BRIEF FOR EXPERT ON NEUROPATHOLOGY

RE: CLAIRE ROBERTS

Introduction

(1) Claire Roberts is one of four children who are the subject of a public inquiry being conducted by John O'Hara QC.

(2) Claire was born on 10th January 1987. She was admitted to the Royal Belfast Hospital for Sick Children ("RBHSC") on 21st October 1996 with a history of malaise, vomiting and drowsiness and she died on 23rd October 1996. Her medical certificate recorded the cause of her death as Cerebral Oedema and Status Epilepticus. That certification was subsequently challenged after a television documentary into the deaths of Adam Strain and two other children (Lucy Crawford and Raychel Ferguson).

(3) The Inquest into Claire's death was carried out nearly 10 years after her death by John Leckey on 4th May 2006. He engaged as experts:

(a) Dr. Robert Bingham Consultant Paediatric Anaesthetist at Great Ormond Street and

(b) Dr. Ian Maconochie Consultant in Paediatric A&E Medicine at St Mary's, London.

The Inquest Verdict found the cause of Claire's death to be: 1(a) Cerebral Oedema due to (b) meningo-encephalitis, hyponatraemia due to excess ADH production and status epilepticus. The Coroner found that hyponatraemia contributed to the development of the cerebral oedema that caused Claire's death, but was not the only underlying cause of her death, the others being meningo-encephalitis and status epilepticus. Each of those 3 factors contributed though in proportions which cannot be determined.

Terms of Reference

(4) The Inquiry was established under the Health and Personal Social Services (Northern Ireland) Order 1972, by virtue of the powers conferred on the Department by Article 54 and Schedule 8 and it continues pursuant to the Inquiries Act 2005.

(5) The original Terms of Reference for the Inquiry as published on 1st November 2004 by Angela Smith (then Minister with responsibility for the Department of Health, Social Services and Public Safety) were revised in 2008 in response to the Crawford family's wish to have Lucy excluded from the Inquiry's work. The Revised Terms of Reference under which the Inquiry is operating are:

> To hold an Inquiry into the events surrounding and following the deaths of Adam Strain and Raychel Ferguson, with particular reference to:
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> 1. The care and treatment of Adam Strain and Raychel Ferguson, especially in relation to the management of fluid balance and the choice and administration of intravenous fluids in each case.
>
> 2. The actions of the statutory authorities, other organisations and responsible individuals concerned in the procedures, investigations and events which followed the deaths of Adam Strain and Raychel Ferguson.
>
> 3. The communications with and explanations given to the respective families and others by the relevant authorities.
>
> In addition, Mr O'Hara will:
>
> (a) Report by 1 June 2005 or such date as may be agreed with the Department, on the areas specifically identified above and, at his discretion, examine and report on any other matters which arise in connection with the Inquiry.
>
> (b) Make such recommendations to the Department of Health, Social services and Public Safety as he considers necessary and appropriate.

The Inquiry

(6) The Inquiry has appointed Inquriy Expert Advisors[1] to assist it in its investigations in respect of all 4 children. Their work is peer reviewed by a team of international experts.[2]

(7) The Inquiry has also engaged Expert Witnesses to deal with a number of discrete issues that are child-specific.

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[1] Dr. Peter Booker (Paediatric Anaesthesia), Dr. Harvey Marcovitch (Paediatrics), Ms. Carol Williams (Paediatric Intensive Care Nursing), and Mr Gren Kershaw (Health Service Management and Patient Safety)

[2] Professor Allen Arieff at the University of California Medical School in San Francisco (Internal Medicine & Nephrology), Dr. Desmond Bohn of the Critical Care Unit at the Hospital for Sick Children in Toronto (Paediatric Anaesthesia), Ms. Sharon Kinney at the Intensive Care Unit and Clinical Quality and Safety Unit at the Royal Children's Hospital in Melbourne (Paediatric and Intensive Care Nursing)

Claire's history and case

Pre-1996 referral

(8) Claire Roberts was born on 10th January 1987. Claire was first admitted to hospital on 23rd July 1987 when she was admitted to The Ulster Hospital in Dundonald ("the Ulster Hospital"), aged 6½ months, because of seizures. Further episodes occurred during August 1987 resulting in treatment with the anticonvulsant, carbamazepine (Tegretol ®). Further convulsions occurred in September 1987, together with findings on examination of being floppy with possible abnormal posture and tone on the left side.

