Analysis of causes that led to rib and skull fractures, sudden illness, intracranial bleeding, and death in the case of toddler Roman Pitts

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Abstract

A male toddler suffered from cardiac arrest on May 26, 1988 after receiving amoxicillin. His stepfather, Daniel Childs, performed cardiopulmonary resuscitation (CPR) and called 911. The child was brought to the hospital, resuscitated, and given epinephrine 0.8 mg endotracheally and IV. He had a blood pH of 6.82, infection, and kidney and liver damage. The child was given sodium bicarbonate, antibiotics, and IV fluids. He died 4 days following admission.

An autopsy was performed and the medical examiner (ME) found separation of the coronal suture in the child's skull, a subarachnoid hemorrhage, brain edema, five healing rib fractures, and one acute rib fracture. It was alleged that the child died as a result of blunt trauma. However, the paramedics, physicians, and nurses at two hospitals did not observe any injury caused by trauma on the child's body. His X-rays and a CT scan of the head did not show skull fracture.

Daniel was accused of killing his stepson. He was convicted and sentenced to life in prison. The medical evidence presented in this report indicates that 1) the child's cardiac and respiratory arrest, pulmonary edema, and liver damage were caused by an allergic reaction to amoxicillin; 2) his subarachnoid bleeding was caused by epinephrine, liver injury, infection, and vitamin K deficiency; 3) the separation of the coronal suture was caused by the increased intracranial pressure which resulted from bleeding and edema; 4) the causes of the healing rib fractures were vitamin K and protein deficiency; 5) the acute rib fracture was caused by CPR; and 6) Daniel is innocent.

Keywords: allergic reactions to amoxicillin, antibiotic, bacterial infection**,** blunt trauma**,** brain edema, cardiopulmonary resuscitation, coronal suture, Daniel Robert Childs, epinephrine, false accusation, intracranial bleeding, metabolic acidosis, rib fracture, protein deficiency, Roman Pitts, skull fracture, subarachnoid bleeding, vitamin K deficiency.

1. Summary of the case and findings

Roman Pitts is a 18-month-old black male from Texas. He suffered from cardiac arrest on May 26, 1988 after receiving his third dose of amoxicillin, while at home with his stepfather, Daniel Robert Childs Jr. Daniel performed cardiopulmonary resuscitation (CPR) and called 911.

The paramedics brought Roman to Northeast Baptist Memorial Hospital (NBMH). Roman was in full cardiac arrest and he was resuscitated successfully. He was intubated and given a total of 0.8 mg epinephrine by endotracheal and IV routes.

The paramedics and the physicians at the ER examined Roman and they did not observe any evidence of injury caused by trauma on his head or the rest of his body. His skull X-ray did not show any bone fracture. His chest X-ray showed his lungs were expanded and clear.

Blood analysis revealed that Roman had a blood pH of 6.82, a blood glucose level of 182 mg/dL, and a white blood cell count of 20.3 x 10^3/μL. Roman suffered from severe metabolic acidosis and infection. In addition, his hematology values indicate that he was anemic.

Roman was transported to Southwest Texas Methodist Hospital (STMH) after staying two hours and 20 minutes at NBMH. The X-ray and CT exams of his head performed at STMH did not reveal any skull fracture. Blood and urine analyses revealed that he suffered from liver and kidney damage and a bacterial infection.

Chest X-rays showed four healed rib fractures and one acute rib fracture on the left side. They also showed fluid in the left lung and the left side of chest. Roman was treated with sodium bicarbonate, antibiotics, IV fluid, and other medications. He died on May 30th.

Dr. Robert C. Bux, performed the autopsy in the County of Bexar on May 31st (Case # 763-88). Prior to autopsy, a blood sample was taken from Roman and tested for alcohol and drugs and revealed negative results. Bux's main findings include separation of the coronal suture in Roman's skull; subarachnoid hemorrhage; brain edema; five healing and one acute rib fractures at the left side of the chest.

Bux alleged that Roman died as a result of blunt trauma to the head. Dr. Martha Morse, who treated Roman at Methodist Hospital, also alleged that Roman's injuries and death were caused by trauma. Daniel was accused of killing Roman and was indicted by Grand Jury in the County of Bexar, Texas on September 14, 1988 (88-CR-4368 and 94-CR-5160). He was put on trial and convicted of killing Roman. He was sentenced to life in prison.

Daniel and his mother contacted me and requested that I evaluate the medical evidence in Roman's case to find the likely causes that led to Roman's illness and death. I am a toxicologist and pathologist with over 20 years experience in these fields. I have published over 40 articles in medical and scientific journals.

In addition, I have evaluated many cases of children who died suddenly from unexplained causes and I was able to explain the causes of death using differential diagnosis. I have also evaluated cases of children and adults who suffered from acute and/or chronic illnesses and I was able to identify the

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causes of their illnesses using differential diagnosis. I have served as an expert witness in many medical-legal cases involving children and adults.

In Roman's case, I reviewed the following documents and the pertinent medical articles cited in this report: 1) Roman's medical records obtained from the paramedics, Baptist Memorial Hospital, and Methodist Hospital cited in this report; 2) the autopsy report; 3) the case history obtained from Daniel covering Roman's health and medications used prior to his cardiac arrest; 4) Daniel's trial transcripts.

I performed differential diagnosis to evaluate the medical evidence, relevant documents and articles cited in this report. Approximately 200 hours were required to evaluate the medical evidence, perform an analysis, and write this report. My findings in this case include:

1) Roman suffered from a bacterial infection as indicated by his elevated blood neutrophils count on May 26th. His segmented and band neutrophil counts were more than twice the upper normal levels. His white blood cell count returned to normal after receiving antibiotic treatment in the hospital.

In addition, Roman had a high serum uric acid level of 13.1 mg/dL that indicates a problem in the clearance of uric acid due to kidney damage. His protein level in urine was high and a moderate amount of bacteria was observed in urine. Roman lost more than five pounds and he had more than a 50% reduction in his thymus weight (Sections 2-5).

2) Roman suffered from cardiac and respiratory arrest on May 26th as a result of an allergic reaction to amoxicillin. In addition, he developed pulmonary edema and fluid in the chest and abdominal cavities, and liver damage as a result of an allergic reaction to amoxicillin. Amoxicillin has been known to cause Type I, II, III and IV allergic reactions and liver damage in children and adults. The clinical observations, biomarkers, and medical studies that indicate Roman died as a result of an allergic reaction to amoxicillin are described in Section 6 of this report.

3) The likely causes of Roman's subarachnoid bleeding are the high dose of epinephrine given in the hospital, liver injury, infection, and vitamin K deficiency. He was given a total of 0.8 mg of epinephrine endotracheally and intravenously on May 26th that raised his heart rate from 0 to 142/min. Intracranial bleeding (intracerebral, subdural and/or subarachnoid hemorrhage) was reported as one of the serious adverse reactions of epinephrine. Bleeding occurred, even when epinephrine was given to individuals at a low dosage level of 0.05 mg subcutaneously, which is equal to 6% of the epinephrine given to Roman in the emergency room.

Furthermore, Roman suffered from severe liver injury as indicated by the high levels of serum liver enzymes, which led to reduction in the synthesis of clotting factors. His serum alanine aminotransferase and aspartate transaminase levels were 14 and 9 times higher than the average normal values, respectively. His alkaline phosphatase and lactic dehydrogenase (LDH) levels in serum were 4 times higher than the average levels. In addition, reduction in food intake and the treatment with antibiotics led to vitamin K deficiency (Section 7).

4) Roman's brain edema was induced by anoxia, treatment with high doses of sodium bicarbonate, and metabolic acidosis. Roman was in full cardiac arrest for more than 40 minutes. His blood pH following admission in the hospital was 6.8. He was treated with high doses of sodium bicarbonate that raised his blood pH to 7.53 (metabolic alkalosis).

5) The likely cause of the separation of the coronal suture observed in Roman's case is the increased intracranial pressure resulted from bleeding and edema. The separation of the coronal suture was not observed on the X-ray or the CT scan of his head performed after admission on May 26th or the X-ray of his head taken on May 27th (Section 8).

6) The likely causes of Roman's healing rib fractures are vitamin K and protein deficiency. CPR is the likely cause for the acute lateral rib fracture of the left 6th.
Daniel, his neighbor, and the paramedics performed CPR on Roman for more than 40 minutes. CPR has caused rib fractures in children and adults.

For example, Dolinak evaluated the incidence of CPR-related rib fractures in a series of 70 consecutive autopsies in infants ranging in age from 2 weeks to 8 months with no history or indications of injury. Fractures of the anterolateral aspects of the ribs were discovered in 8 (11%) of the 70 cases. In 7 of the 8 cases, multiple ribs were fractured (ranging up to 10 rib fractures), and in 5 of these cases, the rib fractures were bilateral. Furthermore, Black *et al*. reviewed the autopsy records of 499 individuals (343 males, 156 females) who received CPR prior to death. Rib fractures were found in 29% (Section 9).

