Analysis of causes that led to Eliza Jane Scovill's cardiac arrest and death

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Abstract

My review of the medical evidence presented in this case and the pertinent medical literature clearly shows that Eliza Jane's death was not caused by *Pneumocystis carinii* Pneumonia (PCP) as alleged by the medical examiner, or any other type of pneumonia. Eliza Jane's lungs did not show an inflammatory response to medically justify a diagnosis of pneumonia. Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma.

Eliza Jane's death resulted from an acute allergic reaction to amoxicillin, which caused severe hypotension (due to the leakage of significant amount of fluid outside the blood vessels), shock, and cardiac arrest. The autopsy revealed that she had pericardial and pleural effusion and ascites. In addition, her organ weights (lungs, heart, liver, and kidneys) were increased significantly. The weight of Eliza Jane's lungs, heart, liver, and kidneys were 184%, 131%, 121%, and 146% of the expected average normal weight for her age, respectively. Also, her liver was significantly enlarged and the hepatocytes show micro-and macrovesicular steatosis. Amoxicillin has been known to induce immune mediated toxic changes in the liver.

Eliza Jane suffered from an upper respiratory tract infection for about three weeks prior to her death on May 16, 2005. My investigation indicates that her respiratory infection was probably caused by Human Parvovirus B19 (HPVB19) infection. HPVB19 has been known to cause upper respiratory tract infection, encephalitis, and aplastic anemia in children and adults. Eliza Jane had non-specific microscopic lesions in the brain consisting of microglia and multineucleated giant cells. These lesions could be caused by HPVB19.

Keywords: Amoxicillin allergic reaction, HPV B19, HIV, Pneumocystis carinii Pneumonia (PCP), thymic atrophy, anemia, cardiac arrest

Summary of the case and findings

Eliza Jane Scovill suffered from cardiac arrest and died following administration of four doses of amoxicillin (400 mg twice a day) to treat an ear infection. She died in Los Angeles, California on May 16, 2005 at the age of 3.5 years. Eliza Jane is a white female child who did not suffer from unusual or serious acute or chronic health conditions prior to her upper respiratory tract infection on April 30, 2005.

Dr. Chanikarn Changsri, the medical examiner at the Los Angeles County Coroner, conducted an autopsy on Eliza Jane on May 18, 2005 (Case No 2005-03767) and investigated this case. The neuropathology consultant conducted an investigation on the brain tissue to check for pathological changes.

They described their findings in a report signed by Dr. Changsri and Dr. James K. Ribe on September 15, 2005. Changsri concluded that Eliza Jane's death was caused by *Pneumocystis carinii* Pneumonia due to Acquired Immunodeficiency Syndrome. The neuropathology consultant reported that Eliza Jane had HIV-induced brain encephalitis.

Christine Maggiore and Robin Scovill, Eliza Jane's parents, requested that I evaluate the medical evidence in their daughter's case to identify the probable cause(s) of her sudden acute illness and death. I evaluated Eliza Jane's medical records, autopsy report, and the pertinent published medical literature using differential diagnosis. I described the medical evidence and my findings in this case in Sections 1-5 of this report, and present my conclusions in Section 6.

My review of the medical evidence presented in this case and the pertinent medical literature clearly shows that Eliza Jane's death was not caused by *Pneumocystis carinii* Pneumonia (PCP) as alleged by the medical examiner, or any other type of pneumonia. Eliza Jane's lungs did not show an inflammatory response to medically justify a diagnosis of pneumonia. Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma.

Eliza Jane's death resulted from an acute allergic reaction to amoxicillin, which caused severe hypotension (due to the leakage of significant amount of fluid outside the blood vessels), shock, and cardiac arrest. The autopsy revealed that she had pericardial and pleural effusion and ascites. In addition, her organ weights (lungs, heart, liver, and kidneys) were increased significantly. The weight of Eliza Jane's lungs, heart, liver, and kidneys were 184%, 131%, 121%, and 146% of the expected average normal weight for her age, respectively. Also, her liver was significantly enlarged and the hepatocytes show micro-and macrovesicular steatosis. Amoxicillin has been known to induce immune mediated toxic changes in the liver.

Eliza Jane suffered from an upper respiratory tract infection for about three weeks prior to her death on May 16, 2005. My investigation indicates that her respiratory infection was probably caused by Human Parvovirus B19 (HPVB19) infection. HPVB19 has been known to cause upper respiratory tract infection, encephalitis, and aplastic anemia in children and adults. Eliza Jane had non-specific microscopic lesions in the brain consisting of microglia and multineucleated giant cells. These lesions could be caused by HPVB19.

In addition, Eliza Jane suffered from severe anemia as shown by her blood analysis and the atrophy of her bone marrow. Amoxicillin has also been known to cause bone marrow depression and anemia. The clinical evidence and the rapid development of anemia indicate that her anemia and bone marrow depression was caused by the amoxicillin exacerbated by synergistic actions with an upper respiratory tract infection most likely caused by HPVB19 infection.

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Furthermore, Eliza Jane's thymus and spleen showed atrophy, which was caused by the stress from her three week illness with an upper respiratory tract infection. Atrophy of the thymus and other lymphoid organs has been widely reported in individuals suffering from a variety of illnesses caused by infections. The degree of atrophy in the thymus is dependent on the duration and the type of illness.

The medical examiner (ME) in Los Angeles County and the neuropathology consultant were assigned to investigate Eliza Jane's case and to find the probable cause(s) of her death. Unfortunately, they overlooked the overwhelming data described in this report that show Eliza Jane died as a result acute allergic reaction to amoxicillin. Also, they failed to explain the significance of the abnormal changes observed in the thymus, bone marrow, spleen, and the liver evidenced in this case. In addition, they did not perform differential diagnosis to find the probable cause(s) for the changes observed in these organs.

The ME based her conclusion that Eliza Jane died as a result of *Pneumocystis carinii* Pneumonia due to Acquired Immunodeficiency Syndrome only on the presence of *Pneumocystis carinii* (PC) and not PCP. The presence of this opportunistic microorganism in the lung tissue alone cannot be the cause of death as Eliza Jane's lungs did not show any inflammatory response as revealed by the ME's microscopic examination of the H&E slides of the lungs. PC has been widely isolated from the lungs of HIV-negative individuals who were suffering from chronic illness and/or treated with immunosuppressive agents. Eliza Jane had severe atrophy of the thymus and bone marrow due to a three week illness as stated above.

The neuropathology consultant called the non-specific microscopic lesions found in the brain HIV encephalitis. He based his assumption on finding non-specific lesions in the brain (microglial nodules and multinucleate giant cells) and the detection of HIV core protein p24 in the brain tissue using immunohistochemical reactions. I find his conclusion in this case scientifically invalid based on the following facts:

1) The presence of multinucleated giant cells and monocytes in the brain is not a pathognomonic lesion to a certain illness. Macrophages appear in the brain tissues in response to infectious and non-infectious agents and giant cell formation appears to be the incidental result of macrophages ingesting material in close apposition to other macrophages.

2) Microglia are phagocytic elements of the central nervous system (CNS). They proliferate and show reactive changes in areas of injury from any cause. Two patterns are recognized, namely, focal microglial nodules and diffuse microgliosis.

3) Brain tissue false positive for HIV infection was detected in tissues with inflammation obtained from HIV-negative individuals using the immunocytochemical approach. No control tissue sections were used in the neuropathology consultant's study having similar conditions to the brain sections in Eliza Jane's case.

Regarding use of immunocytochemical assay, there are three elements in Eliza Jane's case that should be considered when performing immunocytochemical assay: 1) an inflammation was observed in her brain; 2) she suffered from allergic reaction to amoxicillin which has been known to cause type I, II, III, and IV immune mediated reactions; 3) HPV B19 infection has been reported to cause immune mediated reactions. These three elements acting individually or collectively can probably cause a false positive for HIV proteins using an immunohistochemical test.

4) The neuropathology consultant did not consider HPV B19 infection in his differential diagnosis in this case. HPV B19 infection has also been known to cause encephalitis in humans and to induce lesions in the brain consisting of multinucleated giant cells of macrophage/microglia lineage and microglia cells. Eliza Jane also showed other clinical biomarkers for HPV B19 infection as described above.

The autopsy on Eliza Jane's body was performed on May 18, 2005 and the ME released her report on this case on September 15, 2005. The ME and neuropathology consultant had approximately four months to investigate this case and to identify the cause of death. After careful analysis of the medical evidence in this case, I believe they reached the wrong conclusion about the causes of illness and death, and that their incorrect conclusion is due to an incomplete and unscientific investigation.

