Report on

Claire Margaret Roberts (deceased)

Date of birth: 10 January 1987

Date of death 23 October 1996

Medical report on:	Claire Margaret Roberts (d.o.b. 10.01.1987)
Report author:	Prof KAV Cartwright Consultant Clinical Microbiologist
Instructed by:	Ms B Conlon Administrator Inquiry into Hyponatraemia-Related Deaths (IHRD)
Reference:	IHRDNI - Roberts
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Prof KAV Cartwright MA BM FRCP FRCPath FFPH

[redacted]

Tel:
Mobile:
E-mail:

Instructions

I am a consultant medical microbiologist. A brief summary of my curriculum vitae (CV) is appended to this report (Appendix). A full CV is available on request. I am instructed by Ms Bernie Conlon, Administrator, on behalf of Mr John O'Hara QC, Chairman of the Northern Ireland Inquiry into Hyponatraemia-Related Deaths (IHRDNI).

The Inquiry arose after the deaths in hospital of several Northern Ireland children in which it was considered that hyponatraemia (low plasma sodium levels) may have played a part. The Inquiry was established in 2004 by Ms Angela Smith, then Minister with responsibility for Health, Social Services and Public Safety in Northern Ireland. The Terms of Reference of the original Inquiry established the need to inquire into the events surrounding and following the deaths of three children, namely Adam Strain, Lucy Crawford and Raychel Ferguson. Subsequently the family of Lucy Crawford requested that the events surrounding her death be excluded from the Inquiry. Later still, the Terms of Reference of the Inquiry were extended to include investigations into the deaths of two additional children – Claire Roberts and Conor Mitchell. I am instructed to consider solely some aspects of the case of Claire Roberts.

Then aged 9 years, and with a past history of seizures, moderate developmental delay and moderate learning difficulties, Claire was referred by her GP to the Royal Belfast Hospital for Sick Children on 21 October 1996. There was a short history of lethargy, vomiting and slurring, then withdrawal of speech. Claire was afebrile and her neck was not stiff but she did not like light. Muscle tone was increased on the right side and her reflexes were brisk. Her GP queried a post-ictal state or an underlying infection. Following initial assessment, Claire was admitted to the paediatric ward with a differential diagnosis of viral illness or encephalitis. Blood samples were taken and an IV infusion started. Amongst the results of the blood tests were mild hyponatraemia, mild anaemia, a raised white blood cell count and a slightly raised platelet count.

At 7.00 am the next morning (22 October 1996) Claire was more alert, though still not speaking, and late in the morning she became more lethargic. Encephalopathy and status epilepticus were considered. Rectal diazepam was given. She was seen by Dr Webb, consultant paediatric neurologist who was uncertain of the cause of her symptoms, but considered that her motor abnormalities might be longstanding. He wrote "*The picture is of an acute encephalopathy, most probably post-ictal in nature…*".

At 3.30 pm Claire had an overt five minute seizure. Midazolam and phenytoin were started. At 5.00 pm cefotaxime and aciclovir were added, though infective encephalitis was not thought likely. A blood sample taken at around 9.30 pm showed a very low sodium level of 121 mmol/L. Overload with low-sodium fluids or inappropriate anti-diuretic hormone secretion (SIADH) were considered.

At around 2.30 am on 23 October 2006 Claire had a respiratory arrest and developed fixed dilated pupils. She was intubated and transferred to the ICU. Her Glasgow Coma Scale scores remained subnormal thereafter and her pupils remained fixed and dilated. Tests for brain stem death were carried out at 6.00 am and again at 6.25 pm that same day. Ventilation was discontinued at 6.45 pm. The death certificate gave the cause of death as cerebral oedema secondary to status epilepticus. A sample of cerebrospinal fluid (CSF) was taken at a limited post mortem, at which only an examination of the brain was made. The CSF sample showed a number of abnormalities including a very high protein level and a probable high lymphocyte count.

