Analysis of causes that led to subdural bleeding and rib fractures in the case of Baby Patrick Gorman

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Abstract

Patrick and his twin sister, Peyton, were born 5 weeks premature. He suffered from acute abdominal and nonspecific symptoms at the age of 2½ months. CT scans, X-ray, and eye exams revealed that he had subdural and subretinal bleeding and seven rib fractures in various stages of healing. He also had severe anemia, thrombocytosis, low blood creatinine levels, hyperglycemia, and elevated neutrophills and monocyte counts. The treating physicians alleged that Patrick's health problems resulted from shaking [shaken baby syndrome (SBS)] and child abuse. Patrick's parents were accused of causing Patrick's injuries.

My investigation revealed that Patrick's acute symptoms resulted from acetaminophen intoxication. Patrick was treated with Tylenol/cold and he received about 200 mg of acetaminophen per day (64 mg/kg) and 3200 mg per 16 days. He was also treated with Zantac® (ranitidine) and Zantac® potentiates the hepatotoxicity of acetaminophen. The subdural and subretinal bleeding was caused by vitamin K deficiency, intoxication with acetaminophen, and severe anemia. The healed rib fractures occurred due to vitamin K and protein deficiencies and chronic coughing. It seems that the treating physicians alleged that Patrick's health problems resulted from abuse, without considering the clinical data that lead to different causes, or performing differential diagnosis in this case.

Keywords: acetaminophen intoxication; anemia; coughing; differential diagnosis; edema; false accusation; fertility drugs; gastroesophageal reflux; hypothyroidism; pregnancy complications; premature infant; protein deficiency; Ranitidine; retinal and subretinal bleeding; rib fractures; subdural bleeding; thrombocytosis; vitamin K deficiency; Zantac

1. Summary of the case and findings

Patrick is a white male child who lives with his parents in North Carolina. He and his twin sister, Peyton, were born 5 weeks premature on August 25, 2005 via cesarean section. Their mother has suffered from hypothyroidism and infertility problems for several years and they were conceived with the help of a fertility drug.

On the morning of November 5, 2005, Patrick received his doses of Tylenol cold medicine and Zantac. He then consumed about an ounce of formula milk. Patrick made a strange gurgly noise, gagged, and had a mouthful of mucous spit up. Patrick's breathing became labored and his color became ashy gray. Patrick experienced muscle weakness and limpness. He was listless and clammy. He barely kept his head up. His father called 9 11 and Patrick was taken by an ambulance to the Naval Hospital aboard Camp Lejeune (NHCL). He stayed about four hours at NHCL and then was transferred to Pitt County Memorial Hospital (PCMH). He was discharged from PCMH on November 8, 2005.

The CT scans and the X-ray exams revealed that he had subdural bleeding and seven rib fractures in various stages of healing. A physician also examined Patrick's eyes on November 7th and stated that he observed subretinal bleeding. Blood analyses revealed that Patrick suffered from hyperglycemia, severe anemia, and thrombocytosis. He also had very low blood creatinine levels and elevated neutrophills and monocyte counts. Urine analysis was positive for glucose. Patrick's twin sister was also examined but she did not have bleeding or any broken ribs.

The treating physicians at NHCL and PCMH alleged that Patrick's subdural and subretinal bleeding resulted from shaking [shaken baby syndrome (SBS)]. They also alleged that Patrick's healed rib fractures were caused by physical abuse. Patrick's parents were accused of causing Patrick's injuries based on the following theory: The parents used force against Patrick but not against his twin sister because he was fussy and crying and his parents were trying to calm him.

Patrick's parents requested that I evaluate the medical evidence in Patrick's case and provide my opinion concerning the possible causes that led to Patrick's subdural and subretinal bleeding and fractured ribs. I am a pathologist and toxicologist with over twenty years experience in these fields. I have also evaluated many cases of children similar to Patrick's case and have served as an expert witness in these cases.

I reviewed the following documents pertinent to this case. (1) The medical records of Patrick's mother cited in this report (2) Patrick's medical records from birth to December 7, 2005. (3) Peyton's medical records from birth to November 28, 2005. In addition, I reviewed the published medical literature pertinent to Patrick's case. I spent 145 hours in evaluating the

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documents cited above and the pertinent medical literature and writing a detailed report in this case. I used differential diagnosis to identify the causes that led to Patrick's health problems

I presented the clinical data pertinent to this case in Sections 2-6 of this report. In addition, the adverse reactions to vaccines given to Patrick are described in Section 3. The clinical data and studies that indicate Patrick suffered from acute acetaminophen intoxication are presented in Section 7. The causes that led to subdural and subretinal bleeding in Patrick's case are listed in Sections 8 and 9, respectively. Section 10 contains a description of the causes that led to Patrick's rib fractures. My conclusions and recommendations are stated in Section 11. My investigation of this case revealed the followings:

1. Patrick's acute symptoms developed on November 5th and the clinical data collected in the hospitals indicate that he suffered from acute acetaminophen intoxication. Patrick was treated with Tylenol/cold for 16 days (October 20-November 5, 2005). He received about 200 mg of acetaminophen per day (64 mg/kg) and a total of 3200 mg per 16 days (Table 4). Published medical studies show that acetaminophen caused hepatotoxicity in children who received equal or lower doses of acetaminophen than those given to Patrick (Section 7).

In addition, Patrick was diagnosed with gastroesophageal reflux on October 25, 2005. He was treated with Zantac (ranitidine), which has been known to potentiate the hepatotoxicity of acetaminophen. Patrick received 15 mg of ranitidine per day and 165 mg per 11 days orally to relieve his acid reflux.

Furthermore, Patrick was suffering from health problems. He had poor feeding habits and vomited on many occasions, which reduced his food intake. His low weight gain rate (about 50% below normal for his age), low blood levels of creatinine, severe anemia and thrombocytosis indicate that he suffered from protein and vitamin deficiencies. These conditions have been known to increase acetaminophen hepatotoxicity in children.

2. It seems that the physicians who examined Patrick on November 5-7, 2005 did not perform the needed clinical tests to rule out acetaminophen intoxication in Patrick's case. The levels of acetaminophen in the blood and the activities of aspartate aminotransferase and alanine aminotransferase enzymes in serum are usually measured in suspected cases of acetaminophen intoxication (Section 7).

3. The medical evidence indicates that the causes of the subdural bleeding in Patrick's case are vitamin K deficiency and his intoxication with acetaminophen (Section 8). Acetaminophen causes liver damage that reduces the synthesis of clotting factors in the liver. Vitamin K deficiency in infants also causes subdural bleeding. Subdural bleeding has been widely reported in infants suffering from vitamin K deficiency. Patrick had several predisposing factors that led to vitamin K deficiency. These include: a) he was not given 1 mg of vitamin K (IM) following birth as recommended; b) he suffered from health conditions (gastroesophageal reflux, poor feeding and vomiting, cold and upper respiratory problems) and adverse reactions to vaccines and medications that reduced his vitamin K intake.

4. The causes of Patrick's subretinal bleeding observed on November 7, 2005 are severe anemia, vitamin K deficiency, and intoxication with acetaminophen (Section 9). It has been reported that severe anemia causes retinal bleeding and other retinal pathology in children and adults. Patrick's blood analyses performed on November 5-7, 2005 revealed that he suffered from severe anemia and thrombocytosis (Tables 10, 15). Patrick had a low red blood cell count of 2.26 x $10^6/\mu L$ (normal range = 2.7-4.9 x $10^6/\mu L$); hemoglobin level of 7.01 g/dL (normal range = 9.0-14.0 g/dL); and hematocrit value of 20.4% (normal range = 31-55%). His platelet count was 662 x $10^3/\mu L$ (normal range = 150-450 x $10^3/\mu L$).

5. Patrick's CT scan and X-ray exams performed on November 5-7, 2005 showed that he had seven healed rib fractures at various stages of healing (right 1st, 8th, and 9th and left 4th, 5th, 7th, and 8th) as described in Section 10. The medical evidence indicates that Patrick had several risk factors that have been known to cause rib fractures in children and adults and they should be considered in this case.

These factors include: (a) Patrick suffered from vitamin K deficiency and vitamin K is involved in bone metabolism and calcification; (b) Patrick suffered from protein deficiency, which leads to bone fracture. Patrick's average serum creatinine value on November 5th was 22% of normal, which indicates low muscle mass (Table 17). His weight gain rate during the first three months of his life was 50% below normal. (c) Patrick suffered from gastroesophageal reflux and symptoms of cold and he was coughing chronically for long time. Chronic and severe coughing causes rib fractures in children and adults.

Patrick's bones were also examined by X-ray on November 30, 2005 and this examination revealed an additional healed fracture of the 6th rib on the right side that was not observed in the CT san and X-ray exams of November 5-7, 200 (Table 27). This finding indicates that Patrick's rib 6 was fractured after November 7th. The parents did not have access to Patrick during this time frame due to the Department of Social Services Safety Plan Agreement. Patrick suffered from upper respiratory illness between November 7th and November 30th and he was admitted to Onslow Memorial Hospital on November 30th due to complications. His weight gain rate was 1.7 g per day during this period, while his sister Peyton gained 21g per day between October 25th and November 28th (Tables 22, 24). These data show that low food intake and chronic coughing led to the fracturing of rib 6 in Patrick's case.

6. It seems that the physicians who treated Patrick on November 5-8, 2005 alleged that Patrick's health problems resulted from abuse, without considering the clinical data that lead to different causes, or performing differential diagnosis in this case.

7. My review of Peyton's record revealed that she did not develop bleeding or have rib fractures because her health was better than Patrick. For example, Patrick's weight gain rates during the first three months after birth were significantly less than those of his twin sister, Peyton. At birth, he weighted 419 g higher than his sister and at three months of age, Patrick's weight was 464 g less than Peyton's weight. Peyton's weight gain rate was 25 g/day, which was 156% of Patrick's gain rate (16 g/day). These data indicate that Patrick had health problems and he was eating less than his sister.

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8. It seems that the physicians at Pitt County Memorial Hospital (PCMH) discharged Patrick from the hospital on November 8, 2005 without giving him treatment for his severe anemia and thrombocytosis. Iron deficiency is one of the causes of thrombocytosis in children and adults. Patrick continued to suffer from health problem after his release from the PCMH. He developed a respiratory illness that led to his hospitalization on November 30, 2005. He gained very little weight (1.7 g/day) between November 8th and November 30th. The clinical exams of Nov. 30th-Dec. 7th revealed that he had fractured an additional rib (rib 6) as a result of protein and vitamin K deficiency and severe chronic cough. He also had mild brain atrophy.

I believe that the following recommendations will assist Patrick's physicians to better monitor and treat Patrick's health condition: (a) Long term treatment with Tylenol® should be avoided and should not be given with Zantac®. Zantac® potentiates the toxicity of acetaminophen; (b) Vaccinations should be delayed if the child is sick. Sick children are more susceptible to develop adverse reactions to vaccines than healthy children; (c) Patrick should be monitored and treated for vitamins K, B, and folic acid deficiency, protein deficiency, severe anemia, and thrombocytosis. These conditions cause subdural and retinal bleeding, rib fractures, and other health problems.

2. Patrick's birth event and his mother health condition prior and during pregnancy

2.1 Patrick's birth event

Patrick and his twin sister, Peyton, were born 5 weeks premature on August 25, 2005 via cesarean section. Patrick's weight was 6 pounds and 15 ounces (3.15 kg) and his sister weight was 6 pounds (2.727 kg). His one and five minutes Apgar scores were 9 and 9, respectively. Patrick and his sister received Hepatitis B vaccine (IM) on August 25, 2005. However, they did not receive 1 mg of vitamin K injection (IM) as recommended. Patrick was strictly fed formula milk during the first three months of his life [1, 2].

2.2 Pregnancy complications and medications used

Patrick's mother had premature labor at 29-weeks of gestation and she received three injections of magnesium sulfate to stop contractions. She was subsequently put on strict bed rest while taking the oral medication terbutaline (Berthine) every four hours (Table 1). She spent nearly seven weeks in bed and the majority of her time was spent lying on her left side, which was where Patrick was positioned in utero [3].

Furthermore, Patrick's mother went to Onslow Memorial Hospital twice a week in order to monitor the twin's health. Diminished fetal movement was noted and her doctor's visits were increased accordingly. She also went monthly to the Women's Health Specialties Clinic in Wilmington to receive further tests and more extensive ultrasounds [3].

In addition, during her pregnancy, Patrick's mother suffered from Group B Streptococcus infection and hypothyroidism. She was treated with antibiotics and synthroid (Table 1). This is the fifth pregnancy for Patrick's mother and the twins were conceived while she was on the fertility drug [Clomid (clomiphene citrate)].

Patrick's mother suffered from morning sickness with nausea during her pregnancy with the twins. Her appetite was poor and she did not take an increased dose of prenatal vitamins during her pregnancy. She was not even aware that she was having twins until her fifth month of pregnancy. Patrick's mother was 33 years old when she got pregnant with the twins. She does not smoke or consume alcohol [3].

Table 1. Treatments taken by Patrick's mother during her pregnancy with the twins

Medications and doses	Date	Pharmacological
Synthroid (75 μg per day)	Daily during the pregnancy	Treat hypothyroidism
Cephalexin (250 mg caps)	July 11-18, 2005	Antibiotic
Magnesium sulfate	July 2005	Reduce muscle contraction
Terbutaline (5 mg per 4 hr)	July 11-Aug. 24, 2005	Reduce muscle contraction

2.3 Patrick's mother's health problems prior to her pregnancy with the twins

Patrick's mother has suffered from hypothyroidism and has been treated with synthroid since 1996. The results of some of her abnormal thyroid tests are listed in Table 2. In addition, ultrasound exam of her thyroid performed on 10/06/2000 showed both lobes are minimally enlarged and their appearance was molted. It appears to be due to the presence of a small goiter. Similar changes were also observed in her exam of February 25, 1997.

Furthermore, Patrick's mother suffered from fertility problems and she took Clomid to assist with conception. She also tested positive for Streptococcal infection (Table 3) and was treated with antibiotics. Patrick's mother had multiple problems with her previous pregnancies that included a stillbirth at 7 months in 1997 and a miscarriage in 2000. Her second pregnancy was closely monitored because of complications [3].

