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1. Introduction

The Quality Assurance Program (QAP) for Diagnostic Proficiency Testing (DPT) of Inherited Metabolic Diseases is organised by ERNDIM. The DPT centre of Central Europe is one of the four DPT centres of ERNDIM and is located in Nijmegen (NL). The other DPT centres are located in Sheffield (UK) for the region of Northern Europe, in Lyon (F) for the region of Southern Europe, and, in Prague (CZ) for the region of Eastern Europe. Each DPT centre has approx. 20 participants.

The distribution of urine samples is coordinated in Nijmegen and is embedded in SKML, the Netherlands QAP-organization. Urine samples are referred to the Nijmegen centre by the participants of the scheme; each participant has the obligation to refer at least one sample per year. In 2005 the number of samples in stock was still adequate, but all participants are urged to adhere to their obligations in this respect. The diagnostic reports of each set of three urine samples, usually sent out in January and June, are made on standardized forms available through E-mail. The reports are judged by Prof. dr. J.L. Willems are well as by the scientific Advisor of the scheme.
In 2005 dr. A.H. van Gennip, until then scientific Advisor, laid down this task. It was agreed that dr. M. Duran (Academic Medical Center Amsterdam) would take on the responsibility as Scientific Advisor until a permanent replacement could be found.
An evaluation of the diagnostic reports is available to all participants before the Annual Meeting, which in 2005 was held in Paris on the occasion of the Annual Symposium of SSIEM.

2. Participants

In 2005 the DPT centre Central Europe had 21 participants from Germany, The Netherlands, Belgium and the United Kingdom.

Country	Number of participants
Belgium	2
Germany	8
The Netherlands	10
UK	1

3. Logistics of the scheme

Six samples were distributed in 2005; samples S, T, and U in January, and samples X, Y and Z in June. Sample Z of a patient with Tyrosinemia type 2 was the common sample which was distributed by all four DPT-centers. No changes were made in the handling and shipment of samples or the report format.

4. Timetable of the scheme

DPT survey 2005.1:	
Shipment of samples:	10/01/2005
Deadline for returning results:	31/01/2005
Report of survey	14/03/2005
DPT survey 2005.2:	
Shipment of samples:	13/06/2005
Deadline for returning results:	30/06/2005
Report of survey:	12/08/2005

Annual meeting: September 6, 2005 Maison de la Chimie, Paris, France. Twenty-one representatives of the participating laboratories took part in the meeting.

5. Return of reports

Survey 2005.1: Reports on samples S, T, and U were submitted by 20/21 participants
Survey 2005.2: Reports on samples X, Y and Z were submitted by 20/21 participants. The non-submitter was not the same as for 2005.1

6. Scoring of samples and results

Following lengthy discussions in the Scientific Advisory Board, a scoring system was agreed upon in 2002.

For each individual sample a score can be achieved for:

Analytical performance:	Correct results of the appropriate tests	score: 2
	Partially correct or non-standard methods	score: 1
	Unsatisfactory or misleading	score: 0
Interpretative performance:	Good (diagnosis was established)	score: 2
	Helpful but incomplete	score: 1
	Misleading / wrong diagnosis	score: 0
Recommendations:	Helpful	score: 1
(for further investigations)	Unsatisfactory or misleading	score: 0
		=======
	Total:	score: 5

Poor performers are those participants who score less than 15 points out of the maximum 30 in a given year. These poor performers will receive a so-called warning letter from the Scientific Advisor.
At the request of several participants, individual scoring results will be sent to each individual participant.

7. Scores of participants for individual samples

Lab	S	T	U	X	Y	Z	Total 2005
1	5	5	5	5	5	5	30
2	5	5	5	5	5	5	30
3	4	5	5	5	5	5	29
4	5	5	5	3	5	5	28
5	5	5	5	5	5	5	30
6	5	5	5	5	5	5	30
7	5	5	5	5	5	5	30
8	5	5	5	4	0	4	23
9	5	5	5	5	5	5	30
10	5	5	5	5	1	2	23
11	5	5	4	1	5	2	22
12	4	5	5	5	5	2	26
13	5	5	5	5	5	2	27
14	5	1	3	5	5	2	21
15	5	5	5	5	5	2	27
16	4	5	5	4	5	4	27
17	5	5	5	4	5	5	29
18	5	5	5	-	-	-	15 (3)
19	-	-	-	3	5	5	13 (3)
20	5	1	4	3	5	5	23
21	5	5	5	1	5	5	26

