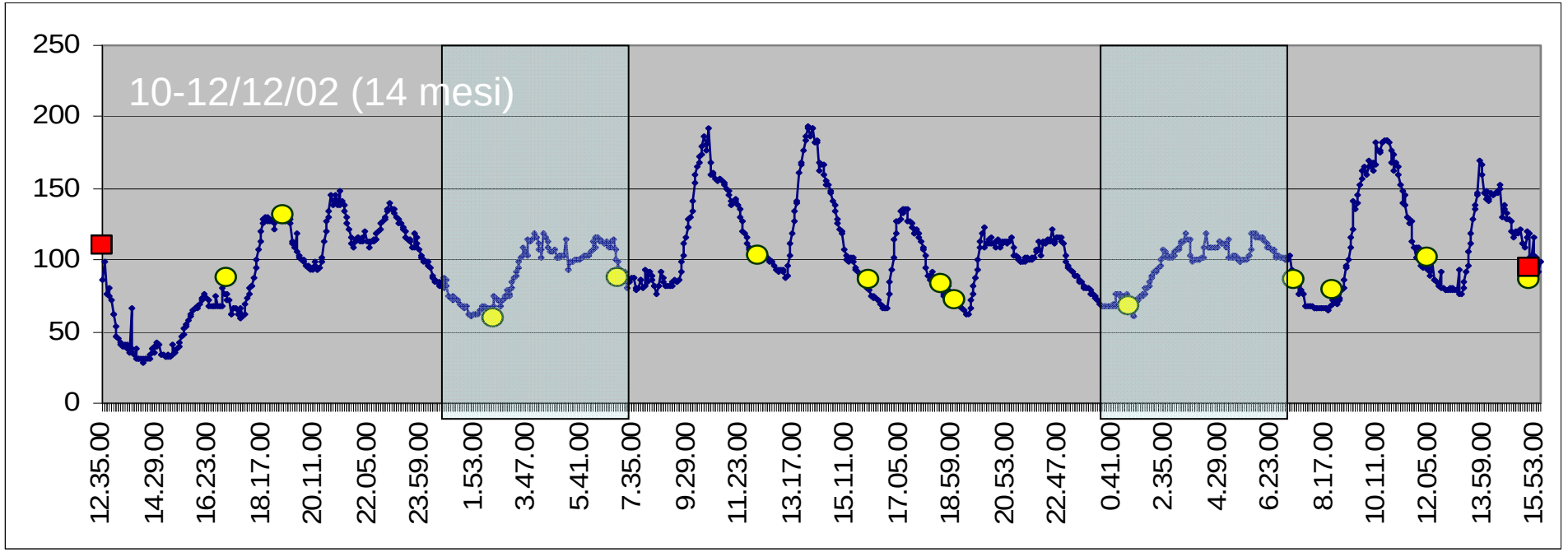
Postprandial blood glucose before (—) and 5 months after (—) Hepatocyte Transplantation

