A True-Life Example of the Consequences of not Recognizing an Organic Acidemia: The Patti Stallings Case

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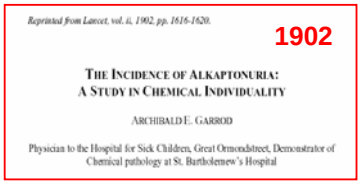
Inborn Errors of Metabolism (IEM)

A genetically-determined biochemical disorder in which a specific protein defect produces a metabolic block that may have pathological consequences

The Beginning

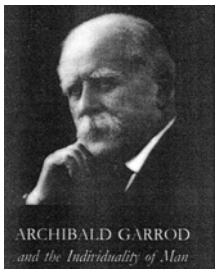

Reprinted from Lancet, vol. ii, 1902, pp. 1616-1620.

1902

THE INCIDENCE OF ALKAPTONURIA:
A STUDY IN CHEMICAL INDIVIDUALITY

ARCHIBALD E. GARROD

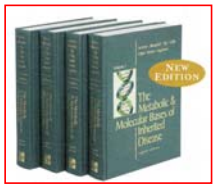
Physician to the Hospital for Sick Children, Great Ormondstreet, Demonstrator of Chemical pathology at St. Bartholomew's Hospital



Inborn Errors of Metabolism arise because an enzyme governing a single metabolic step is reduced in activity, or missing altogether (1909)

Known Inborn Errors of Metabolism

(from Metabolic & Molecular Basis of Inherited Disease)



MMBID, 8th edition
January 2001
4 volumes
255 chapters
6,338 pages

Pathogenesis of IEM

- Disorders of the synthesis or the catabolism of complex molecules (CHRONIC INTOXICATION)
- Disorders of intermediary metabolism (ACUTE INTOXICATION)
- Disorders of energy production (ENERGY DEFICIENCY)

Acute Intoxication/Energy Deficiency

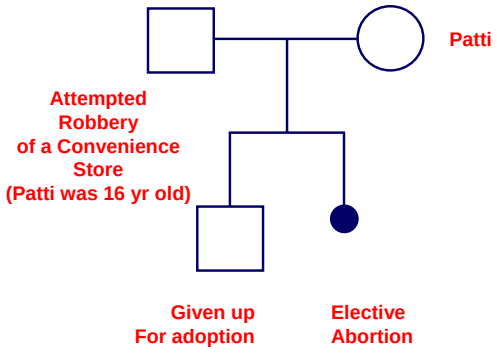
- Amino acid disorders
- Organic acid disorders
- Urea cycle disorders
- Primary lactic acidemias
- Fatty acid oxidation disorders

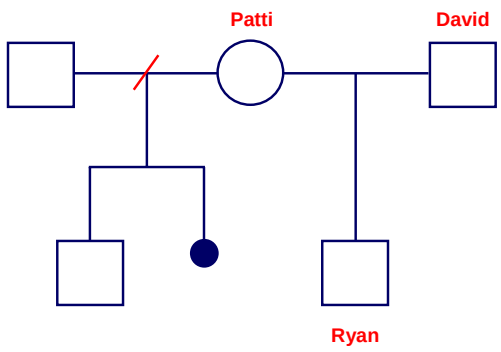
= Life-Threatening Episodes of Metabolic Decompensation

Why Should You Care About IEM?

Common Misdiagnoses

- Sepsis
- Intraventricular brain hemorrhage
- Cerebral palsy
- Seizure disorder
- Developmental delay
- Sudden unexpected death ("SIDS")
- No diagnosis → CHILD ABUSE





Chronology of Events

- July 89 - Ryan (3 mo.) is brought to the ER for severe vomiting, dehydration, lethargy
- Based on lab results, a diagnosis of ethylene glycol and acetone POISONING is made
- The police actively investigates Patti only
- When Ryan recovers he is released to a foster home
- Patti and David are granted one hour of supervised visitation per week

First Episode (July 89)

- History – Full-strength cow's milk was introduced in the diet 48 hours before the onset of symptoms (replacing formula)
- Signs & Symptoms – Poor general conditions, comatose on admission, respiratory distress
- ER lab results
  - Metabolic acidosis (pH 7.02, HCO_3^- 11, AG –27)
  - Glucose 52 mg/dL
  - Urine strongly positive (4+) for ketones

First Episode (July 89)

