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Newborn Urine Screening Experience with over one Million Infants in the Quebec Network of Genetic Medicine

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Summary: We screened urine for chemical individuality in over 1 million newborn infants, by various chromatographic (thin-layer), chemical and spectrophotometric methods, 12 procedures in all. The programme is part of the Quebec Network of Genetic Medicine. Voluntary urine screening began in 1971 and has evolved with changes in choice of tests and times of sample collection. Urine samples were collected on filter paper at either 5, 14 or 21 days after birth; results were best with the 21-day test. Compliance is over 94% with the latter and over 98% with requests for repeat samples. Screening is centralized in one laboratory; follow-up diagnosis, counselling and management are done at four regional centres. Incidence of phenotypes ranged from 1:4300 live births (for expressed cystinuria alleles) to 1 per million (for hyperargininaemia). Over 20 inherited Mendelian disorders were identified. 30 patients required aggressive medical management. We show how this programme can be used for neuroblastoma screening.

Sir Archibald Garrod made the concept of chemical individuality relevant to medicine in 1909 (Garrod, 1909). The Quebec Network of Genetic Medicine, Réseau de médecine génétique du Québec (Laberge *et al.*, 1975; Scriver *et al*, 1978) began voluntary newborn urine screening in 1971. In keeping with accepted goals of genetic screening (*Nat. Acad. Sci.*, 1975), medical intervention for treatable diseases and enumeration of phenotype incidences were ours. We present here the results of 15 years' experience with newborn urine screening over 1 000 000 infants. We describe the evolution of our programme, the tests used, the levels of participation and its costs. We discuss its findings in the context of human biochemical genetics.

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MATERIALS AND METHODS

Urine screening is considered a normal procedure in the Quebec health care system. Participation is voluntary. Parents can abstain from the screening procedure.

Sample collection

Over 99.9% of births in Quebec occur in hospital where the mother is given a kit containing filter paper, return envelope and instructions. The initial (filter paper) urine sample was collected in hospital until October 1973 (Table 1). For 1 year (Nov. 1973–Oct. 1974), paired samples were collected on days 5 and 14, the latter in the home. The 14-day test was then adopted and maintained until we converted to a 21-day in home sample beginning in Jan. 1981. A filter paper (Schleicher and Schuell No. 903 Keene, N.H.) is placed inside a wet diaper (faeces free), pressed to moisten the paper thoroughly, then removed, air dried and mailed to the screening laboratory (at the Centre Hospitalier Universitaire de Sherbrooke).

Table 1 Time of collection of the first urine sample

Age of infant (day)	*Calendar dates*		*Number of samples analysed*
	From	*To*	
5*	Aug. 1971	Oct. 1974‡	218855
14†	Oct. 1973‡	Dec. 1980	500796
14–21†	Jan. 1981	June 1982	127508
21†	July 1982	continuing	364110**

*Sample collected before discharge from nursery
†Sample collected in home (by parents)
‡There was an overlap period of 1 year where paired 5- and 14-day samples were collected on all infants
**As of Dec. 31, 1986

Repeat (liquid urine) samples for repeat tests are collected in the home in a disposable plastic collector, transferred to a plastic mini-vial containing a drop of a 20% solution of thymol in ethanol, and mailed to the screening laboratory. Aliquots were standardized by measuring α-amino nitrogen content (Wells, 1969). We request repeat samples when there is insufficient urine on the filter paper (this can occur with ultra-absorbent diapers), contamination by faeces or diaper creams (Giguère *et al.*, 1980), or a positive finding on the first sample.

Infants with a significant finding (on the first or repeat sample) are referred to one of the four regional centres in the Network for diagnosis.

Sample preparation

We examine the filter paper under ultra-violet light for presence of urine (blue-green fluorescence) and absence of faeces (yellow-orange fluorescence) and other visible contaminants. From a 5 cm disc, we elute urine with 2.75 mL of 0.01 mol L^{-1} ammonium hydroxide in a rotary shaker.

Chromatography

Four TLC glass plates, 20 × 40 cm, are coated with a 300 micron-thick mixture of cellulose, silica gel, water (28 g: 16.8 g: 160 mL) using a spreading device and dried overnight. The coated plates can be kept for months in a dry cabinet.

Aliquots of eluted urine (15 μL) are applied to the plate as 1 cm streaks by a semi-automatic spotting device (Shapcott and Lemieux, 1972), (20 samples and three standard solutions per plate). The plate is developed (one way ascending) in 1-butanol:acetic acid:water, (13 : 3 : 5 by volume), dried, and redeveloped in the same solvent.