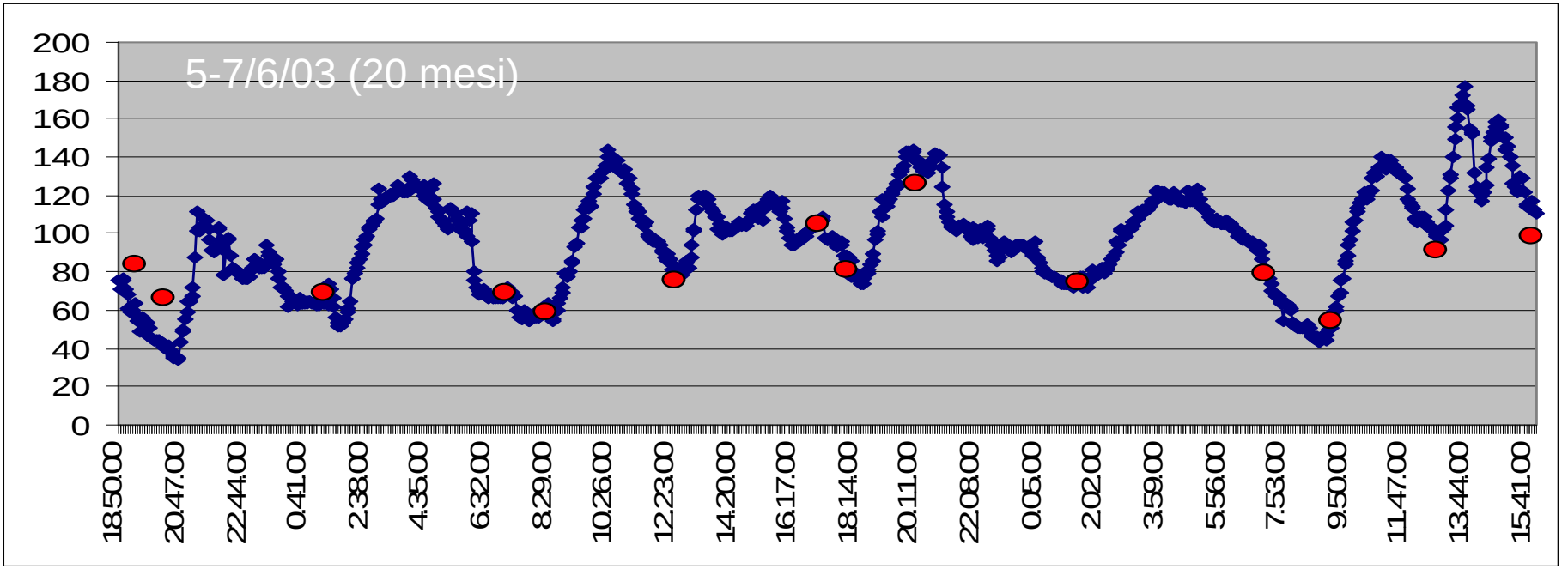


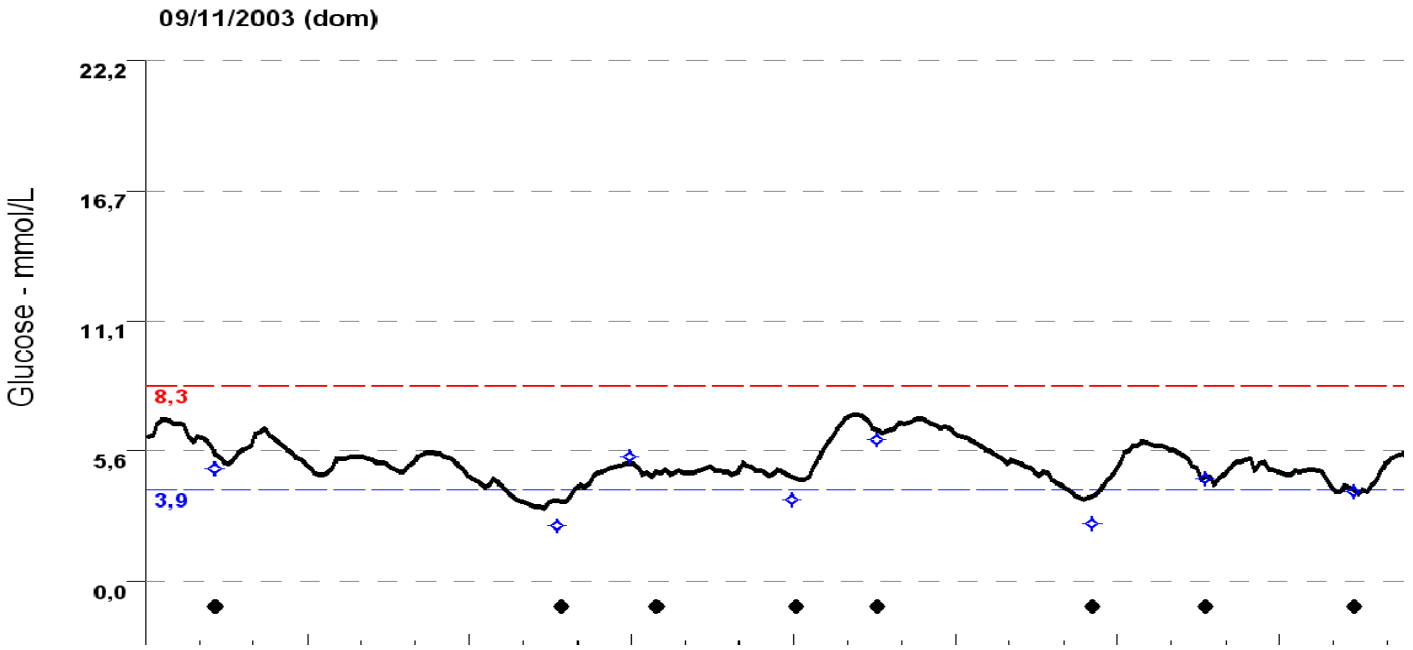
Diapositiva 24

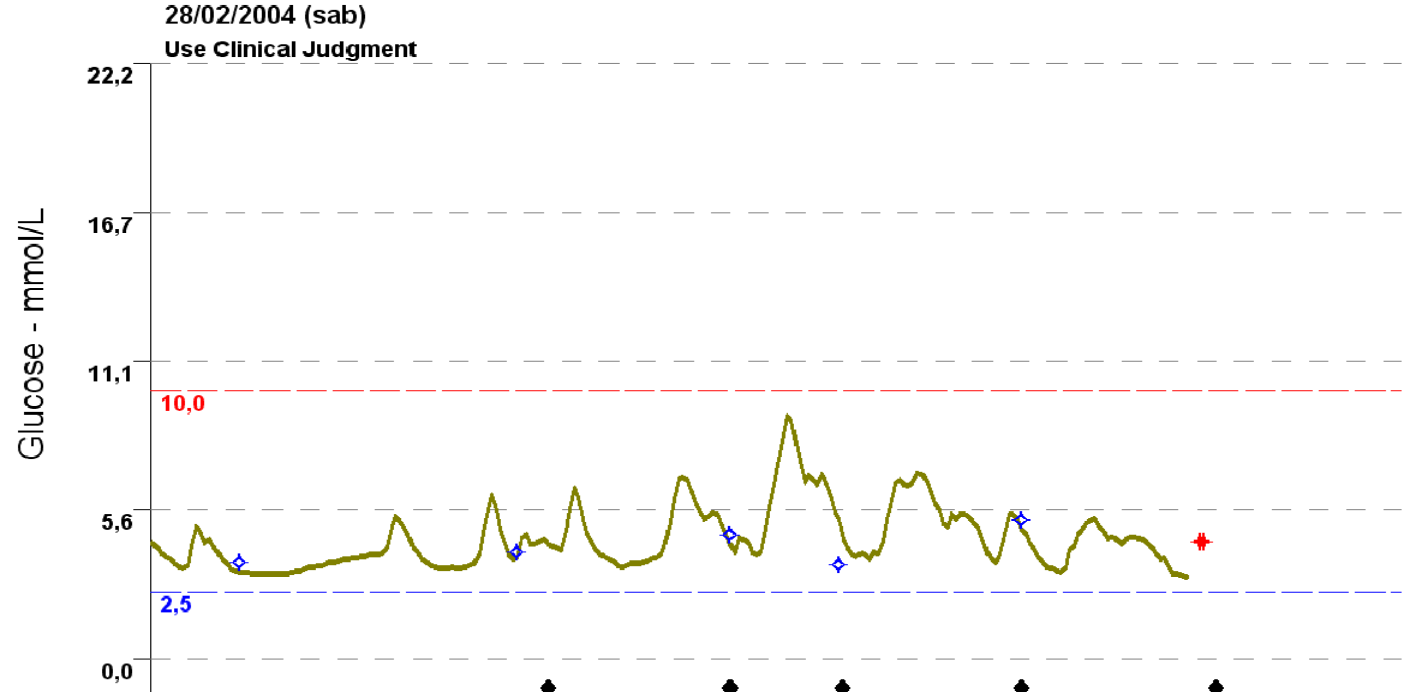
MM1 We documented a striking metabolic improvement following Hepatocyte transplant in a patient with GSDTIa, suffering from severe fasting hypoglicemia due to deficiency of G6Pase, the enzyme which releases glucose from hepatic glycogen. After the procedure, the postprandial rise in blood glucose was much more pronounced and sustained when compared to pre-treat levels

Maurizio Muraca; 13/09/2005


10-12/12/02 (14 mesi)
250
200
150
100
50
0
12.35.00
14.29.00
16.23.00
18.17.00
20.11.00
22.05.00
23.59.00
1.53.00
3.47.00
5.41.00
7.35.00
9.29.00
11.23.00
13.17.00
15.11.00
17.05.00
18.59.00
20.53.00
22.47.00
0.41.00
2.35.00
4.29.00
6.23.00
8.17.00
10.11.00
12.05.00
13.59.00
15.53.00


5-7/6/03 (20 mesi)
200
180
160
140
120
100
80
60
40
20
0
18.50.00
20.47.00
22.44.00
0.41.00
2.38.00
4.35.00
6.32.00
8.29.00
10.26.00