Table 2. Abnormal thyroid tests values observed in Patrick's mother's case

Date	TSH	Thyroxine (T4)	T3 Uptake free	Thyroxine index
08/05/97	1.3	9.9	21L*	2.0
02/17/98	14.67 H[1]	5.2	30	1.5
03/10/98	6.06 H	7.2	32	2.3
Normal range	0.3-5.5 (μIU/mL)	4.5-12.0 μg/dL	24-39	1.2-4.9

[1]L: Lower than normal value; H: higher than normal value

Table 3. Patrick's mother's Streptococcus screening tests results

Testing date	Source	Results
03/20/97	Blood sample	Positive for Beta hemolytic Streptococci
02/18/05	Vaginal sample	Positive for Group B Streptococcus

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3. Patrick's health problems observed during his first ten weeks of life and treatments and vaccines given

3.1 Patrick's belly button problem and treatment given

Patrick was seen at Jacksonville Children's Clinic on September 8, 2005 regarding his umbilical cord granuloma. His belly button was also oozing fluid. A nurse practitioner applied an excessive amount of a concentrated silver nitrate solution to his belly button, which resulted in a severe chemical burn. All of the skin on the lower half of his stomach peeled off on September 9th leaving an open wound.

Mupirocin 2% (Bactroban®) ointment (antibiotic) was applied on the burned area three times a day for more than two weeks to prevent infection and a total of 44 grams of the ointment was used. Patrick's weight was 7.0 lb (3.18 kg) and the total dose of Mupirocin applied on Patrick's skin was 277 mg/kg. The photograph of the burned skin shows that the skin was peeled off completely. In this case, it is expected that a significant portion of the antibiotic was absorbed into the damaged area [1].

3.2 Respiratory system problems and treatment given

Patrick was congested and wheezing on September 6, 2005 and he was given Tylenol® cold/cough medicine. He also had feeding problems. His weight was 6 lb and 14 ounces (3.12 kg), which is one ounce less than his birth weight of 6 lb and 15 ounces recorded on August 25, 2005.

Furthermore, he suffered from cold and upper respiratory system problems (congestion, runny nose, cough, and sneezing) on October 20, 2005. He was treated with Tylenol® cold until November 5th when he started to vomit and appeared very sick. His father called 911 and Patrick was taken to the hospital by the paramedics. Patrick was given Tylenol® cold four to six times per day for 16 days. Table 4 contains information on the doses of compounds in the mixture of Tylenol® cold given to Patrick.

Table 4. Patrick's treatment with Tylenol cold (Oct. 20 to Nov. 5, 2005)

Compounds[1] Given	Daily dose (mg/kg)	Average daily intake (mg)	Total dose per 16 days (mg/kg)	Total intake per 16 days (mg)
Tylenol® (acetaminophen)	64.1	200	1025	3200
Dextromethorphan HBr	2.0	6.25	32	100
Pseudoephedrine HCI	6.0	18.75	96	300

[1]Tylenol® cold contains 80 mg of Tylenol, 2.5 mg of Dextromethorphan HBr, and 7.5 mg of Pseudoephedrine HCI per 0.8 mL. Patrick received 0.4 ml of Tylenol cold 4 to 6 times per day. Patrick weight was 3.12 kg.

3.3 Gastroesophageal reflux and treatment given

Patrick was taken to his pediatrician on October 25, 2005. He was irritable and had poor feeding habits. He was consuming a small amount of formula and he was arching his back in pain. He was bringing his legs up to his chest showing obvious discomfort. His parents had already changed his brand of formula several times and had finally settled on Alimentum. The parents gave this brand of formula before to their oldest son who had allergies to other brands.

Patrick was diagnosed as having gastroesophageal reflux and colic. The doctor prescribed Zantac® (ranitidine) at the dose of 7.5 mg twice per day orally to help with the acid reflux. Patrick was also suffering from a cold and was treated with Tylenol cold as shown in Table 4.

The doctor also recommended that Patrick's parents add rice cereal to Patrick's formula or giving him sugar water instead of formula milk to help with his frequent spitting up. The doctor planned to see Patrick back on November 5, 2005 to reevaluate his feeding regimen.

3.4 Reported adverse reactions to vaccines given to Patrick

The list of vaccines given to Patrick during the first two months of his life is presented in Table 5. On October 25, 2005, Patrick was given full doses of six vaccines when he was suffering for cold and upper respiratory system problems, poor feeding, and gastroesophageal reflux. These vaccines include Diphtheria, tetanus toxoids, acellular pertussis, *Haemophilus influenzae* type b, pneumococcal, and inactivated poliovirus vaccines.

Sick children are usually more susceptible to adverse reactions to vaccines than healthy children. Patrick was treated with Tylenol cold for five days prior to receiving the vaccines and 11 days following his vaccinations (Table 4). Serious adverse reactions and even death due to vaccines given to children have also been described in the medical literature. Below are selective studies that describe symptoms and illnesses in children associated with vaccines similar to those given to Patrick (Table 5). Some of these studies are described in the Physicians' Desk Reference and physicians should be familiar with some of the adverse reactions to vaccines in children [4].

1. The following is a summary of reports on the adverse events of vaccines reported to the USA Vaccine Adverse Event Reporting System (VAERS) from January 1, 1991, through December 31, 2001. VAERS received 128,717 reports and the most commonly reported adverse event was fever (25.8%) followed by injection-site hypersensitivity (15.8%), rash (11.0%), injection-site edema (10.8%), and vasodilatation (10.8%). A total of 14.2% of all reports described serious adverse events, which by regulatory definition include death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [5].

2. In the USA, reports to the Vaccine Adverse Event Reporting System (VAERS), concerning infant immunization against pertussis between January 1, 1995 and June 30, 1998 were analyzed. During the study period, there were 285 reports involving death, 971 nonfatal serious reports (defined as events involving initial hospitalization, prolongation of hospitalization, life-threatening illness, or permanent disability), and 4,514 less serious reports after immunization with any pertussis-containing vaccine [6].

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3. Braun and Ellenberg analyzed reports submitted to the United States Vaccine Adverse Event Reporting System in 1991 through 1994. A total of 38,787 adverse events were reported during the study period without a clearly increasing or decreasing trend in the annual number of total reports or deaths. Of the deaths with known age, 72.4% were reported in the first year of life, and 63.7% of these were male. The peak age for death reports was 1 to 3 months, with a gradual decline through age 9 months, after which death was relatively rare. Adverse events with onset of symptoms the day of vaccination accounted for 45.5% of total reports; 20.4% had onset of symptoms the following day. Onset within 2 weeks after vaccination was noted for 92.5% of all reports [7].

4. Systemic adverse events occurring within 3 days following vaccination of 4,696 Italian infants with DTP at 2, 4, and 6 months of age were recorded. These included fever of more than 100.4 ^{0}F in 7% of total; irritability in 36.3%; drowsiness in 34.9%; loss of appetite in 16.5%; vomiting in 5.8%; and crying for 1 hour or more in 3.9% [4; page 3063].

5. The whole-cell DTP vaccine has been associated with acute encephalopathy. A large case-control study that included children 2 to 35 months of age who received DTP was conducted in England to study the incidence of vaccine related neurological problems. Acute neurological disorders, such as encephalopathy or complicated convulsion(s) occurred in children who were more likely to have received DTP vaccine the 7 days preceding onset than their age-matched controls. Among children presumed to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurological illness occurring within 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 ($p< 0.001$) [4].

6. Two hundred and eleven two month-old infants were vaccinated with IPV and DTaP and some of them developed systemic adverse reactions at 24 hours post-inoculation. These include: Fever > 102.2^{o}F (0.5%); irritability (24.6%); tiredness (31.8%); anorexia (8.1%); and vomiting (2.8%) [4].

7. Three hundred sixty-five infants were inoculated with Hib, and some of them developed systemic adverse reactions. The following adverse reactions and their percentages occurred in two-month-old infants during the 48 hours following inoculation: Fever > 100.8^{o}F (0.6%); irritability (12.6%); drowsiness (4.9%); diarrhea (5.2%); and vomiting (2.7%) [4].

8. Classen and Classen analyzed data from a Hib vaccine trial and identified clusters of extra cases of insulin dependent diabetes (IDDM) caused by the vaccine that occurred between 36 and 48 months post-immunization. In this study, approximately 116,000 children in Finland were randomized to receive 4 doses of the Hib vaccine beginning at 3 months of age or one dose starting after 24 months of age. A control-cohort included all 128,500 children born in Finland in the 24 months prior to the Hib vaccine study. The difference in cumulative incidence between those receiving 4 doses and those receiving 0 doses is 54 cases of IDDM/100,000 ($P = 0.026$) at 7-year (relative risk = 1.26).

Most of the extra cases of IDDM appeared in statistically significant clusters that occurred in periods starting, at approximately 38 months after immunization and lasting approximately 6-8 months [8].

9. The adverse experiences that have been reported with pneumovax vaccines in clinical trials and post-marketing experience in children include: asthenia, malaise, fever >102 ^{o}F, nausea, vomiting, lymphadenitis, serum sickness, arthragia, arthritis, malgia, headache, parestheia, rash, and urticaria (4; page 1862]

10. Wise *et al.* summarized reports of adverse events occurring in children younger than 18 years after vaccination with 7-valent pneumococcal conjugate vaccine (PCV) in the United States during February 2000 through February 2002. A total of 4154 reports of events following PCV were submitted to Vaccine Adverse Event Reporting System (VAERS), for a rate of 13.2 reports per 100,000 doses distributed. The most frequently reported symptoms and signs included fever, injection site reactions, fussiness, rashes, and urticaria.

Serious events were described in 14.6% of reports. There were 117 deaths, 23 reports of positive rechallenges, and 34 cases of invasive pneumococcal infections possibly representing vaccine failure. Immune-mediated events occurred in 31.3% of reports. Thrombocytopenia developed in 14 patients and serum sickness in 6 others. Neurologic symptoms occurred in 38% of reports. Seizures described in 393 reports included 94 febrile seizures [9].

11. The Institute of Medicine (IOM) reviewed the scientific literature on the adverse reactions to vaccines in children in the early 1990s and found that the evidence favored acceptance of a causal relation between some vaccines and systemic illnesses. These include: (1) diphtheria and tetanus toxoids vaccine and the development of Guillain-Barre Syndrome (GBS) and brachial neuritis; (2) oral polio vaccine and the development of GBS; and (3) unconjugated Haemophilus Influenza type b (Hib) vaccines and the susceptibility to Hib disease. The IOM also found the evidence that established causality between vaccines and certain illnesses. These include: (1) diphtheria and tetanus toxoids vaccine and the development of anaphylaxis; (2) oral polio vaccine and the development of poliomyelitis and death from polio vaccine-strain viral infection; and (3) hepatitis B vaccine and the development of anaphylaxis reaction [10].

12. The database from the 1994 National Health Interview Survey (NHIS) in the USA that included 6515 children less than six years of age who received Hepatitis B vaccine were analyzed to evaluate the vaccine related adverse reactions. Hepatitis B vaccine was found to be associated with prevalent arthritis, incident of acute ear infections, and incident of pharyngitis/nasopharangitis [11].

The above selected studies clearly show that vaccines given to Patrick caused serious health problems, even death in healthy infants and older children. The risk of developing adverse reactions to vaccines usually increases in children with pre-existing health problems. Patrick suffered from a cold, poor feeding problems, and gastroesophageal reflux. His cold and coughing continued 11 days following vaccination.

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Table 5. Vaccines given to Patrick between Aug. 25-Oct. 25, 2005

Date	Vaccine given	Trade name	Lot #
08/ 25/05	Hepatitis B	-	-
09/26/05	Hepatitis B		
10/25/05	DTaP (Diphtheria, tetanus toxoids, acellular pertussis)	Infarix	AC14B002BA
10/25/05	Hib (*Haemophilus influenzae* type b)	PedvaxHib	0343R
10/25/05	PneumoConjug (Pneumococcal Vaccine)	Prevar	B08634E
10/25/05	Inactivated poliovirus	IPOL	Y0343-2

3.5 Patrick's health condition on November 4, 2005

Patrick's father called Patrick's pediatrician on 11/04/05 to let him know that they didn't see a marked improvement in Patrick's feeding and his health with the new diet and medications. Patrick was experiencing increased irritability and more vomiting. His appetite was poor and he did not seem to be thriving. They wanted to see if they should try another formula or proceed with other options, including possible X-rays to check for intestinal blockages. The doctor recommended that they switch to Enfamil Gentle Ease or Nestle Good Start with comfort protein, which they planned to start on November 5, 2005. Patrick's father fed Patrick at midnight on November 4th and put him to bed at 0115 on November 5th.

3.6 Patrick's health condition in the morning of November 5, 2005

Patrick's parents were downstairs eating breakfast and Patrick and his twin sister were sleeping in their cribs. They heard Patrick crying on the monitor. His mother picked him up and she saw a small amount of vomit on his sheet.

The parents prepared a bath for Patrick while his bottle was warming. After the bath, he had his dose of Zantac and his Tylenol cough/cold medicine. His mother began feeding him formula milk and he took about an ounce and then he was burped. Patrick's father took Patrick and when he attempted to continue feeding him, Patrick let out a strange gurgly noise, gagged, and had a mouthful of mucous spit up. The father handed Patrick to his mother and called 911.

Patrick's breathing became labored and his color became ashy gray. Patrick experienced muscle weakness and limpness. He was listless and clammy. He could barely keep his head up. The parents thought that he was having a seizure. The mother kept the baby close to the phone so that the operator could listen to his breathing. She walked him around and rubbed his back to keep him stimulated. He was lethargic and very listless.

3.7 The paramedics' assessment of Patrick's condition on November 5, 2005

Patrick's parents called 911 at 0731 on November 5th and the paramedics from Onslow County EMS arrived at Patrick's home at 0747. The paramedics assessed Patrick at home. They found that his color was ashen and his blood glucose levels were highly elevated (279-294 mg/dL). He responded to verbal stimuli but he was very lethargic and he did not respond well to oxygen. His skin was warm and dry. His lung sounds were clear and equal. His abdomen was soft and non-tender. There was no sign of injury caused by trauma.

The Paramedics transported Patrick by an ambulance to the Naval Hospital Camp Lejeune Emergency Department. They left Patrick's house at 0804 and arrived at the emergency room at 0815. Patrick had normal pulse and respiratory rates between 0750 and 0816 as shown in Table 6 [1].

Table 6. Patrick's vital signs recorded by the paramedics on Nov. 5th

Time	Pulse rate per minute	Respiratory rate per minute
0750	156	34
0751	160	32
0804	134	34
0816	152	34
Normal range for infant	100-160	30-40

4. Patrick's assessment at the Naval Hospital Camp Lejeune (NHCL) on November 5, 2005

Patrick arrived by an ambulance to the Emergency Department of the NHCL at 0815 on November 5th. He was examined upon arrival by a physician and no evidence of injury caused by trauma was observed. Patrick weight was 4.93 kg. He had normal temperature of 97.3 ^{o}F. His heart rate, respiratory rate, and blood oxygen saturation level were also normal (Table 7).