I am instructed to consider the difference of opinion with regard to the possible causes of death between (a) consultant paediatrician Dr D Evans arising from his interpretation of the CSF findings and (b) consultant neuropathologist Dr B Harding as a result of his consideration of the brain histopathology.

I am further instructed to comment factually on:

(a) the reliability of using the CSF red blood cell/white blood cell ratio as a guide to the presence or absence of meningeal inflammation;
(b) whether the interpretation of this ratio would differ if the CSF sample was obtained after death;
(c) whether a CSF protein level of 95 g/L means that the sample must have been collected after death;
(d) whether the fact that Claire's total peripheral white blood cell count fell from 16.2 x 10^9/L on admission (on 21 October 1996) to 9.4 x 10^9/L on 23 October 1996 and then to around 5.5 to 5.6 x 10^9/L on 24 October 1996 assists in interpreting the nature of her illness.

Statement of Truth

I understand that my duty as an expert is to provide evidence for the benefit of the Inquiry and not for any individual party or parties, on the matters within my expertise. I believe that I have complied with that duty and confirm that I will continue to do so.

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

I confirm that I have no conflict of interest of any kind, other than any disclosed in this report. I do not consider that any interest that I have disclosed affects my suitability as an expert witness on any issue on which I have given evidence. I undertake to advise the Inquiry Secretariat if there is any change in circumstances that affects the above.

K.A.V. Cartwright

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Prof. KAV Cartwright

Documentation

Claire Roberts' medical records

- Royal Belfast Hospital for Sick Children (RBHSC)

Factual witness statements

- Statement & Deposition of Dr Andrew Sands, then SpR in Paediatric Cardiology
- Statement & Deposition of Dr Heather Steen, Consultant Paediatrician, RBHSC
- Deposition of Dr Brian Herron, Consultant Neuropathologist, Belfast
- Statement & Deposition of Dr David Webb, Consultant Paediatric Neurologist, RBHSC

Expert witness reports

- Report of Dr Dewi Evans, Consultant Paediatrician, Swansea
- Report of Ms Sue Chapman, expert Nursing Adviser, Great Ormond Street Hospital, London
- Report of Dr Brian Harding, Consultant Neuropathologist
- Report of Dr Raj Gupta, Consultant Paediatric Neuropathologist

Inquest documentation

- Death certificate
- Correspondence disclosed to the Coroner
- Statement & Deposition of Mr Alan Roberts (Claire Roberts' father)
- Statement & Deposition of Prof Ian Young, Consultant Clinical Biochemist, Royal Group of Hospitals, Belfast
- Deposition of Dr RM Bingham, Consultant Paediatric Anaesthetist, Great Ormond Street Hospital, London
- Deposition of Dr Ian Maconochie, Consultant in A&E Medicine, Consultant Paediatric Anaesthetist, St Mary's Hospital, London
- Notes taken at Inquest by Dr John Burton
- Inquest Verdict

Inquiry documentation

- Expert microbiologist's brief
- Police Service of Northern Ireland (PSNI) documentation and correspondence

Other documentation

- Chronology of Claire Roberts' final illness provided by Ms Conlon

Summary of my conclusions

1. It is outwith my expertise to assess whether or not hyponatraemia caused or contributed to the cerebral oedema that led to coning and to Claire's death though I observe that inappropriate ADH secretion is a well-recognised complication of both meningitis and encephalitis.
2. Claire did not die from (or with) meningitis, either viral or bacterial.
3. In my view her clinical presentation, the progression of her illness and results of tests on blood and CSF were consistent with an acute and fulminant encephalitis.
4. However, Dr Harding, consultant neuropathologist, found no neuropathological evidence to support such a diagnosis.
5. It would be helpful to gain an understanding from Dr Harding as to whether, in his experience, an acute and fulminant encephalitis causing cerebral oedema, coning and death in the space of three days could occur in the absence of clear neuropathological changes, possibly as a result of the rapidity of development of such an infection.