(9) She was referred to the RBHSC on 3rd September 1987 under the care of Dr. Elaine Hicks, Consultant Paediatric Neurologist[3]. Investigations, including brain CT scanning and electroencephalography, did not define any causative diagnosis for her epilepsy. She was prescribed the anticonvulsant sodium valproate (Epilim®) before discharge, while weaning her from her previously prescribed Tegretol[4].

(10) Claire's convulsions ceased at the age of 4 years (September 1991) and Claire was weaned off Epilim over 3 months from February 1995.[5]

(11) In May 1996, she was seen by Dr. Colin Gaston, Consultant Community Paediatrician in relation to behavioural problems including inattention, easily distracted, obsessions and constant activity. Claire was treated with Ritalin 10 mg daily until 2nd October 1996 when her parents reported "dry mouth, viscous, pacing, ? agitated/unsettled 30 minutes after Ritalin".[6] Dr. Gaston noted his advice to "hold meds" and "restart on a weekend with just 5 mg. Mother to call 5 days later"[7] It is not known whether the Ritalin was restarted. There is no mention of it in her A&E admission notes[8] which record no medication, or in the ward assessment[9].

(12) Claire had no dysmorphic features[10] In Claire's medical records her head circumference is recorded as:

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[3] Ref: 090-018-033, 034
[4] Ref: 090-015-026, 027
[5] Ref: 099-006-008, 099-007-009
[6] Ref:090-013-017
[7] Ref: 090-013-016, 017
[8] Ref: 090-011-013
[9] Ref: 090-022-050
[10] Ref: 099-006-008, 099-013-018

- 43cm on 1st August 1987 when Claire was approximately 7 months old[11]; 46.5cms on 4th February 1988 when Claire was approximately 13 months old[12];
- 48cms on 19th December 1988 when Claire was 1 year and 11 months old[13].

Also, it appears that Claire's head circumference was 53cm on 30th May 1996 when Claire was approximately 9 years and 4 months old, which was about 5 months before her admission to RBHSC in October 1996[14]. We enclose a head circumference chart and a newspaper photograph of Claire to illustrate her facial features/head circumference for your information.

(13) Claire was seen by Professor Norman C. Nevin, Consultant Medical Geneticist, in RBHSC on 3rd April 1995. He did not believe that there was a genetic basis to Claire's developmental delay and fits, but was most likely due a degree of anoxia.[15]

1996 referral

(14) On 21st October 1996 Claire's GP referred her for admission to the RBHSC. She described Claire as a 9-year-old girl with severe learning disability and past history of epilepsy who had been seizure-free for 3 years and had been weaned off anticonvulsant drugs 18 months previously. The referral also stated "No speech since coming home. Very lethargic at school today. Vomited x 3 – speech slurred. Speech slurred earlier"[16]. Claire was described as pale, not liking the light and with no neck stiffness. The GP considered her tone increased on the right side and suggested that Claire was post-seizure and had an underlying infection[17].

(15) Claire was admitted to the RBHSC later on 21st October 1996 exactly 4 months after the conclusion of the Inquest into Adam Strain's death of hyponatraemia at the RBHSC. The A&E note records non-bilious vomiting since the evening. She was drowsy, tired, apyrexial with no other abnormal signs except for increased left sided muscle tone and reflexes. At 20.45, a decision was made to admit Claire to hospital under the care of Dr. Heather Steen, Consultant Paediatrician[18].