Patrick was given fluid and antibiotic via IV route as shown in Table 8. Blood and urine samples were analyzed at 0856 and they show that Patrick was suffering from hyperglycemia, anemia, and possible infection (Tables 9-11). Patrick was also examined by CT scan and X-ray. His examinations revealed that he had subdural bleeding and healed rib fractures. The results of the clinical tests performed on Patrick at NHCL are presented below. Patrick stayed at NHCL about 4 hours and then he was transferred to Pitt County Memorial Hospital at 1230 [1].

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Table 7. Patrick's vital measurements and blood oxygen saturation

Time	Pulse rate per minute	Respiratory rate per minute	Blood oxygen saturation %
0835	132	37	100
0850	125	42	100
0855	156	39	100
0905	170	36	100
1050	147	41	100
1100	136	29	100
1115	136	24	100
1130	142	32	100
1145	162	42	99
1200	156	49	100
1215	166	38	99
Average value	148	38	100
Normal range	100-160	30-40	

Table 8. Treatments given to Patrick at NHCL on Nov. 5th

Time	Treatment Given
0845	80 cc NS Saline IV bolus
0950	D5 ½ NS 16 cc per hour
1025	Rocephin 200 mg IV
1155	D5 1/3 NS 40 cc per hour

4.1 The results of the blood and urine tests performed at 0856-0955 on November 5th.

Patrick's blood and urine analysis show that he had hyperglycemia as indicated by the high glucose levels in the blood and urine (Tables 9 and 11). His blood analysis revealed that he suffered from severe anemia as indicated by the low red blood cell count, hemoglobin level, and hematocrit value. Patrick's high white blood cell and neutrophil counts indicates that he had an infection and /or internal inflammation (Table 10).

Table 9. Patrick's serum analysis results at 0856-0955 on Nov. 5th

Measurements	Values	Normal reference range
Blood glucose (mg/dL)	250 H	60-115
BUN (mg/dL)	17	7-18
Creatinine (mg/dL)	0.5	0.6-1.3
NA+ (mmol/L)	134 L	136-145
K (mmol/L)	5.0	3.5-5.1
Cl- (mmol/L)	102	98-107
CO_2 (mmol/L)	21.2 L	24-31
Ca (mg/dL)	9.8	8.8-10.5

Table 10. Patrick's blood analysis results at 0856-0955 on Nov. 5th

Measurements	Values	Normal reference range
Red blood cell count (x10^6/μL)	2.53 L	3.4-5.3
Hemoglobin (g/dL)	7.9 L	13.5-16.5
Hematocrit (%)	23.1 L	36.0-48.0
MCV (fL)	91.4	87-115
MCH (pg)	31.2	25.8-33.0
MCHC (g/dL)	34.1	33.3-35.5
RDW (%)	15.4 H	12.1-15.2
Platelets (x 10^3/μL)	686 H	169-413
White blood cells (x 10^3/μL)	18.4 H	6.0-17.5
Neutrophil (x 10^3/μL)	14.3 H	1.7-6.7
Lymphocytes (x 10^3/μL)	2.8 H	0.9-2.7
Monocyte (x 10^3/μL)	1.2 H	0.2-0.8

Table 11. Patrick's urine analysis results at 0856 on Nov. 5th

Measurements	Values	Normal reference range
PH	6.0	5.0-8.0
Specific gravity	1.030	1.003-1.031 g/mL
Appearance	Clear	Clear-Turbid
Glucose	+ 2 H	Negative-Trace
Clinitest	1 H (critical)[1]	0-1/4 %
Ketones	Trace	Negative-Trace
Protein	Trace	Negative-Trace
Blood	Negative	Negative-Trace
Bilirubin	Negative	Negative-Trace
Urobilinogen	0.2	0-2.0 EU/dL
Nitrate	Negative	Negative

[1]Clinitest measure reducing agent in urine (glucose, galactose, or other reducing substances)

4.2. Results of the X-rays exams and CT scan taken at NHCL

Patrick had two X-ray exams performed at 0838 and 0914 on November 5th. The first exam was limited to the chest area and the second exam included the entire body. These exams revealed the presence of six healed rib fractures. A Computerized Tomography (CT) scan of Patrick's head region was performed at 0952 and revealed the presence of subdural bleeding. Below are the results of these exams.

4.2.1 The results of the X-ray exam of the chest taken at 0838:

1. No radiographic evidence of cardiopulmonary disease was observed.
2. There were several bilateral healing rib fractures. On the left, the posterior 4th, 5th, 7th, and 8th ribs are involved. On the right, the 8th and 9th ribs are involved.
3. The clavicles and the spine appeared normal.

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4.2.2 The examinations of Patrick's body by X-rays performed at 0914 on November 5th revealed the followings:

1. The osseous structures and the soft tissues of the skull were normal.
2. The lateral radiograph of the cervical spine as well as the frontal and lateral radiographs of the thoracic and lumber spine appeared normal.
3. Lungs and heart appeared normal.
4. There were healing fractures of the posterior ribs on the left at T4, T5, T7, and T8 and the right at T8, T9, and possibly T5.
5. The bowel gas pattern was unremarkable and there was no evidence of free intraperitoneal air.
6. The bones, soft tissues, and the joints of the extremities appeared normal.

4.2.3 The results of the Computerized Tomography (CT) scan of Patrick's head:

1. Subdural blood was seen along the tentorium and also in the left frontoparietal region near the vertex. Some intraaxial blood was also seen on the left near the vertex.

5. Patrick's hospitalization at Pitt County Memorial Hospital on November 5-8, 2005

Patrick was transported from Naval Hospital Camp Lejeune (NHCL) to Pitt County Memorial Hospital (PCMH) via ambulance and arrived at 1242 on November 5th. His examination revealed that his heart rate, respiratory rate, and body temperature were normal (Table 12). His lungs were clear [1].

Patrick's CT scan of the head and the neck region revealed the presence of subdural bleeding and moderate soft tissue edema of the neck. It also showed subacute fracture involving the right lateral first rib and an older subacute fracture involving left posterior rib four. His head's circumference was 39 cm. Patrick was given IV fluid, KCl, Versad, and Zantac as shown in Table 13 [1].

Patrick's blood analyses revealed that he had elevated white blood cell and neutrophil count, severe anemia, and thrombocytosis (Tables 14 and 15). His Prothrombin time measured at 1515 on November 5th was within normal range. However, his partial thromboplastin time was below the normal range (Table 16). His blood creatinine levels were below the normal average and it indicates low muscle mass (Table 17).

A physician examined Patrick's eyes on November 7th and stated that he observed subretinal hemorrhage and a possible macular hole. Patrick continued to have feeding problems. The Nuclear Gastric Emptying and Gastric Reflux study was performed on November 8th and revealed that Patrick was suffering from gastroesophageal reflux and his treatment with Zantac continued.

Patrick was released from the hospital on November 8th. Patrick's weight on November 7th was 4.64 kg and his weight on November 5th was 4.93 kg. He lost 290 grams or 5.9% of his body weight during his three days of hospitalization.

Patrick was not treated for his severe anemia during his hospitalization. Below are the results of Patrick's CT scan and X-ray exams and blood analyses performed at PCMH.

Table 12. Patrick's vital signs taken at PCMH on Nov. 5th

Date & Time	Heart rate /minute	Blood pressure	Respiratory rate/minute	Body temp. (°C)
Nov. 5th				
1242	185	108/72	-	37.2
1515	153	106/66	40	36.3
Nov. 6th				
0615	145	95/45		37.7
1150	142-165	95/53	24-38	37.7
Nov. 7th				
0830	130		36	
1120	153	99/58	48	37.1
Nov. 8th	132-153	99/56	32-48	37.1

Table 13. Treatments given to Patrick on Nov. 5-8 at PCMH

Date & Time	Medications and dose
Nov. 5th	
1546	Versed 0.4 mg IV sedation for CT scan
1810	Ranitidine 5 mg IV Q 8 hrs.
2058	NS bolus 10 cc/kg
2200	D5 1/2NS + 20 mEq KC @ 20 cc/hr
Nov. 6th	
0720	D5 1/4NS + 20 mEq KCl @ 20 cc/hr
1052	D5 1/2NS + 20 mEq KCl @ 20 cc/hr
1510	Ranitidine 5 mg IV Q 8 hrs
Nov. 7th	Ranitidine 4mg/kg/day PO
	D5 1/2NS + 20 mEq KCl @ 20 cc/hr

5.1 The results of Patrick's CT scan exam of the head performed at PCMH

Three CT scans of the head were performed on November 5th, 6th, and 7th. Subdural hematoma was observed on November 5th. The volume and the distribution of the bleeding did not change on November 6th and 7th. There was no mention about the age of the bleeding in this case. There was no bleeding or abnormal change in the brain. There was no evidence of injury involving the soft tissues and the bones of the skull [1].

5.1.1 The result of Patrick's CT scan of the head performed at 1546 on November 5th:

1. There was subdural hematoma involving the high right frontoparietal region, along the flax tentorium, and in the frontal regions bilaterally, left greater than right.
2. The brain appeared normal.
3. There was no skull fracture.

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5.1.2 The result of Patrick's CT scan of the head performed at 0847 on November 6th:

1. Subdural hemorrhage along the right frontoparietal region, flax and tentorium, and frontal regions was seen and it was stable from prior exam of November 5th.

5.1.3 The result of Patrick's CT scan of the head performed at 1630 on November 7th:

1. The results of this exam correlate with the findings of the CT scans of November 5th and 6th cited above (Sections 5.1.1 and 5.1.2).
2. There was no evidence of calvarial fracture.

5.2 The results of Patrick's CT scan exam of spine and abdomen performed at PCMH

The CT scan of the spine showed two healed rib fractures and moderate soft tissue edema in the neck. The CT scan of the abdomen identified four more healed rib fractures. No evidence of acute injury observed in the chest and the abdominal areas.

5.2.1 The result of Patrick's CT scan of the spine performed at 1546 on November 5th:

1. There was a subacute fracture involving the lateral right rib one and an older subacute fracture involving left posterior rib four.
2. Moderate soft tissue edema was noted in the neck
3. No evidence of cervical spine fracture.
4. Imaged portions of the lungs apices were clear.
5. Imaged portions of the skull base were unremarkable.

5.2.2 The result of Patrick's CT scan of the abdomen performed on November 5th:

1. There were healing subacute fractures involving the right posterior ribs eight and nine and left posterior ribs seven and eight.
2. No evidence of acute intra-abdominal injury.

5.3 The results of Patrick's X-ray exam of the chest performed at PCMH

The X-ray exam of the chest performed on November 7th identified seven rib fractures at various stages of healing. These include:

1. There were multiple fractures involving the right lateral first rib, and the 8th and 9th posterior ribs with exuberant callus.
2. There was cortical irregularity noted of the right posterior fifth rib seen along the undersurface that may represent an additional fracture.
3. There were fractures involving the left posterior 4th, 5th, 7th, and 8th ribs with exuberant callus formation involving the 7th and 8th ribs.

5.4 The results of Patrick's blood analyses performed at PCMH

Patrick's blood analyses performed on November 5th, 6th, and 7th revealed the followings:

1. Patrick's neutrophils and monocytes counts were elevated on November 5th and the counts were not reduced by the use of antibiotic (Table 14). Patrick had normal body temperature on November 5th (Table 12). These data indicate that Patrick suffered from internal inflammation and this inflammation was caused by the use of medication (Tylenol) and not as a result of bacterial infection.

2. Patrick suffered from severe anemia (Table 15). His red blood cell count was 59% of the normal average. His average hemoglobin level and hematocrit value were 61% and 47% of the normal average value, respectively.

3. Patrick suffered from thrombocytosis. His average platelet count was 221% of normal average value (Table 15).

4. Patrick's prothrombin time (PT) and partial thromboplastin time (PTT) were measured at 1515 on November 5th (Table 16). Patrick's PT was within the normal range but his PTT was below than normal (Table 16). Patrick suffered from thrombocytosis (Table 15) and the PPT test is usually influenced by high platelet count [12], therefore the result of Patrick's PPT test is probably not valid in this case.

5. Patrick's average serum creatinine value was 22% of normal average and it indicates low muscle mass (Table 17).

6. Patrick's blood glucose levels returned to normal at or before 1415 on November 5th (Table 18).

Table 14. Patrick's white blood cell counts on Nov. 5-6, 2005

Date & Time	White Blood cells x 10^3/μL	Neutrophil x 10^3/μL	Lymphocyte x 10^3/μL	Monocyte x 10^3/μL
Nov. 5th				
1515	19.0	13.8 H	3.5	1.60 H
1630	19.7 H	13.9 H	3.8	1.80 H
Nov. 6th	22.0 H	10.7 H	9.10	2.00 H
Nov. 7th				
0430	14.2			
1120	11.1	3.8	5.9	1.22 H
Normal range	5.0-19.5	1.9-9.0	2.5-16.5	0-0.8

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Table 15. Patrick's hematology values on Nov. 5-7, 2005[1]

Date & Time	Red blood cell (x 10^6/µL)	Hemoglobin (g/dL)	Hematocrit %	Platelets x 10^3/µL
Nov. 5th				
1515	2.18L	6.9L	19.5L	615H
1630	2.16L	6.5L	19.1L	675H
Nov. 6th				
0205	2.32L	7.2L	20.9L	687H
Nov. 7th				
0430	2.45L	7.5L	22.1L	678H
0835	2.19L	6.8L	19.5L	656H
1700	-	7.4L	21.5L	-
Nov. 8th				
0315	-	7.0L	20.6L	-
1140	-	6.8L	20.0L	-
Patrick's average value (1)	2.26L (n=5)	7.01L (n=8)	20.40L (n=8)	662H (n=5)
Normal range	2.7-4.9	9.0-14.0	31-55	150-450
Average normal value (2)	3.8	11.5	43	300
1 as % of 2	59	61	47	221

[1]L: Value is lower than normal; H: value is higher than normal, n: number of observation.