1. Eliza Jane's Clinical History from Birth to Death On May 16, 2005

1.1 Eliza Jane's clinical history prior to her respiratory illness on April 30, 2005

Eliza Jane is a 3.5-year-old white female. She was born on December 3, 2001 by natural birth. She was a healthy newborn. Her body weight at birth was 7 pounds (10^{th} percentile). She was breast-fed. Three pediatricians examined and monitored Eliza Jane's health during her life. She did not suffer from any unusual or serious acute or chronic illness prior to an upper respiratory tract infection on April 30, 2005. She enjoyed good health and gained 22 pounds during her life. She was never vaccinated.

1.2 Eliza Jane's upper respiratory illness and her treatment with amoxicillin

Eliza Jane suffered from an upper respiratory tract infection on April 30, 2005.

Her cough and nasal congestion resolved, however pediatricians noted fluid in her eardrums at all visits and recommendations were given to treat this condition with non-pharmaceutical remedies. On May 14^{th}, one of her physicians noted redness in addition to fluid in her right eardrum and prescribed amoxicillin (400 mg/twice a day). The physician who examined Eliza Jane on May 14^{th} found her lungs were clear. [1]. Her lungs were also found to be clear on prior visits with other pediatricians on April 30^{th} and May 5^{th}.

1.3 Acute symptoms developed following treatment with amoxicillin

Eliza Jane's treatment with amoxicillin (400 mg/twice a day) started at about 18:25 on May 14^{th}. Eliza Jane was never treated with antibiotics before this time [1]. Eliza Jane's condition appeared to worsen after receiving the second dose of amoxicillin. Her mother described Eliza Jane's condition during the course

of her treatment with amoxicillin as follows: On May 15th, Eliza Jane vomited several times throughout the day and was pale. After dinner, she seemed agitated and then, at some point, lethargic. She had a fever of 101.1-degrees F, but her extremities felt cold to the touch [1, 2]. She suffered from cardiac arrest shortly after receiving the fourth dose on the evening of May 15th.

Eliza Jane's parents called the physician that had prescribed the amoxicillin just before midnight on May 15th to report the new symptoms and ask for advice. Eliza Jane stopped breathing as they were talking with the physician. They hung up and called 911. The 911 call was placed at 0003 on May 16th and the paramedics arrived at Eliza Jane's house at 0006 [1,2]. Eliza Jane's father stated that Eliza Jane was not looking well, seemed to be deteriorating, and in front of him she became incoherent, then her arms seemed to change color, her eyes rolled up, and she collapsed. She was without a pulse and was not breathing. The father started CPR as the ambulance was in arrival with compressions and mouth-to-mouth resuscitation per instructions from the 911 operator.

1.4 Treatment given by paramedics

The Los Angeles City Fire Department RA 239 was dispatched on May 16th at 0003 and arrived at Eliza Jane's home at 0006 [1,2]. Upon the paramedics' arrival, Eliza Jane was found pulseless and apneic on the floor. She was cyanotic with cold extremities and asystolic on the cardiac monitor. Eliza Jane was transported to Valley Presbyterian Hospital (VPH). CPR and ventilations were done via-bag-valve-mask en route to the hospital. She was presented at the emergency room at 0026 and was intubated on arrival [2].

2. Description of clinical events and treatment at Valley Presbyterian Hospital

Eliza Jane was presented at the emergency room of Valley Presbyterian Hospital (VPH) at 0026 on May 16th. On arrival, she was pulseless, had no spontaneous respiration, and appeared very pale. Her pupils were mid position and fixed. Her rectal temperature was 100.6 F. CPR was continued and Eliza Jane was intubated with # 5 ET tube orotracheally. There were no significant secretions in the orophyranx. Breath sounds were heard bilaterally [2].

The treating physician examined Eliza Jane and found that her abdomen and her liver were distended. Her extremities were cold and poorly perfused with non-palpable pulses. Her oral mucous membranes were pink and there was a lesion on her lower lip.

An IV was started in the left hand and Eliza Jane was given epinephrine 0.3mg IV push. This was followed by sodium bicarbonate13 mEq IV push. The epinephrine was repeated three minutes after the first dose, this time with higher dose of epinephrine 1.3 mg IV push. She remained in asystole and CPR was continued. She was given another 13 mEq of sodium bicarbonate.

Eliza Jane started to have a spontaneous electrical impulse, though it was very slow. She was given atropine 0.26 mg IV push and this was followed by epinephrine 1.3 mg IV push. Approximately after the atropine and the last epinephrine, her heart rate came up to 122 b/minute, then to 152 b/min at approximately 0039.

At 0105, her heart rate began to slow down into the 40-60 b/min range and she did not have a palpable pulse. CPR was restarted. She was bagged with 100% O2 and given high-dose epinephrine 1.3 mg, atropine 0.26 mg, and sodium bicarbonate 13 mEq. Her heart rate began to increase, it came up to 113 b/minute, and she had a palpable pulse.

At 0137, no blood pressure could be obtained and Eliza Jane was started on dopamine drip at 5 microgram/kg per hour. Her blood pressure reached to 41/28 and was taken to CT scan. While in CT scan, she had another episode of asystole and she was given epinephrine, atropine, and sodium bicarbonate. She developed a pulse again and was transferred to the Pediatric ICU.

At the PICU, her heart rate reached approximately 120 b/min but she did not have a pulse. She was given fluid boluses, as well as being placed on dopamine 10 microgram/kg per hour and dobutamine 10 microgram/kg per hour. She did not have a pulse and her blood pressure was not obtainable in spite of these treatments. She was also started on antibiotics.

Approximately at 0500, Eliza Jane had another episode where she became bradycardic. She received a dose of atropine. She had another arrest episode. She was given epinephrine, multiple doses of bicarbonate, calcium, and atropine. In spite of prolonged time of chest compression and resuscitation, she continued to be in asystole every time they stopped chest compression. She was pronounced dead at 0540 on May 16, 2005 [2].

3. Pre-autopsy clinical tests and their indications

Several clinical and blood tests were performed at VPH and prior to autopsy to check for injuries caused by trauma, abuse, and exposure to drugs and alcohol as described below. These tests show that Eliza Jane did not die as a result of trauma, drug intoxication, or abuse. In addition, her body weight measured at autopsy indicates that she did not suffer from malnourishment. Her blood and CSF bacterial culture did not reveal bacterial infection. However, her blood analysis shows that she suffered from severe anemia [1,2]. Below are the descriptions of the clinical tests and the results.

3.1 No evidence of traumatic injury or abuse

Trauma and abuse was excluded as the cause of Eliza Jane's injury and death based on the following tests and observations:

1) The treating physicians examined Eliza Jane at VPH on May 16th and found no evidence of traumatic injury or abuse.
2) A CT scan of the head was performed. On CT scan, there was no evidence of cerebral edema and no hemorrhage and no evidence of trauma noted.
3) The ME examined Eliza Jane's body at the Los Angeles County's Coroner (Case No 2005-03767) on May 18, 2005 and found no evidence of injury caused by trauma.

4) Eliza Jane's entire body was fluoroscoped and twelve pre-autopsy x-rays were taken of the full body. There is no radiographic evidence of abuse or non-accidental inflicted trauma. There is no radiographic evidence of skeletal dysplasia or musculoskeletal anomaly.

3.2. No evidence of alcohol and drugs or exposure to toxic volatiles

On May 18th, a blood sample was obtained from Eliza Jane's heart and analyzed by LA County's Forensic Science Laboratories for the presence of more than 12 drugs and solvents (Table 1). No evidence of exposure to any of these chemicals was detected.

Table 1. Chemicals tested in Eliza Jane's blood at the time of autopsy

Drugs	Results
Acetaminophen	Not Detected
Alcohol (Ethanol)	Negative
Barbiturates	Not Detected
Cocaine and Metabolites	Not Detected
Methamphetamine	Not Detected
Opiates (Codeine)	Not Detected
Opiates (Morphine	Not Detected
Phencyclidine	Not Detected
Salicylate	Not Detected
Volatiles (Acetone)	Not Detected
Volatiles (Methanol)	Not Detected
Volatiles (Isopropanol)	Not Detected

3.3 Eliza Jane's pre-autopsy weight appears within the normal range for her age

Eliza Jane's weight measured prior to autopsy was 29 pounds which is at the 10th percentile rank. My review of her medical record revealed that her birth weight (7 lbs) was also at the 10th percentile. Her body weight measurements at different intervals during her life are listed in Table 2. She gained 22 pounds during her life.

Her body weight reached the 25th percentile level at the age of one year. It went down to 5th at the age of 1 year and 9 months and her weight stayed at the 5th to 10th percentile ranks during the 21 months period prior to her death on May 16, 2005. Thus Eliza Jane's weight (29 lbs) measured on May 16, 2005 does not indicate that she suffered from malnourishment. A physician also examined her at VPH on May 16th and stated that she appeared to be within normal ranges [2].