Location of substances

Methylmalonic and amino acids were located by the sequential use of orthodianisidine and ninhydrin sprays respectively (viz. Figure 1) (Lemieux *et al.*, 1974; Auray-

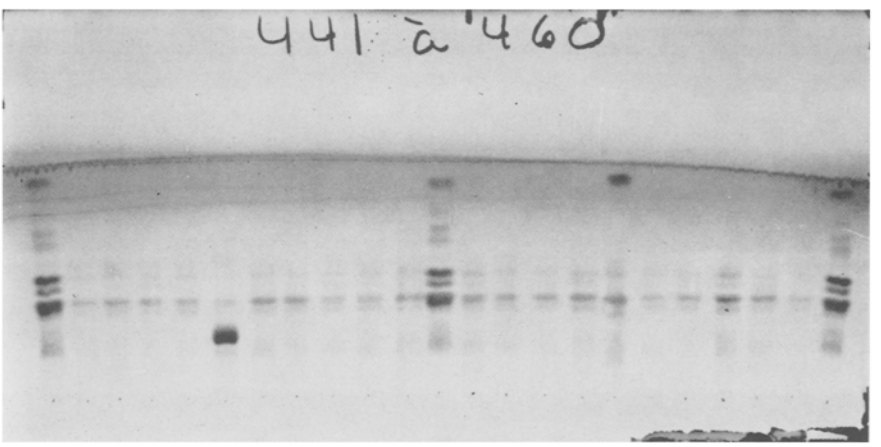

Figure 1 Combined development and staining of amino acids and methylmalonic acid on the same TLC plate (see Methods) with three standard solutions. Patient samples no. 5 and 15 contain excesses of argininosuccinic acid and methylmalonic acid respectively

Blais *et al.*, 1979; 1982b). We use Ehrlich's reagent for location of citrulline and hydroxyproline, the Sakaguchi reagent for arginine, and iodoplatinate for cystathionine (Smith, 1969).

Chemical tests

Aliquots of eluate are applied to powder mixtures. Sulphur amino acids are identified with Brand's reagent (Cystinuria-Actessa, Luxembourg); a pink colour signifies a positive reaction for cystine or homocyst(e)ine. Reducing sugars are identified by blackening of a mixture of sodium hydroxide, bismuth oxychloride and sodium silicate (63 : 12 : 25 w/w) respectively (Auray-Blais *et al.*, 1978).

Other analyses

We have used conventional automated spectrophotometric methods to measure uric acid by a modification of the molybdate reduction technique (Nishi, 1967), creatinine by the Jaffe reaction (Chasson *et al.*, 1961), keto acids by formation of hydrazones with dinitrophenylhydrazine and measurement of the colour produced by adding alkali (Katsuki *et al.*, 1971), methylmalonic acid by formation of the green complex with *p*-nitroaniline (Giorghio *et al.*, 1969), and orotic acid by the method of Paradis *et al.* (1980).

Changes in tests

Our use of the above-mentioned methods evolved during operation of the programme (Table 2). The changes reflect deletion of unproductive tests and improvements in analysis. The current protocol is shown in the flow diagram (Figure 2).

Table 2 Protocol of analyses by calendar year

Type of analysis	*Date*		*Number of samples analysed*
	From	*To*	
Thin layer chromatography			
Amino acids	Aug. 1971	continuing	1 106 094*
Specific sprays for amino acids	June 1975	continuing	864 514*
Methylmalonic acid	June 1975	continuing	864 514*
Powder tests			
Sulphur amino acids†	Aug. 1971	continuing	573 316*
Reducing sugars	Feb. 1974	Nov. 1978	373 674
Spectrophotometric analyses			
Uric acid/creat.	Aug. 1971	Oct. 1974	218 855
Keto acids/creat.	Oct. 1973	Oct. 1974	105 175
Methylmalonic acid/creat.	Oct. 1973	March 1975	129 734
Orotic acid	Jan. 1979	Jan. 1980	88 607

*As of Dec. 31st, 1986
†Since 1980, test done only on samples with amino acid patterns indicating potentially increased cystinuria or homocystinuria

RESULTS

Participation at the first test was 83% at inception of the programme, rose to 91% within 5 years, and then to 94%. Compliance with repeat tests was 98%.

When we changed the time of sample collection to 14 days, there was a 5-fold increase in the incidence of case detection and a marked reduction of false-positive findings. This improvement persisted when the sample was collected at 21 days of age.