Opinion

Preamble

The chronology of Claire's final illness has been laid out in considerable detail both in the contemporaneous medical records and in many experts' reports. I do not propose to reiterate it again in this report.

The reliability of using the CSF red blood cell/white blood cell (RBC/WBC) ratio as a guide to the presence or absence of meningeal inflammation

Normal CSF contains no RBCs and essentially no WBCs. The normal level of protein is between 0.15 and 0.4 g/L. The normal glucose level is > than 70% of that found in plasma.

In both viral and bacterial meningitis (and in some other inflammatory CNS conditions), the WBC count in CSF is elevated, sometimes markedly so. In bacterial meningitis the CSF WBC count can be normal in the first few hours, but then rises rapidly. Counts are variable, sometimes rising to 10^3 to 10^4 per mm^3. Most of the WBCs are polymorphs (=neutrophils).

In viral meningitis (and to a lesser extent in encephalitis) the CSF WBC count usually rises but not to the same extent as in bacterial meningitis. Counts of greater than 10^3 per mm^3 are unusual. In viral CNS infections the WBCs in the CSF usually comprise almost entirely lymphocytes – a mononuclear cell type - though polymorphs may sometimes be present in quite large proportions early in the infection. Also in viral CNS infections, the glucose level is usually similar to, or only marginally reduced from the plasma level and while the CSF protein level may be elevated it is not normally as high as the levels seen in bacterial meningitis. Typical results for these three conditions are laid out below in tabular form:

Condition	WBCs	Cell type	RBCs	Protein	Glucose	Microscopy	Culture
Normal	< 5 per mm^3	-	None	< 0.4 g/L	> 70% of plasma level	Negative	Negative
Bacterial meningitis	Raised +++	Polymorphs	A few	Raised ++	Low	Bacteria present	Positive
Viral meningitis	Raised +	Lymphocytes	None	Normal or raised ±	Normal or slightly low	Negative	Negative

In patients with suspected acute CNS infection collecting CSF is often straightforward, yielding fluid with no (or almost no) blood contamination, but sometimes the lumbar puncture needle nicks a small blood vessel and the resulting CSF can be contaminated with blood. Such contamination can be minor, gross, or anywhere between.

The normal ratio of RBCs to (total) WBCs in the peripheral circulation is around 500 to 1,000:1 (RBCs about 4 - 5 x 10^9/L and WBCs approximately 5 – 10 x 10^9/L). If blood-stained CSF is obtained from a patient with possible meningitis and the RBC/WBC ratio is the same as in whole blood (i.e. between 500:1 and 1,000:1) this suggests that there is little or no inflammatory process occurring within the meninges (the linings of the brain). Conversely, if the ratio is lower (i.e. there are relatively more white blood cells than would be expected), this suggests that the relative excess of white blood cells may have resulted from inflammation within the CSF.

In my experience the RBC/WBC ratio is a crude tool in assessing the likelihood of a truly raised CSF WBC count when the CSF is bloodstained. I would only be suspicious of the possibility of an underlying meningitis if the ratio were lower than around 250:1. It is often forgotten that in bacterial or viral meningitis the peripheral WBC count is often markedly raised e.g. to 15 – 20 x 10^9/L whereas the RBC count remains relatively constant, so ratios of 250:1 or more need to be considered quite critically before significance is attributed to them. The clinical status of the patient and the other findings (peripheral WBC count and differential, CSF glucose and protein) all need to be taken into account and evaluated carefully before attributing significance to a CSF RBC/WBC ratio.

The interpretation of the CSF RBC/WBC ratio when the CSF sample is obtained after death

In common with most clinicians I have almost no personal experience of assessing this ratio in CSF samples obtained after the patient has died. Blood contamination of CSF is much less likely to occur when samples are collected after death. Also, since CSF is only likely to be collected after death when there has been suspicion of intracranial pathology during life, such post mortem collection of CSF is usually accompanied by direct examination of the brain and meninges, and this is generally much more informative and more reliable than examination of post mortem CSF in isolation.