Table 2. Eliza Jane's body weight measured at different time intervals

Date	Age	Weight	Percentile
12-03-01	Birth	7 lbs	10
01-21-02	7 weeks	9 lbs & 13 Ounces	20
05-20-02	5.5 mos.	14 lbs & 6 Ounces	30
12-03-02	1 year	18 lbs & 10 Ounces	25
09-05-03	1 year & 9 mos.	20 lbs & 5 Ounces	5
02-02-04	2 years & 2 mos.	21 lbs & 6 Ounces	5
01-21-05	3 years & 1 mo.	23 lbs & 9 Ounces	5
03-02-05	3 years & 3 mos.	25 lbs	10
05-16-05	3.5 years	29 lbs	10

3.4 Blood and CSF analysis and bacterial culture

Blood and CSF samples were obtained from Eliza Jane on May 16th at VPH and analyzed. The blood analysis revealed that she suffered from severe hypochromic anemia and neutropenia. The CSF was clear and normal.

In addition, some blood and CSF samples were used for bacterial culture and showed no bacterial growth [1,2]. Below are the results of these tests.

1) A blood sample was drawn from Eliza Jane at 0240 on May 16th and analyzed. The results are presented in Table 3.

Table 3. Eliza Jane's blood values at 0240 on May 16, 2005

Measurements	Values	Normal range
PH	6.92*	7.38-7.44
PCO2 (mmHg)	135**	35-45
PO2 (mmHg)	25.6*	80-100
Hemoglobin (g/dl)	6.3*	12-16
Hematocrit (%)	21*	37-48
MVC (fl)	75.6*	86-98
MCH (pg/dL)	22.4*	28-33
MCHC (g/dL)	29.6*	32-36
White blood cell count (k/µL)	14.5	5.5-15.5
Neutrophil %	12*	45-74
Lymphocyte %	75%**	16-45
Absolute Lymphocyte count (cell/µL)	10,800**	2000-8000
Monocyte %	8	4-10
Platelets count k/µL	214	130-400
Bicarbonate (meq/L)	26.3	21-30

* Values lower than normal
** Values higher than normal

2) Lumbar puncture was performed and five ml of clear CS fluid was obtained.

   The CSF was sent for Gram stain, culture, glucose, protein, cell counts, and bacterial antigens. CSF protein 48 mg/dL (normal: 20-50 mg/dL), glucose 58 mg/dl (normal: 40-70 mg/dL), and no cells were observed. CSF culture showed no bacterial growth at one day [1,2].
3) Two chest x-rays were taken at VPH at 0039 and at about 0500 on May 16th. The first x-ray showed small patchy infiltrates and the second x- showed more diffuse pulmonary edema pattern [1].
4) Eliza Jane had a 12-lead EKG at 0345 on May 16th which did not show any signs of prolonged QT, but it was stated that she had sinus tachycardia and possible right ventricular hyperatrophy [2].

4. Autoposy findings and medical examiner's methods of diagnosis

Dr. Chanikarn Changsri, the medical examiner at the Los Angeles County Coroner, conducted an autopsy on Eliz Jane's body at 1045 on May 18, 2005 (Case No 2005-03767). In addi-

tion, she examined thirteen H&E stained tissue sections from several organs microscopically. She also examined Gomori methenamine silver stained (GMS) sections of the lungs [1].

The formalin–fixed brain was sent to the neuropathology consultant for evaluation. He examined H&E stained tissue sections of Eliza's brain and performed select immunohistochemical reactions on paraffin sections of the brain to check for HIV core protein p24 and HSV 1 and 2 [1].

They described their findings of this case in a report signed by Changsri and Dr. James K. Ribe on September 15, 2005 [1]. The main objective of the autopsy and the investigations conducted by the medical examiner and neuropathology consultant is to identify the cause(s) of death in this case. Trauma, intoxication with drugs and alcohol, and child abuse were excluded as the cause of death in Eliza Jane's case as described in Section 3 of this report.

Changsri concluded that Eliza Jane's death was caused by *Pneumocystis carinii* Pneumonia (PCP) due to Acquired Immunodeficiency Syndrome. She based her diagnosis in this case only on the identification of the *Pneumocystis carinii* in the alveoli of GMS stained lung sections. Her microscopic examination of five H&E stained lung sections revealed **no evidence of inflammation or interstitial fibrosis.** She stated that all lobes show pink foamy casts in the alveoli **with no inflammatory response**. Changsri's observations clearly indicate that Eliza Jane did not suffer from pneumonia caused by *Pneumocystis carinii* or any other type of pneumonia. Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma [3; pp566]. I describe the problem with the diagnosis given by the medical examiner concerning the lungs and her unscientific approach in reaching a diagnosis in Section 4.1.

My review of this case also revealed many other significant problems with Changsri's approach in evaluating this case. I describe these problems and the medical data to support my conclusions in Sections 4.1-4.5 and 5 of this report. Below is a list of some of the problems with the ME's approach used in evaluating the evidence in Eliza Jane's case:

1) ME examined H&E slides of the thymus, spleen, and bone marrow microscopically and observed atrophy in these tissues. However, she did not explain the significance of her findings in relation to the case or present a probable cause for these changes [1]. My explanation of the medical significance of the atrophy observed in these tissues and present discussion for the probable cause follows in Sections 4.2 and 4.3 of this report.
2) There are significant increases in the weights of the lungs (184% of expected normal), heart (131% of normal), and kidneys (146% of normal). However, ME did not explain the medical significance of her findings in relation to the case or present a probable cause for the increases in organ weights [1]. I explain the significance of the changes observed in organs weight and present discussion for the probable cause in Sections 4.1 and 5 of this report.
3) ME reported that Eliza Jane's liver was enlarged and her liver weight was 121% of normal. She also examined H&E stained liver section and observed micro-and macrovesicular steatosis. Steatosis is accumulation of fat in hepatocytes and this lesion indicates that liver cells were not normal [1]. However, she did not explain the medical significance of her findings in relation to the case or present a probable cause for these abnormal changes in the liver. I explain the significance of the changes observed in liver and present discussion for the probable cause in Sections 4.5 and 5 of this report.
4) ME reported that Eliza Jane suffered from hydrothorax, pericardial effusion, and ascites [1]. However, she did not explain the medical significance of these abnormal changes or provide probable cause for these abnormal conditions. I explain the medical significance of these changes in relation to the case and present a discussion for the probable cause in sections 4 and 5.
5) Eliza Jane was treated with amoxicillin, which has been known to cause acute allergic reaction in children and adults. However, ME did not consider amoxicillin allergic reaction in this case. I describe the clinical indicators of the acute allergic reaction to amoxicillin observed in this case in section 5 of this report.

I also find serious problems with neuropathology consultant's conclusion in calling the non-specific microscopic brain lesions observed in this case as lesions caused by HIV and that this lesion is pathognomonic for an infection with HIV. I present a detailed discussion addressing this issue in Section 4.4.

The overwhelming clinical data observed in Eliza Jane's case as described in this report clearly show that she suffered from an upper respiratory tract infection most likely caused by HPVB19. Infection with HPVB19 causes anemia and the non-specific microscopic lesions in the brain. Her thymus and spleen atrophy was caused by stress from an infection, most likely as a result of HPV B19 infection. Her death resulted from acute allergic to amoxicillin. I present the medical data that support my conclusions in Sections 4 and 5 of this report.

4.1Eliza Jane did not suffer from *Pneumocystis carinii* Pneumonia

Eliza Jane's lung weight at autopsy was 306 g and her lung weight was increased tremendously (184% of expected normal weight for age). The ME examined her lungs grossly and her lungs were congested and edematous. The ME also examined five H&E stained lung sections (two from the left lung and three from the right lung) microscopically and observed evidence of edema only and **no evidence of inflammation or interstitial fibrosis.** The ME stated that all lobes show pink foamy casts in the alveoli **with no inflammatory response**. The ME's observation clearly indicate that Eliza Jane did not suffer from pneumonia. Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma [3:566].

The ME examined additional lung sections from the lung that was stained with Gomori methenamine silver stain (GMS) to search for the presence of microorganisms. The GMS stains show teacup-shaped microorganisms in the foamy material in the alveoli. Based on this observation, the ME claimed that Eliza Jane's death was caused by *Pneumocystis carinii* Pneumonia

(PCP) due to AIDS. I find the ME's methods of investigation and the diagnosis given are not medically valid based on the following clinical and scientific facts:

1) Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma [3; pp566]. The microscopic examination of Eliza Jane's lungs revealed no inflammation. The ME did not observe any inflammatory response in the alveoli or in the interstitial tissue to justify a diagnosis of *Pneumocystis carinii* Pneumonia (PCP) or any other form of pneumonia.