Table 16. Patrick's clotting factors at 1515 on Nov. 5th

Measurements	Values	Normal range
PT	10.9	9.6-12.0 seconds
PTT	18.1 L	23.0-29.0 seconds
INR	1.0	2-3

Table 17. Patrick's BUN and Creatinine levels

Date	Time	Creatinine (mg/dL)[1]	BUN (mg/dL)
Nov. 5th	1415	0.2L	10
Nov. 6th	0205	0.3L	7
Nov. 7th	0430	0.2L	4L
	0830	0.2L	3L
Nov. 8th	0315	0.2L	8
Patrick's Avg. value (1)		0.2L	6.4
Normal range		0.6-1.2	6-20
Avg. normal value (2)		0.9L	13
(1) as % of (2)		22%	49%

[1]L: value is lower than normal

Table 18. Patrick's blood glucose levels on Nov. 5-8, 2005

Date	Time	Glucose	Anio Gap
Nov. 5th	1415	76	11
Nov. 6th	0205	93	10
Nov. 7th	0430	90	7
	0830	99	9
Nov. 8th	0315	85	9
Normal range		70-105 mg/dL	4-12 mEq/L

6. Patrick's hospitalization on November 30, 2005

Patrick was diagnosed with Respiratory Syncicial Virus (RSV) on 11/21/05 and his parents and grandmother were given instructions for in home care. Patrick's illness did not resolve and he was taken to his doctor on November 28th. Patrick's illness got worse and he was admitted to Onslow Memorial Hospital on November 30th due to RSV complications and bronchitis [1].

Patrick's body weight was 10.31 pounds (4.678 kg), which is 38 grams higher than his weight on November 7th (4.640 kg). His daily weight gain rate between November 7th and 30th was 1.7 g/day. Patrick received antibiotics to treat his infection and continued with breathing treatments. He was released from the hospital on December 1, 2005.

The CT scan and the MRI exam of Patrick's head region showed an old subdural bleeding and mild atrophy of the brain. Patrick's eyes were examined by two physicians and they did not see retinal bleeding or any abnormal change. His X-ray skeletal survey revealed healed fractures of four ribs (4th, 5th, 7th, and 8th) which were also observed on November 5th and 7th. In addition, it showed a healed fracture of the 6th rib that was not noted on the exams of November 5th and 7th. Patrick's blood analysis revealed that he had normal levels of calcium and vitamin D (Table 19). Below are the results of Patrick's clinical tests.

Table 19. Results of Patrick's blood analysis of Dec. 7, 2005

Measurements	Values	Normal range
Calcium	10.4	9.0-11.0 mg/dL
Phosphorous	6.7	4.8-8.1 mg/dL
Alkaline phosphotase	193	145-320 U/L
Vitamin D (1,25)	52	22-67 pg/mL
Vitamin D (25 OH)	53	25-80 ng/mL

6.1.The results of Patrick's CT scan and the MRI exam of the head

CT scan and the MRI exams of Patrick's head region were performed on November 30th and December 1st of 2005, respectively. These exams showed an old subdural bleeding and mild diffuse cortical atrophy of the brain. No evidence of bone fracture in the skull was observed [1]. Below are the results of these exams.

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6.1.1 The findings of the CT scan include:

1. Subacute bilateral posterior subdural hematoma was noted
2. There was mild diffuse cortical atrophy.
3. There was prominence of the extra-axial CSF spaces that likely reflect mostly chronic subdural hematomas, although a component of this appearance may be a secondary to the atrophy.
4. No evidence of bone fracture was observed.

6.1.2 The findings of the MRI exam include:

1. Findings consistent with bilateral posterior small subdural hemotomas (1 week to months old), left greater than right. This was also extended along the tentorium.

2. Prominent CSF signal overlying the frontal lobes bilaterally which is seen with chronic subdural hematomas. This is also seen as prominent spaces, a normal variant.

6.2 The results of the X-ray exam of Patrick's body

6.2.1 The chest X-ray exam of Nov. 30th revealed the following:

1. Healed fractures of the posterior aspect of right 6th and 8th ribs.
2. Healed fractures of the posterior aspect of the left 4th and 5th ribs.
3. Questionable healed fractures of the posterior aspect of the left 7th and 8th ribs.
4. The lungs were clear.
5. The cardiothymic contour was with normal limits.

6.2.2 Skeletal bone survey of December 1, 2005:

The survey of the skeletal bone revealed old healing fractures of the posterior aspect of the left 4th, 5th, 7th, and 8th ribs as well as healing fractures of the posterior aspect of the right 6th and 8th ribs. No other bone fractures or bone abnormalities were observed in other regions of Patrick's body [1].

6.3. Patrick's eye exams (December 1-9, 2005)

Dr. Johnston examined Patrick's eyes on December 1, 2005 and his eyes appeared normal. Johnston didn't agree with the findings of the physician at Pitt County Memorial Hospital (PCMH) that he had identified subretinal bleeding. Johnston recommended that Dr. Westra, a retinal specialist, examine Patrick's eyes to get a second opinion concerning retinal hemorrhages. Dr. Westra examined Patrick's eyes on December 9th and his examination revealed clear corneas and clear lenses. On dilated exam, the optic nerve and the macula were normal. Patrick had very blonde fundus but there was no sign of retinal hemorrhages nor any other pathology.

7. The likely causes of Patrick's acute illness observed on November 5, 2005

Patrick was sleeping in his crib at about 0700 on November 5th and his parents heard him crying on the monitor. His mother picked him up and found a little vomit on his sheet. She gave him a bath. Patrick was given his medicine orally (7.5 mg of Zantac® and 0.4 ml of Tylenol® cough/cold) and then he was fed formula milk.

Patrick took about an ounce of formula then he let out a strange gurgly noise, gagged, and had a mouthful of mucous spit up. Patrick breathing became labored and his color became ashy gray. Patrick experienced muscle weakness and limpness. He was listless and clammy. He could barely keep his head up. Patrick's parents called 911 at 0731 and the paramedics assessed Patrick and found him very lethargic.

On November 4th, Patrick experienced increased irritability and more vomiting than previous days. Patrick's father called Patrick's pediatrician and let him know that they didn't see a marked improvement in Patrick's feeding and his health with the new diet and medications. Patrick's appetite was poor and he did not seem to be thriving. The doctor recommended that the parents switch Patrick's formula to Enfamil Gentle Ease or Nestle Good Start with comfort proteins. Patrick's father fed Patrick at midnight on November 4th and put him to bed at about 0115 on November 5th.

The likely cause of Patrick's acute illness described above is Tylenol® cough/cold. He developed acute toxicity to acetaminophen. Zantac® (ranitidine) potentiated the hepatotoxic action of acetaminophen in this case. Patrick was given 0.4 mL of Tylenol® cough/cold (40 mg of acetaminophen, 1.25 mg of Dextromethorphan HBr, and 3.75 mg of Pseudoephedrine HCI) orally four to six times per day for 16 days. He received about 200 mg of acetaminophen per day and 3200 mg per 16 days (Table 4), which caused liver toxicity and kidney problems.

Patrick also received 15 mg of ranitidine per day orally and 165 mg per 11 days to relieve his acid reflux. Ranitidine has been known to potentiate the hepatotoxic action of acetaminophen in experimental animals. Furthermore, Patrick had other predisposing factors that led to acetaminophen toxicity.

It seems that the physicians who examined Patrick on November 5-8, 2005 in the hospitals overlooked the followings important clinical data that show Patrick was suffering from acute symptoms of acetaminophen toxicity:

1. Patrick's non-specific acute symptoms are similar to those of children suffering from acute acetaminophen toxicity and the acute symptoms of acetaminophen hepatotoxicty in children are non-specific.

2. Patrick received a toxic dose of acetaminophen (about 3200 mg in 16 days) and even less than this dose is capable of inducing liver toxicity in some children.

3. Patrick was treated with Zantac® (ranitidine) at the same time of receiving acetaminophen and ranitidine has been known to potentiate the hepatotoxic action of acetaminophen by reducing the conversion of acetaminophen to non-toxic metabolite.

4. Patrick was suffering from gastroesophageal reflux, poor feeding problems, and severe anemia and had low blood levels of creatinine. These factors have been known to increase acetaminophen hepatotoxicity in children.

5. Patrick's blood neutrophils and monocyte counts were elevated on November 5-6, 2005 and his body temperature was normal. These data indicate that Patrick suffered from chemically induced inflammation in one or more organs.

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6. Patrick had fluid retention and subcutaneous edema (neck region). This datum indicates that Patrick was suffering from kidney problems.

In addition, the levels of acetaminophen and aspartate aminotransferase and alanine aminotransferase enzymes were not measured in Patrick's serum on November 5, 2005 to rule out acetaminophen toxicity. The levels of acetaminophen and liver enzymes in serum are usually elevated in children intoxicated with acetaminophen.

7.1. Patrick received a toxic dose of acetaminophen

Patrick was treated with Tylenol/cold for 16 days (October 20-November 5, 2005). He received about 200 mg of acetaminophen per day (64 mg/kg) and a total of 3200 mg per 16 days (Table 4). Published studies show that acetaminophen caused hepatotoxicity in children who received equal or lower doses than the total dose of acetaminophen given to Patrick. The results of published clinical studies on acetaminophen toxicity in children are presented in Tables 20 and 21 and described below.

1. Table 20 contains the clinical data of three children who developed liver toxicity after receiving acetaminophen at daily dose levels similar to Patrick (60-61 mg/kg per day) but were treated for significantly less time than Patrick.

2. Table 21 shows the clinical data of five children who developed hepatotoxicty after receiving about half or less of the total dose of acetaminophen given to Patrick in 16 days.

3. Heubi *et al.* evaluated 47 reports of acetaminophen hepatotoxicity in children (age range, 5 weeks to 10 years) received 60 to 420 mg/kg/day for 1 to 42 days.
Twenty-four of 43 patients (55%) died, with an additional three surviving after orthotopic liver transplantation. Six of these children received doses that were only slightly above the recommended 10 to 15 mg/kg/dose for up to 5 doses per day or 50 to 75 mg/kg/day. These data suggest that the therapeutic index for acetaminophen is 1 to 1.7 in ill and febrile child. They stated that parents should be advised about the potential hepatotoxicity of acetaminophen when given to ill children in doses exceeding weight-based recommendations [13].

4. Shahroor *et al.* reported two children, who developed severe hepatic damage, with renal insufficiency as well in 1, after receiving acetaminophen at dose level of 15-20 mg/kg six times per day for 3-4 days during an intercurrent febrile illness. They stated that the risk for severe acetaminophen toxicity are increased in children who are vomiting or have sharply reduced caloric intakes when given in doses as low as 20 mg/kg at frequent intervals for a number of days. They also stated that increased caution and awareness of the toxic effects of acetaminophen are needed, and it should be dispensed with appropriate package-label warnings [14].

5. Pershad *et al.* reported a case of fatality from chronic acetaminophen toxicity in an 18-month-old toddler. This toddler received less than the standard toxic threshold of the pediatric suspension of acetaminophen for 4 days prior to presentation. This child was born 14 weeks premature and was put on prolonged total parenteral nutrition (TPN) as an infant [15].

Table 20. Children developed liver toxicity after receiving acetaminophen at similar daily dose of Patrick but treated for less time

Source & (Age)	Daily dose (mg/kg)	Duration of admin. (days)	AST[2] (IU/L)	ALT[2] (IU/L)
Patrick (10 w)	64	16	NM	NM
(13) 4.0y[1]	61	1	>10,000	>10,000
(13) 4.5y[1]	60	3	2,970	5,060
(13) 2.5y[1]	60	6-8	1,180	480
Normal range[3]			0-35	0-35

[1](13) Heubi *et al.* 1998 [13].
[2]NM: not measured; AST: aspartate aminotransferase; ALT: alanine aminotransferase;
[3]Fauci et a., 1998 [16].

Table 21. Comparison between Patrick's total dose of acetaminophen (mg/kg) and the total doses (mg/kg) received by other children who developed hepatotoxicity

Source & (Age)	Sex (M/F)	Total dose (mg/kg)	Duration of admin. (days)	SGOT IU/L	Treatment given	Outcome of the case
Patrick 10 w	M	1024	16	NM[2]	Supportive	Survival
6 w	M	200	2	3,000	Acetylcysteine	Survival
1.5y	F	288	2	1,576	Supportive	Survival
3.5y[1]	F	336	1	22,000	Supportive	Death
7 w	F	200-400	6-8	1,180	Supportive	Survival
1.4y	M	600	4	10,230	Supportive	Survival

[1]Smith *et al.* 1986 [17].
[2]NM: Not measured; SGOT (AST) normal range = 0-35 IU/L [16].

7.2 Patrick's treatment with Zantac potentiates the hepatotoxicity of acetaminophen

In addition to receiving toxic doses of acetaminophen, Patrick was treated with Zantac® (ranitidine), which has been known to potentiate the hepatotoxicity of acetaminophen. It decreases the conversion of acetaminophen to non-toxic metabolite in the liver. Patrick received 15 mg of ranitidine per day and 165 mg per 11 days orally to relieve his acid reflux. He was diagnosed with gastroesophageal reflux on October 25, 2005.

Acetaminophen is metabolized extensively in the liver by three main pathways (sulphation, glucuronidation, and oxidation) and approximately 5% is excreted unchanged in the urine. In the therapeutic doses most of acetaminophen undergoes glucuronidation or sulphation, producing non-toxic metabolites that are excreted in the urine. Approximately 5% to 10% of the drug is oxidized by CYP450-dependent pathways to a toxic electrophilic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is detoxified by glutathione and eliminated in urine or bile [18, 19, 20].

As sulphation and glucuturonidation pathways become saturated, an increasing portion and quantity of the drug is metabolized by the cytochrome P-450 system, resulting in an increased production of NAPQI. If the hepatic synthesis of glutathione becomes overwhelmed, the manifestations of toxicity appear producing centrolobular necrosis [18, 21].

Zantac® (ranitidine) has been found to increase the hepatotoxicity of acetaminophen in experimental animals as shown by the studies described below. It inhibits the formation of aceta-

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minophen glucuronide in the liver and leaving a higher portion of the dose to be converted to toxic metabolite by P-450 enzymes. I believe that ranitidine also increased the toxicity of acetaminophen in Patrick's case.

1. Leonard *et al.* studied ranitidine-acetaminophen interaction in rats and found that **r**anitidine administration at 50 mg per kg or less enhanced acetaminophen hepatotoxicity. They administered acetaminophen to F344 rats (750 mg per kg, p.o.) and assessed the hepatotoxicity of acetaminophen at 24 hours after treatment by measuring the glutamic pyruvic transaminase (SGPT) activity in serum and the level of hepatic necrosis microscopically. They found that ranitidine pretreatment 30 minutes prior to acetaminophen treatment increased the toxicity of acetaminophen. Ranitidine potentiated acetaminophen hepatotoxicity in a dose-dependent manner (600 to 1,000 mg per kg). Inhibition by ranitidine of acetaminophen conjugation is proposed as a possible mechanism of this potentiation [22].