The request rate for repeat positive samples at the first analysis is approximately 1.5%. There was a 0.3–0.5% increase in 'positive' tests over the 14 years of the

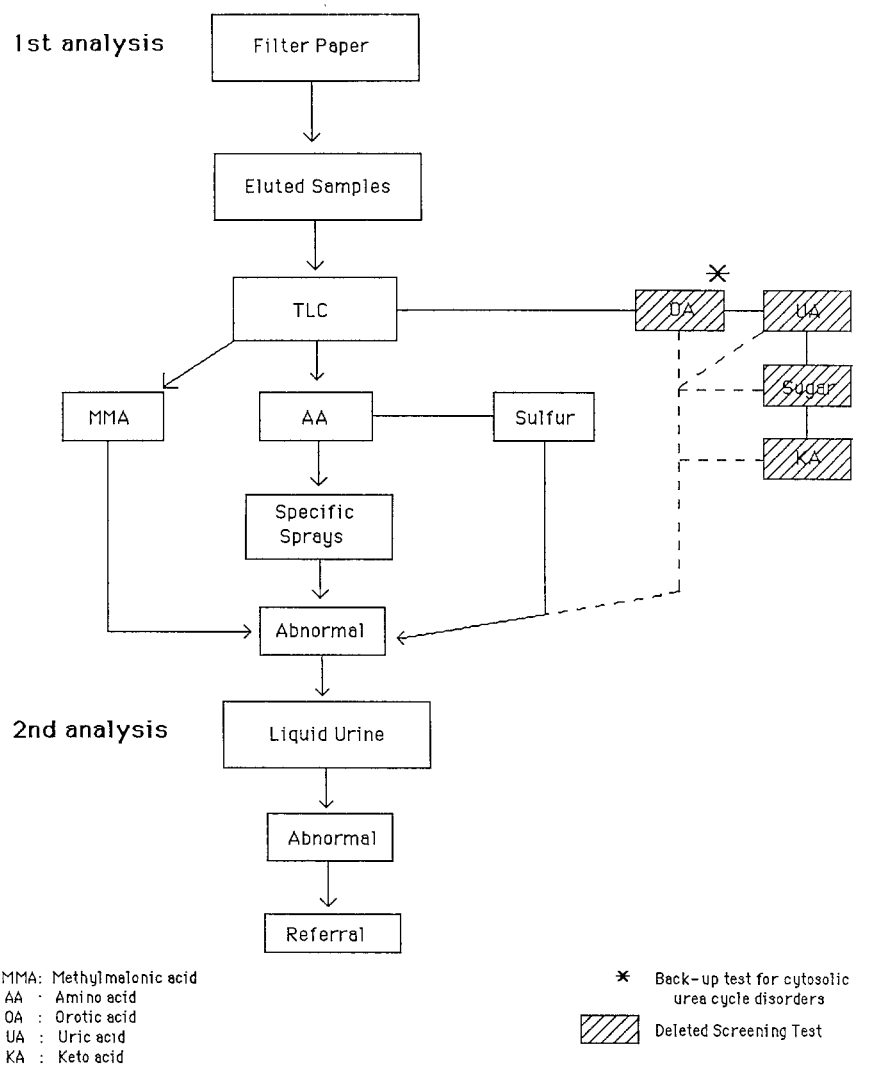

Figure 2 Flow sheet depicting processing of samples in the urine screening programme

Table 3 Observed incidence of confirmed findings in urine specimens collected between 14 and 21 days of age

Disorder	*McKusick no.*	*Number of identified cases*	*Incidence*
Disorders requiring early medical intervention			
Methylmalonic aciduria(s)	25100, 25110, 27738*	14	1: 61 000
Argininosuccinic aciduria	20790	11	1: 90 000
Citrullinaemia	21570	2	1: 500 000
Ketotic hyperglycinaemia	23200, 23205	2	1: 500 000
Hyperargininaemia	20780	1	1: 990 000
Conditions requiring only counselling and surveillance			
Transport disorders			
Cystinuria (incomplete)†	22010	232	1: 4300
Iminoglycinuria‡	24260	55	1: 7400
Cystinuria (complete)	22010	36	1: 28 000
Dicarboxylic aminoaciduria	22273	34	1: 29 000
Hartnup disorder	23450	24	1: 41 000
Dibasic aminoaciduria	22269	11†	1: 90 000
Generalized aminoaciduria(s)	(several)	8	1: 124 000
Renal glucosuria	23310	7	1: 142 000
Metabolic disorders			
β-Aminoisobutyric aciduria‡	21010	80	1: 5100
Histidinaemia	23580	142	1: 7000
Sarcosinaemia	26890	36	1: 28 000
Cystathioninuria	21950	8	1: 124 000
Prolidase deficiency	26413	2	1: 500 000