7) Drs. Bux and Morse's allegations that Roman's injuries and death were caused by trauma are not supported by the medical data and studies described in this report. Physical examinations, X-rays and CT scan of the head conducted during the six days prior to autopsy did not reveal any evidence of trauma to Roman's head or the rest of his body.

It seems Bux and Morse that did not perform differential diagnosis to consider the roles of many factors and agents involved in causing injuries and death in this case. These include an allergic reaction to amoxicillin, a bacterial infection, adverse reaction to epinephrine and sodium bicarbonate, liver and kidney damage, vitamin K and protein deficiency, and CPR.

8) My review of the medical evidence in this case and the testimonies of the state's expert witnesses reveal that Daniel was convicted based on a false theory and that he is innocent.

2. Review of Roman's medical history prior to his hospitalization on May 26, 1988

Roman Pitts is a 18-month-old black male from Texas. He was born on December 2, 1986. His birth weight was 7 pounds and 8 ounces (3.4 kg). The pregnancy was complicated by gestational diabetes.

Roman suffered from cardiac arrest on May 26, 1988 and he died four days later in the hospital. Daniel Robert Childs, Jr. (Roman's stepfather) stated that Roman's health was good until

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15 days prior to his hospitalization on May 26th. He became irritable and cried a lot. His parents thought that he was teething and his mother treated him with oral gel applied on the gums [1].

Roman suffered from an upper respiratory infection during the five days prior to his cardiac arrest on May 26, 1988. He did not eat well and his mother stated that he lost a significant amount of weight (5-10 lbs). He was treated with Tylenol.

On May 25th, Roman appeared very lethargic and ate a small amount of food. Daniel and Roman's mother took Roman to the city clinic. A pediatrician examined Roman and his examination revealed that Roman had significant congestion of the chest, breathing problem, halitosis (foul breath), and a fever. He believed that Roman had an obstruction of the nasal passage as a result of a foreign body.

The pediatrician prescribed two medications to treat Roman's infection and the congestion in his chest, one of them is an antibiotic. Roman was also given Tylenol for his fever. The information that I collected from Daniel and the records indicat that Roman was given amoxicillin in liquid form [1-6].

Roman was given the first dose of amoxicillin (one teaspoon) at 1800 on May 25th. Daniel gave Roman the second dose of amoxicillin (5 mL) at about 1030 on May 26th. Daniel believes that his wife gave Roman a third dose of dose of antibiotic between 1300 and 1400 on May 26th [5]. A teaspoonful of amoxicillin liquid (5 mL) contains 150-250 mg of amoxicillin [7].

Roman was sitting on the sofa at home while Daniel was in the kitchen preparing a dinner. Daniel heard Roman was making an unusual sound and then began to gasp for breath, raised his arms and clenched his fists. Daniel rushed to Roman's side and began to shake him.

Roman went limp and Daniel began cardiopulmonary resuscitation (CPR). Then he stopped and ran to get help from his neighbor. He was gone for a minute and when he returned, he restarted the attempts at CPR. His neighbor also performed CPR. Daniel stated that when he tried to do CPR, large amounts of mucus came out of Roman's nose.

The Emergency Service (EMS) was called at 1720 on May 26, 1988 and arrived at the scene at 1727. The EMS found Roman unresponsive and without respiration and pulse, and Daniel's neighbor performing CPR. The EMS performed CPR, placed a bag mask on Roman's face, and administered oxygen at 10-15 L/min.

The EMS transported Roman by ambulance to Northeast Baptist Emergency room and arrived at 1740. On arrival, Roman was intubated. No injuries or abnormalities on Roman's head or the rest of his body were observed by the EMS [8].

3. Clinical tests performed at Baptist Memorial Hospital and treatment given

The EMS brought Roman to Northeast Baptist Memorial Hospital (NBMH) at about 1740 on May 26th. Roman was in full cardiac arrest and he was resuscitated successfully. He was intubated and given a total of 0.8 mg epinephrine by endotracheal and IV routes. Then, he was transported to Southwest Texas Methodist Hospital at 2000 on May 26th [2].

Blood analysis revealed that Roman had a blood pH of 6.82, a blood glucose level of 182 mg/dL, and a white blood cell count of 20.3 x 10^3/μL. He suffered from severe metabolic acidosis and infection. In addition, his hematology values indicate that he was anemic.

The paramedics and the physicians at the ER examined Roman and they did not observe any evidence of injury caused by trauma on his head or the rest of his body. His skull and chest X-rays did not show any bone fracture. His chest X-ray showed his lungs were expanded and clear.

3.1 Resuscitation effort and epinephrine dose given

The EMS brought Roman to Northeast Baptist Memorial Hospital (NBMH) in full cardiac arrest. He was intubated by the ER physician and given 0.2 mg epinephrine endotracheally at 1741. Furthermore, he was given three more injections of epinephrine (0.2 mg/injection) IV between 1747 and 1752 (Table 1). Roman received a total of 0.8 mg and his weight was 10.2 kg (22.4 lb).

Roman's first measured heart rate was 40's beats/minute at 1741. His heart rate was raised to 132 beats/minute by 1815. His blood pressure was 86/46 mm Hg at 1810 (Table 2). Roman's temperature was 95.6 °F rectally at 1805 [6].

Table 1. Epinephrine doses given to Roman on May 26, 1988

Time	Epinephrine dose and route
1741	0.2 mg endotracheal
1747	0.2 mg IV
1751	0.2 mg IV
1752	0.2 mg IV

Table 2. Roman's heart rate and blood pressure measured on May 26th at BSA

Time	Heart rate (beats/minute)	Blood pressure (mm Hg)*
1741	40's	-
1754	154	-
1801	162	-
1810	144	86/46
1825	134	102/44
1840	136	96/40
1905	148	96/30
1930	142	86/52
Normal range	100-130	

* -: not measured

3.2 Indicators of metabolic and respiratory acidosis and treatment given

Roman's blood analysis performed at 1800 showed that he was suffering from severe metabolic and respiratory acidosis (Table 3). His blood pH was 6.82 and he was treated with sodium bicarbonate 5 mEq IV that raised his blood pH to 7.17. He was also given 5 mEq sodium bicarbonate IV at 1902.

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Table 3. Indicators of acidosis measured on May 26th at BSA

Measurements	Values at 1800	Values at 1839	Reference range
PH	6.82	7.17	7.34-7.45
PCO_2 (mmHg)	50.7	27.0	33-44
HCO_3 (mEq/L)	8.0	10.0	21-28
Base difference (mEq/L)	-28.0	-17.7	-3-3

3.3 Roman's chest and skull X-rays did not show bone fracture

Roman's first chest X-ray performed at 1806 showed both lungs were expanded and clear. It also showed left pleural effusion. No rib fracture was observed. Roman's head X-ray showed his skull was intact. It also showed the sella, petrous ridges and soft tissues of posterior nasopharynx were normal.

3.4 Evidence of bacterial infection

Roman's blood analysis performed on May 26th showed that he had high white neutrophils count. His segmented and band neutrophil counts were more than twice the upper normal levels (Table 4). These data indicate that Roman had a bacterial infection.

Table 4. Roman white blood cell counts on May 26th

Measurements	1843	1910	Reference range x 10^3/µL
WBC	20.3	19.4	3.0-17.5
Neutrophils	15.2	15.2	1.9-8.0
Seg. neutrophills	12.6	10.2	1.5-7.5
Bands neutrophills	2.0	1.8	0-1
Lymphocytes	2.6	3.7	0.9-5.2
Monocytes	1.0	0.4	0-0.8

3.5 Indicators of anemia

Roman's blood analysis performed at about one hour after admission showed that he suffered from anemia. His hematocrit and hemoglobin values were 81% and 84% of the low normal values, respectively (Table 5). His anemia resulted from not eating well as reported by his parents.

Table 5. Roman hematology values on May 26th

Measurements	1843	1910	Reference range
RBC x 10^6/µL	3.57	3.89	4.7-6.1
Hemoglobin (g/dL)	10.1	10.3	12-18
HCT %	29.7	30.9	37-50
MCV (fl)	80.9	79.5	80-98
MCH (pg/cell)	27.2	26.5	28-33
MCHC (g/dL)	33.7	33.3	32-36
RDW	15.1	15.3	1.5-15
Platelet x 1000/µL	399	382	130-400

3.6 Evidence of hyperglycemia and hypocapnia

Roman's serum analysis at 1910 showed that he had an elevated glucose value of 184 mg/dL and a very low CO_2 level (Table 6). His calcium level was slightly below normal.