2. Rogers *et al.* administered ranitidine (50 mg/kg p.o.) to male Fischer 344 rats 30 minutes before treating these rats with acetaminophen (750 mg/kg p.o.). They found that ranitidine increased the plasma concentrations of acetaminophen at 2 hour (193%) and 4 hour (277%) after the treatment with acetaminophen as compared with the animals treated with acetaminophen alone. They also found that the urinary excretion (0-24 hr) of acetaminophen and acetaminophen glucuronide were reduced in ranitidine-pretreated animals to 64 and 66% of control, respectively. These data indicate that in vivo ranitidine altered acetaminophen conjugation with glucuronic acid [23].

Furthermore, Patrick was suffering from gastroesophageal reflux, poor feeding, and severe anemia, and had low blood levels of creatinine. These factors have been known to increase acetaminophen hepatotoxicity in children by enhancing the formation of toxic metabolites in liver and reducing the rates of detoxifications. For example, the American Academy of Pediatrics reported that fasting, vomiting, and/or diarrhea are associated with increased acetaminophen hepatotoxicity in humans [19].

These conditions may increase the activity of liver P-450 enzymes which lead to an increase in the formation of NAPQI. Detoxification may be reduced in individuals with chronic protein-calorie malnutrition, who also have low glutathione levels [19]. The combination of fasting and repeated acetaminophen administration may lead to even greater reductions in hepatic glutathione, increases in turnover, and reduced syntheses [13.

7.3 Clinical data that indicate Patrick developed acetaminophen toxicity

Patrick's acute symptoms developed on November 5th and some of the clinical data collected in hospitals indicate that he suffered from acute toxicity of acetaminophen. However, the treating physicians overlooked to consider acetaminophen intoxication in their diagnosis. Below are descriptions of studies that outline the diagnostic values of the clinical data collected in Patrick's case in relation to acetaminophen toxicity.

7.3.1. Patrick's acute symptoms observed on November 5th

Patrick's non-specific acute symptoms developed on November 5th are similar to those of children suffering from acute acetaminophen hepatotoxicity at the early stage. The first phase of acetaminophen intoxication in children consists of anorexia, nausea, vomiting, malaise, and diaphoresis (excessive sweating) [19]. Muniz *et al.* stated that initial signs and symptoms of acetaminophen hepatotoxicity are nonspecific in infants and biochemical evidence of hepatic damage may not become evident for 24 to 36 hours [24].

In addition, the American Academy of Pediatrics reported that the diagnosis and treatment of acetaminophen intoxication in children is more likely to be delayed in unintentional cases of toxicity because the symptoms of acetaminophen intoxication are nonspecific [19]. Roach *et al.* also stated that because the signs and symptoms of acetaminophen overdose in children mimic common illnesses, the real diagnosis might go undetected [25].

7.3.2. Biomarkers of inflammation observed in Patrick's case:

Patrick's blood neutrophils and monocyte counts were significantly elevated on November 5-6, 2005 (Tables 10, 14). However, his body temperature was normal (Table 12). On November 5th, Patrick's neutrophils and monocyte counts were 213% and 150% of the normal upper limit for the neutrophils and monocyte count, respectively. Patrick was treated with antibiotic at 1025 on November 5th but the antibiotic did not reduce the neutrophils or the monocyte count. These data indicate that acetaminophen was causing the inflammation in tissues and the elevation of the neutrophils and monocytes counts was not resulted from bacterial infection.

It has been reported that extensive acetaminophen induced hepatocellular necrosis triggers an inflammatory response. The released postinflammatory cytokines activate neutrophils and cause their accumulation in sinusoids. The general purpose of this early neutrophil infiltration is to remove dead or dying cells as prerequisite for wound repair and regeneration [26]. Below are descriptions of clinical and experimental studies that show acetaminophen induced inflammatory mediators and increased neutrophils and monocytes numbers in tissues.

1. James *et al.* 2001 measured the levels of interleukin 8 in the blood of children and adolescents (n=35) with acetaminophen overdose to evaluate relationships between cytokine elevation and hepatotoxicity. Peak cytokine levels were examined relative to biochemical evidence of hepatocellular injury, nomogram risk assessment, and prothrombin time. Peak interleukin 8 correlated with hepatotoxicity (Mann-Whitney exact test, $P < .001$) [27].

2. James *et al.*, 2005 found that monocyte chemoattractant protein 1 and other cytokines were elevated in the blood of individuals received acetaminophen overdose. They collected blood samples from 111 individuals (90 females; mean age 13.6 years) following acute ingestions of acetaminophen and measured the plasma concentrations of interleukin 6, interleukin 8, interleukin 10, and monocyte chemoattractant protein 1. Indi-

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viduals were stratified by the severity of acetaminophen toxicity as defined by the maximal values of hepatic transaminase elevation.

They found that the levels of interleukin 6, interleukin 8, and monocyte chemoattractant protein 1 were higher in individuals with serum alanine aminotransferase > 1000 IU/L. In addition, monocyte chemoattractant protein 1 values were higher in individuals with greater delays in N-acetylcysteine treatment. Their study showed that monocyte chemoattractant protein 1 had the strongest association with toxicity [28].

3. Lawson *et al.* conduced study to characterize the neutrophilic inflammatory response after treatment of C3Heb/FeJ mice with 300 mg/kg acetaminophen. A time course study showed that neutrophils accumulate in the liver parallel to or slightly after the development of liver injury. The number of neutrophils in the liver was substantial (209 +/- 64 PMN/50 high-power fields at 12 h) compared to baseline levels (7 ± 1).

Serum levels of TNF-alpha and the C-X-C chemokines KC and MIP-2 were also increased by 28-, 14-, and 295-fold, respectively, over levels found in controls during the injury process. They stated that inflammation observed after acetaminophen overdose may be characteristic for a response sufficient to recruit neutrophils for the purpose of removing necrotic cells [29].

4. Liu *et al.* reported that liver natural killer (NK) and NKT cells play a critical role in mouse model of acetaminophen-induced liver injury by producing interferon gamma (IFN-gamma) and modulating chemokine production and subsequent recruitment of neutrophils into the liver. They gave C57BL/6 mice an intraperitoneal toxic dose of acetaminophen (500 mg/kg), which caused severe acute liver injury characterized by significant elevation of serum ALT, centrilobular hepatic necrosis, and increased hepatic inflammatory cell accumulation. Flow cytometric analysis of isolated hepatic leukocytes demonstrated that the major fraction of increased hepatic leukocytes at 6 and 24 hours after acetaminophen was neutrophils [30].

7.3.3 Patrick had fluid retention and subcutaneous edema:

The following clinical observations show that Patrick developed fluid retention during the period of his treatment with Tylenol cold and Zantac, which is a sign of liver and kidney toxicity. Patrick's treatment with Tylenol started on October 20, 2005 and ended on November 5th (Table 4).

1. Patrick's weight gain rate between October 25, 2005 and the morning of November 5th was 46 g/day, which is 212% of his weight gain rate (22 g/day) for the period between September 26 to October 25 (Tables 22 and 23).

2. Patrick's CT scan of the head and the neck region taken on November 5th at 2146 showed moderate soft tissue edema in the neck.

3. Patrick lost 290 g during his three days stay in the hospital between November 5th and November 7th (97g per day) as shown in Tables 22 and 23. However, he gained 265 g between November 7th and 21st (19 g/day). These data indicate that he was losing fluid following the cessation of his treatment with Tylenol cold.

Table 22. Patrick's body weights from birth to November 30, 2005

Date & time	Patrick's weight[1]
08/25/05	3.146 kg (6.92 lb)
09/06/05	3.119 kg (6.86 lb)
09/16/05	3.402 kg (7.48 lb)
09/26/05	3.771 kg (8.31 lb)
10/25/05	4.423 kg (9.75 lb)
11/05/05 (0950)	4.930 kg (10.85 lb)
11/05/05 (1810)	4.780 kg (10.52 lb)
11/06/05	4.700 kg (10.34 lb)
11/07/05	4.640 kg (10.21 lb)
11/21/05	4.905 kg (10.79 lb)
11/25/05	4.678 kg (10.29 lb)
11/30/05	4.678 kg (10.29 lb)

Table 23. Patrick's weight gain rates at various intervals between his birth on 8/25/05 and November 30, 2005

Period	Duration days	Weight gain (g)	Weight gain rate (g/day)
08/25-09/26	32	625	20
09/26-10/25	30	625	22
10/25-11/05	11	507	46
11/05-11/07	3	-290[1]	-97
11/07-11/21	14	265	19
11/21-11/30	10	0	0

[1]Patrick lost 290 in three days in the hospital as a result of losing fluid that was retained in his body due to kidney problems.

7.4 The blood levels of acetaminophen and liver enzymes were not measured

It seems that the physicians who examined Patrick on November 5th did not perform the needed clinical tests to rule out acetaminophen intoxication in Patrick's case. The level of acetaminophen in the blood and the activities of aspartate aminotransferase and alanine aminotransferase enzymes in serum are usually measured in suspected cases of acetaminophen intoxication. Below are clinical studies that show these tests are routinely performed in cases of children with history of recent treatment with acetaminophen and developing sudden illness.

1. Daly *et al.* evaluated 249 cases of individuals aged 12 years and older who took acetaminophen at dosage greater than 4 g per 24 hours. At presentation, serum aspartate aminotransferase levels of 50 to 1,000 IU/L were observed in 47 individuals, and in 37 individuals, the aspartate aminotransferase levels were above 1,000 IU/L. No individual with an aspartate aminotransferase level below 50 IU/L at presentation developed hepatotoxicity (aminotransferase >1,000 IU/L).

Seven individuals with aspartate aminotransferase levels of 50 to 1,000 IU/L at presentation subsequently developed hepatotoxicity and one of them died. In addition, six individuals with aspartate aminotransferase levels above 1,000 IU/L at presentation died or received liver transplants. They recommended that individuals with serum acetaminophen level above

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10 mg/L or aspartate aminotransferase level above 50 IU/L to be treated with acetylcysteine [31].

2. James *et al.* collected serum samples from 51 children and adolescents with acetaminophen overdose at the time of routine blood sampling for clinical monitoring. They found that six subjects developed "severe" hepatotoxicity (transaminase elevation > 1,000 IU/L), and 6 subjects had transaminase elevation of 100 to 1,000 IU/L [32].

3. Heubi *et al.* evaluated 47 reports of acetaminophen hepatotoxicity in children (age range, 5 weeks to 10 years) who received 60 to 420 mg/kg/day in 1 to 42 days. The mean peak serum aspartate aminotransferase level was 10,225 IU/L (n = 45), and the mean serum alanine aminotransferase level was 7355 IU/L (n = 31 [13].

4. Tsai *et al.* evaluated the outcome and risk factors for acetaminophen-induced hepatotoxicity in 75 Taiwanese individuals with acute acetaminophen intoxication. They collected data on the serum acetaminophen concentrations and serum aminotransferase concentrations in these individuals. The primary outcome measure was the development of major hepatotoxicity, which was defined as a serum aminotransferase concentration greater than 1000 IU/L. Individuals with a serum acetaminophen concentration above the possible risk line on the nomogram were treated with oral N-acetylcysteine [33].

7.5 Was overlooking acetaminophen intoxication in Patrick's case medically justified?

I am surprised to learn that the treating physicians in two hospitals overlooked to consider acetaminophen intoxication in Patrick's case. Patrick's history shows that he received a high total dose of acetaminophen (Table 4). His acute symptoms and the clinical data described above point toward acetaminophen toxicity.

In addition, the relative high incidence of acetaminophen toxicity in children has been known worldwide. Physicians should consider acetaminophen intoxication when dealing with an ill child who received multiple therapeutic doses of acetaminophen. Larsen and Fuller stated that acetaminophen poisoning is a significant medical problem in the United States [34].

Furthermore, Conejo *et al.* conducted study in Spain to establish the incidence of poisoning caused by oral antipyretics in the Spanish pediatric population occurred between January 1998 to December 2000. All cases of poisoning due to antipyretic ingestion in children aged up to 14 years old were recorded and tabulated. A total of 13,044 cases of drug poisoning were identified. Acetaminophen accounted for 11.0 %, acetylsalicylic acid (ASA) for 3 % and ibuprofen for 1.5 % of the cases ($p < 0.001$). The risk of acetaminophen poisoning was 5.6 higher than that of ibuprofen poisoning (RR: 5.6; 95 % CI: 4.8-6.5) [35].

8. The likely causes of Patrick's subdural bleeding observed on November 5, 2005

On the morning of November 5th, Patrick suffered from acute symptoms of acetaminophen intoxication as described in Section 7 of this report. He was admitted to the Naval Hospital Camp Lejeune (NHCL). The Computerized Tomography (CT) scan of Patrick's head region performed at 0952 revealed the presence of subdural bleeding but the age of the bleeding was not stated. No evidence of skull fracture was observed (Section 5).

Patrick was transported from NHCL to Pitt County Memorial Hospital (PCMH) via ambulance and arrived at 1242 on November 5th. A CT scan of Patrick's head was performed at 1546 on November 5th and it also revealed the presence of subdural bleeding. The age of the bleeding was also not given. The brain appeared normal and no evidence of skull fracture was observed (Section 6).

The treating physicians at both hospitals alleged that the subdural bleeding in Patrick's case was by shaking force [shaken baby syndrome (SBS)]. However; Patrick's CT scans of the head region taken on November 5th did not show evidence of skull fracture or injury caused by trauma. In addition, the age of the subdural bleeding in Patrick's case was not given. Therefore, it cannot be stated medically that the bleeding occurred on November 5th.

Furthermore, it seems that the physicians did not do differential diagnosis or consider all the clinical data collected in this case (Sections 2-7). They made their assumptions cited above based on a theory. Below is a list of some of the clinical data that were not considered by the physicians in Patrick's case.

1. The medical evidence indicates that the main causes of the subdural bleeding in Patrick's case are vitamin K deficiency and his intoxication with acetaminophen. Acetaminophen causes liver damage that reduces the synthesis of the clotting factors. Vitamin K deficiency in infants also causes subdural bleeding. Subdural bleeding has been widely reported in infants suffering from vitamin K deficiency. Patrick had several predisposing factors that led to vitamin K deficiency. These include: a) he was not given 1 mg of vitamin K (IM) following birth; b) he suffered from gastroesophageal reflux, poor feeding problems, and cold and upper respiratory problems. He vomited on many occasions. Patrick suffered from severe anemia, poor weight gain, and low muscle mass as indicated by low creatinine levels in the blood. These biomarkers indicate that his food and vitamin K intake were below normal.