After death, WBCs and RBCs begin to lyse (break down), with the former deteriorating faster than the latter. Also, if blood contamination of CSF is severe, blood may clot. These factors make the interpretation of the CSF RBC/WBC ratio after death increasingly unreliable. The longer the interval between death and the collection of a CSF sample the greater will be the uncertainty attaching to the ratio.

The interpretation of a CSF protein level of 95 g/L

The upper limit of the normal CSF protein level in life is 0.4 g/L. The highest CSF protein levels I have ever encountered in living patients have been around 10 - 12 g/L in cases of severe and advanced untreated tuberculous meningitis. I would view a CSF protein level of 95 g/L as being incompatible with life and therefore having been obtained only after death. Even in a "CSF" sample obtained after death I would be highly sceptical of the validity of the result and would query whether the sample analysed was indeed CSF at all.

I am unable to offer any meaningful theory as to how such a CSF level could be anything other than a "rogue" false result, since the level is appreciably higher than the upper limit of the normal total protein level in serum or plasma (around 80 g/L), so even in a heavily bloodstained specimen it should not be possible to achieve a level of 95 g/L (unless the sample comprised entirely blood, and no CSF, and in addition the patient had a paraproteinaemia such as myeloma (which was not remotely likely in this case).

The interpretation of a rapid fall in Claire's total peripheral white blood cell count (from 16.5 x 10^9/L on the day of admission (21 October 1996) to 9.4 x 10^9/L on 23 October 1996, then to 5.7 x 10^9/L later that day and to finally 5.5 x 10^9/L on 24 October 1996

A blood sample for a full blood count was taken shortly after Claire's admission to hospital on 21 October 1996. This showed a markedly elevated total peripheral white blood cell count of 16.5 x 10^9/L. On 23 October 1996 two further blood counts showed a falling white cell count of 9.4 x 10^9/L then 5.6 x 10^9/L. A final white blood cell count of 5.5 x 10^9/L was obtained on 24 October 1996. It is very unlikely that any of these results was unreliable for technical reasons. Haematology blood cell counters are highly reliable and are checked several times daily for the accuracy of their results using standardised test samples.

A total white blood cell count of 16.5 x 10^9/L is well above the upper limit of normal (which is about 11.0 x 10^9/L). Taken in isolation, and considered in the context of Claire's illness, I would view such a level as being strongly suggestive of an acute infective process. Unfortunately the laboratory did not provide a differential white blood cell count. Had this been done and reported, it would have given a good indication as to whether such (putative) infection was viral or bacterial.

In the great majority of bacterial infections in which an elevated total white blood cell count is found, the elevation is due almost entirely to an increase in the numbers (and the proportion) of neutrophils. In contrast, in viral infections, such an elevation would almost always be due to an excess of lymphocytes.

Can the white blood cell count change as was apparently the case here? The answer is in the affirmative. Though not particularly common, but especially when elevated, total peripheral white blood cell counts can change markedly (and by at least as much as was documented here) within even a few hours, let alone from day to day.

Do such large changes reduce the significance of the initial high white blood cell count? In my opinion they do not. I repeat my view that in the context of Claire's illness, I would view a total white blood cell count of 16.5 x 10^9/L as being strongly suggestive of (albeit not proof of) an infective process, though whether viral or bacterial cannot be determined from this single result without a differential white blood cell count. The later fall to normal levels of white blood cell counts by the following day does not diminish the significance of the initial high value.

The nature of Claire Roberts' final illness

Claire had a history of developmental delay and moderate learning difficulty and also some modest motor handicap, though it appears that when well she was able to walk and run and hold simple conversations. Though there was a past history of epilepsy, she had had no fits for three years including eighteen months after discontinuation of her anticonvulsant treatment. Two days before her referral to hospital, she had been in contact with her cousin who had a gastrointestinal upset.