8. Distribution of total scores 2005

		Number of labs
Better than 75%	(23-30 points)	17
Less than 75%	(<23%)	4
Less than 50%	(<15 points; poor performer)	1

9. Summary of scores

Sample	Diagnosis	Correct diagnosis made
S	5-Oxoprolinase deficiency	20/20
T	MCAD-deficiency	18/20
U	No inborn error	19/20
C	MPS 1-Hurler/Scheie	18/20
Y	3-Methylglutaconic aciduria type 1	18/20
Z	Tyrosinemia type 2	14/20

The cumulative score in 2005 of the participants submitting results was 89%, a very good figure indeed.
The program of the 2005 Annual Meeting was so tight that no time could be found for a general discussion between participants of all DPT-centers on the common sample. This discussion was postponed until the 2006 Annual Meeting.

10. Minutes of the meeting for participants of the Diagnostic Proficiency Test (DPT) Centre of Metabolic Diseases for Central Europe held during the SSIEM Symposium in Paris, September 6, 2005

Present: Duran (Amsterdam) chairman, Abeling (Amsterdam) secretary on behalf of Holtrop (Amsterdam), Dorland (Utrecht), Eyskens (Antwerpen), Gerlo (Brussel), Sass (Freiburg), Onkenhout (Leiden), Ruitenbeek (Nijmegen), Spaapen (Maastricht), Poorthuis (Leiden), Reijngoud (Groningen), Wamelink (Amsterdam), De Sain (Utrecht), Ruijter Rotterdam), Kluijtmans (Nijmegen), Haas (Heidelberg), Okun (Heidelberg), Jakobs (Tilburg).
Apologies for absence: Van Gennip (Maastricht), Holtrop (Amsterdam), Huijmans (Rotterdam)

1. Welcome.

The chairman welcomes the participants.
He explains that the president, Albert van Gennip, after 15 years of intensive engagement with ERNDIM, decided to stand down for retirement by october 1. The chairman shortly commemorates the highly valued contribution of Albert van Gennip as a Scientific Advisor for the purines and pyrimidines scheme, member of the Executive Board, and of the SKML, for we all feel very thankful.
Sjoukje Holtrop, our secretary, is unable to attend the meeting because of high priorities related to accreditation of the laboratory.

2. Minutes of the meeting held at August 31, 2004 in Amsterdam.

Text. page 4 , line 7 from bottom : ' methylene blue test' should be : 'dimethylene blue (DMB) test'.There were no further corrections with respect to the text.
Matters arising: 4. Annual contribution of DPT samples:

The new data form for samples in stock is not received by all. The forms will be sent out again. Action: Holtrop

Duran again stipulates the importance of sending samples, particularly also for the other DPT Centres.

Spaapen : how to prepare and send the samples ?

Duran: heat-inactivate and send at room temperature. Action: all

5. Discussion of the results:

Poorthuis: Sample O was discussed with respect to the question which method for MPS would be better: 1-dimensional or bidimensional. The statement in the minutes about 2-dimensional being the better is not according to the discussion in Amsterdam.

Duran: this will come back when we will discuss the 2005-samples.

The minutes were agreed, with thanks to the secretary (Holtrop) for preparation.

Annual Report 2004: correction on page 2 : Meeting of participants: august 31, instead of september 2.

3. Information from Trust Board, Scientific Advisory Board, executive Committee.

The numbers of participants in the 4 DPT Centers in Europ are steadily growing. In total we have 95 participants now.
The planning is to set up a 5th Center if the number exceeds 100.
Changes will take place in Committee members, with Albert van Gennip and Jim Bonham standing down this year, Brian Fowler in 2006.