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 protein C, protein S, and protein Z. All of these vitamin K-dependent proteins contain the amino acid γ-carboxyglutamic acid and the carboxyl groups of the glutamic acid residues provide the vitamin-K-dependent proteins with characteristic calcium and phospholipid binding properties [36-40]. The clinical data, clinical studies, and biomarkers that indicate Patrick was suffering from vitamin K deficiency are described below.

2. Patrick's partial thromboplastin time (PTT) measured at 1515 on November 5th was lower than normal (Table 16). Patrick suffered from thrombocytosis (Table 15) and high blood platelet count can influence the result of PPT test [12]. Therefore, Patrick's PPT value is probably not valid in this case.

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3. Patrick's prothrombin time (PT) was measured at 1515 on November 5th and his value was within the normal range (Table 16). However, his normal value does not rule out that the involvement of vitamin K deficiency in causing the subdural bleeding. The PT test was performed at about 9 hours after Patrick's acute nonspecific illness appeared and there is no medical evidence to indicate that his subdural bleeding occurred on November 5th. High PT value can be lowered with less than 8 hours if the infant receives adequate amount of vitamin K.

8.1 Predisposing factors to vitamin K deficiency observed in Patrick's case

8.1.1 Patrick's food and vitamin K intake was lower than normal:

Patrick suffered from gastroesophageal reflux, poor feeding, and cold and upper respiratory problems. He also vomited on many occasions. Patrick's parents reported to Patrick's pediatrician on many occasions that Patrick had feeding problems. For example, on September 6, 2005, Patrick was reported to have a feeding problem and his weight was 6 lb and 14 ounces (3.12 kg). It was one ounce less than his birth weight (6 lb and 15 ounces) recorded on August 25, 2005.

Furthermore, Patrick was diagnosed with gastroesophageal reflux on October 25, 2006 and he was treated with Zantac. The doctor also recommended that Patrick's parents add rice cereal to Patrick's formula or giving Patrick sugar water instead of formula milk to help with his frequent spitting up. The doctor planned to see Patrick again on November 5, 2005 to reevaluate the feeding regimen. On November 4th, Patrick's father called Patrick's pediatrician to let him know that they didn't see marked improvement in Patrick's feeding and his health with the new diet and medications. Patrick was experiencing increased irritability and more vomiting. His appetite was poor and he did not seem to be thriving.

Patrick's severe anemia, low blood creatinine levels, and poor weight gain indicate that his food intake is lower than normal. Patrick's blood analyses performed at PCMH on November 5th, 6th, and 7th revealed that he suffered from severe anemia. His average red blood cell count was 59% of average normal. His average hemoglobin level and hematocrit value were 61% and 47% of the average normal values, respectively (Table 15).

He also suffered from thrombocytosis and thrombocytosis is usually associated with iron deficiency anemia [41, 42]. His average platelet count was 221% of average normal value (Table 15). In addition, Patrick's average serum creatinine value was 22% of the average normal, which indicates that he had low muscle mass (Table 17).

Patrick's weight gain rate was below normal for his age and it was also less than those of his twin sister, Peyton. At birth, he weighted 419 g higher than his sister and after two months their weights became equal (Table 24). Furthermore, at three month of age, Patrick's weight was 464 g less than Peyton's weight. Peyton's weight gain rate was 25 g/day, which was 156% of Patrick's weight gain rate of 16 g/day.

Patrick's weight gain rates at one month and three months of age were also significantly less than the rates of babies at his age as shown in Tables 25 and 26. His weight gain rate at three month of age was about 50% of the rate of a baby with a similar age (Table 26). These data indicate that his food intake was about 50% of normal.

Table 24. Comparison between Patrick's weight and Peyton's weight at birth to November 30, 2005

Date & time	Patrick's weight (1)[1]	Peyton's weight (2)[2]	1 – 2 = (g)
08/25/05	3.146 kg (6.92 lb)	2.727 kg (6 lb)	+ 419
09/26/05	3.771 kg (8.31 lb)	3.380 kg (7.44 lb)	+ 391
10/25/05	4.423 kg (9.75 lb)	4.423 kg (9.75 lb)	0
11/28-30/05	4.678 kg (10.29 lb)	5.142 kg (11.31 lb)	-464

[1]Patrick's weight gain rate between 8/25/05 and 11/30/05 was 16 g/day.
[2]Peyton's weight gain rate between 8/25/05 and 11/30/05 was 25 g/day.

Table 25. Weight gain rates of premature and full term infants during the first month of life

Gestation period (weeks)	Birth weight (g)	Weight (g) at three-month	Weight gain (g per 90 days)	Weight gain rate (g/day)
32	1818	3200	1382	46.1
33	1450	3600	2150	71.7
37	2877	4032	1155	38.5
40	3362	4510	1148	38.3

*Thompson and Cohle [43].

Table 26. Weight gain rates of premature and full term infants at the first three-month of life

Gestation period (weeks)	Birth weight (g)	Weight (g) at three-month	Weight gain (g per 90 days)	Weight gain rate (g/day)
30	1405	4460	3055	33.9
32	1673	4200	2527	28.1
35	2314	5133	2819	31.3
37	2559	5100	2541	28.2
40	3283	6161	2878	32.0

*Thompson and Cohle [43].

8.1.2 Patrick was not given the recommended dose of vitamin K after birth:

It has been recommended that 1mg of vitamin K (IM) to be given to the newborn infant following birth to avoid future development of vitamin K deficiency and bleeding. However, this recommendation was not followed in Patrick's case. The validity of this recommendation is supported by the following clinical observations:

1. Vitamin K is essential because the 1, 4 naphthoquinone nucleus cannot be synthesized by the body and the transfer of vitamin K from mother through placenta to infant is very poor. Bacteria in the intestinal tract synthesize vitamin K and can supply part of the vitamin K requirement but this is not the case in the newborn infant. The neonatal gut is sterile during the first few days of life. The neonatal liver is immature with respect to prothrombin synthesis. Thus, the newborn infant has undetectable level of vitamin K in serum with abnormal amounts of the coagulation proteins and undercarboxylated prothrombin [36-38].

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2. Vitamin K concentrations in human milk are very low. The daily requirement for vitamin K in an infant is about 1μg/kg and breast milk contains 1 to 3 μg vitamin K/L. Plasma phylloquinone concentrations in the infants fed human milk remained extremely low (mean less than 0.25 ng/mL) throughout the first 6 months of life [36-38, 44,45].

Some studies have shown that treating infants with 1 mg of vitamin K (IM) after birth is not enough to maintain high blood levels of vitamin K beyond their first month of life that needed to protect them from developing bleeding. For example, Widdershoven *et al.* treated thirteen breast-fed infants with 1 mg vitamin K1 (IM) at birth. The levels of vitamin K in their plasma reached as high as 32711 ± 25375 pg/mL shortly after birth. However, at one month of age, the vitamin K1 levels in the plasma of these infants were down to 698 ± 536 (n= 9) and this is the range found in breast-fed infants not receiving vitamin K prophylaxis [39]. In addition, Verity *et al.* reported three infants who developed the late-onset form of Hemorrhagic Disease of the Newborn at the age of 4-7 weeks. These infants received one mg of vitamin K at birth [46]. Furthermore, Cornelissen *et al.* treated breast-fed infants at the ages of 2, 4, 8 and 12 weeks with either once 1 mg vitamin K1 orally (n = 165) or intramuscularly (n = 166), or weekly 1 mg orally (n = 48), or daily 25 micrograms orally (n = 58). They found that the two single administrations of 1 mg were insufficient to prevent the appearance of PIVKA-II and vitamin K deficiency after the age of 1 month. When vitamin K was administered at 1 mg per week or 0.025 mg per day, significantly higher concentrations of vitamin K1 were found and no PIVKA-II was detectable [47].

Patrick was fed formula milk that contains higher levels of vitamin K than breast milk (5.3 μg per 100 grams or 3.3 fluid ounces). However, the clinical data presented above show that he did not eat well and he did not receive adequate amount of vitamin K to protect him from developing subdural bleeding. For example, his weight gain rate during his first three months of life was about of 50% of average normal (Table 26). It was also 36% less than those of his twin sister Peyton (Table 24). These data indicate that Patrick food intake was about 50% of average normal.

8.2 The occurrence of intracranial bleeding in infants with vitamin K deficiency

The occurrence of intracranial bleeding in infants due to vitamin K deficiency has been reported worldwide. Infants with unexpected bleeding should be tested for vitamin K deficiency. Choo *et al.* conducted a retrospective study of 42 newborns who were admitted to the hospital for spontaneous bleeding due to vitamin K deficiency. Subdural hemorrhage was the commonest form of intracranial hemorrhage and followed by subarachnoid hemorrhage [48].

In addition, Chaou *et al.* reported late-onset intracranial hemorrhage related to vitamin K deficiency in 32 breast-fed infants (1/2 to 6 months of age). Their CT scans showed mild to severe intracranial hemorrhage. Most (90.6%) had subarachnoid hemorrhage, either alone or in combination with subdural hemorrhage (37.5%), parenchymal hemorrhage (31.3%), or intraventricular hemorrhage (12.5%) [49].

Furthermore, Hanawa *et al.* reported 543 cases of vitamin K deficiency occurring in infants over 2 weeks of age. They divided these infants into three groups based on the causes that led to vitamin K deficiency in these infants. The first group consisted of 427 infants who showed no obvious reasons for vitamin K deficiency. In this group, 387 cases (90.0%) were entirely breast-fed and intracranial hemorrhage was observed in 353 cases (82.7%) of this group. 269 cases (63.0%) developed bleeding episodes between the 1st and 2nd months of age. The second group included 57 cases who had bleeding episodes due to vitamin K deficiency associated with obvious hepatobiliary lesions, chronic diarrhea, long-term antibiotic therapy, etc. The third group, consisting of 59 cases in which a hemorrhagic tendency, without any obvious clinical hemorrhage, was discovered by Normotest, at the time of mass screening [50].

Also, Aydinli *et al.* conducted a retrospective study included 11 babies between 30 and 119 days of age, who developed bleeding due to vitamin K deficiency. The localizations of the intracranial hemorrhage were as follows: intracerebral (91%), subarachnoid (46%), subdural (27%), and intraventricular (27%) [51].

9. The likely causes of a subretinal bleeding in Patrick's case

A physician examined Patrick's eyes at Pitt County Memorial Hospital (PCMH) on November 7th and stated that Patrick has subretinal hemorrhage and a possible macular hole. He alleged that theses lesions were caused by shaking-force. Dr. Johnston examined Patrick's eyes on December 1, 2005 and she didn't agree with the findings that the physician at PCMH had identified subretinal bleeding.

In addition, Dr. Westra examined Patrick's eyes on December 9th and his exam showed clear corneas and clear lenses. On dilated exam, the optic nerve and the macula were normal. Patrick's had very blonde fundus, but there was no sign of retinal hemorrhages, nor any other pathology.

The medical evidence described in Sections 7 and 8 of this report indicate that Patrick suffered from acetaminophen intoxication and vitamin K deficiency. These factors are responsible for causing the subdural bleeding in Patrick's case and can also cause bleeding in other locations of the body.

Furthermore, Patrick blood analyses performed on November 5-7, 2005 revealed that he suffered from severe anemia and thrombocytosis (Tables 10, 15). It has been reported that both of these conditions cause retinal bleeding and other retinal pathology in children and adults. Patrick had low red blood cell count of 2.26 x 10^6/μL (normal range = 2.7-4.9 x 10^6/μL); hemoglobin level of 7.01 g/dL (normal range = 9.0-14.0); and hematocrit value of 20.4% (normal range = 31-55%). His platelet count was 662 x 10^3/μL (normal range = 150-450 x 10^3/μL). Below are clinical studies that show that severe anemia and/or thrombocytosis cause retinal problems.

1. Asien *et al.* evaluated the occurrence of clinically apparent retinal changes in 35 anemic patients and 35 age-and sex-matched healthy control subjects. Retinal photographs of all subjects were obtained and all vascular and extra vascular retinal lesions were recorded. No retinal abnormalities were ob-

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served in the control subjects. Seven (20%) of the anemic patients exhibited extra vascular lesions (flame-shaped hemorrhages, hard exudates, and cotton-wool spots). Within the group of anemic patients, the mean hemtocrit reading for those with extravascular lesions (N=7) was 24.7%. A significant negative correlation was determined between venous length and the level of hematocrit, thereby implying that retinal venous tortuosity is directly related to severity of anemia [52].

2. Carraro *et al.* conducted a cross-sectional study involved 226 patients with anemia and/or thrombocytopenia to evaluate the incident of retinopathy among these patients. A 47 healthy age-matched subjects were used as control. Retinopathy was observed in 28.3% of the patients as a whole, the presence of fundus lesions being closely associated with severe anemia (Hb < 8 g/dL) and severe thrombocytopenia (PLT < 50 x 10^9/L). Among the patients with concomitant anemia and thrombocytopenia, the incidence of retinopathy was 38%. Retinal hemorrhages were found in all of the patients with concomitant severe anemia and thrombocytopenia [53].

3. Kacer *et al.* reported two cases of individuals with ophthalmologic complications associated with mild iron deficiency anemia. The first case is a 37-year-old female who suffered from blurred vision in her left eye for four days. Ophthalmoscopic and angiographic findings were consistent with the diagnosis of central retinal vein occlusion
Further hematologic investigation into possible causes disclosed mild iron deficiency anemia (Hb 9.4 g/dl, hematocrit 30.5%).

The second case is a 50-year-old female, presented with a 1-week-history of blurred vision and metamorphopsia. Her visual acuity was 20/200. Further examination revealed a nonarteritic ischemic optic neuropathy and an iron deficiency anemia as the underlying disease (Hb 7.3 g/dl, hematocrit 25%). They stated that clinicians involved in the management of chronic iron deficiency anemia should be aware of possible ophthalmic manifestations in this disease [54].

4. Nobacht *et al.* reported a case of a 24-year-old man who developed acute vitreous hemorrhage of the right eye. Fluorescein angiography of the right eye showed an avascular peripheral retina with marked capillary nonperfusion, arteriovenous anastomosis, and sea fan neovascularization. Blood studies showed thrombocytosis without other associated systemic diseases. They concluded that the avascular retina in this man was associated with thrombocytosis. They also stated that thrombocytosis may cause an avascular peripheral retina with neovascularization and vitreous hemorrhage in otherwise healthy persons [55].

10. The likely causes of the healed fractured ribs observed in Patrick's case

The CT scan exams of November 5th showed three healed rib fractures on the right side (1st, 8th, and 9th) and four healed rib fractures on the left side (4th, 5th, 7th, and 8th). These fractures were also noted on the X-ray bone survey performed on November 7, 2005 (Table 27).