The lesions of PCP usually comprise an interstitial infiltrate of plasma cells and lymphocytes; an interstitial fibrosis; an interstitial diffuse alveolar damage; and hyperplasia of type II pneumocytes; the alveoli are filled with characteristic foamy exudates [3, 4]. For example, Chen et al. examined lung biopsies from twenty-three individuals who developed PCP using electron and light microscopes. Their examination showed alveolar exudate, inflammation in interstitium and alveolar space, interstitial fibrosis, and alveolar epithelial damage in all patients [4]. The ME observed none of these lesions in Eliza Jane's case.

2) The presence of *Pneumocystis carinii* (PC) alone in the alveoli does not justify the diagnosis of pneumonia, AIDS or HIV infection. PC was isolated from the lungs of HIV-negative immunocompetent individuals and individuals suffering from immune deficiency resulting from malnutrition and/or treatment with corticosteriods as shown by the following clinical studies.

a) Contini et al. evaluated the presence of *Pneumocystis carinii* (PC) in the respiratory tract in 36 specimens obtained from 28 HIV-negative immunocompetent children who suffered from chronic lung disorders (CLD). They used a nested polymerase chain reaction (PCR) assay. In addition, Gomori methenamine silver stain (GMS) and indirect immunofluorescence assay (IFA) were performed in parallel. Of the 36 specimens, 12 were PC PCR-positive compared to 10 positive by GMS-IFA. These results suggest an association between PC and exacerbations of CLD in childhood, in the absence of HIV infection or other immunodeficiency syndromes [5].

b) Takahashi et al. analyzed bronchoalveolar lavage (BAL) specimens obtained from 45 non-HIV immunosuppressed individuals for the presence of *Pneumocystis carinii* (PC) by staining and by PC 5S rDNA determined by PCR. PC was observed by staining of BAL specimens in 20% of these patients. P. C 5S rDNA was also detected by PCR assay in four (8.9%) of these patients for whom staining was negative. None of these patients developed PCP within the follow-up period [6].

3) Even, if an individual shows clinical and pathological evidence of PCP, it does not justify the assumption that PCP was caused by HIV. The development of PCP does not require HIV and the treating physicians and medical examiners must perform differential diagnosis to rule out treatments and health conditions that lead to immune suppression. PCP has been reported in children and adults treated with immunosuppressant agents and /or who suffered from chronic health conditions. The following eight clinical studies that include 525 patients show PCP can be developed in immunocompromised individuals as a result of treatments with immunosuppressive agents and/or chronic health conditions:

a) Yale and Limper retrospectively analyzed the medical records of 116 patients who developed PCP. Regardless of the associated underlying disease, corticosteroids had been administered systemically in 105 patients (90.5%) within 1 month before the diagnosis of PCP. The median daily corticosteroid dose was equivalent to 30 mg of prednisone; however, 25% of patients had received as little as 16 mg of prednisone daily. The median duration of corticosteroid therapy was 12 weeks before the development of pneumonia; however, PCP developed after 8 weeks or less of corticosteroid therapy in 25% of these patients [7].

b) Godeau et al. conducted retrospective analysis of 34 HIV-negative individuals with connective tissue diseases (CTD), who developed PCP. The majority of patients (25/34 patients; 74%) presented with PCP during the first 8 months following the diagnosis of CTD. At the time of diagnosis of PCP, most patients (32/34; 94%) were receiving corticosteroids (mean prednisone equivalent dose: 1.2 mg/kg/day) associated in 24 cases with cytotoxic agents (cyclophosphamide, n = 19; methotrexate, n = 5). Most patients were lymphocytopenic at the onset of PCP: 91% (31/34) of patients had fewer than 1500 circulating lymphocytes per µL of blood and 76% (26/34) had fewer than 800/ µL [8].

c) Gluck et al. determined the CD4+ and CD8+ T-lymphocyte counts in seven HIV-negative patients who developed PCP as a complication of immunosuppressive treatment. CD4+ T-lymphocyte counts (T-helper phenotype) were less than 200/µL in all seven patients (mean 90.6/µL) [9].

d) Arend et al. evaluated the charts of 78 patients with PCP. They found that these patients were previously treated with immunosuppressive medication consisting of prednisone or other corticosteroids in 72 (92%) of 78 patients, cytotoxic drugs in 55 (71%) of 78 patients, and both in 50 (64%) of 78 patients. The overall mortality rate for patients was 35% (27/78). PCP occurred at all levels of immunosuppression; no threshold level could be defined. A trend toward a higher mortality in patients with previous corticosteroid use was detected (P =0.06). They concluded that PCP might complicate a variety of immunocompromised states, with considerable mortality [10].

e) Saksasithon et al. conducted a retrospective study of PCP in 19 patients without HIV infection. They found that all patients had underlying immunocompromised diseases. 94.7 per cent of the cases received immunosuppressive drugs. PCP occurred at a mean duration of 26.4 months after the diagnosis and treatment of underlying diseases [11].

f) Sepkowitz et al. conducted a retrospective review of 140 patients with morphologically proved PCP. These patients had hematological malignancy (47%), solid tumor (31%), or bone marrow transplantation (18%). All but seven patients had previously established predisposing factors for PCP, including corticosteroid use in 87% [12]

g) Gerrard reported the development of PCP in 28 HIV-negative individuals who received corticosteroids combined with other immunosuppressive agents before the on-

set of PCP symptoms. The symptoms appeared within six months of immunosuppression [13].

h) Roblot et al. evaluated 103 HIV-negative patients diagnosed with PCP. 71 (69%) patients received cytotoxic drugs, 57 (55%) were treated with long-term corticotherapy, and 15 (14.7%) underwent bone marrow transplantation [14].

4) Eliza Jane's lung weight was increased to 184% of expected normal weight as shown in Table 4. Five H&E stained tissue sections from five lobes were examined microscopically by the medical examiner and all lobes show pink foamy casts in the alveoli (edema) with no inflammatory response. These data indicate that the increase in lung weight resulted from accumulation of fluid (edema). The clinical data in this case indicate that the accumulation of fluid in the lungs resulted from cardiac problems and vasodilatation of blood vessels. These problems were caused by the release of histamines and other mediators induced by the allergic reaction to amoxicillin given to Eliza Jane prior to her cardiac arrest. Vasodilatation and cardiac problems can lead to edema in lungs and other organs [3]. The following clinical data support my conclusions:

a) In addition to pulmonary edema, Eliza Jane's pleural cavities contained approximately 20 cc of clear serous fluid. No adhesions were observed.

b) She had pericardial effusion and her heart weight was increased by 31% of the expected average normal weight for age (Table 4).

c) She suffered from ascites. There were approximately 60 cc of serous fluid in the peritoneal cavity. This fluid was not caused by inflammation. The peritoneal cavity was without evidence of peritonitis and there were no adhesions.

d) Eliza Jane's kidneys weighed 146% of average normal weight for age (Table 4). No pathological lesion in kidneys was observed by the medical examiner grossly and microscopically. The increase in kidney weight indicates accumulation of fluid resulted from vasodilatation and other cardiovascular problems.

Table 4. Significant increases in Eliza Jane's organ weights

Organ	Weight (g)	Expected average weight (g) for age	% of normal expected weight
Heart	77	59	131
Left lung	138	77	179
Right lung	168	89	189
Both lungs	306	166	184
Liver	500	413	121
Left kidney	75	49	153
Right kidney	67	48	140
Both kidneys	142	97	146

4.2 The probable cause for Eliza Jane's bone marrow atrophy and severe anemia

The ME examined H&E stained section of decalcified vertebrae in Eliza Jane's case and observed marked atrophy. The ME's examination revealed hypocellular marrow with reduction of all three cell lines. Megakaryocytes are hypolobulated. Analysis of blood sample on May 16th also showed that she suffered from severe anemia. Her hematocrit and hemoglobin values were 21% and 6.3 g/dl (Table 3).

The ME did not discuss the significance of these important findings in relation to the case or provide probable cause(s) for the changes observed in bone marrow and her severe anemia. My investigation revealed that hypoplastic bone marrow and anemia are commonly associated with variety of illnesses including HPV B19 infection [15-19]. Eliza Jane suffered from an upper respiratory tract infection for about three weeks. HPV B19 infection is known to cause upper respiratory tract infection in children and can be transmitted through respiratory secretions [20-24]. In addition, amoxicillin is also known to cause bone marrow depression and anemia. The clinical evidence and the rapid development of Eliza Jane's anemia indicate that her anemia and her bone marrow depression was caused by amoxicillin exacerbated by the synergistic actions of a viral infection, most likely HPV B19.