Sample	Test	Unit	Result	Interpretation
SERUM	Iron	(mg/dL)	15.0	normal
	Lactate	(mM)	2.0	normal
	Ethanol	"	nd	negative
	Methanol	"	nd	negative
	Isopropanol	"	nd	negative
	Salycilate	(mg/dL)	3.8	normal
	Acetone	(mg/L)	169	POISONING
	EG	(mg/L)	180	POISONING
URINE	Drug screen		Negative	negative
	Oxalate	(mg/24h)	2.0	normal

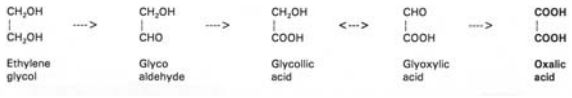
Child Protection Services (July 12)

"*This is a double ingestion of toxin. This could not have been accidentally ingested by child* "

Impression: CHILD ABUSE

Ethylene Glycol

- Sweet, colorless, odorless liquid
- Easily available (antifreeze)
- Minimum lethal dose: ~100 mL (adults)
- EG metabolites are highly toxic

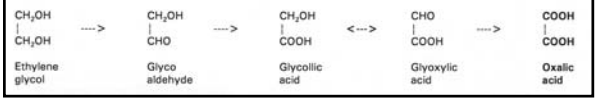


Clinical Features Of Ethylene Glycol Poisoning

Time after Ingestion (h)	Clinical Features
0 - 12	NEUROLOGIC MANIFESTATIONS
	Patient appears intoxicated
	Nausea, vomiting
	Coma, seizures
12 - 24	CARDIO-PULMONARY FAILURE
	Respiratory distress, cianosis
	Tachycardia, hypertension
24 - 72	OLIGURIC RENAL FAILURE
	Systemic tissue precipitation
	Of Ca^{++} oxalate crystals

Laboratory Findings Of Ethylene Glycol Poisoning

Body fluid	Laboratory finding
BLOOD	Metabolic acidosis
	High osmolality
	Hypocalcemia
URINE	Glycolic aciduria
	Hyperoxaluria
	Crystalluria
	Low specific gravity



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Fasting or
Excessive energy consumption

↓

CHO → CHO

↓ Ins ↑ Gluc

Tissue glycogen depletion

↓

FA → FA

Mobilization of fatty acids from adipose tissue

↓

FA → Acetyl -CoA

FATTY ACID OXIDATION

↓

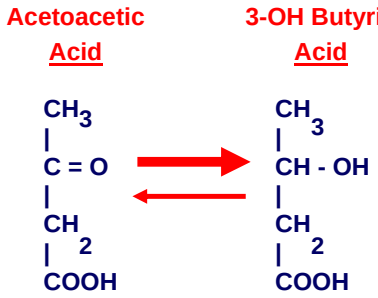
Acetyl -CoA → Ketone bodies

Hepatic synthesis of ketone bodies

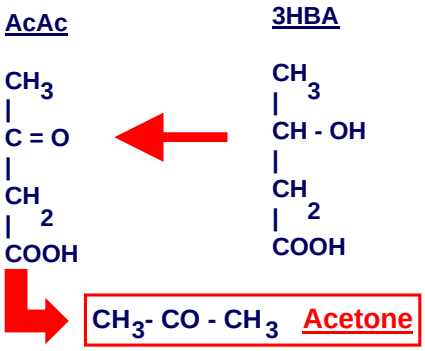
↓

Peripheral Utilization

Ketone Bodies



Conventional Method to Measure KB



Conventional Method to Measure KB

"Acetone" = 3HBA + AcAc + Acetone

= Total Ketone Bodies

CH_3- CO - CH_3 Acetone

Chronology of Events

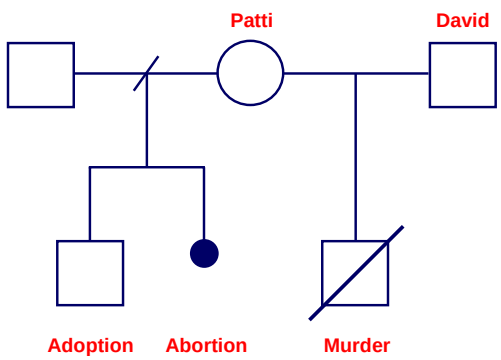
- September 89 – Three days after a visit, Ryan suffer a second episode with the same symptoms
- Again laboratory results point to EG poisoning
- Diagnosis confirmed by an independent toxicology lab using a different method (GC/MS)
- Traces of EG found in a bottle of formula used to feed Ryan during last parental visit