On her admission to hospital on 21 October 1996 there was a short history (< 1 day, as confirmed by her father) of vomiting, pallor, lethargy, drowsiness, and slurred speech progressing to a lack of vocalisation. On examination she was afebrile and without neck stiffness but with a dislike of light. Her pupils were equal and reactive to light. There was increased muscle tone and the reflexes were brisker on the left than on the right. (The referring GP had noted an upgoing right plantar reflex). Other than increased muscle tone, brisk reflexes bilaterally and a marked decrease in responsiveness there was little abnormal to find on physical examination. The working diagnosis was either encephalitis or a viral illness. A full blood count revealed a markedly elevated total white blood cell count of 16.5 x 10^9/L, mild anaemia (haemoglobin 10.4 g/dL), a marginally raised platelet count of 422 x 10^9/L and a slightly low sodium of 132 mmol/L. Claire was observed overnight. By the morning (22 October 1996) she was thought by the nurses to be improved and brighter. There had been one further vomit overnight.

During the morning Claire was reviewed by Dr Sands, SpR in Paediatric Cardiology, who noted that she was still retching and remained vague and vacant with little speech, even with her parents. She remained on IV fluids. He summarised as: "*Impression – non fitting status. Plan – rectal Diazepam. Dr Webb to review.*". After Dr Sands' ward round, neurological observations were commenced.

When Dr Webb, Consultant Paediatric Neurologist, reviewed during the early afternoon he wrote: "*Impression – I don't have a clear picture of the prodrome and yesterday's episodes. Her motor findings today are probably long-standing but this needs to be checked with the clinical notes. The picture is of an acute encephalopathy, most probably post-ictal in nature. I note the normal biochemistry profile.*". He advised starting phenytoin, an anticonvulsant, and instituting hourly neurological observations. A CT was advised for the next day if Claire did not "*wake up*". Midazolam and phenytoin were started. The next major event was a "*strong seizure*" lasting 5 minutes at around 3.30 pm.

When seen again by Dr Webb at 5.00 pm, Claire continued to be "*largely unresponsive*". He suggested she be started on cefotaxime (a broad-spectrum antibiotic) and aciclovir (an antiviral) although in the absence of fever and meningism he did not think an infective meningoencephalitis was likely.

Further seizures followed during the late afternoon and early evening. At 11.30 pm the results of blood tests that had been taken earlier in the evening (at 9.30 pm) became available. The major abnormality was a markedly low plasma sodium of 121 mmol/L. After discussion between the Paediatrics SHO and SpR it was thought that this hyponatraemia was most likely to have been caused by either inappropriate secretion of anti-diuretic hormone (SIADH) or by fluid overload with low sodium fluids. The rate of fluid infusion was decreased by two thirds.

At 2.30 am (now 23 October 1996) the nurses noted that Claire suffered a respiratory arrest. By the time the first doctor arrived Claire's pupils were fixed and dilated. Oxygen and suction were given but attempted intubation was initially unsuccessful. When an anaesthetist arrived Claire was successfully intubated and then transferred to the ICU at 3.25 am where she was hyperventilated and started on mannitol and dopamine. At around 5.30 am she was taken to the Royal Victoria Hospital for a brain scan. This showed severe, diffuse hemispheric swelling with complete effacement of the basal cisterns, but no other focal abnormality i.e. the brain was severely swollen. Following fluid restriction Claire's plasma sodium levels returned to normal.

At 6.00 am and then again at 6.25 pm brain stem functional evaluations demonstrated absence of brain stem activity. Throughout the day Claire remained unresponsive. The ventilator was turned off at 6.45 pm and Claire passed away.

A limited autopsy (of the brain alone) was carried out. The autopsy was carried out on 24 October 1996, the day after Claire's death. The post mortem CSF sample was probably obtained on the same day. The CSF yielded the following results:
Appearance: bloodstained
Supernatant: straw-coloured
Protein: 95.0 g/L
Globulin: present +++
Red blood cells: 300,000 per mm^3
White blood cells: 4,000 per mm^3
Cytology: mostly lymphocytes

Other test results that became available after Claire's death included: no bacterial growth from the blood cultures (that had probably been taken on 22 October 1996 and probably before antibiotics had been started), a normal urine microscopy and negative culture, and negative serology results for mumps, measles, *Herpes simplex, Herpes zoster* and CMV (cytomegalovirus). There were also negative serology results for adenovirus, Q fever, PLGV, *Mycoplasma pneumoniae* and influenza A and B viruses.