Below is a list of clinical studies that show HPV B19 caused aplastic anemia in previously healthy children and adults similar to the changes observed in Eliza Jane's case.

a) Qian et al. conducted a study to explore the relationship between HPV B19 infection and aplastic anemia (AA) and to investigate the role of HPV B19 in the occurrence of AA. The presence of HPV B19 DNA was detected in the peripheral blood samples of 60 patients with AA (children 38 and adults 22) by nested polymerase chain reaction (PCR) assay, and 30 healthy persons were selected as controls. Sixteen (26.7%) of 60 AA cases were HPV B19 DNA positive, while all the samples in the control group were negative for HPV B19 ($P = 0.000914$). Among the case group, the positive rates of HPV B19 DNA were 21.4% (6/28), 30.0% (3/10), 20.0% (1/5) and 35.3% (6/17) in children with acute AA (AAA), children with chronic AA (CAA), adults with AAA and adults with CAA respectively, which were significantly higher than rates in the control group [15].

Furthermore, there was no remarkable difference between children with AA and adults with AA in the 16 HPV B19 DNA positive patients; neither was there between AAA and CAA. They concluded that HPV B19 infection is not only correlated with the occurrence of AAA and CAA in children, but also with AAA and CAA in adults, and might be an important viral cause for AA in humans [15].

b) Mishra et al. conducted a clinical study to determine the role of HPV B19 in aplastic anemia patients. Aplastic anemia is characterized by pancytopenia with hypoplastic bone marrow. 27 aplastic anemia patients and 20 healthy controls were tested for the presence of parvovirus B19 infection by detecting parvovirus B19-specific IgM by ELISA and viral DNA by PCR. Parvovirus B19 IgM and viral DNA were detected in significantly higher numbers of patients in comparison to the controls

(40.7% vs. 5%, P < 0.01; 37% vs. 0%, P < 0.001, respectively). The presence of parvovirus DNA in aplastic anemia patients indicates active or recent infection [16].

c) Qian et al. diagnosed six cases of children with severe aplastic anemia who showed active or recent parvovirus B19 infection, as shown by B19 DNA viraemia, positive B19 specific IgM antibodies, or both. They did not identify other plausible causes in these patients. They suggested that parvovirus B19 infection might be associated with severe aplastic anaemia [17].

d) Yetgin et al. described a case of a previous healthy, 10 year-old girl with severe aplastic anemia associated with HPV B19 infection. The patient underwent bone marrow transplantation from her HLA-identical sibling resulting in complete recovery. They also reviewed a number of reports that described cases of severe aplastic anemia associated with HPVB19 infection in patients without an underlying disease. They concluded that HPVB19 infection should be considered as one of the causes of aplastic anemia in patients without an underlying disease [18].

e) Osaki et al. reported a case of aplastic anemia in a previously healthy boy without any underlying diseases following asymptomatic infection with the HPB19 virus. Laboratory examination initially showed thrombocytopenia, mild leukopenia in the peripheral blood, and severe hypoplastic bone marrow. Serological and histological analysis revealed an underlying infection with the B19 virus. They concluded that HPV B19 infection must be considered one of the causes of aplastic anemia in patients without underlying hemolytic anemia and an apparent episode of the viral infection [19].

In addition to aplastic anemia and bone marrow depression, a second biomarker is identified in Eliza Jane's case that indicates her respiratory illness was most likely caused by HPV B19 infection. Parvovirus B19 infection is also known to cause brain lesions that contain multinucleated giant cells of macrophage/microglia lineage that are similar to the lesions observed in brain sections in Eliz Jane's case. For example, Isumi et al. did a postmortem examination of a fetus brain infected with human parvovirus B19. Their examination revealed **multinucleated giant cells of macrophage/microglia lineage** predominantly in the cerebral white matter**.** Parvovirus B19 genome DNA was detected in the nucleus of the multinucleated giant cells and solitary endothelial cells by polymerase chain reaction amplification and in situ polymerase chain reaction methods. Capsid antigen was also demonstrated in the cytoplasm of the endothelial cells by immunofluorescent assay [25].

In Eliza Jane's case, the medical examiner did not do any test to rule out HPV B19 infection in spite of the presence of many indicators in her case that point to HPV B19 infection. The diagnosis of HPV B19 infection can also be confirmed by immunological assay. Borreda et al. evaluated 24 pediatric patients with HPV B19 infection. In every case, the diagnosis was established by a positive capture immunoassay for IgM antibodies against the HPV B19 [26].

4.3 The probable cause for Eliza Jane's thymus and spleen atrophy

The ME measured the weight of Eliza Jane's thymus and spleen and noted severe atrophy of the thymus. The weights of the thymus and the spleen are 8 g and 40 g, respectively, which are 32% and 85% of the expected normal average weight for age. [1]. The ME also examined H&E stained sections of the thymus and spleen microscopically and observed thymic atrophy and fibrosis. The ME noted marked reduction in the white pulp of the spleen. However, the ME did not consider the significance of these findings in Eliza Jane's case or attempt to identify the probable cause for these significant changes in her thymus and spleen.

My investigation revealed that significant reduction in the thymus and lymphoid organs weight has been reported in individuals suffering from a variety of illnesses. The degree of atrophy is dependent on the type and the duration of illness. Eliza Jane was ill for three weeks with an upper respiratory tract infection and her body suffered from stress as a result of her illness. The atrophy of the thymus and spleen can explain the finding of *Pneumocystis carinii* (PC) in Eliza Jane's lungs. PC is commonly found in the lungs of individuals with immune depression as explained by the studies presented in Section 4.1 above. Below are the results of four clinical studies that show thymus and spleen atrophy caused by stress.

a) Zhang reviewed thymuses, spleens, lymph nodes, tonsils and appendices from 621 autopsy cases. He found that more than 130 different illnesses cause atrophy of the thymus. For example, cases of infection with a course less than 5 days showed mild atrophy of the thymus and those cases with a longer course might show moderate or severe degree of atrophy. In 81% of the cases, the degree of thymus atrophy was in accordance with those of the other immune organs [27].

b) Liang et al. studied 70 thymuses obtained at autopsy from children who died of various diseases using histological, immunohistochemical and ultrastructural methods. In the immunohistochemical study, antibodies against 8 lymphocyte differentiation antigens, including CD4, CD8, CD3, CD1, CD2, CD25, CD22 and T9 as well as those against keration and S-100 protein were used. The findings suggest that thymus involution can occur in different diseases [28].

c) The characteristics of the normal adult thymus in both sexes were determined in 50 cases of accidental death by a simplified quantitative histologic technique. A table of normal values derived from these findings was used for making comparisons with the thymuses from autopsies of 50 additional patients suffering terminal illness. Changes ascribed to disease included accelerated involution of the thymus accompanied by loss of septae, smaller lobules, increased adipose tissue and fusiform cells, a reduced number of lymphocytes and Hassall's corpuscles and a relative increase in the number of cystic corpuscles. No lymphoid follicles were observed. Changes were not identical in all disease conditions [29].

d) Kitonyi reviewed one hundred anteroposterior chest radiographs of children under the age of five years suspected of having chest infection. Thymocardiac ratio is determined. It is concluded that in children under five years, the thymus generally decreases in size with age and that often the thymus will undergo atrophy as a primary response to infection [30].

4.4 The probable cause for microscopic non-specific lesions in the brain

The ME examined Eliza Jane's brain and the dura matter grossly and did not detect any abnormality. The fresh weight of Eliza Jane's brain at the time of removal was 1070 grams [1].

The neuropathology consultant examined three H&E stained slides of the brain microscopically and observed the following non-specific lesions. He stated that scattered throughout the white matter with relative sparing of cortex are a number of variable sized microglial nodules characterized by multinucleate giant cells. These zones are associated with moderate pallor and myelination, occasional microphages and have an angiocentric pattern. Necrosis and organisms are not identified. Similar encephalitic changes were noted in the thalamus. The neuropathology consultant stated that these preliminary sections are strongly suggestive of HIV encephalitis [1].

The neuropathology consultant also performed select immunohistochemical reactions on the paraffin blocks (1-3, 2-3, and 3-3). These studies included the HIV core protein, p24 and HSV 1 and 2. He stated that strongly positive p24 reactivity was detected in all three sections in the previously described zones of subcortical and deep white matter focal demyelination with microglial-giant cell reaction. No signal was recognized for HSV 1 or 2. The neuropathology consultant concluded that the immunohistochemical study confirms the presence of HIV core protein in the brain sections confirming a diagnosis of HIV encephalitis [1].