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[11] Ref: 099-059-077
[12] Ref: 099-0579-088
[13] Ref: 099-031-043, 099-059-093
[14] Ref: 099-059-099
[15] Ref: 099-005-007.
[16] Ref: 090-011-013
[17] Ref: 090-011-013
[18] Ref: 090-012-014

(16) The admission note (timed at 20:00) refers to Claire as vomiting at 3pm and every hour since and to her having experienced a loose bowel motion 3 days previously. The admitting doctor, Dr. O'Hare, noted that Claire had severe learning difficulties but normally had meaningful speech and referred to the recent trial of Ritalin and its apparent side effects[19]. Dr O'Hare also noted that Claire sits-up and stares vacantly and was ataxic. She was not responding to her parents' voice and only intermittently responding to a deep pain stimulus. She had cogwheel rigidity of her right arm and increased tone in all other limbs. Tendon reflexes were brisker on the right than the left and there was bilateral ankle clonus[20].

(17) The admission diagnoses were noted as: (1) Viral illness; (2) Encephalitis (but this was subsequently scored through)[21]. Treatment was noted as "IV fluids, IV diazepam if seizure activity".

(18) A medical note at midnight stated that she was slightly more responsive'and had no meningism. It was noted that she would be observed and reassessed in the morning. Directly beneath that note is an for the blood biochemical and haematological results:

> Sodium 132; Potassium 3.8; Urea 4.5; Glucose 6.6; Creatinine 36; Chloride 96; Haemoglobin 10.4; Packed cell volume 31; White cell count 16.5; platelets 422,000

The white cell count result of 16.52 on admission was from a sample taken at approximately 22.00/22.30 on 21st October 1996.[22] Claire's white cell count results then dropped to 9.4 as recorded in the medical notes at 04.00 on 23rd October 1996[23] which appears to have the printed lab report result of 09.35.[24] There are also printed lab reports for white cell count results of 5.70 from a specimen on 23rd October 1996,[25] and of 5.54 from a specimen on 24th October 1996.[26]

(19) In the late morning of 22nd October 1996 Claire, who was usually very active, became lethargic and vacant. She was seen by Dr. Sands (Registrar, Paediatric Cardiology) who concluded "status epilepticus – non-fitting" and rectal diazepam given.[27] She was described in the note of the ward

[19] Ref: 090-022-050
[20] Ref: 090-022-051
[21] Ref: 090-022-052
[22] Ref: 090-022-052, 090-032-108
[23] Ref: 090-022-057
[24] Ref: 090-032-111
[25] Ref: 090-032-112
[26] Ref: 090-032-110
[27] Ref: 090-040-141

round as apyrexial, pale and showing little response compared to normal. Her pupils were sluggish to light. The impression was of non-fitting status. A different hand has added "encephalitis/ encephalopathy" but the time at which that note was made and it author is not known.[28]

(20) The fluid chart for 22nd October 1996[29] does not note the solution given. However, an undated prescription chart[30] referred to 500 ml of no.18 solution at 64 ml/hr. A total of 562 ml was given over eight hours from 08.00, i.e. 70 ml/h.

(21) At 15.10 Claire was reported as having a 5-minute strong seizure at 15.25. At 16.30, her teeth tightened slightly[31]. Dr. Webb saw Claire and noted a history of vomiting and listless followed by a prolonged period of poor responsiveness. He added that she had appeared to improve after rectal diazepam, given at 12.30. She was afebrile and pale with no meningism. She opened her eyes to voice, was non-verbal, withdrew [limb] from painful stimulus and had (questionably) reduced movements on the right side. He found mildly increased tone in her arms and symmetrical brisk reflexes, sustained ankle clonus and upgoing plantar responses. Claire was sitting up with eyes open and looking vacant, not obeying commands. She did not have papilloedema[32]. Dr Webb's impression was that Claire's motor findings are probably long-standing, which should be checked with notes but that the picture was of acute encephalopathy, most probably postictal in nature. He noted the normal biochemistry profile[33]. He suggested starting Claire on the anticonvulsant phenytoin intravenously: 18 mg/kg as a first dose, followed by 2.5 mg/kg 12 hourly. He asked for hourly neurological observations and a CT scan the following day if she did not wake up[34].