Table 6. Roman's serum values on May 26th

Measurements	1910	Reference range
Sodium (mEq/L)	138	136-145
K^+ (mEq/L)	4.1	2.7-3.9
Cl^- (mEq/L)	105	97-107
CO_2 (mEq/L)	7	21-30
BUN (mg/dL)	14	10-20
Glucose (mg/dL)	184	75-115
Calcium (mg/dL)	8.3	9-10.5

4. Clinical tests performed at Methodist Hospital and treatment given

Roman was transported to Southwest Texas Methodist Hospital (STMH) after staying two hours and 20 minutes at Baptist Memorial Hospital. He arrived at the emergency room at 2005 on May 26th. The X-ray and CT exams of his head performed at STMH did not reveal any skull fracture. Blood and urine analyses revealed that Roman suffered from liver and kidney damage and a bacterial infection.

Chest X-rays showed four healed rib fractures and one acute rib fracture on the left side. They also showed fluid in the left lung and the left side of chest. Roman was treated with sodium bicarbonate, antibiotics, IV fluid, and other medications. He died on May 30th.

The results of the clinical exams and tests performed at STMH and treatment givens are described below.

4.1 Physical exam

Dr. Martha Morse examined Roman at 2105 on May 26th and her examination revealed that he had an occasional spontaneous respiration. His heart rate and blood pressure were 125 beats/min and 115/71 mm Hg, respectively. His temperature was 92.7°F rectally. His weight was 10.2 kg.

Roman's sclerae and conjunctivae were clear. His pupils were fixed and dilated. His fundi showed sharp discs. His nose was normal. Her examination did not reveal any sign of injury caused by trauma on Roman's head. She noticed only a blue area in the submandibular region that resulted from the EMS bagging of the child.

Examination of the chest revealed decreased breath sounds on the left side with some course rhonchi (sound caused by secretion in bronchial airways). His heart had a regular rate and rhythm without murmur. His abdomen was soft and there was no organomegaly. No bowel sounds were heard.

His genitalia were those of a normal, uncircumcised male. His extremities revealed 2+ pulses. His neurological exam was remarkable in that he was areflexic. He had no corneal reflexes, no doll's eyes, and no response to pain. The examination of Roman's body did not reveal any sign of injury caused by trauma.

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4.2 Roman's metabolic acidosis continued until May 27th

Roman was treated with high doses of sodium bicarbonate IV on May 26th at two hospitals. However, his blood pH stayed below normal at 2305 due to the severity of his acidosis (Table 7). He was treated again with high doses of sodium bicarbonate that raised his pH to 7.53 (metabolic alkalosis).

Table 7. Roman's blood pH, PCO_2, and HCO_3 levels measured on May 26-30.

Date	Time	PH	PCO_2	HCO_3
26th	2033	7.28	28.8	13.7
	2350	7.30	33	17
27th	0550	7.53	19.8	16.4
	0900	7.50	27	19.9
28th	0430	7.40	29	19
	0800	7.45	26.2	18.5
	1230	7.43	29.7	19.7
30th	0830	7.44	26.7	18.3
Normal range		7.34-7.45	33-44	21-28

4.3 Evidence of liver damage

Roman had elevated serum liver enzymes and he suffered from liver damage. His alanine aminotransferase (Alt) and aspartate transaminase (AST) levels were 14 and 9 times higher than normal levels, respectively. His alkaline phosphatase (ALP) and lactic dehydrogenase (LDH) levels were 4 times higher than normal (Table 8). It is possible that some of the LDH was released from damaged cardiac muscle.

Table 8. Roman's serum enzymes levels

Enzymes[1]	05/26 at 2059	05/28 at 0609	05/30 at 0629	Reference Range (U/L)
ALP	580	374	437	50-136
LDH	800	375	338	100-190
AST	346	55	46	7-40
ALT	501	265	111	3-36
GGT	147	98	86	5-85

[1]ALP: alkaline phosphatase; LDH: lactic dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase.

4.4 Evidence of kidney damage

Roman's serum analysis showed that he had a high uric acid level of 13.1 mg/dL, which indicates a problem in the clearance of uric acid due to kidney damage (Table 9). The urine analysis performed on May 27th indicates that he suffered from kidney damage and a bacterial infection. The protein level in his urine was high. A moderate amount of bacteria was also observed in his urine (Table 10).

Table 9. Roman's serum level of uric acid

Date	Value (mg/dL)
05/26	13.1
05/28	7.7
05/30	4.1
Normal range	2.2-9.0

Table 10. Roman's urine analysis performed at 1230 on May 27th

Measurements	Values	Reference range
pH	5.0	5.0-6.0
Specific gravity (g/mL)	1.030	1.010-1.025
Glucose	Negative	Negative
Bilirubin	Negative	Negative
Protein (mg/dL)	30	0-15
WBC/HPF	2-4	0-2
RBC/HPF	2-4	0-5
Urate crystal	+ 4	
Bacteria	Moderate	

4.5 The results of serum analysis and their significance

Roman's serum analyses performed on May 26-30 indicate that his protein, albumin, creatinine and calcium levels were below than the normal range (Table 11). His average creatinine value was 0.2 mg/dL, which is 40% of low normal. These data indicate that Roman had low food intake and low muscle mass.

Table 11. Results of Roman' serum analyses

Measurements	5/26/1988 (2059)	5/28 0609	5/30 0629	Reference range
Sodium	139	155	135	135-153 mmol/L
Potassium	3.7	4.3	3.9	3.5-5.3 mmol/L
Chloride	105	123	106	95-110 mmol/L
Carbon dioxide	14	20	18	24-31 mmol/L
Glucose	178	140	106	70-110 mg/dL
Urea nitrogen	11	4	4	5-25 mg/dL
Creatinine	0.4	0.2	0.1	0.5-1.4 mg/dL
Total bilirubin	1.0	0.4	0.3	0.0-1.0 mg/dL
Calcium	7.7	8.8	8.3	8.7-10.2 mg/dL
Phosphorus	4.2	4.1	4.1	2.5-4.9 mg/dL
Cholestrol	164	135	120	120-239 mg/dL
Total protein	6.0	5.3	4.9	6.0-8.0 g/dL
Albumin	3.5	3.0	2.5	3.6-4.9 g/dL

4.6 X-ray and CT scan exam of Roman's head did not show bone fracture

Roman's X-ray and the CT scan of the head taken on May 26th did not show any skull fracture. Also, the X-ray exam of the head performed on May 27th did not reveal any skull fracture. The CT san of May 26th showed edema of the brain (Table 12).

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Table 12. Findings on Roman's X-ray and CT scan of the head taken within 24 hours following admission

Date & time	Test type	Findings
May 26th at 1806	X-ray-head	• Showed skull was intact and the sella, petrous ridges and soft tissues of posterior nasopharynx were normal.
May 26th at 2057	CT-head	• The ventricles were slit-like but midline. • No shift of the ventricular system was observed. • No suspicious intra-axial or extra-axial absorption densities were found. • No skull fracture was observed.
May 27th at 1624	X-ray-head	• Bone structures were normal.

4.7 Changes observed in Roman's lungs

Roman's chest X-ray taken at 1806 on May 26th showed both lungs were clear. However, the chest X-ray taken at 2059 on May 26th revealed near complete opacification of the left lung. Ultrasound exam also indicated the presence of fluid in the left chest. Chest X-rays and ultrasound exam taken on May 27th-29th showed that the amount of the fluid in the chest was increasing with time (Table 13).

A flexible bronchoscopy was performed on May 27th and showed no foreign body or abnormality present in Roman's airways. In this procedure, the left and the right main stems were entered and all orifices were visualized and appeared patent. However, some white mucus discharge was observed in the right stem.

4.8 Rib fractures observed and their healing stages

Four healed rib fractures of left 6th, 7th, 8th, and 9th were identified on the chest X-rays of May 27th. The absence of any definite callus formation on these fractures indicate that these fractures were probably less than 10 days old. In addition, acute fracture of the left 6th rib (anterolaterally) was identified by the X-ray and radionuclide bone scan performed on May 27th. The radiologist indicated that the acute rib fracture might be the result of resuscitative efforts.

4.9 Results of spinal fluid analysis and electroencephalogram

A spinal tap was performed at 2256 on May 26th and spinal fluid was collected and analyzed. It revealed the presence of blood, which indicates bleeding in the subarachnoid space. The electroencephalogram (EEG) of the brain performed on May 27th at 0550 revealed no electrocerebral activity.