12.23.00
14.20.00
16.17.00
18.14.00
20.11.00
22.08.00
0.05.00
2.02.00
3.59.00
5.56.00
7.53.00
9.50.00
11.47.00
13.44.00
15.41.00


09/11/2003 (dom)
Glucose - mmol/L
22,2
16,7
11,1
8,3
5,6
3,9
0,0


28/02/2004 (sab)
Use Clinical Judgment
Glucose - mmol/L
22,2
16,7
11,1
10,0
5,6
2,5
0,0

CASE II : OCT DEFICIENCY

Patient A.M. born 30/05/07

Acute neonatal hyperammonaemic crises

At day 4 : HT (2 applications) by ombelical catheter

3 mo :weight : kg 5.256; l: cm 57.5; cc: hc 38.5 (10 percentile)

Natural protein intake : 6.3 g/kg/d(1.2 g/kg/d)

aa mixture : 1.25 g/kg/d (0.25 g/kg/d)

Therapy:

- **Na benzoate: 190 mg/Kg/ d**
- **Ammonaps : 190 mg/Kg/ d**
- **Citrulline: 190 mg/Kg/ d**
- **FK-506 : 0.6 mg/d**

BIOCHEMICAL DATA

		1mo	2mo	3mo	6 mo
NH_3 (µmol/l)	22	44	18	<10	
Glutammine	454	708	639	1024	
Arginine	17	14	35	37	
Citrulline	0	0	3	2	
Isoleucine	54	41	35	63	
B-FK 506 (µg/l)	6.2	6.7	18	9.1	

RINGRAZIAMENTI

COLLABORATORI

TUTTI I PAZIENTI

COMETA -ASMME