(22) The SHO noted calculations of phenytoin dose at 14.30 and ordered a dose of 18 mg x 24 h which he wrongly calculated as 632 mg rather than 432 mg. The calculation of the continuing dose of 2.5 mg/kg 12 hourly is then stated as 60 mg 12 hourly[35].

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[28] Ref: 090-022-052, 053
[29] Ref: 090-038-135
[30] Ref: 090-038-136
[31] Ref: 090-042-144
[32] Ref: 090-022-053, 054
[33] Ref: 090-022-054
[34] Ref: 090-022-054
[35] Ref: ibid

(23) The nursing notes record a stat dose of phenytoin given at 14.45pm[36], with a second dose at 2300 following blood sampling for phenytoin levels[37].

(24) The next medical note (untimed) referred to Claire being seen by Dr. Webb and being 'still in status.' It went on to calculate a dose of the anticonvulsant/ sedative midazolam to be given as a first dose of 0.5 mg/kg (12 mg) followed by 2 mcg/kg/minute, calculated as 2.88 mg/h. The prescription chart records the once only dose of 120mg, the time of administration 15.25[38] but the actual dose administered to Claire is not known. The continuing infusion of midazolam was ordered as 69 mg in 50 ml normal saline to be given at 2 ml/h, which is confirmed by the fluid charts as having been given from 16.30[39]. Also from 16.00, no 18 solution was continued with 452 ml given over 7 h to 23.00 (64 ml/h])[40].

(25) At 17.00, Dr Webb described Claire as largely unresponsive with intermittent vomiting and chewing. He prescribed the antibiotic cefotaxime and the anti-viral drug acyclovir for 48 hours, although he noted that he did not think meningoencephalitis very likely. He noted that stool, urine, blood and a throat swab should be checked for evidence of enterovirus infection. He also suggested an additional anticonvulsant intravenous infusion: sodium valproate 20 mg/kg as an initial dose, followed by 10 mg/kg over 12 h[41]. A nursing note at 17.15 referred to Claire being given a stat dose of Epilim and being responsive only to pain, remaining pale and having the occasional episode of teeth clenching.[42] A further attack of "teeth clenched and groaned" for "1 min[ute]" is recorded at 19.15.

(26) At 21.00, a nurse reported that Claire had a 30-second episode of screaming and drawing up of her arms with her pulse rising to 165. A doctor was informed[43].

(27) At 23.30, an SHO noted that a blood sample likely to have been taken when the doctor attended at 21.00 - 2130, showed a sodium concentration of 121 mmol/L, potassium 3.3 mmol/L, urea 2.9 mmol/L and creatinine 33 µmol/L. The phenytoin level was 23.4 mg/L (reference range 10-20 mg/L). It was noted: 'Hyponatraemic - ? Fluid overdose with low sodium fluids. ? SIADH' and 'Imp[ression]. ? need for↑ sodium content in fluids. Discussed

[36] Ref: 090-026-075, 090-040-141
[37] Ref: 090-040-138, 090-038-135, 090-026-077
[38] Ref: 090-040-141
[39] Ref: 090-038-135, 136
[40] Ref: 090-038-135
[41] Ref: 090-022-055
[42] Ref: 090-040-141, 090-142-144
[43] Ref: 090-042-144

with registrar - ↓ fluids to ⅔ of present value – 41 ml/h. Send urine for osmolality'[44].

(28) In fact, between 23.00 and 02.00 Claire received 56 ml of No 18 solution (18.5 ml/h) and 7.6 ml of normal saline. Also between 22.00 and 01.00 Claire received 170 ml of other fluids, recorded as IV Acyclovir 60 (presumably 'ml') and Phenytoin 110 (? 'ml') recorded in the oral fluids columns. The exact nature of the fluids in which the Acyclovir and Phenytoin were dissolved is not stated[45].