I do not agree with neuropathology consultant's assumption that the non-specific microscopic lesions observed in Eliza Jane's brain were induced by HIV. I base my position on the following clinical studies and medical principles:

1) The clinical and the pathologic evidence described in this report shows that Eliza Jane suffered from aplastic anemia and an upper respiratory tract infection. The medical examiner examined H&E stained tissue section of Eliza Jane's bone marrow microscopically and her examination revealed hypocellular marrow with reduction of all three cell lines. Megakaryocytes were hypolobulated. Analysis of a blood sample on May 16th also showed that Eliza Jane suffered from severe anemia. Her hematocrit and hemoglobin values were 21% and 6.3 g/dl [Table 3]. I present in this report the findings of several clinical studies that show infection with human parvovirus B19 causes aplastic anemia in children and adults (Section 4.2).

Furthermore, HPV B19 infection is also known to cause encephalitis in human and to induce lesions in the brain consisting of multinucleated giant cells of macrophage/microglia lineage and microglia [25]. However**,** the neuropathology consultant did not include HPV B19 infection in his differential diagnosis. Also he did not perform immnohistochemical and other immunological tests to check for HPV B19. There are clinical tests available to check for evidence of parvovirus B19 infection as described in this report (Section 4.2). Below are medical data that show HPV B19 infection in human caused encephalitis and brain lesions that contain multinucleated giant cells of macrophage and microglia cells.

a) Isumi et al. did a postmortem examination of a fetus brain infected with human Parvovirus B19. Their examination revealed **multinucleated giant cells of macrophage/microglia lineage** and many small calcifications around the vessels, predominantly in the cerebral white matter**.** HPV B19 genome DNA was detected in the nucleus of the multinucleated giant cells and solitary endothelial cells by polymerase chain reaction amplification and in situ polymerase chain reaction methods. Capsid antigen was also demonstrated in the cytoplasm of the endothelial cells by immunofluorescent assay [25]**.**

b) Barah et al. tested samples of cerebrospinal fluid from 162 patients with undiagnosed meningoencephalitis using nested PCR for B19 genes. Seven patients were positive; an incidence of 4.3% [31].

c) Bakhshi et al. evaluated a case of 13 year-old girl with hemoglobin Sbeta(+) thalassaemia who developed simultaneous aplastic crisis and encephalopathy associated with HPV B19 infection. Brain magnetic resonance imaging findings were consistent with central nervous system (CNS) vasculitis and her symptoms resolved with steroid therapy. They stated that HPVB19 induced CNS hypersensitivity vasculitis and must be considered in the differential diagnosis of encephalopathy [32]**.**

d) Bilge et al. reported a case of a 12 year-old boy with a renal transplant who had chronic HPVB19 infection with skin eruptions and recurrent episodes of encephalopathy with focal neurological deficits. HPV B19 DNA was detected in blood, bone marrow, and skin biopsy specimens. Repeat cranial magnetic resonance (MR) imaging during each episode of encephalopathy showed variable focal findings, and MR angiography revealed vasculitic changes with narrowing of the cerebral arteries [33].

2) The presence of multinucleated giant cells and monocytes in the brain is not a pathognomonic lesion to a certain illness. Macrophages appear in the brain tissues in response to infectious and non-infectious agents and giant cell formation appears to be the incidental result of macrophages ingesting material in close apposition to other macrophages. Chambers and Spector stated that giant cells are commonly seen in granulomas produced by a wide variety of known and unknown agents. It is widely accepted that giant cell formation results from fusion of mononuclear phagocytes. Both experimental and circumstantial evidence suggests that fusion takes place following the attachment of more than one macrophage to the same endocytic material. The material responsible for fusion may either be the visible particulate cause of granuloma formation or the denatured macromolecules formed by the inflammatory process [34]**.**

For example, an inflammatory response was induced by the implantation of cover-slips into the brains of rabbits. The cytomorphology of the glass-adhering cells were characterized. Mononuclear cells with foamy cytoplasm and multinuclear gi-

ant cells were observed. Multinuclear giant cells increased in number after prolonged implantation. [35]**.**

3) Microglia are phagocytic elements of the central nervous system (CNS). They proliferate and show reactive changes in areas of injury from any cause. Two patterns are recognized, namely, focal microglial nodules and diffuse microgliosis [3]. Wirenfeldt et al. also stated that microglia, the resting macrophage population in the brain and spinal cord, has a central role in inflammatory processes and in acute and chronic degenerative diseases of the central nervous system [36]**. These studies clearly show that the microglial nodules observed in Eliza Jane 's brain are not specific** lesions and do not justify a diagnosis for HIV as the neuropathology consultant claimed.

4) The neuropathology consultant also based his assumption that Eliza Jane's brain lesions were induced by HIV on the finding of a positive signal for p24 in the brain tissue. I believe that his assumption is not valid based on the following facts:

a) False positive for HIV infection was detected in tissues with inflammation obtained from HIV-negative individuals. For example, Nadasdy et al. conducted study to evaluate the immunocytochemical approach in detecting HIV infection in a variety of routinely fixed archival tissues using antibodies to various viral proteins. They found that false positive staining with the IgG1 standard or with the antibodies to HIV proteins was frequently seen in tissues of HIV-negative individuals with pathologic findings (inflammation, hyalin degeneration), particularly following protein digestion. Protein digestion also had a major impact on specific staining [37].

In this study, they examined paraffin sections with a large panel of commercially available monoclonal antibodies against the various HIV proteins (5 antibodies to p24, 1 to p17, 1 to gp41, and 1 to gp120) using a streptavidin-biotin method. A polyclonal antibody against p24 was also tested. Formalin-fixed, paraffin-embedded HIV infected CEM E5 T cells were used as positive controls. Tissues from AIDS patients included 31 kidneys, 8 lymph nodes, 2 spleens and 3 brains. Non-AIDS tissues examined were 6 renal biopsies with focal segmental glomerulosclerosis, 5 with interstitial nephritis, 6 reactive lymph nodes, and a brain with encephalitis, all from patients not known to be at high risk for HIV infection [37].

Additional negative controls were also used. These included: 1) replacement of primary antibody with a hybridoma derived mouse monoclonal IgG1 standard, 2) omission of the primary antibody, and 3) sections of formalin-fixed paraffin-embedded CEM E5 T cells cultures not infected with HIV. Competition experiments with excess recombinant p24 protein were also performed [37].

b) No control tissue sections were used in the neuropathology consultant's study having similar conditions to the brain sections in Eliza Jane's case. Inflammation was observed in Eliza Jane's brain. In addition, Eliza Jane suffered from allergic reaction to amoxicillin and probably from HPVB19 infection as indicated by the overwhelming medical evidence presented in this report. Both amoxicillin and HPVB19 have been known to cause immune illnesses. Immune reactions caused by one or both of these agents may cause a false positive on a p24 immunocytochemical test and should be taken into consideration in this case.

4.5 The probable causes for liver injury and ascites

The ME reported that Eliza Jane's liver was enlarged. Her liver weight was 500 grams and the expected average weight for age 413 grams [1]. Her liver weight was 121% of normal. The color of her liver was tan-brown. The ME examined H&E stained liver sections and observed micro-and macrovesicular steatosis. Steatosis is accumulation of fat in hepatocytes and this lesion indicates that liver cells were not normal [1].

The increase in the liver weight (21%), the accumulation of fat in the liver cells, and the accumulation of the fluid in the peritoneal cavity indicate that the liver injury in Eliza Jane's case was serious. The ME collected approximately 60 cc of serous fluid from the peritoneal cavity. This fluid was not caused by inflammation. The peritoneal cavity was without evidence of peritonitis and there were no adhesions.

The treating physician at VPH examined Eliza Jane on May 16th and reported an enlargement of liver and the distention of the abdomen. Eliza Jane's physician examined her on May 14th and did not notice any enlargement of her liver or the distention of her abdomen. No enlargement of the liver or distention of the abdomen was noted in examinations with other pediatricians on April 30, May 5, and May 7. These clinical data clearly show that the injuries in the liver and the accumulation of fluid in the peritoneal cavity occurred during the course of treatment with amoxicillin. She was treated with amoxicillin (400 mg twice a day) for about 36 hours prior to her cardiac arrest. Her treatment started on May 14th at about 18:25 and she received four doses.

Amoxicillin has been known to cause serious allergic liver injury in children and adult allergic to amoxicillin and penicillin type antibiotics [38-50]. The clinical data observed in this case indicate that Eliza Jane suffered from a serious allergic reaction to amoxicillin. The 11 clinical studies cited below show that both amoxicillin and amoxicillin/clavulanic acid caused hepatotoxicity in individuals treated for bacterial infections with these medications:

a) Gresser conducted a medline search of case reports and reviews on amoxicillin-clavulanic acid induced adverse effects. The criteria of a consensus conference on the reporting of drug-induced liver disease were applied. Amoxicillin-clavulanic acid has been associated with drug-induced cholestatic hepatitis in 208 reported patients. Infection and cholestasis from other reason were ruled out in most patients**.** Liver injury was classified according to laboratory parameters to be hepatocellular in 35 patients, cholestatic in 24 patients and mixed in 83 patients [38].