*One case of the cblF phenotype (McKusick 27738)
†Heterozygous phenotype only
‡Based on 407 124 samples

programme associated with an increase in the birth rate of premature babies (who have various hyperaminoacidurias associated with immature metabolic and renal functions), and the increased use of hyperalimentation in very-low-birthweight babies (who have hyperaminoaciduria). Insufficient or contaminated samples accounted for 1.2% of all the first samples.

The incidence of confirmed metabolic phenotypes identified by urine screening in 14–21-day-old babies is shown in Table 3. The overall incidence of disorders requiring early medical intervention was about 1 : 33 000 livebirths. Conditions requiring early counselling and surveillance have a higher overall incidence; they include transport disorders (about 1 : 2900 livebirths); and benign metabolic disorders (about 1 : 5300 livebirths). We also observed 'physiological' phenotypes, such as familial renal iminoglycinuria (McKusick 24260; incidence 1 : 7500) and β-aminoisobutyric aciduria (McKusick 21010; incidence 1 : 6000). Repeat specimens have not been requested for either of these disorders since 1978 and we no longer counsel families about these two findings.

We calculated the average cost per analysis, taking into account salaries, fringe

benefits and laboratory supplies, for a full year (approximately 85 000 analyses). Parents now pay the mailing costs. The cost per analysis was $1.77 (Can.) in 1986.

DISCUSSION

We used filter paper to collect the urine sample for reasons of cost, convenience, and reasonable stability of metabolites when samples are stored at room temperature in a dry location (viz. Levy *et al.*, 1972). We chose the TLC method because it was convenient, less expensive than filter-paper partition chromatography; and application of samples to TLC plates could be semi-automated (500 samples in 90 min). Development and spraying of TLC plates was rapid and simple and could be completed in a single working day. We used a relatively inexpensive TLC spreading machine and reusable glass plates to reduce costs further.

The 5-day samples were collected, in the initial stages of the programme (Table 1), in the nursery by hospital staff. Because of low compliance (only 83%) with this protocol, we gave the urine collection kits to the parents, beginning in 1973, with instructions to collect the urine sample at 14 days. In 1981, we changed to a 21-day test. Parental compliance was excellent (over 94%), and it did not decrease when they assumed the costs of postage (after 1981). A recent survey of 100 families with positive tests and an equal number with negative tests revealed that both groups considered this voluntary programme worthwhile (Scriver *et al.* 1987).

The merits of the various tests were repeatedly evaluated and we changed or retained them accordingly. For example, the method of McInnes *et al.* (1971) to detect hyperuricosuria was performed for 3 years. There were many positive findings during the first week of life; all were normal on repeat examination. There were no positive tests when sampling was performed at 14 days after birth. The test was dropped after 220 000 tests. Only one case of Lesch-Nyhan syndrome was identified by clinical diagnosis after the cessation of our pilot study.

Maple Syrup Urine Disease (MSUD) (McKusick 24860) is readily recognized in the Quebec health care system which encourages early admission. Accordingly, diagnosis of MSUD patients occurs before they would be found by the newborn urine screening programme. Six cases of proven MSUD have been diagnosed in the past 15 years in Quebec (Clow *et al.*, 1981), all by clinical signs (approximate incidence 1 : 150 000 births). The corresponding keto acid test was discontinued after 100 000 analyses without a positive finding.

We used a spectrophotometric method to measure methylmalonic acid (MMA) in a pilot study, and had an unacceptably high number of false-positive findings. Because MMA screening is considered worthwhile (Coulombe *et al.*, 1981), we adopted the TLC method which has a low rate of false-positives (less than 0.1%) is sensitive at 1 mg/dL (about 3 times normal levels in the newborn) and could be combined with the amino acid screening test. MMA screening in our programme led to the discovery of a new disease, a disorder of lysosomal vitamin B_{12} release, McKusick 27738 (Rosenblatt *et al.*, 1986), two treatable cases with B_{12} responsive MMA, McKusick 25110/25111 (Mitchell *et al.*, 1986) and 11 other cases with various degrees of clinical manifestations.