The initial (limited) autopsy (of the brain alone) was carried out by Dr B Herron, Consultant Neuropathologist. Summarising his findings, he wrote: "*.. the features here are those of cerebral oedema with neuronal migrational defect and a low grade subacute meningoencephalitis. No other discrete lesion has been identified to explain epileptic seizures. The reaction in the meninges and cortex is suggestive of a viral aetiology, though some viral studies were negative during life and on post mortem CSF. With the clinical history of diarrhoea and vomiting, this is a possibility though a metabolic cause cannot be entirely excluded. As this was a brain only autopsy it is not possible to comment on other systemic pathology in the general organs. No other structural lesion in the brain like corpus callosal or other malformations were identified.*".

In contrast, Dr Brian Harding, Consultant Neuropathologist at Great Ormond Street Hospital for Children, London, found on re-examination of the sections and blocks of brain tissue: (a) brain swelling (determined by the recorded weight of the brain (1606 g), (b) acute hypoxic damage to nerve cells, (that he regarded as probably terminal), (c) no evidence of acquired or inherited disease. He went on to state that there was no evidence of acquired infection (meningitis or encephalitis) and also that the cause of death as stated on the death certificate and in the Inquest verdict was not concordant with his observations. In his report dated 22 August 2007 he elaborated as follows:

"*1. The only relevant observation, albeit macroscopic (naked eye) is of brain swelling, as judged by the excessive brain weight (1606 g, the normal at this age in girls is 1200 g), 'effacement of the gyri' and 'uncal prominence'. However these are rather weak indicators, not supported by major downwards shift of the brain and cerebellum which is common in severely swollen brains and by the microscopy (lack of vacuolation of white matter). I can find no mention of the head circumference on the records which I have been given to indicate whether this child had a normal head circumference*

during her life, against which to judge the brain weight. During the terminal illness the CT scan was reported to show cerebral oedema (swelling).

2. *We have no information regarding the other internal organs of the body, which might help us, for example to exclude a cardiac cause of sudden death.*
3. *If cerebral oedema is present (inquest cause of death 1a), then we require a cause of it. The inquest records 1b 'meningoencephalitis, hyponatraemia due to excess ADH production and status epilepticus'.*
4. *I consider meningoencephalitis excluded, both by microbiology and the post mortem neuropathology.*
5. *Hyponatraemia has been identified from the chemical-pathology data. There is a history of vomiting which when severe may result in electrolyte disturbance. Hyponatraemia is known to cause brain swelling. But there is no other specific neuropathological indicator for hyponatraemia that I am aware of.*
6. *The child was said to suffer from seizures. None were witnessed prior to hospital admission, and certainly not status epilepticus. Moreover the neuropathological sequelae of status were not present. Nor was there damage to the hippocampus which may be seen in children with chronic epilepsy.*".

Dr Harding's conclusion (by a process of elimination of other possibilities) was that "*the evidence suggests that brain swelling was the immediate cause of death and hyponatraemia is the only causative factor that has been positively identified.*".

Thus, the two neuropathologists appear to agree that the proximate cause of Claire's death was cerebral oedema, but as observed in my instructions, take contrary views as to the likely cause of that cerebral oedema. My views on the cause of death are as follows:

1. Both CT scanning and post mortem evidence (the weight of the brain) were strongly suggestive of the presence of cerebral oedema. The clinical episode that occurred at 2.30 am on 23 October 1996 was almost certainly an episode of coning, in which raised intracranial pressure (caused by cerebral oedema) causes (a) the bases of the cerebral hemispheres to be pushed unnaturally through the tentorium, the fibrous membrane that normally supports the cerebral hemispheres, and/or (b) the brainstem and/or the cerebellar tonsils to be similarly pushed unnaturally into the constriction of the foramen magnum, the opening at the base of the skull at which the brain and spinal cord are linked.