Table 13. Changes observed in Roman's lungs during his hospitalization

Date & time	Method	Findings
May 26th at 1806	Chest X-ray	• Showed both lungs were well expanded and clear. • Pleural effusion may be present at the left side.
May 26th at 2059	Chest X-ray	• Showed near complete opacification of the left hemithorax with a slight mediastinal shift from right to left. • Right lung was clear.
May 27th at 0126	Chest X-ray	• Almost complete opacification of the left lung. • Right lung well aerated.
May 27th at 0848	Chest X-ray	• Continued opacification of the left hemithorax compatible with atelectasis of the left lung. • There was some pleural fluid and/or infiltrate. • Right lung remained clear.
May 27th At 0916	Ultra-sound	• Revealed a large fluid collection in the left side of the chest.
May 28th At 0550	Chest X-ray	• Left lung was completely opaque. • Right lung well aerated.
May 29th at 0215	Chest X-ray	• Interval partial re-expansion of the left lower lung field with persistent consolidation of the left upper field. • Right lung remained clear.

4.10 Treatments given

Roman was admitted to the hospital on May 6th and died on May 30th. He was maintained on a ventilator with total life support. He was treated with antibiotics, sodium bicarbonate, and IV fluid. He also developed diabetes insipidus and was treated with a synthetic antiduretic hormone (ADH) called DDAVP intranasally (Table 14). The EEG taken on May 30 also showed no electrocerebral activity. Roman was declared brain dead at 1047 on May 30th.

Table 14. Treatments given to Roman

Date	Treatments
05/26/1988	• Fluid D5 ½ NS at 25 cc/hr • 10 mg NaHCO3 IV • Maalox 20 cc q 3 hr • Fluid D5 ½ NS + KCl at 22 cc/ hr
05/27-30/1988	• Cefalexin 350 mg IV each 8hr • Decadon 2 mg IV each 6 hr • DS1/4 + 2 mEq KCL/100 cc • DDAVP 0.05 ml intranasally each 6-8 hr. • NS 200 cc over 2 hrs

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5. Autopsy findings in case of Roman Pitts

Roman was admitted to the hospital on May 26th and died on May 30th. Dr. Robert C. Bux, performed the autopsy in the County of Bexar on May 31st (Case # 763-88). Prior to autopsy, a blood sample was taken and tested for alcohol and drugs and revealed negative results [3].

Bux's main findings include separation of the coronal suture in Roman's skull; subarachnoid hemorrhage; brain edema; five healing and one acute rib fractures; and minor contusions on the scalp and the back. He alleged that Roman died as a result of blunt trauma to the head. His findings are described in Section 5.1-5.6 below.

My review of the medical evidence reveals that Roman's health problems and death were caused by adverse reactions to medications, a bacterial infection, and metabolic problems. Bux did not perform differential diagnosis to consider the following specific medical evidence:

1) Roman suffered from cardiac and respiratory arrest due to an allergic reaction to amoxicillin given to him on May 25th and 26th to treat a bacterial infection (Section 6).

2) Roman's subarachnoid hemorrhage was caused by the high doses of epinephrine given to him in the hospital, liver damage, and vitamin K deficiency (Section 7).

3) Roman's brain edema was induced by anoxia, treatment with high doses of sodium bicarbonate, and metabolic acidosis (Section 8).

4) The separation of the coronal suture in Roman's skull resulted from the increased intracranial pressure due to edema and bleeding (Section 8).

5) The fractures of the healing ribs were caused by metabolic problems and vitamin K deficiency. The likely cause of the acute rib fracture is CPR. The medical data that support these conclusions are presented in Section 9 of this report.

5.1 External examination, body measurements, and description of minor bruises

Dr. Bux described Roman's body as that of a well developed and nourished16 month-old black toddler. His weight and length were 24 lbs (10.91 kg) and 32.5 inches (81.3 cm)..

The evidence presented in this report shows Roman was born on December 2, 1986 and died on May 31, 1988. His age was about 18 months instead of 16 months. His mother stated that Roman was sick for five days and he had lost 5-10 pounds. Blood and urine analyses indicated that he had a bacterial infection and suffered from liver and kidney damage (Section 4).

Bux reported the presence of two small contusions on Roman's head. In addition, the reflection of the scalp revealed the presence of bleeding of various sizes in four areas (Table 15). Bux did not give information about the age of the contusions and the bleeding. The paramedics and the physicians who examined Roman in two hospitals did not report the presence of contusions on Roman's head.

Furthermore, Bux's examination of Roman's back revealed the presence of a small area (1 cm in diameter) of subcutaneous hemorrhage on the left side, near the midline. He did not give information about the age of the bleeding. The paramedics and the physicians who treated Roman for four days in the hospital did not report any sign of trauma on Roman's back.

Table 15. Lesions observed outside Roman's skull at autopsy

Area	Lesions
Skin	• A 0.5 cm in diameter area of faint contusion present on the left upper forehead, near the hairline. Lateral and slightly inferior to this was a 1 cm in diameter area of contusion.
Under the scalp	• An area of scalp hemorrhage (11 x 5 cm) observed in the right temporoparietal region of the scalp, above the level of the right ear attachment. • A scalp hemorrhage (1 cm in diameter) found in the left temporal region, near the crown. Just posterior to this a 0.5 cm in diameter scalp hemorrhage was also found. • A 4 x 3 cm area of scalp hemorrhage observed in the left temporoparietal region directly above the left ear attachment.

5.2 Examination of the skull

Bux examined Roman's skull and observed the separation of the coronal suture (bilaterally and along the left side) with a small area of surrounding hemorrhage. His microscopic examination of H & E stained section of the suture revealed the presence of acute hemorrhage in the intra-osseous spaces adjacent to the suture.

The coronal suture is a dense fibrous connective tissue joint that separates the frontal and parietal bones of the skull**.** The separation of the suture was not observed on the X-ray and the CT scan of the head performed after admission on May 26th and the X-ray of the head taken on May 27th. The increased intracranial pressure due to bleeding and edema can explain the separation of the coronal suture.

5.3 Examination of the brain and surrounding membranes

Bux observed diffuse subarachnoid hemorrhage along all aspects of the cerebral hemispheres bilaterally. Roman was injected with 0.8 mg epinephrine following admission on May 26th. Intracranial (intracerebral, subdural and/or subarachnoid hemorrhage) bleeding has been reported in some children and adults treated with epinephrine [9-14].

Bux also found severe diffuse cerebral edema with central herniation and widespread encephalomalacia. On cross section, there was no evidence of infection or tumor. The brain weight was 1200 g.

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On May 26th, Roman was stayed without a pulse for more than 20 minutes. Roman's blood pH was 6.8 following admission. He was treated with high doses of sodium bicarbonate that raised his pH to 7.53. Anoxia and high doses of sodium bicarbonate cause brain edema [14, 15].

5.4 Fractured ribs

Bux found acute fracture of the left anterior lateral 6th rib with surrounding hemorrhage. In addition, he observed healing rib fractures involving the left 5th through the 9th ribs in the posterior aspect of the left chest rib cage, less than ½ inch from the posterior spine articulation. Bux' microscopic examination of H & E stained section of the posterior 6th left rib revealed abundant callous formation and no other abnormalities were seen.

Bux alleged that these fractures were caused by trauma. However, his external examination of the thorax region did not reveal any evidence of injury caused by trauma. In addition, the paramedics and the physicians who examined Roman in two hospitals did not report any sign of trauma on Roman's chest.

5.5 Examination of the chest cavity, heart, lungs, and thymus

Bux's examination of the chest cavity and organs revealed the following:

1) There was a significant amount of serous fluid present in the right chest cavity (20 mL), the left chest cavity (30 mL), and the pericardial sac (10 mL). No evidence of inflammation or infection was observed. Bux did not provide a cause for the accumulation of the fluid in these cavities. The likely cause for the accumulation of clear fluid in these cavities is allergic reaction to amoxicillin.

2) The epicardial and endocardial surfaces were smooth and glistening. The myocardium, the cardiac valves and great vessels appeared normal. The heart weighed 68 g.

3) The capsule of the thymus was smooth and glistening. On section, the thymus appeared unremarkable grossly. The weight of the thymus was 14 g. The expected thymus weight in a child similar to Roman's age is between 30-50 g. Bux did not examine H & E stained section of thymus microscopically to check for atrophy.

4) The weights of the right and the left lungs were 102 g and 68 g, respectively. The pleural surfaces were smooth and glistening and had a purple red appearance. On cross section, the parenchyma appeared congested. There were no pulmonary emboli.

5.6 Examination of the abdominal and the pelvic regions

Bux's external and internal examination of Roman's abdominal and pelvic regions did not reveal any evidence of trauma. He found 20 mL of serous fluid in the abdominal cavity. The likely cause for the accumulation of this fluid is allergic reaction to amoxicillin, which also caused the accumulation of significant amount of clear fluid in the chest cavity.