Patrick's bones were also examined by X-ray of on November 30th and it showed healed fracture of rib 6th on the right side that was not observed on November 7th. The bone survey of November 30th also revealed the presence of four healed rib fractures (4th, 5th, 7th, and 8th) that were observed on November 7th. However, it did not show the healed fractures of the 1st and 9th ribs that were observed on November 7th (Table 27).

The physicians who treated Patrick on November 5-7, 2005 alleged that these healed rib fractures were the result of physical abuse. However, these physicians did not find evidence of injury caused by trauma in Patrick's chest or his back. In addition, the physician who examined Patrick on October 25, 2005 and the paramedics who examined Patrick on November 5th did not report signs of injuries caused by trauma.

The medical evidence indicates that Patrick had several risk factors that have been know to cause rib fractures in children and adults and they should be considered in this case.
These factors include: 1) Patrick suffered from vitamin K deficiency and vitamin K is involved in bone metabolism and calcification. 2) Patrick suffered from protein deficiency and it leads to bone fracture. Patrick suffered from gastroesophageal reflux. He had feeding problems and vomited on many occasions. His weight gain rate during the first three months of his life was 50% below normal. 3) Patrick suffered from gastroesophageal reflux and symptoms of cold and he was coughing for long time. Chronic and severe coughing has been reported to cause rib fractures.
It seems that the treating physicians alleged that Patrick's healed rib fractures were caused by physical trauma without considering the clinical data collected that point toward metabolic problem. They also did not perform differential diagnosis in this case to consider all the possible causes that lead to rib fracture. Below are descriptions of clinical studies that explain the roles of vitamin K and protein deficiency and chronic and sever coughing in causing rib fractures in Patrick's case and other cases.

10.1 Vitamin K deficiency causes bone fractures in children and adults

Some of the bone matrix proteins necessary for normal bone metabolism are vitamin K-dependent. Vitamin K is a coenzyme for glutamate carboxylase, which mediates the conversion of glutamate to gamma-carboxyglutamate (Gla). Gla residues attract Ca^{2+} 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 [36-38, 56, 57]. The following clinical studies show that bone fractures occurred in individuals suffered from vitamin K deficiency.
1. Fenton *et al.* reported two cases of infants who had massive intracranial hemorrhage with no history of trauma. In addition, their radiographic exam of the head revealed the presence of linear parietal fractures that raised the possibility of nonaccidental trauma.

Both infants had severe coagulopathy that resulted from vitamin K deficiency in one infant and disseminated herpes simplex virus infection in the second infant. Both infants died. At autopsy, the parietal bone abnormalities were found to be not

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fractures, but proved to be an anomalous suture in 1 and a connective tissue fissure in the other [58].

2. Bugel stated 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 [56].

He also stated that the current dietary recommendation for vitamin K is one μg /kg of body weight per day is based on saturation of the coagulation system and not on the requirement in relation to bone health. The present daily dietary vitamin K intake in European population is estimated to be in the range 124-375 μg/day and a deficiency based on the hepatic coagulation system would be unusual at these levels. However, recent data suggest that the requirement in relation to bone health might be higher [56].

3. 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) participating in the Framingham Heart Study in 1988-1989. incidence of hip fractures was recorded from 1988 to 1995.

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 [59].

The clinical data and studies described in Section 8 of this report indicate that Patrick suffered from vitamin K deficiency and vitamin K deficiency played a role in the rib fractures observed on November 5-7, 2005. In addition, Patrick's bone survey of November 30th revealed that he had a new rib fracture (rib # 6). The rib 6th fracture also correlates with his poor weight gain and his respiratory tract illness.

Patrick's body weights on November 7th and 30th were 4.678 kg and 4.640 kg, respectively. He gained 1.7 g per day during this period (Table 22). However, his sister Peyton gained 21g per day between October 25th and November 28th (Table 24). Patrick was diagnosed with Respiratory Syncicial Virus (RSV) on 11/21/05 and his parents and grandmother were given instructions for in home care. Patrick's illness did not resolve and he was taken to his doctor on November 28th. Patrick's illness got worse and he was admitted to Onslow Memorial Hospital on November 30th due to RSV complications and bronchitis.

10.2 Protein deficiency causes bone fracture

Tanaka *et al.* stated that protein malnutrition increases the fracture risk due to decreased bone mineral density and muscle weakness [60]. 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 [61]. The clinical data described in this report clearly indicate that Patrick suffered from protein deficiency and it contributed to his rib fractures.

Patrick was diagnosed with gastroesophageal reflux on October 25, 2005. He was irritable and had poor feeding habits. He was consuming a small amount of formula. His parents had changed his brand of formula several times. The doctor also recommended that Patrick's parents add rice cereal to Patrick's formula or to give Patrick sugar water instead of formula milk to help with his frequent spitting.

Furthermore, Patrick's father called Patrick's pediatrician on 11/04/05 to let him know that they didn't see a marked improvement in Patrick's feeding and his health with the new diet and medications. Patrick was experiencing increased irritability and more vomiting. His appetite was poor and he did not seem to be thriving.

Rice cereal and rice milk contain relatively low concentrations of protein compared to the formula milk and feeding these products to infants for significant time instead of formula can result in severe protein deficiency. For example, Carvalho *et al.* reported a case of a 22-month-old male child who developed severe malnutrition. He was breastfed until 13 months of age. Because of a history of chronic eczema and perceived milk intolerance, he was started on a rice beverage after weaning and he consumed about 1.5 L of this drink daily. His intake of solid foods was very poor [62].

Rice beverage is extremely low in protein content and his daily protein intake was 0.3 g/kg/day, which is only 25% of the recommended dietary allowance. Laboratory evaluation was remarkable for a serum albumin of 1.0 g/dL (10 g/L), urea nitrogen <0.5 mg/dL (<0.2 mmol/L), and a normocytic anemia with marked anisocytosis. Evaluation for other causes of hypoalbuminemia was negative [62].

Patrick's low weight gain rate and blood creatinine levels and his severe anemia indicate that he suffered from protein deficiency. His weight gain rate during the first three months of his life was about 50% of normal (Tables 25, 26). His average serum creatinine value on November 5th was 22% of normal, which indicates that he had low muscle mass (Table 17). Patrick's blood analyses on November 5th, 6th, and 7th revealed that he suffered from severe anemia (Table 15). He also suffered from thrombocytosis and thrombocytosis is usually associated with iron deficiency anemia. His average platelet count was 221% of average normal value (Table 15).

10.3 Severe and chronic coughing cause rib fracture

Patrick was diagnosed with gastroesophageal reflux (GER) on October 25, 2005 and gastroesophageal reflux disease (GERD) is associated with severe and chronic cough in many cases. GERD occurs when gastric contents irritate mucosal surfaces of the upper aerodigestive tract. Cezard reported that GER and GERD have a higher prevalence among infants than among children or adults. This is linked to the immaturity of the esophagus and stomach and the higher liquid intake of infants [63].

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Poe and Kallay evaluated one hundred eighty-three individuals with chronic cough (with cough of ≤ 3 weeks) and found that fifty-six of these individuals (30.6%) had gastroesophageal reflux disease (GERD) [64]. Furthermore, Issing *et al.* conducted study included 40 patients, who presented to the department of Otolaryngology with chronic complaints of at least one of the following symptoms or disorders during a minimum period of 3 months: dysphagia (n = 28), sensation of globus pharyngeus (n = 28), hoarseness (n = 20), odynophagia (n = 22), heartburn (n = 16), postnasal drip (n = 15), sore throat (n = 22), cough (n = 14), throat clearing (n = 11), laryngospasm (n = 6), and voice fatigue (n = 6). Gastroesophageal reflux disease (GERD) was diagnoses in 48% of these individuals [65].

It has been reported that chronic and severe coughing cause rib fracture in people with low bone density and people with normal bone density as shown by the clinical studies described below. I believe that Patrick's chronic coughing also contributed significantly to his rib fractures.

1. Hanak *et al.* conducted a retrospective study to define the demographic, clinical, and radiological features of individuals with cough-induced rib fractures and to assess potential risk factors. They identified 54 individuals (78% female), mean age of 55 years, with cough-induced rib fractures who were diagnosed at the Mayo Clinic in Rochester, Minnesota, between 1996 and 2005. These individuals presented with chest wall pain after onset of cough. Rib fracture was associated with chronic cough (≥ 3 weeks'
duration) in 85% of these individuals. The most common causes of the chronic cough were postnasal drip, chronic bronchitis, and gastoesophageal reflux. Rib fractures were documented by chest radiography, rib radiography, computed tomography, or bone scan.

They found 112 fractured ribs in these individuals and one half of these individuals had more than one fractured rib. Right-sided rib fractures alone were present in 17 individuals (26 fractured ribs), left-sided in 23 individuals (35 fractured ribs), and bilateral in 14 individuals (51 fractured ribs). The most commonly fractured rib on both sides was rib 6. The fractures were most common at the lateral aspect of the rib cage. They found that cough-induced rib fractures occurred in individuals with reduced bone density and in individuals with normal bone density [66].

2. De Maeseneer *et al.* reported three individuals who developed stress fractures of the ribs induced by coughing. Bone scintigraphy, performed 1 to 2 weeks after initial onset of symptoms, showed a focal area of increased uptake along the chest wall in all cases. Thin section angulated helical CT directly visualized the subtle rib fractures [67].

3. Suga *et al.* reported two individuals with cough related stress fractures of the ribs. These individuals complained of cough and chest pain with respiratory infection. The initial chest radiographs showed only an infiltrative shadow due to bronchopneumonia in the lung field but it failed to reveal any definite osseous abnormality of the ribs. Follow up chest radiographs revealed a callus formation in the fracture sites.

In both individuals, fracture sites were multiple and located at the axillary line, and radionuclide bone scan disclosed focal abnormal concentrations of activity in these characteristic locations of the lesions. Moreover, there were abnormal accumulation sites in the adjacent above and below ribs, and this finding also seemed to be characteristic of cough related stress fractures of the ribs [68].

4. Prasad and Baur reported a case of a first rib fracture in an 11-year-old boy secondary to pertussis infection. He developed a sudden onset of severe right-sided pleuritic chest pain following a 6 week history of a coughing illness and considerable weight loss. Pertussis was clinically suspected and proven on serology and the pain was determined to be due to a first rib fracture [69].

5. Rob *et al.* evaluated a case of a 54-year-old man with pneumonia who developed severe pain in the lateral and basal part of the left thorax after a severe coughing bout. The chest radiograph demonstrated fractures of the eighth to tenth rib on the left and extrathoracic sickle-shaped collection of air in the left laterobasal area. Computed tomography additionally showed prolapsed of pulmonary tissue on pressing. This was a case of "cough fracture", complicated by herniation of lung tissue [70].

6. Roberge *et al.* reported a case of multiple rib fractures induced by a paroxysm of coughing in an elderly woman. They stated that this disorder may be under diagnosed and should be considered in any individual with an acute onset of chest pain following coughing or sneezing [71].

Table 27. Patrick's healed rib fractures observed on November 5th, 7th, and 30th

Date	Exam type	Rib fractures and positions
11/05/05	CT scan of spine	1) A subacute fracture involving the lateral right rib 1st. 2) An older subacute fracture involving left posterior rib 4th.
11/05/05	CT scan of the abdomen	1) Healing subacute fractures involving the right posterior ribs 8th and 9th. 2) Healing subacute fractures involving left posterior ribs 7th and 8th.
11/05/05	Skeletal Survey (X-ray)	1) Multiple fractures involving the right lateral ribs 1st, 8th, and 9th posterior ribs with exuberant callus. 2) Multiple fractures involving the left posterior 4th, 5th, 7th, and 8th ribs with exuberant callus formation involving the 7th and 8 ribs.
11/30/05	Chest X-ray exam	1) Healed fractures of the posterior aspect of right 6th and 8th ribs. 2) Healed fractures of the posterior aspect of the left 4th and 5th ribs. 3) Questionable healed fractures of the posterior aspect of the left 7th and 8th ribs.
12/01/05	Skeletal Survey (X-ray)	1) Old healing fractures of the posterior aspect of the right 6th and 8th ribs. 2) Old healing fractures of the posterior aspect of the left 4th, 5th, 7th, and 8th ribs

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11. Conclusions and recommendations

The medical evidence clearly shows that the likely causes for Patricks's subdural and subretinal bleeding and the old rib fractures are his health problem, adverse reactions to vaccines, intoxication with acetaminophen, and vitamin K and protein deficiency. Zantac® (ranitidine) potantiated the hepatotoxicity of acetaminophen. Patrick's rib fractures resulted from the synergistic actions of vitamin K and protein deficiency and severe and chronic coughing caused by his acid reflux. In addition, Patrick suffered from severe anemia and thrombocytosis and these conditions cause retinal bleeding and other abnormalities.

The physicians who examined Patrick on November 5-7, 2005 alleged that Patrick's subdural and subretinal bleeding resulted from shaking force [shaken baby syndrome (SBS)]. They also alleged that Patrick's healed rib fractures were caused by physical abuse. It seems that these physicians alleged that Patrick's health problems were the result of abuse without performing differential diagnosis in this case or considering the clinical data that point to different causes.

Furthermore, these physicians overlooked the clinical evidence and Patrick's treatment history with Tylenol that indicate he was suffering from acute acetaminophen intoxication. In addition, they did not perform tests to measure the levels of acetaminophen and liver enzymes in Patrick's serum to rule out acetaminophen intoxication involvement in Patrick's case.

The physicians at Pitt County Memorial Hospital (PCMH) discharged Patrick from the hospital on November 8, 2005 without giving him treatment for his severe anemia and thrombocytosis. Iron deficiency is one of the causes of thrombocytosis in children and adults. Patrick continued to suffer from health problem after his release from the PCMH. He gained very little weight (1.7 g/day) between November 8th and November 30th and his rib 6 was fractured during this period as a result of protein and vitamin K deficiency and severe chronic cough. He developed respiratory illness that led to his hospitalization on November 30, 2005.

Patrick's pediatrician treated Patrick with Zantac® and Tylenol® cold for 11-16 days without considering the synergistic actions between these medications in causing liver toxicity. In addition, Patrick was vaccinated with six vaccines on October 25, 2005 while he was sick and receiving Tylenol® cold treatment. It has been shown that ill children are more susceptible to develop adverse reactions to vaccines than healthy children.

I believe that the following recommendations will assist Patrick's physicians to better monitor and treat Patrick's health condition: a) long term treatment with Tylenol® should be avoided and should not be given with Zantac®. Zantac® potentiates the toxicity of acetaminophen; b) vaccinations should be delayed if the child is sick. Sick children are more susceptible to develop adverse reactions to vaccines than healthy children; c) Patrick should be monitored and treated for vitamins K, B, and folic acid deficiency, protein deficiency, severe anemia, and thrombocytosis. These conditions cause subdural and retinal bleeding, rib fractures, and other health problems.