Because orotic acid is increased in several disorders of the urea cycle, we measured this metabolite for 1 year (88 000 samples) and found no confirmed positive tests, and an unacceptable rate of false-positive tests. The screening test was discontinued but retained as a follow-up procedure for confirmation of suspected urea cycle abnormalities (Lemieux *et al.*, 1983).

We found seven cases of renal glucosuria (McKusick 23310) (Table 3) by the chemical tests for reducing sugars but none of galactosaemia (McKusick 23020, 23035, 23040), fructosaemia (McKusick 22960) or glucose-galactose malabsorption (McKusick 23160). We discontinued the test in 1978. The test for galactosaemia in the newborn blood screening programme had already been discontinued because of low yield (<1 per 200 000 births) and replaced by the highly cost-effective tests for congenital hypothyroidism (Laberge, 1975; Scriver *et al.*, 1978; Dagenais *et al.*, 1985).

The chemical test for sulphur amino acids, in combination with the TLC screening method for amino acids, detects a high frequency of 'cystinuria' in the newborn. About 80% of the probands are heterozygous, not homozygous or compound, for cystinuria alleles (Scriver *et al.*, 1985). Accordingly, follow-up of these cases is essential for accurate counselling.

Our screening method for hyperaminoacidurias has remained unchanged since its inception. It revealed the incidence of several disorders of amino acid metabolism (Table 3). We incidentally found two cases of phenylketonuria where blood screening had not yet been completed (it was also positive). Follow-up studies of subjects with renal iminoglycinuria (McKusick 24260) revealed useful information about the ontogeny of the corresponding renal transport systems (Lasley and Scriver, 1979). β-Aminoisobutyric aciduria (McKusick 21010), a benign metabolic polymorphism, is prevalent by virtue of gene flow in the Amerindian and Inuit populations covered by the Quebec programme.

The incidence of dicarboxylic aminoaciduria (McKusick 22273) is noteworthy in the Quebec population. Because it is high, it may reflect a founder effect here; occurrence is low in other populations (Levy *et al.*, 1980). Follow-up studies, as yet incomplete, suggest it is a benign disorder (S. Melançon, 1986 personal communication).

Hartnup disorder (McKusick 23450) is symptomatic in only about 10% of cases according to our follow-up observations (Scriver *et al.*, 1987). Whereas the urine phenotype (specific hyperaminoaciduria) is monogenic, the disease is polygenic and multifactorial and those at risk can be predicted by appropriate follow-up studies. Accordingly, early diagnosis of Hartnup probands permits prospective counselling and prevention of disease in high-risk probands.

Histidinaemia (McKusick 23580), next to cystinuria and β-AIBuria, is the most common disorder detected by newborn urine screening in Quebec (Auray-Blais *et al.*, 1982a). Prospective and retrospective studies (Scriver and Levy, 1983) imply that it is a benign disorder. It is not treated in Quebec but follow-up studies of the cohort continue.

The incidence of sarcosinaemia (McKusick 26890) is high in Quebec relative to Massachusetts, for example (Levy *et al.*, 1984). A prospective study of Quebec

cases is underway to examine the medical significance of this disorder and to discern whether it is a homogenous entity. Prolidase deficiency (McKusick 26413) detected by the associated iminodipeptiduria (Lemieux *et al.*, 1984), is still under investigation in two cases.

14 cases with disorders of the urea cycle were identified by urine screening. None had fulminating neonatal manifestations. We diagnosed 11 patients with argininosuccinic aciduria (McKusick 20790), two with citrullinaemia (McKusick 21570), and one with hyperargininaemia (McKusick 20780) (Qureshi *et al.*, 1983). All but one patient (a case of ASAuria) have been treated.

Others have discontinued their newborn urine screening programme (Wilcken *et al.*, 1980) or compromised by passing the costs on to the participants as a fee for service (H. Levy, personal communication), an option not permitted in Quebec. We have a reason to continue the urine programme in Quebec. We recently performed a feasibility study of neuroblastoma screening in Quebec (Scriver *et al.*, 1987; Tuchman *et al.*, 1987) which showed that the incidence of neuroblastoma is about 10^{-4} livebirths in Quebec. The disease can be diagnosed at the early clinical stages by chemical tests or by TLC of metabolites in filter paper urine samples. Early diagnosis will be highly cost-effective, and it will greatly improve prognosis of the disease. Citizens have been consulted and they support the principle of screening for neuroblastoma. Accordingly, we will do a pilot study of neuroblastoma screening by incorporating the tests for this disease into the existing metabolic screening programme.

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