Bux stated that he examined the following organs grossly and they appeared normal. These include: esophagus; stomach; small and large bowel and appendix; pancreas; adrenal glands; spleen; kidneys; and urinary bladder. The right and the left kidneys weighed 42 g and 40 g, respectively. The weight of the spleen was 50 g.

Bux reported that Roman's liver was normal but congested. The weight of the liver was 500 g. However, Bux did not examine H & E stained sections of the liver and the kidney microscopically. The clinical evidence presented in Section 4 showed that Roman suffered from liver and kidney damage. Roman's serum liver enzymes and uric acid were highly elevated on May 27th. A significant amount of protein and bacteria were also present in Roman's urine.

6. The likely cause of Roman's cardiac and respiratory arrest

Roman suffered from cardiac and respiratory arrest at about 1-2 hours following his third dose of amoxicillin on May 26th. In addition, he developed pulmonary edema and fluid in the chest and abdominal cavities as a result of an allergic reaction to amoxicillin.

Roman's blood analysis indicated that he had liver damage. Amoxicillin has been known to cause type I, II, III and IV allergic reactions and liver damage in children and adults [7, 16-38]. Below are clinical observations, biomarkers, and medical studies that indicate Roman died as a result of an allergic reaction to amoxicillin.

6.1 Laryngeal spasm and increased bronchial secretions

Daniel stated that he heard Roman was making an unusual sound and then began to gasp for breath, raise his arms, and clenche his fists. Daniel also stated that when he tried to do cardiopulmonary resuscitation (CPR), large amounts of mucus came out of Roman's nose. These signs indicate that Roman was suffering from laryngeal spasm and the spasm of the respiratory muscles. Allergic reactions to amoxicillin induce the release of histamine and other bioactive amines from tissue. Histamine causes laryngeal spasm, bronchial construction, and increases bronchial secretions [39].

6.2 Pulmonary edema and leakage of fluid outside the blood vessels

Progressive development of pulmonary edema and accumulation of fluid in the chest was observed in Roman's case. Roman's chest X-ray performed at 1806 on May 26th showed both lungs were expanded and clear. Then, his chest X-ray taken at 2059 on May 26th revealed near complete opacification of the left lung. In addition, the chest X-rays taken on May 27-30 showed the amount of the fluid in Roman's left lung and chest was increasing with time.

Furthermore, at autopsy, the medical examiner collected total of 50 mL, 10 mL, and 20 mL of clear fluid from Roman's chest cavity, the pericardial sac, and the abdominal cavity, respectively. No adhesion or inflammation was observed in the pleural and peritoneal cavities and pericardial sac. These observations indicate that the pulmonary edema and the accumula-

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tion of fluid in these cavities resulted from cardiovascular problems.

Allergic reactions to amoxicillin induce the release of histamine and other vasoactive mediators from the granules stored in mast cells and basophils. These mediators exert immediate biological effects following their release. Histamine induces constriction of vascular and non-vascular smooth muscle, causes microvascular dilation, and increases the permeability of venules, which results in the leakage of fluid outside the blood vessels. In the lung, histamine is responsible for the early manifestations of immediate hypersensitivity, including bronchospasm, vascular congestion, and edema [34-36, 39].

Roman's symptoms and lesions that developed following receiving amoxicillin are similar to those reported in Eliza Jane's case who also died as a result of an allergic reaction to amoxicillin. Eliza Jane developed cardiac arrest shortly following receiving her third dose of amoxicillin which was prescribed to treat an ear infection [16]. Table 16 contains a list of symptoms and lesions observed in Roman and Eliza Jane's case following their treatment with amoxicillin.

Table 16. Symptoms and lesions developed in Roman and Eliza Jane's case following their treatment with amoxicillin[1]

Observations and biomarkers	Roman	Eliza Jane
Number of amoxicillin doses give prior to cardiac arrest	3	3
Progressive development of pulmonary edema	+	+
Accumulation of clear fluid in the chest cavity	+	+
Accumulation of clear fluid in the abdominal cavity	+	+
Total amount of fluid collected from the chest and abdominal cavities (mL)	80	80
Evidence of pneumonia	None	None
Evidence of liver injury	+	+
Evidence of inflammation and adhesion in the chest and abdominal cavities	None	None

[1] Roman and Eliza Jane's ages are 18 months and 3.5 years, respectively.

6.3 Liver injury

Roman's serum analysis performed following admission on May 26th revealed that his serum liver enzymes were elevated. His alanine aminotransferase (Alt) and aspartate transaminase (AST) levels were 14 and 9 times higher than the average normal value, respectively. His alkaline phosphatase (ALP) and lactic dehydrogenase (LDH) levels were 4 times higher than the average normal level (Table 8).

It has been known that amoxicillin causes serious allergic liver injury in children and adults [7, 16-20, 22-31, 37, 38]. Below are clinical studies that show amoxicillin and amoxicillin/clavulanic acid have caused hepatotoxicity in individuals treated for bacterial infections with these medications.

1) Gresser conducted a Medline search of case reports and reviews on amoxicillin-clavulanic acid induced adverse effects. Amoxicillin-clavulanic acid has been associated with drug-induced cholestatic hepatitis in 208 reported individuals. Liver injury was classified according to laboratory parameters to be hepatocellular in 35 individuals, cholestatic in 24 individuals and mixed in 83 individuals [17].

2) Maggini *et al.* reviewed the medical records of 118 potential cases of acute liver injury. These cases were identified through the regional hospital information system in the Friuli-Venezia Giulia region of Italy. Overall, 12 cases of acute liver injury were identified. Three of these cases (25%) occurred in the amoxicillin exposure category and two (17%) among the amoxicillin/clavulanic acid category [18].

3) Larrey *et al.* reported 15 cases of hepatitis related to a combination of amoxicillin-clavulanic acid intake. Histological examination of the liver performed in 7 individuals showed centri- or panlobular cholestasis in all cases. Serum aminotransferase activities were increased in all individuals and were generally 2 to 10 times the upper limit of normal. Serum alkaline phosphatase activity was considerably increased, from two to seven times the upper limit of normal [19].

4) Garcia Rodriguez *et al.* conducted a retrospective study in the United Kingdom to estimate the risk of acute liver injury associated with use of amoxicillin and amoxicillin-clavulanic acid. The user's ages were between 10 and 79 years and were followed up from 1991 through 1992. They found 14 cases of acute liver injury among users of amoxicillin alone and 21 cases among users of amoxicillin-clavulanic acid [20].

5) Reddy *et al.* reviewed 18 cases of individuals who developed jaundice and hepatic dysfunction following their treatment with amoxicillin/clavulanate potassium. These cases revealed a predominantly cholestatic syndrome in 7 cases, a mixed hepatocellular-cholestatic picture in 6 cases, and a hepatocellular pattern in 4 cases. All cases had reversal of hepatic dysfunction upon cessation of the drug [37].

6) Mari *et al.* reported 9 individuals who developed hepatitis after receiving treatment with amoxicillin and clavulanic acid. Other causes of hepatitis were excluded [22].

7) Ryley *et al.* reported liver injuries in 5 individuals treated with amoxicillin/clavulanic acid. They developed cholestatic illness within 8 weeks of a course of amoxicillin/clavulanic acid. Hepatic histology revealed a distinctive focal destructive cholangiopathy in all individuals and granulomatous reaction in two. The clinical picture indicated a direct link between the illness and the medication. [23].

8) Hautekeete *et al.* reported 8 cases of liver injury related to amoxycillin/clavulanate. Liver biopsy performed in 7 individuals revealed the presence of injury to interlobular bile ducts. Lesions included irregularity of the nuclei, vacuolization of the cytoplasm, lymphocytic infiltration, destruction and endothelialization of the bile duct epithelium [24].

9) Bralet and Zafrani described the clinical and pathological findings of 5 cases of acute hepatitis due to amoxicillin/clavulanic acid intake. Liver biopsies revealed cholestasis in all cases. It was associated with varied degrees of interlobular bile duct injury in four cases [25].

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10) Stricker *et al.* reported 5 cases of individuals developed cholestatic hepatitis associated with the intake of amoxicillin and clavulanic acid. Biopsy in 2 individuals showed extensive cholestasis [26].

11) Chawla *et al.* reported a rapidly progressing liver disease with ductopenia and portal fibrosis in a 3 year-old boy treated with amoxicillin/clavulanic acid [27].

12) Habior *et al.* reported 2 cases with liver injury due to amoxicillin/clavulanic acid. Liver biopsy revealed mixed hepatocellular-cholestatic liver injury in both cases [28].