(29) A nursing note at 21.30 referred to Claire receiving midazolam at 3 ml/h, completed by 22.40. At 2300, she was given IV phenytoin over 1 hour. In addition, the fluid chart refers to two 'small mouthfuls' of vomit/aspirate recorded at 24.00 and 01.00[46]. It is unclear whether these were discussed with the doctors, as they are not referred to in the medical or nursing notes. As a result of instructions from 'a registrar', 20 mmol of potassium chloride was added to the No 18 solution and the rate reduced to 41 ml/h.

(30) The neurological observation chart, started at 1300 on 22nd October 1996, shows that at 1300 she was noted as *opening her eyes to speech* and at 1430 as *opening eyes to pain*. Thereafter, hourly recordings until 0200 on 23.10.96 all stated there was *no eye opening*. 'Best verbal response' was noted as *none* from 1300 to 1800 and thereafter as *incomprehensible sounds*. Her 'best motor response' was noted as *obey commands* at 1300 and at 2000, *localise pain* between those times and *flexion to pain* thereafter[47].

(31) Her Glasgow Coma Scale (GCS) score was given as 9 on first checking and thereafter was 6 - 7, except recorded as 8 at 2000. There was a rise in temperature from normal to between 37.5 C and 38 C from 1900 and of pulse rate from <90 at 1300 to 115 at 1800, thereafter remaining at 100-105. There was no significant change recorded in blood pressure[48].

(32) At 02.30, a nurse noted 'Slight tremor of right hand noted lasting few seconds. Breathing became laboured and grunting. Respiratory rate 20 per minute. Oxygen saturations 97%. Claire stopped breathing. The medical note states that Claire 'had been stable when suddenly she had a respiratory arrest and developed fixed dilated pupils.' The doctor who attended noted she was 'Cheyne-Stoking'. Oxygen was being administered

[44] Ref: 090-022-056
[45] Ref: 090-038-135
[46] Ref: 090-038-135
[47] Ref: 090-039-137
[48] Ref: 090-039-137

by a facemask and 'bagging' with oxygen saturation in the 'high 90s' and a 'good volume pulse.'

(33) Claire was transferred to intensive care at 3.25 am'[49] on 23rd October 1996 with the first ICU note at 04.00. It noted that Claire was "now intubated and ventilated. Pupils fixed and dilated. Bilateral papilloedema [swelling of the optic discs visible using an ophthalmoscope and implying raised intracranial pressure] L>R. No response to painful stimuli". She was given mannitol to reduce the cerebral oedema and dopamine and a brain CT scan was requested. At that time, a second serum sodium concentration was recorded at 121mmol/L, which was equivalent to the result recorded at 2330 on 22nd October 1996[50]. It is not clear precisely when those bloods were taken or the laboratory results communicated but the phenytoin result states that it was received at 0420 and vetted at 0438[51]. The blood could therefore have been taken between 0315 and 0400.

(34) Dr. Webb noted, at 04.40, "SIADH (syndrome of inappropriate antidiuretic hormone secretion] – hyponatraemia, hyposmolarity, cerebral oedema + coning following prolonged epileptic seizures. Pupils fixed and dilated following mannitol diuresis. No eye movements "[52]

(35) The CT scan was reported as showing "severe diffuse hemispheric swelling with complete effacement of the basal cisterns. No focal abnormality identified"[53].

(36) Dr. McKaigue, ICU Consultant, ordered a dopamine infusion to maintain blood pressure and a 'close check on serum sodium and osmolality and urine output. He changed the IV infusion fluid to 0.9% saline and at 08.10 or 08.50 requested 2 hourly measurements of urea and electrolytes[54].

(37) An untimed note (possibly between 08.10 and 18.25) is made by Dr. Taylor who was the Paediatric Anaesthetist for Adam's kidney transplant on 27th November 1996. It refers to Claire becoming hypotensive (BP 70/?) "with DI [diabetes insipidus], given HPPF 500 ml, needing DDAVP to limit polyuria and having a serum sodium level of 129 (from 121)".