Second Episode (Sept. 89)

Sample	Test	Unit	Result	Interpretation
SERUM	Ammonia	(ug/dL)	298	Elevated
	Acetone	(mg/L)	320	POISONING
	EG	(mg/L)	911	POISONING
URINE	Drug screen		negative	negative
	Oxalate	(mg/24h)	Not done	

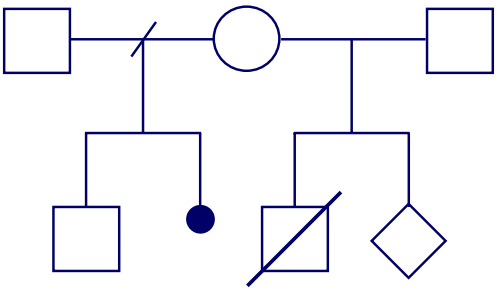
Chronology of Events

- September 89 – Three days after a visit, Ryan suffer a second episode with the same symptoms
- Again laboratory results point to EG poisoning
- Despite aggressive treatment, Ryan dies
- Ca^{++} oxalate crystals found at autopsy in kidney and brain
- Patti is arrested, charged with 1st degree murder and remanded without bail



Chronology of Events

- **September 89 – Three days after a visit, Ryan suffer a second episode with the same symptoms**
- **Again laboratory results point to EG poisoning**
- **Despite aggressive treatment, Ryan dies**
- **Patti is arrested, charged with 1st degree murder and remanded without bail**
- **While in jail, she finds out to be pregnant**

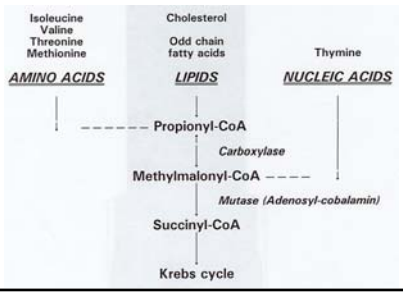


Chronology of Events

- **February 90 – Patti gives birth to David Jr., who is immediately taken from her and placed in foster care. Although he was not a suspect, David Sr. is denied custody**
- **At two weeks of age, David Jr. becomes ill with the same symptoms seen previously in Ryan**
- **A diagnosis of Methylmalonic Acidemia is made in another hospital**

Methylmalonic Acidemia

- **Autosomal recessive inheritance (1967)**
- **Defect of methylmalonyl-CoA mutase**

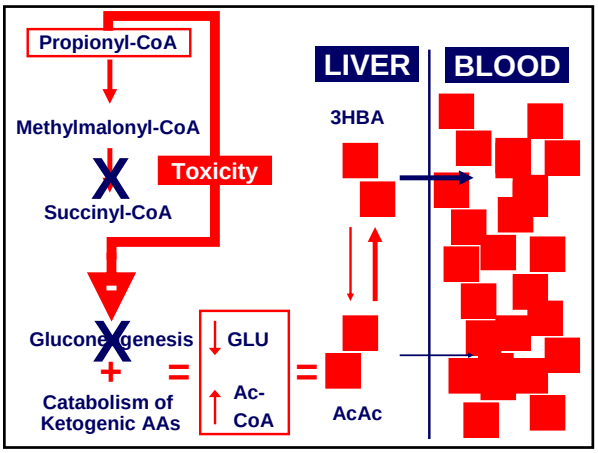


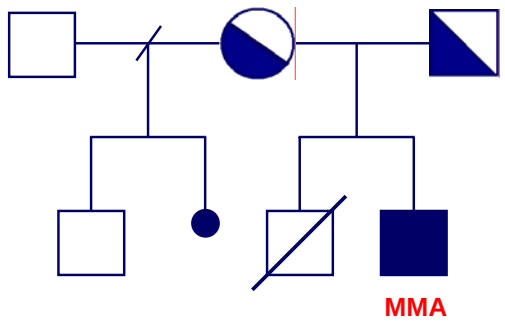
Clinical Features of Methylmalonic Acidemia

- **Lethargy, coma**
- **Recurrent vomiting, dehydration**
- **Respiratory distress**
- **Hypotonia, failure to thrive**
- **Developmental delay**