Coning often causes sudden death and in survivors, irreversible brain damage. When it does not cause death, if the raised intracranial pressure is later reversed or moderated, the displaced parts of the brain may recover their original anatomical positions, but if this occurs, damage incurred during coning will often have proved irreversible. As observed by Dr Harding, this then begs the question: what caused cerebral oedema and raised intracranial pressure?

2. I am not an expert metabolic physician or clinical biochemist and it is outwith my expertise to assess what role, if any, may have been played by low plasma sodium levels on 22 October 1996. However, from my general clinical experience I would add my voice to those of the other experts in this case who concluded that the plasma sodium level on admission, though low, was not sufficient of itself to cause brain swelling and cerebral oedema. I also observe that inappropriate ADH secretion is a well-recognised complication of meningitis and encephalitis.
3. What evidence was there that Claire's illness might have resulted from an infection? Dr Harding concluded that there was no microbiological evidence to support an infection, but like Dr Evans (whose report I deliberately did not read until I had completed a first draft of my report), I formed a different view. As I have stated earlier in this report, in my view, and in the clinical context of a child with relatively sudden onset of vomiting and diminished responsiveness, the total peripheral white blood cell count of 16.5×10^9/L in the blood sample collected on the day of admission was highly suggestive (although not diagnostic of) infection. The lack of a differential white blood cell count made it impossible to determine whether such putative infection was viral or bacterial.
4. I agreed completely with Dr Evans' interpretation of the (post mortem) CSF sample. There was indeed a substantial relative excess of white blood cells in this specimen that could not be explained by blood contamination.
5. Dr Evans highlighted a further extremely important point, namely that cytology studies of these CSF white blood cells revealed them to be predominantly lymphocytes. In the absence of a mononuclear cell CSF infiltration caused by a malignancy (which was highly unlikely in this case), such a finding makes a viral CNS infection a real possibility.
6. I am unable to account for or interpret the reported CSF protein level. Even though the CSF protein level will rise when there is blood contamination, the reported level was higher than the upper limit found in undiluted plasma or serum.

6. If there was viral CNS infection, is it possible to draw any conclusions about its nature? Though Dr Herron found evidence at post mortem of "*focal meningeal thickening and a cellular reaction in the meninges and perivascular space in the underlying cortex*" that he interpreted as being consistent with a "*low grade subacute meningoencephalitis*" in contrast, Dr Harding found no neuropathological evidence at all of meningoencephalitis.
7. Clinically, meningitis in a child of Claire's age would normally be manifested by a combination of fever, headache, stiff neck, sometimes accompanied by photophobia (dislike of bright lights). The first three of these were all absent and the latter is a subjective sign. Thus there was no real clinical evidence of meningitis. Further, had there been meningitis, it would have been obvious at autopsy. Thus meningitis, either bacterial or viral, can be safely excluded.
8. In my view a viral encephalitis remains a material possibility. The apparent lack of supportive evidence from the battery of negative serological tests for encephalitis agents that were undertaken should not be misinterpreted. These negative results were diagnostically meaningless and of no value in the context of such a short history of illness. It takes a minimum of 6-8 days for antibody levels to rise in such infections, and often longer. Thus a battery of negative antibody test results on specimens collected only 2 – 3 days into the clinical illness provides no diagnostic information at all, either positive or negative.
9. I have considered earlier in this report the possibility of poor reliability of the CSF RBC/WBC ratio in post mortem specimens of CSF but in this case the interval between death and autopsy was only one day. This means that degeneration of the cellular elements in CSF would have been very limited, enabling one to place somewhat more confidence in the validity of the ratio.
10. I note Dr Harding's view that there was no neuropathological evidence of encephalitis but would pose the question whether such evidence always present, even in cases where encephalitis has only been present for three days before causing death.