13) Barrio *et al.* reported two cases of acute hepatotoxicity after treatment with amoxicillin/clavulanic. Viral hepatitis serology and autoantibodies were negative. Biliary tree obstruction and other etiologies were excluded. Discontinuation of the drug resulted in favorable clinical improvement and normalization of liver tests [29].

7. The likely causes of Roman's intracranial bleeding

Roman died in the hospital four days following admission on May 26th and Dr. Bux conducted the autopsy on May 31st. He reported the presence of diffuse subarachnoid hemorrhage along all aspects of the cerebral hemispheres bilaterally. Bux alleged that the bleeding in the subarachnoid space was caused by trauma.

The medical evidence in this case indicates that the likely causes for the subarachnoid bleeding are the high dose of epinephrine given in the hospital, liver injury, infection, and vitamin K deficiency. It seems that Bux did not perform differential diagnosis in this case to consider the medical data and studies described below, and that his conclusions are medically invalid.

7.1 No evidence of trauma was observed in Roman's case

Physical examinations, X-rays and CT scan of the head conducted during the six days prior to autopsy did not reveal any evidence of trauma to Roman's head or the rest of his body. Roman was examined by a pediatrician and the paramedics on May 25th and May 26th, respectively and they did not observe any injury caused by trauma.

Furthermore, physicians and nurses who examined and treated Roman for four days in two hospitals did not report the presence of injuries induced by trauma. In addition, Roman's X-rays of the head taken on May 26th and 27th did not reveal bone fracture or any injury induced by trauma. Also, the CT scan of his head performed on May 26th did not show evidence of any skull fracture or injury caused by trauma.

7.2 High doses of epinephrine cause intracranial bleeding

Roman was brought to the hospital on May 26th with cardiac arrest. He was given a total of 0.8 mg of epinephrine endotracheally and intravenously, which raised his heart rate from 0 to 142/min. (Tables 1, 2). Intracranial bleeding (intracerebral, subdural and/or subarachnoid hemorrhage) has been reported as one of the serious adverse reactions of epinephrine [9, 11]. Bleeding occurred, even when epinephrine was given to individuals at a low dosage level of 0.05 mg subcutaneously, which is equal to 6% of the epinephrine given to Roman in the emergency room [9].

Furthermore, I reported intracranial bleeding in two children who received less doses of epinephrine at the emergency room than Roman [12, 14]. In addition, Horowitz *et al.* reported the development of fatal subarachnoid hemorrhage in an individual who suffered from allergic reaction and was treated with epinephrine subcutaneously [10].

7.3 Liver damage leads to reduction in the synthesis of clotting factors

Roman suffered from severe liver injury as indicated by the high levels of serum liver enzymes. On May 26th, his serum alanine aminotransferase and aspartate transaminase levels were 14 and 9 times higher than the average normal values, respectively. His alkaline phosphatase and lactic dehydrogenase (LDH) levels in serum were 4 times higher than the average normal level (Table 8).

The liver plays a central role in the clotting process. Injury and diseases of the liver are usually associated with coagulation disorders due to multiple processes. These include reducing the synthesis of clotting and inhibitor factors; decreasing the clearance of activated factors; producing quantitative and qualitative platelet defects; causing hyperfibrinolysis, and accelerating intravascular coagulation [40-46].

The extent of the coagulation abnormalities depends upon the degree of disturbed liver functions. The high levels of liver enzymes in serum observed in Roman's case indicate that he had significant liver injury. It is likely that his injury led to reduction in the vitamin K-dependent factors (prothrombin; factors VII, IX, and X; proteins C and S) [42].

7.4 Sepsis causes bleeding

Many clinical indicators showed Roman suffered from bacterial infection prior to his cardiac arrest on May 26th. These indications include: 1) A white blood cell count of 20.3 x 10^3/μL, neutrophil count of 15.2 x 10^3/μL and band neutrophil count of 2 x 10^3/μL (Table 4). His white blood cell count returned to normal (9.3 x 10^3/μL) following his treatment with antibiotic; 2) A kidney infection as indicated by his elevated serum uric acid level of 13.1 mg/dL and other parameters. His serum uric acid level returned to normal level (4.1 mg/dL) following his treatment with antibiotic (Table 9); 3) his thymus weight was 14 g and the expected thymus weight in a child similar to Roman's age is between 30-50 g.

Septicemia is frequently accompanied by changes in the plasmatic as well as cellular coagulation systems and by microclot formation. The activation of coagulation by endotoxin is mediated by synthesis of tissue factor by monocytes and endothelial cells.

Some microorganisms have specific properties which affect individual components of hemostasis and thus increase their virulence. Furthermore, thrombocytopenia, thrombocytopathy and endothelial cell damage caused by a direct effect of the toxic agent contribute to the bleeding diathesis [47, 48].

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The occurrence of a hemorrhagic diathesis and microthrombosis is best explained by the syndrome disseminated intravascular coagulation (DIC). Widespread intravascular coagulation and hemostatic defect are common in individuals with sepsis. The main cause of hypercoagulation state during sepsis seems to be the inhibition of fibrinolysis as a result of overproduction of plasminogen activator inhibitor-1 in later stages of the disease [47-51].

Levi *et al.* reviewed articles and published peer-reviewed abstracts on the mechanism of the initiation of disseminated intravascular coagulation DIC in sepsis. They found that significant coagulation activation was detected after the appearance of endotoxin in the circulation. This activation is preceded by an increase in the serum levels of various cytokines, such as tumor necrosis factor and interleukins. The activation of coagulation seems to be amplified by impaired function of the protein C-protein S inhibitory pathway. [52].

7.5 Vitamin K deficiency causes bleeding

Vitamin K controls the formation of coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor), and X (Stuart factor) in the liver. Other coagulation factors that depend on vitamin K are proteins C, S, and Z. Furthermore; two bone matrix proteins necessary for normal bone metabolism are vitamin K-dependent.

These vitamin K-dependent proteins contain the amino acid γ-carboxyglutamic acid and the carboxyl groups of the glutamic acid residues that provide the vitamin-K-dependent proteins with characteristic calcium and phospholipid binding properties. Vitamin K deficiency leads to the production of abnormal vitamin K-dependent factors, which lack gamma-carboxy glutamic acid residues in the NH2-terminal part of their molecules [42; 53-57].

In humans, the body does not synthesize the 1, 4 naphthoquinone nucleus of vitamin K and gets it from food. In addition, the bacteria in the intestinal tract synthesize vitamin K and can supply part of the vitamin K requirement. Significant reduction of food intake occurs in serious illness and treatment with high therapeutic doses of antibiotics for a significant time can lead to vitamin K deficiency and intracranial bleeding in children [53, 54, 59-62].

Roman suffered from bacterial infection and lost more than 5 pounds. His thymus weight was 14 g (expected weight for age is 30-50 g). The significant reduction in his thymus weight indicates that he was ill for a significant period of time. He was treated with antibiotics prior to his cardiac arrest and in the hospital. Serious illness, reduction in food intake, and treatment with antibiotics can lead to vitamin K deficiency and bleeding in children.

7.5.1. Relationship between thymus weight and infections

Roman had more than a 50% reduction in thymus weight. The following clinical studies show that significant reduction in the thymus weight indicates serious infection. Zhang reviewed thymuses from 621 autopsy cases. He found cases of infection with a course less than 5 days showed mild atrophy of the thymus and those cases with a longer course might show moderate or severe degree of atrophy. In 81% of the cases, the degree of thymus atrophy was in accordance with those of the other immune organs [63].

Furthermore, Kitonyi reviewed one hundred anteroposterior chest radiographs of children under the age of five years suspected of having chest infection. Thymocardiac ratio is determined. It is concluded that in children under five years, the thymus generally decreases in size with age and that often the thymus will undergo atrophy as a primary response to infection [64**]**.

7.5.2 Treatment with antibiotics leads to vitamin K deficiency in some children

The following clinical studies show that the treatment of ill children with antibiotics for a significant period of time has caused vitamin K deficiency and bleeding:

1) Bhat and Deshmukh conducted a prospective non-randomized study on children receiving antibiotic therapy. Coagulation abnormalities were seen in children with malnutrition, receiving a prolonged course of antibiotics, and in children who were critically ill in intensive care. Inhibition of intestinal microorganisms by antibiotics was thought to be a likely explanation of this phenomenon. They suggested Vitamin K prophylaxis in severely ill individuals, on extended periods of antibiotics and inadequate diet to prevent morbidity and mortality [60].

2) Sunakawa *et al.* found that the incidences of diarrhea after administering oral antibiotics in children were high for amoxicillin and amoxicillin + clavulanic acid. In some individuals with depressed immunity, decreases in intestinal bacteria after doses of antibiotics led to increases in pathogenic bacteria. They invaded the circulating blood, leading to septicemia.