Major Laboratory Findings of Methylmalonic Acidemia

- Metabolic acidosis
- Ketonemia / ketonuria
- Hyperammonemia
- Hypoglycemia
- Hyperglycinemia

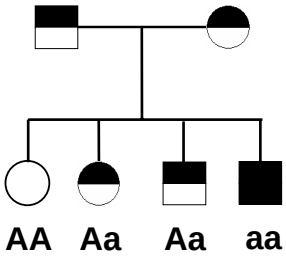




Autosomal Recessive Inheritance

	A	a
A	AA	Aa
a	Aa	aa

A = normal allele
a = mutant allele

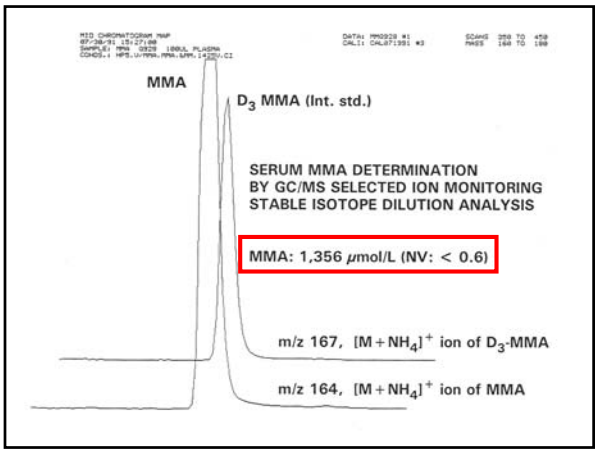


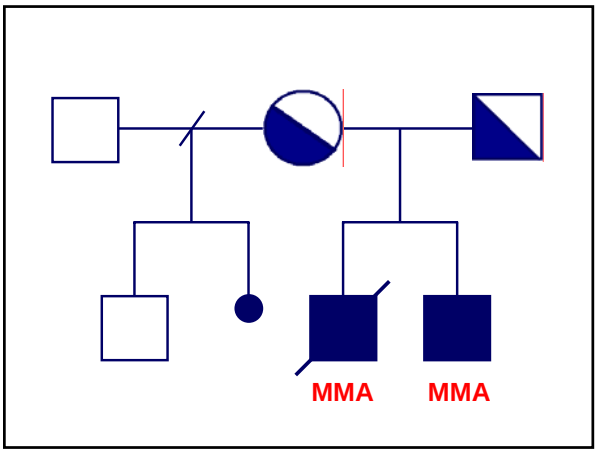
Chronology of Events

- May 90 - Patti is released from jail pending trial
- January 91 - Judge rules that no evidence could be introduced at trial about David Jr. presentation and diagnosis
- March 91 - Patti is found guilty of first degree murder and sentenced to life in jail without possibility of parole
- May 91 - *Unsolved Mysteries* airs on NBC
- June 91 - Patti gets a new lawyer
- July 91 - A new trial is granted

Prosecutor's Questions

- Was Ryan affected with MMA, too?
- Was the identification of EG in blood correct?
- Could two independent (and reputable) labs make the same mistake?





Reference GC Method For Determination of Serum Ethylene Glycol

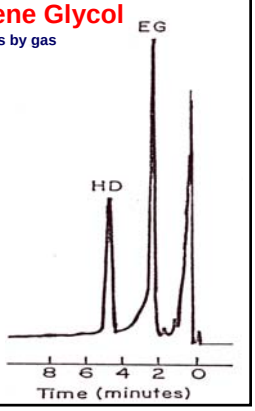
Bost RO, Sunshine I. Ethylene glycol analysis by gas chromatography. J Anal Toxicol 1980; 4:103

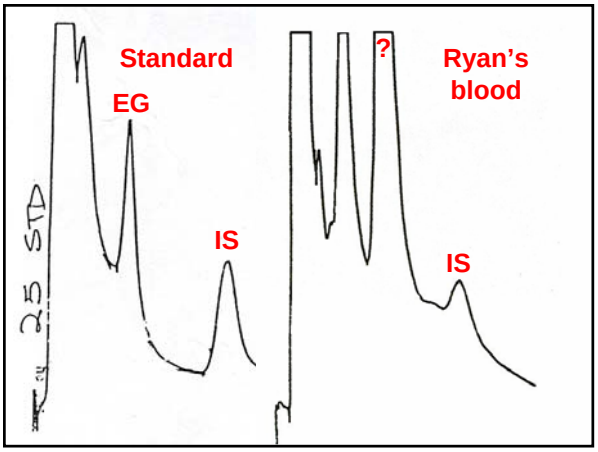
Sample: Serum 1.0 mL
I.S. 2,5-hexanedione