Appendix

Prof KAV Cartwright

Relevant qualifications and experience

I qualified in medicine from Oxford University in 1971 (BM BCh). In 1977 I obtained the Membership of the Royal College of Pathologists, becoming a Fellow of the College in 1987. I have worked in clinical microbiology for more than thirty years and as a consultant clinical microbiologist since 1978. I took partial early retirement from the NHS in July 2004.

From 1981 to 1995 I was Director of Gloucester Public Health Laboratory, providing microbiology services for 500,000+ people in Gloucestershire. In July 1995 I was appointed Director of PHLS South West, a group of seven (later 10) Public Health Laboratories from Hereford to Truro, serving a population of over five million and with a throughput of more than one million specimens per annum. Following the abolition of the PHLS and the creation of the Health Protection Agency (HPA) in 2003, my last post was that of Head of Intervention Policy and R&D for the HPA. I continued to work part-time for the HPA until the end of 2007.

In 1997 I was awarded a personal chair in clinical microbiology by the University of Bristol. In 2003 I was elected a Fellow of the Faculty of Public Health and in 2008 I was elected a Fellow of the Royal College of Physicians. I was President of the Association of Clinical Pathologists in 2004-05.

My principal research interest is in the identification, management and prevention of severe community-acquired infections, and particularly bacterial meningitis. I have published extensively in this area and am sole editor of the first book devoted entirely to meningococcal disease. I am an author of more than 100 peer-reviewed papers and many book chapters on a range of infection-related topics. Until my retirement, I was a member of the HPA Systemic Infections Committee and the chairman of the HPA Pneumococcus and Meningococcus Working Groups. Until 2008 I continued a programme of research into bacterial vaccines and severe community-acquired infections and I was a member of the Department of Health's Joint Committee on Vaccination and Immunisation, advising the Department on UK vaccination policy until the end of 2006. From 1998 to 2003 I chaired the Wellcome Trust Advisory Committee on Medical Microbiology Clinical Training Fellowships. From 1994 to the time of my (partial) retirement I was a senior editor of the journal “Epidemiology & Infection” reviewing 20 – 50 papers annually. I refereed papers for many journals and grant proposals for many institutions and I examined candidates for higher degrees for several universities. I remain a member of a scientific advisory panel providing a steering function for the University of Liverpool DH-funded Biomedical Research Centre (£5m + annual budget).

I have provided a total of over 200 reports for various Courts on a diverse range of topics including most types of severe hospital and community-acquired infections, including orthopaedic infections. My reports have been written on the instructions of solicitors acting both for Claimants (about 40%) and for Defendants (about 50%), as well as for HM

Coroners, and include instructions from Australia, USA, Scotland and Ireland, as well as England & Wales. I have given evidence in various Courts on about a dozen occasions.

I am a non-executive director of the Medical Defence Union, the UK's largest doctors' defence organisation. I am also the chair of the MDU's Cases Committee and Advisory Medical Committee and a member of Council.

The MDU Council

The MDU Council is a forum for discussion and analysis of professional, scientific and allied matters referred to it by the Board of the MDU. Council considers matters such as the implications for MDU members of changes in hospital disciplinary procedures and professional regulation, and court judgments that set precedents in the medico-legal field. The Council may provide input to MDU staff on matters such as general guidance for members. The Council has no responsibility for decision making in individual cases involving MDU members.

The MDU Cases Committee

The MDU Cases Committee considers and provides advice upon reports from case handlers on individual cases involving MDU members. The advice given is for internal purposes only. Members of the Cases Committee are excluded from any discussion or advice relating to a case in which they have provided a report for litigation.

The MDU Claims Management Committee and Advisory Medical Committee

The MDU Claims Management Committee and Advisory Medical Committee exercise delegated powers of the Board in relation to individual cases. The members of the Committees are drawn from the Council. A Committee member who has provided an expert report for any party is excluded from any discussion or decision-making in relation to that case.