Septicemia originating in the intestinal tract was frequently associated with the development of vitamin K deficiency. Besides changes in the intestinal flora, a reduction in oral food intake and the presence of a methylthiotetrazole group in the structure of the administered antibiotics were also found to play a crucial role in causing vitamin K deficiency [61].

3) de Montalembert evaluated the medical records of 43 cystic fibrosis individuals and found a significant correlation between PIVKA-II concentrations and the administration of antibiotics in these individuals [62].

8. The likely causes of the brain edema and separation of the coronal suture observed in Roman's case

Dr. Bux stated that Roman had severe diffuse cerebral edema with central herniation and widespread encephalomalacia. He also reported the separation of the coronal suture in Roman's skull. The coronal suture is a dense fibrous connective tissue joint that separates the frontal and parietal bones of the skull**.**

His microscopic examination of H & E stained section of the suture revealed the presence of acute hemorrhage in the intra-

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osseous spaces adjacent to the suture. No evidence of inflammation or healing was observed.

Bux alleged that the brain edema and separation of the suture were caused by blunt trauma to the head. However, physicians and nurses who examined Roman during the five days prior to his death did not report the presence of injury caused by trauma on Roman's head (Section 7). Roman died on May 30, 1988 (four days following hospital admission) and Bux conducted the autopsy on May 31st.

My review of the clinical and the scientific evidence pertinent to this case indicates that Roman's brain edema was induced by anoxia, treatment with high doses of sodium bicarbonate, and metabolic acidosis. The separation of the coronal suture in Roman's skull resulted from the increased intracranial pressure due to edema and bleeding. Below are medical data and studies that describe the causes and the progress of these lesions.

8.1 Brain edema and herniation

Roman's CT scan of the brain taken following admission to the hospital on May 26th showed that Roman had a brain edema without herniation. However, at autopsy, Bux observed severe and diffuse cerebral edema with central herniation and widespread encephalomalacia. These observations indicate that fluid accumulated in the brain mostly during Roman's four days of hospitalization as a result of the following factors:

1) Roman suffered from cardiac arrest for more than 20 minutes and anoxia causes brain damage and edema. Roman suffered from cardiac arrest prior to 1720 on May 26th and he was in full cardiac arrest at 1740. Roman's first measured heart rate was 40's beats/minute at 1741.

2) Roman had severe metabolic acidosis. His blood pH following admission was 6.8. Metabolic acidosis can cause brain edema as shown by the clinical studies cited below. Edge *et al.* stated that cerebral edema complicating diabetic ketoacidosis (DKA) remains the major cause of morbidity and mortality in children with type 1diabetes [65].

a) Hanas *et al.* reviewed the records of 292 cases of diabetic ketoacidosis (pH < 7.30), aged 0.8-19.9 years. They found two children (11 years old) had overt symptoms of cerebral edema and one developed neurological sequelae. In addition, symptoms of subclinical cerebral edema after admission (headache, vomiting, lethargy) were recorded in additional 16 cases. In 2 of these cases mannitol was given, and both recovered within 1-2 h [66].

b) Glaser *et al.* measured the intercaudate width of the frontal horns of the lateral ventricles using magnetic resonance imaging (MRI) in children with diabetic ketoacidosis (DKA) during treatment and after recovery from the DKA episode. They found that narrowing of the lateral ventricles is evident in just over half of children being treated for DKA. They concluded that clinical evidence of cerebral edema in children with DKA is more common than previously reported [67].

c) Marcin *et al.* evaluated the medical records of 61 children with diabetic ketoacidosis who developed cerebral edema. They found 17 (28%) children died or survived in a vegetative state; 8 (13%) survived with mild to moderate neurologic disabilities; and 36 (59%) survived without sequelae. Factors associated with poor outcomes included greater neurologic depression at the time of diagnosis of cerebral edema, a high initial serum urea nitrogen concentration, and intubation with hyperventilation to a PCO2 <22 mm Hg [68].

3) Roman was treated with high doses of sodium bicarbonate that raised his blood pH from 6.8 to 7.53. Treatment with high doses of sodium bicarbonate causes anoxia and brain edema [13-15].

8.2 Separation of the coronal suture

The following clinical and medical studies indicate that the separation of the coronal suture in Roman's case occurred in the hospital due to the increased intracranial pressure which resulted from bleeding and edema.

1) The separation of the suture was not observed on Roman's X-ray and the CT scan of the head performed after admission on May 26th and his X-ray of his head taken on May 27th. The clinical studies described below show that X-ray and CT scan are used as dependable diagnostic tools in detecting suture abnormalities, skull fracture, and other abnormalities of the skull.

a) Andronikou *et al.* assessed the usefulness of skull radiographs in detecting skull fracture and other abnormalities in children with minor head injury (MHI). Three hundred and eighty-one children were included with a mean age of 6 years. Retrospective review of CT scans and skull X-rays (SXR) showed 49 percent of all children had fractures either on CT or SXR [69].

b) Agrawal *et al.* used radiography as a tool to determine the pattern of postoperative suture reformation in children who underwent surgery for isolated sagittal synostosis. Records were retrospectively reviewed for 42 consecutive infants who had surgery for isolated sagittal synostosis and for whom postoperative skull radiographs were available.

The median age at surgery was 3.9 months (range 1.9-7.6 months). The mean duration of follow up was 32.2 months (range 6-144 months). The radiographs were evaluated for sagittal suture morphology and patency of the coronal and lambdoid sutures. They were able to determine that the sagittal suture had reformed in only seven (16.7%) of the children at follow up [70].

c) Losee *et al.* used computed tomography (CT) scans as a tool to characterize morphological differences in the lambdoid suture between nonsynostotic occipital plagiocephaly and lambdoid craniosynostosis. The lambdoid suture is a dense, fibrous connective tissue joint that separates the parietal and temporal bones of the skull from the occipital bone.

CT scans of children clinically diagnosed with nonsynostotic occipital plagiocephaly (n = 26) were compared with CT scans from children diagnosed with lambdoid craniosynostosis (n = 7). Suture and cranial morphology, ear position, and endocranial base angles were qualitatively and quantitatively compared.

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d) Keller *et al.* used computed tomography (CT) as a tool to evaluate the degree of coronal synostosis in infants. The purpose of this study was to test whether the severity of the cranial phenotype in Muenke syndrome infants with unicoronal synostosis is greater than in infants with nonsyndromic unicoronal synostosis.

A total of 23 infants included in the study who had a computed tomography (CT)-verified synostosis of the coronal suture. These include 11 infants in the Muenke group and 12 infants in the non-Muenke control group. Their study found differences with regard to severity of increased digital markings and craniofacial asymmetry between the infants with Muenke syndrome and the infants with nonsyndromic unilateral coronal synostosis [72].

e) Cerovac *et al.* evaluated 109 cases of children with simple craniosynostosis using CT scan and radiography. CT scans with 3D reconstructions provided diagnostic confirmation in 100% of the children, while radiography was able to confirm the diagnosis in 91% of the children [73].

f) Paperno *et al.* examined 27 cadavers with cranial computed tomography (CT) prior to autopsy to assess the diagnostic value of postmortem CT in comparison to autopsy. They found that the detection of skull fractures was equal for both methods (n=3) [74].

2) The increased intracranial pressure in Roman's case led to herniation of the brain and it can also lead to separation of the suture. I reported a skull fracture in a child (Averial) resulted from accumulation of fluid caused by anoxia and that treatment with sodium bicarbonate. The head circumference in Averial's case was increased from 37 cm to 38.25 cm [(14]. Averial had brain edema without herniation and Roman had herniation of the brain, which indicates that his brain was subjected to a higher intracranial pressure than Averials.

9. The likely causes of rib fractures observed in Roman's case

Roman died on May 30th and Dr. Bux conducted the autopsy on May 31th. He found five healing rib fractures involving the left 5th through 9th ribs. These fractures were located in the posterior aspect of the left chest rib cage, less than ½ inch from the posterior spine articulation. His microscopic examination of the H & E stained section of the posterior 6th left rib revealed abundant callous formation.

In addition, Bux found acute fracture of the left anterior lateral 6th rib with surrounding hemorrhage. Bux alleged that these fractures were caused by trauma. However, his external examination of the thorax region did not reveal any evidence of injury caused by trauma. Furthermore, the paramedics and the physicians who examined Roman in two hospitals did not report any sign of trauma on Roman's chest.