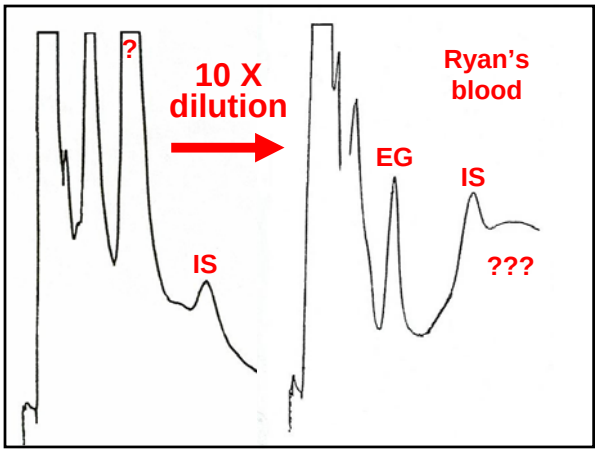
Procedure
Serum and IS solution are mixed
3.0 uL injected

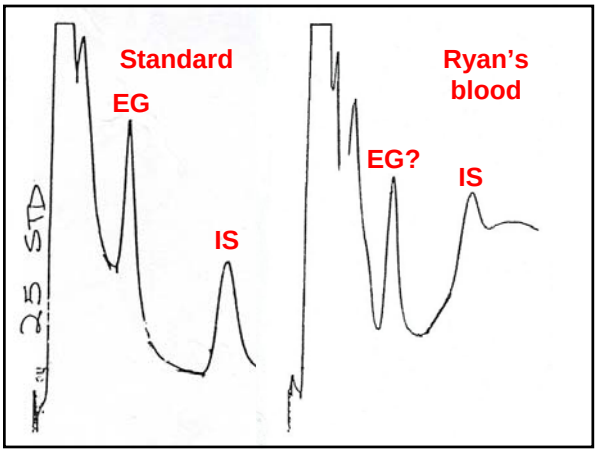
No deproteinization
No extraction
No derivatization

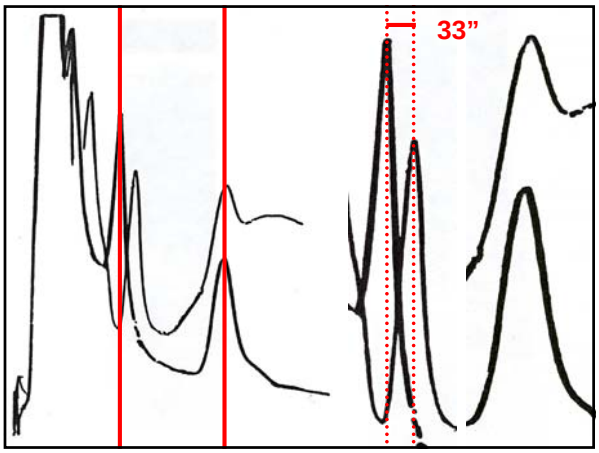
GC
1.8 m x 0.3 mm SS column
Phase: 5% Carbowax 20M
Carbopack B, 60-80 mesh
INJ 215°C
OVEN 170°C
DET 220°C
Carrier N_2, 3 mL/min