References

[1] Patrick's medical records from birth to December 7, 2005.
[2] Peyton's medical records from birth to November 28, 2005.
[3] Patrick's mother's medical records (1996-2005).
[4] Physicians' Desk Reference, Edition 53, 1999. Medical Economics Company, Inc, Montavale, NJ, USA.
[5] Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, Haber P, Pless RP, Mootrey G, Ellenberg SS, Braun MM, Chen RT. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)--United States, 1991-2001. MMWR Surveill Summ. 2000; 52(1):1–24.
[6] Braun MM, Mootrey GT, Salive ME, Chen RT, Ellenberg SS. Infant immunization with acellular pertussis vaccines in the United States: assessment of the first two years' data from the Vaccine Adverse Event Reporting System (VAERS). Pediatrics 2000;106(4):E51.
[7] Braun MM and Ellenberg SS. Descriptive epidemiology of adverse events after immunization: reports to the Vaccine Adverse Event Reporting System (VAERS), 1991-1994. J Pediatr. 1997;131(4):529–35.
[8] Classen JB and Classen DC. Clustering of cases of insulin dependent diabetes (IDDM) occurring three years after haemophilus influenza B (HiB) immunization support causal relationship between immunization and IDDM. Autoimmunity 2002; 35(4):247–53.
[9] Wise RP, Iskander J, Pratt RD, Campbell S, Ball R, Pless RP, and Braun MM. Postlicensure safety surveillance for 7-valent pneumococcal conjugate vaccine. JAMA 2004;292(14):1702–10.
[10] Stratton KR, Howe CJ, Johnston RB. Adverse Events associated with Childhood Vaccines Other Than Pertussis and Rubella. JAMA 1994; 271:1602–5.
[11] Fisher MA, Eklund SA, James SA, and Lin X. Adverse Events Associated with Hepatitis B Vaccine in U.S. Children less than six years of age, 1993 and 1994. AEP, 2001; 11(1)::13–21.
[12] Activated Partial Thromboplastin Time [CO003400]. Available online at http://www.massgeneral.org/pathology/coagbook/co000100.htm#co000100
[13] Heubi JE, Barbacci MB, Zimmerman HJ. Therapeutic misadventures with acetaminophen: Hepatoxicity after multiple doses in children. J Pediatr. 1998 Jan; 132(1):22–7.
[14] Shahroor S, Shvil Y, Ohali M, Granot E. Acetaminophen toxicity in children as a "therapeutic misadventure". Harefuah. 2000 Apr 16;138(8):654–7, 710.
[15] Pershad J, Nichols M, King W. "The silent killer": chronic acetaminophen toxicity in a toddler. Pediatr Emerg Care. 1999 Feb;15(1):43–6.
[16] Fauci AS, Braunwald E, Isslbacher KJ, Wilson, JD, Martin JB, Kasper DL, Hauser SL, Longo DL. Harrison's Principles of Internal Medicine. McGraw-Hill Companies, Inc. New York USA, ed. 14, 1998.
[17] Smith DW, Isakson G, Frankel LR, Kerner JA Jr. Hepatic failure following ingestion of multiple doses of acetaminophen in a young child. J Pediatr Gastroenterol. Nutr. 1986 Sep-Oct;5(5):822–5.
[18] Arana A, Morton NS, Hansen TG. Treatment with paracetamol in infants. Acta Anaesthesiol Scand. 2001 Jan;45(1):20–9.
[19] American Academy of Pediatrics. Committee on Drugs. Acetaminophen toxicity in children. Pediatrics. 2001 Oct;108(4):1020–4.
[20] Mitchell MC, Schenker S, Speeg KV Jr. Selective inhibition of acetaminophen oxidation and toxicity by cimetidine and other histamine H2-receptor antagonists *in vivo* and *in vitro* in the rat and in man. J Clin Invest. 1984 Feb;73(2):383–91.
[21] Gibson JD, Pumford NR, Samokyszyn VM, Hinson JA. Mechanism of acetaminophen-induced hepatotoxicity: covalent binding versus oxidative stress. Chem Res Toxicol. 1996 Apr-May;9(3):580–5.
[22] Leonard TB, Morgan DG, Dent JG. Ranitidine-acetaminophen interaction: effects on acetaminophen-induced hepatotoxicity in Fischer 344 rats. Hepatology. 1985 May-Jun;5(3):480–7.
[23] Rogers SA, Gale KC, Newton JF, Dent JG, Leonard TB. Inhibition by ranitidine of acetaminophen conjugation and its possible role in ranitidine potentiation of acetaminophen-induced hepatotoxicity. J Pharmacol Exp Ther. 1988 Jun;245(3):887–94.
[24] Muniz AE, Rose SR 2nd, Liner SR, Foster RL. Unsuspected acetaminophen toxicity in a 58-day-old infant. Pediatr Emerg Care. 2004 Dec; 20(12):824–8.

doi: 10.1588/medver.2006.03.00120

[25] Roach JA, Stacey B. Acetaminophen toxicity. Orthop Nurs. 1997 May-Jun;16(3):49–53; quiz 54–5.
[26] Jaeschke H. How relevant are neutrophils for acetaminophen hepatotoxicity? Hepatology. 2006 Jun;43(6):1191–4.
[27] James LP, Farrar HC, Darville TL, Sullivan JE, Givens TG, Kearns GL, Wasserman GS, Simpson PM, Hinson JA. Elevation of serum interleukin 8 levels in acetaminophen overdose in children and adolescents. Clin Pharmacol Ther. 2001 Sep;70(3):280–6.
[28] James LP, Simpson PM, Farrar HC, Kearns GL, Wasserman GS, Blumer JL, Reed MD, Sullivan JE, Hinson JA. Cytokines and toxicity in acetaminophen overdose. J Clin Pharmacol. 2005 Oct;45(10):1165–71.
[29] Lawson JA, Farhood A, Hopper RD, Bajt ML, Jaeschke H. The hepatic inflammatory response after acetaminophen overdose: role of neutrophils. Toxicol Sci. 2000 Apr;54(2):509–16.
[30] Liu ZX, Han D, Gunawan B, Kaplowitz N. Neutrophil depletion protects against murine acetaminophen hepatotoxicity. Hepatology. 2006 Jun; 43(6):1220–30.
[31] Daly FF, O'Malley GF, Heard K, Bogdan GM, Dart RC. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med. 2004 Oct;44(4):393–8.
[32] James LP, Farrar HC, Sullivan JE, Givens TG, Kearns GL, Wasserman GS, Walson PD, Hinson JA, Pumford NR. Measurement of acetaminophen-protein adducts in children and adolescents with acetaminophen overdoses. J Clin Pharmacol. 2001 Aug;41(8):846–51.
[33] Tsai CL, Chang WT, Weng TI, Fang CC, Chen WJ. Acute acetaminophen intoxication in Taiwan: outcomes and risk factors. J Formos Med Assoc. 2004 Nov; 103(11):830–5.
[34] Larsen LC, Fuller SH. Management of acetaminophen toxicity. Am Fam Physician. 1996 Jan;53(1):185–90.
[35] Conejo Menor JL, Lallana Dupla MT. Antipyretic poisoning. An Esp Pediatr. 2002 Apr;56(4):318–23
[36] Al-Bayati MA. Analysis of Causes That Led to Baby Lucas Alejandro Mullenax-Mendez's Cardiac Arrest and Death in August-September of 2002. Medical Veritas 2005; 1(1):45–63.
[37] Al-Bayati MA. Analysis of causes that led to bleeding, cardiac arrest, and death in the case of Baby Nadine. Medical Veritas 2006; 3(2): 997–1012.
[38] The Merck Manual of Diagnosis and Therapy. Beets MH, Berkow R, eds. 17th ed., 1999. Published by Merck Research Laboratories, Whitehouse Station, N.J.
[39] Widdershoven J., Labert W., Motohara K., *et al.* Plasma concentrations of vitamin K1 and PIVKA-II in bottle-fed and breast-fed infants with and without vitamin K prophylaxis at birth. European Journal of Pediatrics. 1988;148:139–42.
[40] Sutor AH, von Kries R, Cornelissen EA, McNinch AW, Andrew M. Vitamin K deficiency bleeding (VKDB) in infancy. ISTH Pediatric/Perinatal Subcommittee. International Society on Thrombosis and Haemostasis. Thromb Haemost. 1999; 81(3):456–61.
[41] Diagne I, Sall MG, Camara B, Ndiaye O, Sarr M, Ba M, Sow HD, Kuakuvi N. Major thrombocytosis associated with severe anemia in children. Diagnosis of 9 Cases. Dakar Med. 2002;47(1):52–6.
[42] Tamura T, Konno K, Matsumoto S, Gotou T. An infantile case of cerebral infarction associated with thrombocytosis. No To Hattatsu. 1992 May; 24(3):257–61.
[43] Thompson WS, Cohle SD. Fifteen-year retrospective study of infant organ weights and revision of standard weight tables. J Forensic Sci. 2004 May; 49(3):575–85.
[44] Greer FR. Vitamin K status of lactating mothers and their infants. Acta Paediatr. 1999; Suppl 88(430):95–103.
[45] Greer FR, Marshall S, Cherry J, Suttie JW. Vitamin K status of lactating mothers, human milk, and breast-feeding infants. Pediatrics. 1991; 88(4):751–6.
[46] Verity CM, Carswell F, Scott GL. Vitamin K deficiency causing infantile intracranial haemorrhage after the neonatal period. Lancet 1983; I: 1439.
[47] Cornelissen EA, Monnens LA. Evaluation of various forms of vitamin-K prophylaxis in breast-fed infants. Ned Tijdschr Geneeskd 1993; 137(43):2205–8.
[48] Choo KE, Tan KK, Chuah SP, Ariffin WA, Gururaj A. Haemorrhagic disease in newborn and older infants: a study in hospitalized children in Kelantan, Malaysia. Ann Trop Paediatr. 1994; 14(3):231–7.
[49] Chaou WT, Chou ML, Eitzman DV. Intracranial hemorrhage and vitamin K deficiency in early infancy. J Pediatr. 1984; 105(6):880–4.
[50] Hanawa Y, Maki M, Murata B, Matsuyama E, Yamamoto Y, Nagao T, Yamada K, Ikeda I, Terao T, Mikami S, *et al.* The second nation-wide survey in Japan of vitamin K deficiency in infancy. Eur J Pediatr. 1998; 147(5):472–7.
[51] Aydinli N, Citak A, Caliskan M, Karabocuoglu M, Baysal S, Ozmen M. Vitamin K deficiency--late onset intracranial haemorrhage. Eur J Paediatr Neurol. 1998; 2(4):199–203.
[52] Aisen ML, Bacon BR, Goodman AM, Chester EM. Retinal abnormalities associated with anemia. Arch Ophthalmol. 1983;101(7):1049–52.
[53] Carraro MC, Rossetti L, Gerli GC. Prevalence of retinopathy in patients with anemia or thrombocytopenia. Eur J Haematol. 2001;67(4):238–44.
[54] Kacer B, Hattenbach LO, Horle S, Scharrer I, Kroll P, Koch F. Central retinal vein occlusion and nonarteritic ischemic optic neuropathy in 2 patients with mild iron deficiency anemia. Ophthalmologica. 2001 Mar-Apr;215(2):128–31.
[55] Nobacht S, Cruysberg JR, Deutman AF. Peripheral retinal nonperfusion associated with essential thrombocytosis. Am J Ophthalmol. 1999 Jan;127(1):101–2.
[56] Bugel S. Vitamin K and bone health. Proc Nutr Soc. 2003 Nov;62(4):839–43.
[57] Iwamoto J, Takeda T, Sato Y. Effects of vitamin K2 on osteoporosis. Curr Pharm Des. 2004;10(21):2557–76.
[58] Fenton LZ, Sirotnak AP, Handler MH. Parietal pseudofracture and spontaneous intracranial hemorrhage suggesting nonaccidental trauma: report of 2 cases. Pediatr Neurosurg. 2000 Dec;33(6):318–22.
[59] Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, Wilson PW, Ordovas J, Schaefer EJ, Dawson-Hughes B, Kiel DP. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr. 2000 May;71(5):1201–8.
[60] Tanaka K, Nakanishi Y, Kido S. Role of nutrition in the treatment of osteoporosis. Clin Calcium. 2005 Apr;15(4):666–72.
[61] Rizzoli R, Ammann P, Chevalley T, Bonjour JP. Protein intake and bone disorders in the elderly. Joint Bone Spine. 2001 Oct;68(5):383–92.
[62] Carvalho NF, Kenney RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. Pediatrics. 2001 Apr;107(4):E46.
[63] Cezard JP. Managing gastro-oesophageal reflux disease in children. Digestion. 2004;69(Suppl 1):3–8.
[64] Poe RH, Kallay MC. Chronic cough and gastroesophageal reflux disease: experience with specific therapy for diagnosis and treatment. Chest. 2003 Mar;123(3):679–84.
[65] Issing WJ, Gross M, Tauber S. Manifestations of gastroesophageal reflux in the otorhinolaryngology tract. Laryngorhinootologie. 2001 Aug; 80(8):464–9.
[66] Hanak V, Hartman TE, Ryu JH. Cough-induced rib fractures. Mayo Clin Proc. 2005 Jul;80(7):879–82.
[67] De Maeseneer M, De Mey J, Debaere C, Meysman M, Osteaux M. Rib fractures induced by coughing: an unusual cause of acute chest pain. Am J Emerg Med. 2000 Mar;18(2):194–7.
[68] Suga K, Nishigauchi K, Fujita T, Kawata Y, Yoneshiro S, Oono T, Arita T, Nakanishi T, Utsumi H, Yamada N. Bone scintigraphy in two cases with cough related stress fractures of rib. Kaku Igaku. 1992 Apr; 29(4):495–9.
[69] Prasad S, Baur LA. Fracture of the first rib as a consequence of pertussis infection. J Paediatr Child Health. 2001 Feb;37(1):91–3.
[70] Rob PM, Link J, Dalhoff K. Extrathoracic prolapse of the pulmonary parenchyma after a bout of coughing with spontaneous serial rib fractures. Dtsch Med Wochenschr. 1993 May 14;118(19):701–4.
[71] Roberge RJ, Morgenstern MJ, Osborn H. Cough fracture of the ribs. Am J Emerg Med. 1984 Nov;2(6):513–7.

doi: 10.1588/medver.2006.03.00120