The study conclusions include the following: 1) amoxicillin-clavulanic acid which is marketed for treatment of respiratory infections and sinusitis/otitis may in some cases induce severe adverse effects and death in patients of different age, especially if they are on multi-drug regimens; 2) in consideration of this fact many authors recommend to reflect carefully whether amoxicillin-clavulanic acid is necessary in treatment of patients with localized or uncomplicated infections; 3) if amoxicillin-

clavulanic acid is prescribed, transaminase, alkaline phosphatase and bilirubin tests should be obtained within the first two weeks and after four to five weeks after beginning of treatment to recognize undesired hepatic side effects [38].

b) Maggini *et al.* reviewed the medical records of 118 potential cases of acute liver injury. These cases were identified through the regional hospital information system in the Friuli-Venezia Giulia region of Italy. Overall, 12 cases of acute liver injury were identified. Three of these cases (25%) occurred in the amoxicillin exposure category and two (17%) among the amoxicillin/clavulanic acid category [39].

c) Garcia *et al.* conducted a retrospective study in the United Kingdom to estimate the risk of acute liver injury associated with use of amoxicillin and amoxicillin-clavulanic acid. The users' ages were between 10 and 79 years and were followed up from 1991 through 1992. They found 14 cases of acute liver injury among users of amoxicillin alone and 21 cases among users of amoxicillin-clavulanic acid [40].

d) Mari *et al.* reported 9 patients who developed hepatitis after receiving treatment with amoxicillin and clavulanic acid. Other causes of hepatitis were excluded. Clinical and biological signs of hypersensitivity may suggest an immunoallergic reaction [41].

e) Chawla *et al.* reported a rapidly progressing liver disease with ductopenia and portal fibrosis in a 3 year-old boy treated with amoxicillin/clavulanic acid [42].

f) Nathani *et al.* reported a case of a 40 year-old woman with amoxicillin/clavulanate-related cholestatic hepatotoxicity and multiple duodenal erosions, whose diagnosis was delayed until inadvertent rechallenge with the antibiotic combination. Immunological hypersensitivity is considered to be the most likely mechanism resulting in liver injury [43]**.**

g) Habior *et al.* reported two cases with liver injury due to amoxicillin-clavulanic acid. Liver biopsy revealed mixed hepatocellular-cholestatic liver injury in both cases [44].

h) Ryley *et al.* reported liver injuries in 5 patients treated with amoxicillin/clavulanic acid. These patients presented with cholestatic illness within 8 weeks of a course of amoxicillin/clavulanic acid. The clinical picture indicated a direct link between the illness and the drug. Hepatic histology revealed a distinctive focal destructive cholangiopathy in all 5 patients. In addition, two of these patients showed a granulomatous reaction. Parallels are drawn with other diseases displaying bile duct destruction, and it is suggested that immunologically mediated drug-induced biliary damage may be involved [45].

i) Verhamme *et al.* reported 2 cases of cholestatic hepatitis after treatment with an amoxicillin/clavulanic acid [46].

j) Bralet and Zafrani described the clinical and pathological findings of 5 cases of acute hepatitis due to amoxicillin-clavulanic acid intake. Liver biopsies revealed cholestasis in all cases, associated with varied degrees of interlobular bile duct injury in four patients [47].

k) Larrey *et al.* reported 15 cases of hepatitis related to a combination of amoxicillin- clavulanic acid intake. Histological examination of the liver, performed in 7 patients, showed centri- or panlobular cholestasis in all cases, associated with granulomatous hepatitis in one. Serum aminotransferase activities were increased in all patients and were generally 2 to 10 times the upper limit of normal. Serum alkaline phosphatase activity was considerably increased, from two to seven times the upper limit of normal. The association of hepatitis and signs of hypersensitivity may suggest an immunoallergic mechanism of hepatotoxicity in some patients [48].

5. Clinical indicators of acute allergic reaction to Amoxicillin observed in Eliza Jane's case

Eliza Jane received the first dose of amoxicillin (400 mg twice a day) at about 18:25 on May 14, 2005. Her condition appeared to worsen after receiving the second dose of amoxicillin. Her mother described Eliza Jane's condition during the course of her treatment with amoxicillin as follows: On May 15th, Eliza Jane vomited several times throughout the day and was pale. After dinner, she seemed agitated and then, at some point, lethargic. She had a fever of 101.1ºF, but her extremities felt cold to the touch [1,2]. She suffered from cardiac arrest shortly after receiving the fourth dose on the evening of May 15th.

Eliza Jane's acute symptoms developed following receiving the amoxicillin and the other clinical observations and biomarkers described in her case indicate clearly that she died from acute allergic reaction to amoxicillin. Amoxicillin and other penicillin type antibiotics have known to cause serious and fatal allergic reactions in children and adults. Amoxicillin has been known to induce anemia, bone marrow depression, and Type I, II, III and IV allergic reactions in children and adults [38-62]. The clinical evidence and the rapid development of Eliza Jane's anemia indicate that her anemia and bone marrow depression was caused by the synergistic actions of amoxicillin and a viral infection, most likely HPV B19.

Below is a list of clinical observations and biomarkers that show Eliza Jane died from acute allergic to amoxicillin:

1) The weight of Eliza Jane's lungs was 306 g and the expected average normal weight for her age is 166 g (Table 5). The microscopic examination of the lung sections did not reveal inflammation of the lungs and that the excess in lung weight (140 g) resulted from edema. The clinical data collected in this case indicate that the fluid observed in the lungs developed following treatment with amoxicillin on May 14th. These include:

a) Physicians examined Eliza Jane on May 14th and prior visits and found her lungs clear.

b) Two chest x-rays were taken at VPH on May 16th. The first x-ray was taken at 0039 and showed small patchy infiltrates. The second x-ray was taken at about 0500 and showed more diffuse pulmonary edema pattern [2]. These observations indicate that some fluid moved from the blood vessels into the lungs during Eliza Jane's hospitalization at VPH.

2) Accumulation of fluid also observed in the pleural and peritoneal cavities and pericardial sac which indicates cardiovascular problems. Eliza Jane's pleural cavities contained approximately 20 cc of clear serous fluid. In addition a 60 cc of serous fluid was collected from the peritoneal cavity. No adhesions or inflammation were observed in the in the pleural and peritoneal cavities and pericardial sac. These observations indi-

cate that the excess fluid in these compartments resulted from cardiovascular problems. Allergic reaction to amoxicillin causes the release of many vasoactive mediators such as histamine, which induces vasodilatation and leakage of fluid outside the blood vessels [54-56].

3) Excess in organ weight was also observed in heart (18 g) and kidneys (45 g) as shown in Tables 5. The gross and the microscopic examination of these organs by the medical examiners did not reveal the presence of inflammation or other abnormalities that influence their weights. These data indicate that the excess weight in these organs resulted from accumulation of fluid due to cardiovascular problems caused by the allergic reaction to amoxicillin.

4) Excess in liver weight (87 g) and the abnormal accumulation of fat in hepatocytes were also reported in this case. Allergic reaction to amoxicillin has known to cause liver problem as shown in the studies described in Section 4.5 of this report.

5) The estimated total excess in organ weights (lungs, heart, liver, and kidneys) is 290 gm which is approximately equal to 290 mL of fluid (Table 5) In addition, the total amount of fluid collected from the pleural and peritoneal cavities was 80 mL. These data indicate that about 370 mL of fluid leaked from the blood vessels to the tissues and cavities described above. Eliza Jane's weight measured on May 16th is 29 lbs (13.2 kg) and her estimated total blood volume is 924 mL (7% of body weight) [1,2]. The estimated amount of the fluid leaked out side the blood vascular system in this case is about to 40% of her blood volume.

The acute loss of 40% of the circulatory fluid in any person will cause shock and cardiac arrest. Eliza Jane's physician examined her on May 14th prior to her treatment with amoxicillin and did not observe lung or cardiovascular problems, liver enlargement, or distention of the abdomen. In medical exams on April 30, May 5 and May 7, doctors did not observe lung or cardiovascular problems, liver enlargement or distention of the abdomen. These data show clearly that Eliza Jane's cardiovascular problems developed following her treatment with amoxicillin and was caused as a result of allergic reaction to amoxicillin. Bacterial infection, intoxication with alcohol and drugs, and trauma were excluded as the cause of death as described in Section 3 of this report.

Unfortunately, the medical examiners overlooked the overwhelming data described in this report that show allergic reaction to amoxicillin. In addition, the medical examiners and the physicians who treated Eliza Jane at Valley Presbyterian Hospital did not order blood tests to check for the presence of specific IgE for amoxicillin [62].