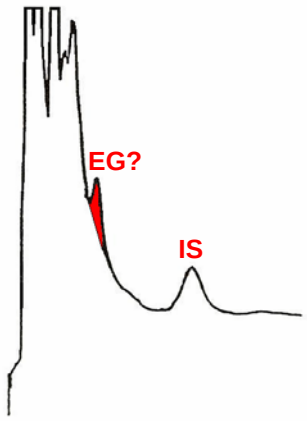


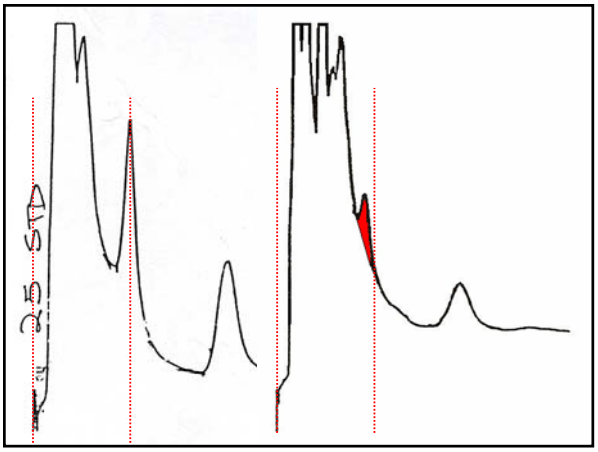


Ethylene Glycol	Propionic Acid
CH_2-OH | CH_2-OH	CH_3 | CH_2 | COOH
$C_2 H_6 O_2$	$C_3 H_6 O_2$

The “Smoking Gun”

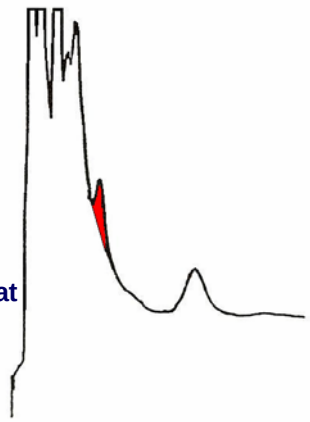
- Trace amounts of EG found in bottle used to feed Ryan

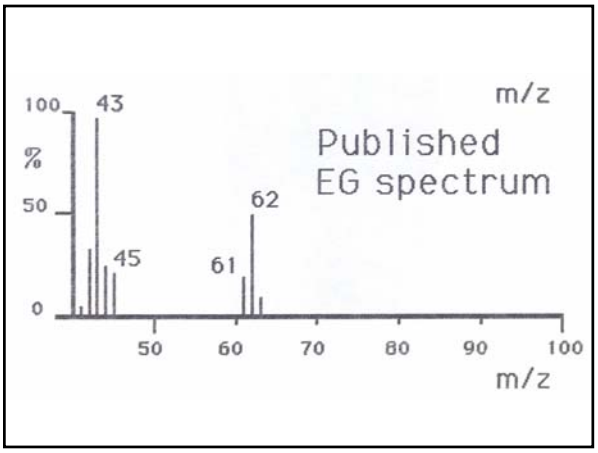


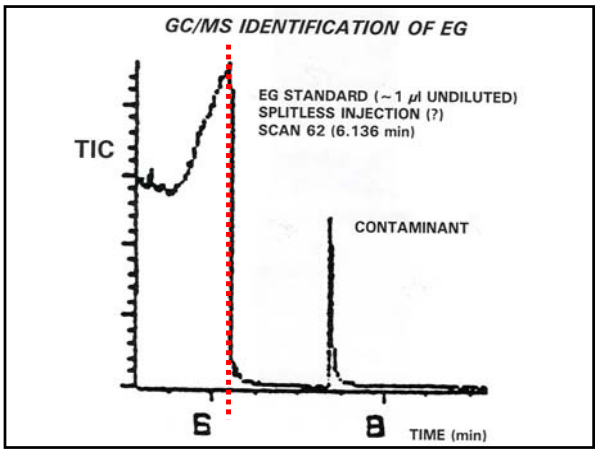


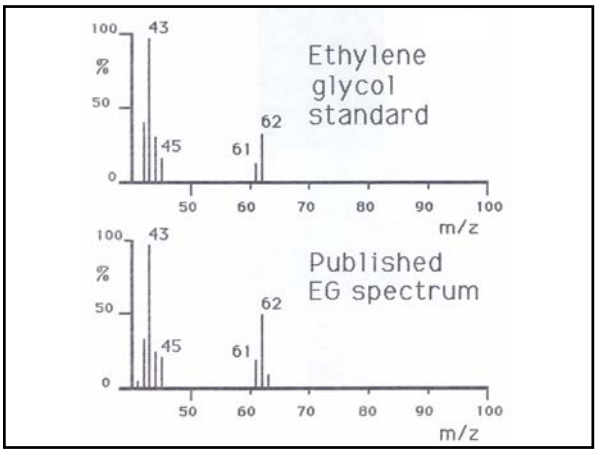
The “Smoking Gun”