The medical data and the pertinent medical studies indicate that the likely causes of Roman's healed rib fractures are vitamin K and protein deficiency. Cardiopulmonary resuscitation (CPR) is the likely cause for the left anterior lateral 6th rib fracture. The following are clinical observations and studies that explain the roles of vitamin K and protein in bone synthesis and describe rib fractures caused by CPR:

9.1 Vitamin K deficiency results in bone weakness and fractures

The medical evidence described in Section 7 of this report indicates that Roman was suffering from vitamin K deficiency. Some of the bone matrix proteins necessary for normal bone metabolism are vitamin K-dependent. Vitamin K is a coenzyme for glutamate carboxylase that mediates the conversion of glutamate to gamma-carboxyglutamate (Gla).

Gla residues attract Ca2+ and incorporate these ions into the hydroxyapatite crystals. There are at least three Gla proteins associated with bone tissue, of which osteocalcin is the most abundant and best known. Osteocalcin is the major non-collagenous protein incorporated in bone matrix during bone formation [54; 75-77].

Bugel found that vitamin K deficiency in people results in an increase in undercarboxylated osteocalcin, a protein with low biological activity. Several studies have demonstrated that low dietary vitamin K intake is associated with low bone mineral density or increased fractures.

Additionally, vitamin K supplementation has been shown to reduce undercarboxylated osteocalcin and improve the bone turnover profile. Some studies have indicated that high levels of undercarboxylated osteocalcin are associated with low bone mineral density and increased hip fracture [76].

Booth *et al.* conducted study to determine the associations between vitamin K intake and hip fracture in a population-based cohort of elderly men and women. Dietary vitamin K intake was assessed with a food-frequency questionnaire in 335 men and 553 women (average age: 75.2 y) and incidence of hip fractures was recorded.

They found that individuals in the highest quartile of vitamin K intake (median: 254 μg per day) had a significantly lower fully adjusted relative risk (0.35; 95% CI: 0. 13, 0.94) of hip fracture than did those in the lowest quartile of intake (median: 56 μg/day). They concluded that low vitamin K intakes were associated with an increased incidence of hip fractures in this cohort of elderly men and women [78].

Furthermore, Shiraki *et al.* investigated the effectiveness of vitamin K2 (menatetrenone) treatment in preventing incidence of new fractures in osteoporotic individuals. A total of 241 osteoporotic individuals were enrolled in a 24-month randomized open label study, the control group (without treatment; n =121) and the vitamin K2-treated group (n = 120), which received 45 mg/day orally vitamin K2.

These individuals were followed for lumbar bone mineral density (LBMD); measured by dual-energy X-ray absorptiometry (DXA) and occurrence of new clinical fractures.

Serum level of Glu-osteocalcin (Glu-OC) and menaquinone-4 levels were also measured at the end of the follow-up period. They found that the incidence of clinical fractures during the 2 years of treatment in the control group was higher than the vitamin K2-treated group (chi2 =10.935; p = 0.0273) [79].

I reviewed the medical records of an infant who had several rib fractures at various degree of healing. These include the lateral right rib 1st; right posterior ribs 6th, 8th and 9th; left posterior ribs 4th, 5th, 7th and 8th. No evidence of trauma was observed

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in this case. These fractures were caused by vitamin K and protein deficiency [80].

In addition, Fenton *et al.* reported 2 cases of infants who died as a result of massive intracranial hemorrhage caused by vitamin K deficiency in one infant and by disseminated herpes simplex virus infection in the second infant. Their radiographic exams of the head taken prior to death revealed the presence of linear parietal fractures. At autopsy, the parietal bone abnormalities were found one not to be fractures, but proved to be an anomalous suture in 1 and a connective tissue fissure in the other [81].

9.2 Protein deficiency and bone metabolism

Tanaka *et al.* stated that protein malnutrition increases the fracture risk due to decreased bone mineral density and muscle weakness [82]. Rizzoli *et al.* also reported that protein deficiency contributes to the occurrence of osteoporotic fractures not only by decreasing bone mass but also by altering muscle function [83].

Roman suffered from a bacterial infection and lost a significant amount of weight. His thymus weight was 14 g, which is less than 50% of normal for age. His average serum creatinine level for the period of May 26-30, 1988 was 0.23 mg/dL, which is 46% of low normal (Table 11). These observations indicate that Roman had low protein intake as a result of his illness, which contributed to his rib fractures.

9.3 Rib fractures associated with CPR

Roman was admitted to the hospital on May 26th and no evidence of injury was observed on Roman's chest by the paramedics, physicians, and nurses who treated him for five days. Acute lateral rib fracture of the left 6th was observed on the chest X-ray performed on May 27th. Roman suffered from cardiac arrest on May 26th and Daniel, his neighbor, and the paramedics performed cardiopulmonary resuscitation (CPR) for more than 40 minutes. The following medical studies show that CPR has caused rib fractures in children and adults:

1) Dolinak evaluated the incidence of CPR-related rib fractures in a series of 70 consecutive autopsies in infants ranging in age from 2 weeks to 8 months, with no history or indications of injury. Subtle fractures of the anterolateral aspects of the ribs were discovered in 8 (11%) of the 70 cases. In 7 of the 8 cases, multiple ribs were fractured (ranging up to 10 rib fractures), and in 5 of these cases, the rib fractures were bilateral [84].

2) Black *et al.* reviewed the autopsy records of 499 individuals (343 males, 156 females) who received CPR prior to death. Rib fractures were found in 29% and sternal fracture in 14%. There was no significant difference in the number of left or right ribs fractured (P=0.631) [85].

3) Rabl *et al.* evaluated complications arising from techniques of cardiopulmonary resuscitation (CPR) and active compression-decompression (ACD) CPR. They analyzed the autopsy protocols of 25 individuals who died after receiving standard (Std) CPR and 31 who died after receiving ACD-CPR, 15 of them preceded by Std CPR.

After Std CPR (n = 25), rib fractures were detected in 28% and sternal fractures in 16%. After ACD-CPR (n = 16), rib fractures occurred in 68% and sternal fractures in 68%. After ACD-CPR following Std CPR (n = 15), rib fractures were detected in 93% and sternal fractures in 93% [86].

4) Baubin *et al.* evaluated the autopsy records of 35 individuals who suffered cardiac arrest and received active compression-decompression cardiopulmonary resuscitation (ACD-CPR) or received STD-CPR. The ACD-CPR group included 20 individuals and the STD-CPR group contained 15 individuals. They found significantly more sternal fractures with ACD-CPR versus STD-CPR (14/15 vs. 6/20; P <0.005) and rib fractures (13/15 vs. 11/20; P < 0.05) [87].

5) Lederer *et al.* reviewed the plain chest radiography (CXR) and autopsy results of CPR-related chest injuries in 19 individuals. Rib and sternum fractures were diagnosed in 9 of 19 patients by means of radiology and in 18 of 19 patients by autopsy (rib fractures in 6/19 versus 17/19, P=0.002; sternum fractures in 5/19 versus in 9/19, P=0.227. The total number of isolated bone fractures detected by CXR was 18 (12 rib and 6 sternum fractures) and by autopsy 92 (83 rib and 9 sternum fractures) [88].

10. Conclusions

The medical evidence presented in this report reveals the following:

1) Roman Pitts suffered from cardiac arrest on May 26, 1988 as a result of an allergic reaction to an antibiotic (amoxicillin) prescribed by his physician to treat a bacterial infection.

2) The subarachnoid bleeding observed in Roman's case was caused by the high dose of epinephrine given in the hospital, liver injury, infection, and vitamin K deficiency.

3) Roman's brain edema and herniation was induced by anoxia, metabolic acidosis, and treatment with high doses of sodium bicarbonate.

4) The separation of the coronal suture in Roman's skull resulted from increased intracranial pressure due to edema and bleeding.

5) The likely causes of Roman's healed rib fractures are vitamin K and protein deficiency.

6) Cardiopulmonary resuscitation (CPR) is the likely cause for the left anterior lateral 6th rib fracture.

7) Dr. Robert Bux's allegation that Roman's injuries and death were caused by trauma are not supported by the medical and scientific data described in this report. It seems that Bux did not perform differential diagnosis to consider the role of many factors and agents involved in causing injuries and death in this case. These include an allergic reaction to amoxicillin, a bacterial infection, adverse reaction to epinephrine and sodium bi-

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carbonate, liver and kidney damages, vitamin K and protein deficiency, and CPR.

8) Dr. Martha Morse's allegation that Roman's injuries and death were caused by trauma are not supported by the medical and scientific data described in this report. It seems that Morse did not perform differential diagnosis to consider the role of many factors and agents involved in causing injuries and death in this case. These include an allergic reaction to amoxicillin, bacterial infection, adverse reaction to epinephrine and sodium bicarbonate, liver and kidney damages, vitamin K and protein deficiency, and CPR.

9) My review of the medical evidence in this case and the testimonies of the state's expert witnesses reveals that Daniel Robert Childs Jr. was convicted based on a false theory and that he is innocent.

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