4. Discussion of the results of the survey 2005:

2005-1: samples S, T, U
2005-2: samples X,Y,Z

Sample 2005.1 – S: 5-Oxoprolinuria

Results:

Sample S was a very old sample, but appeared to be very well preserved.
Creatinin values were very close. One exception (112 mM) presumably was a typing error (probably 11.2).
Uric acid: 286 ? Unclear. Wrong units ? Typing error ? Result came from a routine lab to participant's lab.
Amino acids: unknown peaks have been seen by various participants, not clearly identified.
Organic acids: large variation in 5-oxoproline, possibly by variable extraction efficiency for this compound. Exact quantification is felt to be unnecessary for 5-oxoproline.
Purines/pyrimidines: may be useful because of mention of renal stones.
Mucopolysaccharides, oligosaccharides and sialic acid: not relevant.
Duran (knowing this sample, which originally was analyzed in Utrecht) states that oxalic acid had been elevated in 1979, but apparently had precipitated and is now normal.

Advice for further investigations:

Why measure 5-oxoproline in RBC ?
Acylcarnitines in a bloodspot ? Carnitine-ester formation is very unlikely, because also no CoA-ester will be formed.
Reijngoud: How is the hemolytic anemia explained ?
Duran: not by the defect. Presumably 'normal' drug effect.
Advice to clinician and Remarks:
Wamelink: we have given a text for this and for Remarks, but it was not mentioned in the report.

Sample 2005.1 – T: MCAD deficiency

Results:

Organic acids
Duran: Organic acids pattern chracteristic for older MCAD patient.
Reijngoud: Disagree. We have seen a substantial variation between different MCAD patients within one family. This phenomenon was observed in various families.
Two participants missed the diagnosis. Do they participate in the quantitative OA scheme ?
GC-only users ? Anyway, GC-only users can easily miss this diagnosis. Obsolete configuration nowadays.
Dorland: who measures glycine conjugates ?
Duran, Spaapen: routinely done in our labs.
Duran: Iso-hexanoylglycine ? Where from ?
Sass: we find it regularly (with methylation) in MCAD !
Onkenhout: we too.
Reijngoud: might originate from phytanic acid, and thus characteristic for vegetarian MCAD patients ?

Other analyses:

Duran: acylcarnitines in urine can be highly informative, also for detection of GA I .

Advice for further investigations:

Duran: (113) why exclude MADD ?

Sample 2005.1 – U: No Inborn Error of Metabolism

Results:

One participant made a diagnosis prolidase deficiency. The arguments were not known, because the participant was not present.
Preinvestigations: The urine was clearly alkaline. This raised a discussion about refusal of bad samples.
Duran: criteria for refusal ?
Spaapen: alkaline samples with pH > 8.

More opinions were exchanged, but no consensus was reached.
Page 24 of the report: Spaapen and Eyskens did not provide the 'N' for benzoic acid. This has to be corrected.
Page 25 : Guanidinoacetate should have been measured.

Sample 2005.2 – X: Mucopolysaccharidosis, Hurler-Scheie
Results:
Page 5 : Duran:glucuronic acid ?
Spaapen: maybe from conjugates?
Duran: is this relevant. Report it ?
Spaapen: yes, to get information about medication.
Duran is not convinced of relevance.
The discussion about 1- or 2-dimensional electrophoresis now focused on the presence and recognition of heparin sulphate, which discriminates Hurler from Maroteaux-Lamy. Some participants concluded Maroteaux-Lamy, which is contra-indicated if clearly HS is found. Poorthuis states that some HS was seen in 1-dim electrophoresis, but not much, which is rather unusual for Hurler.
Duran: possibly more HS is isolated with Alcian Blue.
Poorthuis: possible, but Alcian Blue is hardly used .
Conclusion: unusual patient.
One participant missed the diagnosis because the dilution factor for the urine sample in the DMB-test was not accounted for by the technician.

Sample 2005.2 – Y: 3-methylglutaconic aciduria type 1
Duran: this sample is from the patient in the original publication of the disorder.
The finding of high lactate and 3-OH-butyrate is strange, because it was not mentioned in the original publication.
This sample was not further discussed by lack of time.

Sample 2005.2 – Z: Tyrosinemia type II
This diagnosis, or at least the tyrosyluria was found by all participants.

5. Scoring and reporting
Duran: the planning is that scoring and reporting will be done via the ERNDIM website in the near future.
The scores will be made in September.

5. Any other business
None.

6. Date and venue of next DPT-meeting; linked to ICIEM 2006 ?
The proposal is Maastricht, because it will be impossible to have full attendance for the DPT-meeting in Japan.

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Paris, september 6, 2005
N.G.G.M. Abeling