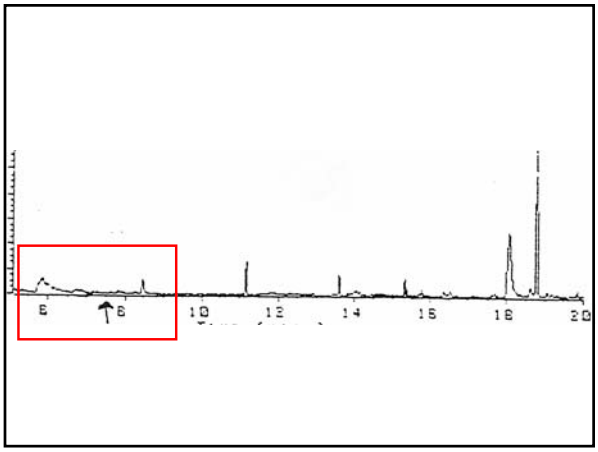
- After the feeding, the bottle was washed by hand, went through a dishwasher cycle, and filled with Pedialyte
- The jury was told at trial that leftover formula tested positive for EG

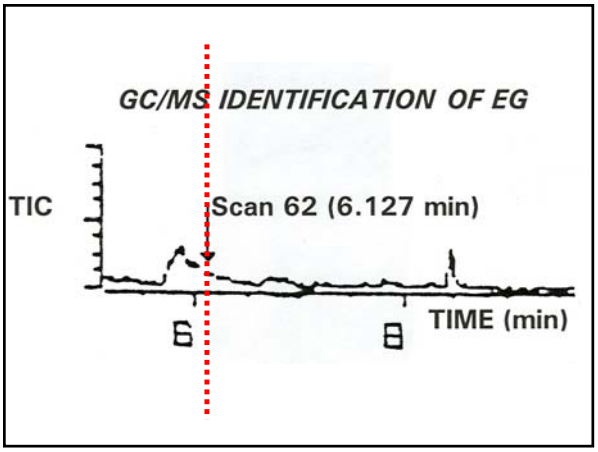


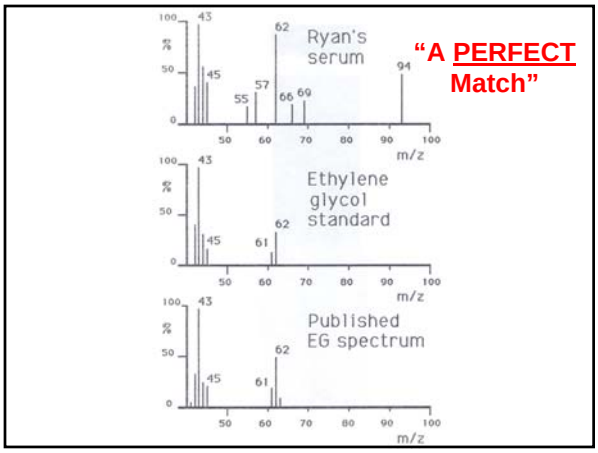












"A PERFECT Match"

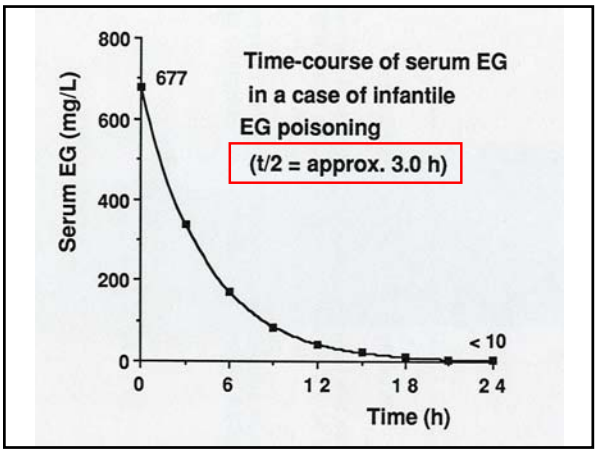
Prosecutor's Questions

- Was Ryan affected with MMA, too? **YES**
- Was the identification of EG in blood correct? **NO**
- Could two independent (and reputable) labs make the same mistake? **NO**

YES

How Could They??

- Lack of motive (but she was a "bad person")
- Unexplained massive ketosis / ketonuria
- Strong odor and taste of acetone
- Symptoms became evident 86 hours after last contact with Patti (she was briefly left alone with Ryan and fed him)
- EG level of 911 mg/L found 108 hours after bottle feeding



Chronology of Events

- September 91 – The prosecutor dismisses all charges
- David Jr. is returned to the custody of his parents