Table 5. Excess weight observed in Eliza Jane's organs

Organ	Eliza Jane's Organ Weight (g)	Expected average weight (g) for age	Estimated weight* increase (g)
Heart	77	59	18
Left lung	138	77	61
Right lung	168	89	79
Both lungs	306	166	140
Liver	500	413	87
Left kidney	75	49	26
Right kidney	67	48	19
Both kidneys	142	97	45

*Estimated total weight (g) increase for lungs, liver, kidneys, and heart = 290

6. Conclusions

My review of the medical evidence presented in this case and the pertinent medical literature clearly show that Eliza Jane's death was not caused by *Pneumocystis carinii* Pneumonia or any type of pneumonia. Her lungs did not show an inflammatory response to medically justify a diagnosis of pneumonia of any kind. Pneumonia is a term that refers to inflammation and consolidation of the pulmonary parenchyma.

Eliza Jane's death resulted from acute allergic reaction to amoxicillin which caused severe hypotension (due to the leakage of significant amount of fluid outside the blood vessels), shock, and cardiac arrest. The autopsy revealed that Eliza Jane had pericardial and pleural effusion and ascites. In addition, her organ weights (lungs, heart, liver, and kidneys) were increased significantly. The weight of her lungs, heart, liver, and the kidneys were 184%, 131%, 121%, and 146% of the expected average normal weight for age, respectively. Also, Eliza Jane's liver was significantly enlarged and the hepatocytes show micro-and macrovesicular steatosis. Amoxicillin has been known to induce immune mediated toxic changes in the liver.

Eliza Jane suffered from an upper respiratory tract infection for about three weeks prior to her death on May 16, 2005. My investigation indicates that her upper respiratory tract infection was probably caused by HPV B19 infection. HPVB19 has been known to cause upper respiratory tract infection, encephalitis, and aplastic anemia in children and adults. Eliza Jane had nonspecific microscopic lesions in the brain consisting of microglia and multineucleated giant cells. These lesions were probably caused by HPV B19.

In addition, Eliza Jane suffered from severe anemia as shown by her blood analysis and the atrophy of her bone marrow. Amoxicillin has also been known to cause bone marrow depression and anemia. The clinical evidence and the rapid development of her anemia indicate that the anemia and bone marrow depression was caused by the synergistic actions of amoxicillin and an upper respiratory tract infection most likely, HPV B19.

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Furthermore, Eliza Jane's thymus and spleen showed atrophy which was caused by stress resulting from her three week illness with an upper respiratory tract infection. Atrophy of the thymus and other lymphoid organs has been widely reported in individuals suffering from a variety of illnesses caused by infections. The degree of atrophy in the thymus is dependent on the duration and the type of illness.

The ME and the neuropathology consultant were assigned to investigate Eliza Jane's case and find the probable cause(s) of her death. Unfortunately, they overlooked the overwhelming data described in this report that show Eliza Jane died as a result acute allergic reaction to amoxicillin. Also, they did not explain the significance of the abnormal changes observed in the thymus, bone marrow, spleen, and the liver in relation to this case. In addition, they did not perform differential diagnosis to find the probable cause(s) for the changes observed in these organs.

The ME based her conclusion that Eliza Jane died as a result of PCP on only the presence of *Pneumocystis carinii* (PC) in her lungs and with no evidence of pneumonia. The presence of this opportunistic microorganism in the lung tissue alone cannot cause death. Eliza Jane's lungs did not show any inflammatory response as revealed by the ME's microscopic examination of the H&E slides of the lungs. PC has been widely isolated from the lungs of HIV-negative individual who were suffering from chronic illness and/or treated with immunosuppressive agents. Eliza Jane had severe atrophy of the thymus and bone marrow due to a three week upper respiratory tract infection as stated above.

The neuropathology consultant called the non-specific microscopic lesions found in the brain an HIV disease. He based his assumption on finding non-specific lesions in the brain (microglial nodules and multinucleate giant cells) and the detection of p24 in the brain tissue using immunohistochemical reactions. I find his conclusion in this case scientifically invalid based on the following facts:

1) He did not consider HPV B19 infection in his differential diagnosis in this case. HPV B19 infection has also been known to cause encephalitis in humans and to induce lesions in the brain consisting of multinucleated giant cells of macrophage/microglia lineage and microglia cells. Eliza Jane also showed other clinical biomarkers for HPV B19 infection as described previously.

2) The presence of multinucleated giant cells and monocytes in the brain is not a pathognomonic lesion to a certain illness. Macrophages appear in the brain tissues in response to infectious and non-infectious agents and giant cells formation appears to be the incidental result of macrophages ingesting material in close apposition to other macrophages.

3) Microglia are phagocytic elements of the central nervous system (CNS). They proliferate and show reactive changes in areas of injury from any cause. Two patterns are recognized, namely, focal microglial nodules and diffuse microgliosis.

4) False positive reactions for HIV infection have been detected in tissues with inflammation obtained from HIV-negative individuals using the immunocytochemical approach. No control tissue sections were used in the neuropathology consultant's study having similar conditions to the brain sections in Eliza Jane's case. Three elements in this case should be considered when performing immunocytochemical assay: 1) an inflammation was observed in Eliza Jane's brain; 2) she suffered from allergic reaction to amoxicillin which has been know to cause type I, II, III, and IV immune mediated reactions; 3) HPV B19 infection has been reported to cause immune mediated reactions. These three elements acting individually or collectively may cause a false positive reaction for p24 using an immunocytochemical test.

The autopsy on Eliza Jane's body was performed on May 18, 2005 and the ME released her report on this case on September 15, 2005. The ME and neuropathology consultant had approximately four months to investigate this case and to identify the cause of death. After careful analysis of the medical evidence in this case, I believe they reached the wrong conclusion about the causes of illness and death, and that their incorrect conclusion is due to an incomplete and unscientific investigation.

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Comments from Dr. Harold E. Buttram

For the past several years I have had the privilege of becoming familiar with the work of Dr. Mohammed Ali Al-Bayati through mutually shared cases involving alleged parental child abuse in the form of shaken baby syndrome (SBS). In these cases, each of us wrote medical reports defending parents whom we believed were falsely accused.

Regarding my own background, in the past six years I have written approximately 80 medical reports in defense of parents whom I believed to have been falsely accused of violent physical child abuse, largely involving charges of SBS. With few exceptions in these cases, I have observed a troubling pattern of abandonment of the usual thoroughness one finds in medical centers once suspicions of SBS were raised. In most cases that I have reviewed, in my opinion, there have been varying degrees of negligence in working through differential diagnoses, sometimes missing the most obvious of alternate non-traumatic causes.

In the present case of the autopsy report on Eliza Jane Scovill, in my opinion, there is a similar pattern; that is, diagnostic assumptions have been made based on superficial evaluation with little if any attempt to investigate other possible causes of the child's three-week illness culminating in death.

Regarding Dr. Al-Bayati, I consider him to be a master craftsman in a broad field of medical expertise. His workups are exhaustive and meticulous, yet plainly written so as to be accessible to reasonably educated non-medical people. He makes no statements or claims that he does not document in the medical literature.

In the case of Eliza Jane Scovill, I first reviewed the autopsy report, which did in fact give rise to personal concerns and doubts. However, after going through Dr. Al-Bayati's report point-by-point, he put all doubts to rest. There is no question in my mind that his report accurately describes the true causes in the death of Eliza Jane Scovill.

Dr. Maniotis' letter

As a Professor of Pathology at the University of Chicago, Illinois, one of the nation's largest medical schools, I analyze many similar reports in the course of a single week. I find Dr. Al-Bayati's report perhaps one of the most thorough, if not the most thorough and well-studied investigations I have ever reviewed. If more pathologists used Dr. Al-Bayati's same logical and scientific methodology, there would be little need for inquests, charges of medical malpractice and fraud, and certainly less medical error in autopsies, diagnosis, treatment, and critical care practices.

I would like to emphasize what Dr. Al Bayati developed quite adequately from a technical standpoint by noting how the independent neuroconsultant failed to perform the proper controls for the p24 staining of the microglia and neurons. It should not escape the attention of readers, especially those not familiar with the technical language of these reports, that the detection of the p24 antigen is not in any way diagnostic of the presence of HIV, or any other virus or pathogenic state. Positive staining for p24 in this case, as in all cases in the published literature, is without scientific basis since positive staining can also be found in normal tissues and contexts. Further, I believe Dr. Al-Bayati's analysis and report represent the state of the art in terms of methodology, completeness, and accuracy, and should be presented in the textbooks as models of how to conduct a differential diagnosis.

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