[49] Ref: 090-040-138, 139
[50] Ref: 090-022-057
[51] Ref: 090-031-101
[52] Ref: 090-022-057
[53] Ref: 090-022-058
[54] Ref: 090-022-059, 060

(38) Following two negative brain stem tests, ventilation was discontinued at 18.45 on 23rd October 1996. The Death Certificate issued for Claire gave the cause of death as cerebral oedema secondary to status epilepticus[55].

Post-mortem findings

(39) Certain pathological investigations requested during her life were reported after Claire's death. These included a blood culture that was sterile, an unremarkable urine specimen, absence of blood antibody to mumps, measles, herpes simplex, herpes zoster, cytomegalovirus, adenovirus, Q Fever, PLG virus, Mycoplasma pneumoniae, and Influenza A & B. A cerebrospinal fluid sample [taken post-mortem] was bloodstained with protein 95 gm/L (normal 0.15 -0.45 gm/L), globulin present +++, red cells 300,000/μL and white cells 4000/μL – mostly lymphocytes. No organisms were cultured[56].

(40) An autopsy of the brain only was carried out on 24th October 1996 by Dr. Herron. The clinical summary referred to Claire's vomiting, increasing drowsiness, that 'she was felt to have subclinical seizures' and mentioned her anticonvulsant treatment and that her serum sodium concentration had decreased to 121mmol/L. There was a query of inappropriate ADH secretion. There is a statement that Claire had 'iatrogenic epilepsy since 10 months'[57].

(41) Dr. Herron noted Claire's brain weighed 1606 g. His evidence to the Coroner's Inquest was that he would have expected it to be 1300 g. There was no cortical venous thrombosis or meningeal exudate. There was symmetrical brain swelling with effacement of gyri, confirmed on sectioning. He reported observing focal meningeal thickening over the cortex and a cellular reaction in the meninges and perivascular space. In the deep white matter, there were focal collections of neurones arranged in a 'rather haphazard manner.' Dr. Herron also described focal collections of neuroblasts in the subependymal grey matter suggestive of a migration problem. There was focal haemorrhagic necrosis in the brain stem.

(42) Dr. Herron's diagnosis was cerebral oedema with neuronal migrational defect and a low-grade sub acute meningoencephalitis. He concluded that the reaction in meninges and cortex was suggestive of a viral aetiology although viral studies were 'negative during life and on a post-mortem

[55] Ref: 090-022-061, 091-012-077
[56] Ref: 090-030-092 to 098
[57] Ref: 090-003-003

cerebrospinal fluid'. Dr. Herron could not rule out a metabolic cause.[58] There was no other discrete lesion identified to explain epileptic seizures.

(43) A brief handwritten summary and a typed précis written by Dr. S. Mannam, an ICU SHO, dated 29th October 1996 records the principal diagnosis is recorded as Cerebral Oedema, other diagnoses are listed as Status Epilepticus and finally hyponatraemia. This summary dealt only with the events in ICU, not those preceding it.[59]

Inquest in 2006

(44) The Inquest into Claire's death was carried out on 4th May 2006 by the Coroner who engaged as experts Dr. Robert Bingham, Consultant Paediatric Anaesthetist at Great Ormond Street Hospital ("Great Ormond Street") and Dr. Ian Maconochie, Consultant in Paediatric A&E Medicine at St Mary's, London ("St Mary's"). The Inquest Verdict found the cause of Claire's death to be Cerebral Oedema with Hyponatraemia as a contributory factor.

(45) Dr Bingham considered the admission diagnosis was reasonable and acute encephalopathy (viral or ictal) a likely cause of the presenting illness. He concluded that if the reported sodium concentration of 121 mmol/L was accurate, then it was the likely cause of her deterioration and death. He could not exclude the possibility of an inaccurate reading given the subsequent ICU measurements, in which case acute encephalopathy was involved or even central. He considered it possible that the aggressive treatment at 21.00 when her coma score reduced from 8 to 6 had been effective.

(46) In his evidence at the Inquest, Dr. Bingham stated he agreed with Dr. Maconochie's formulation of cause of death and that he considered her neurological illness caused ADH secretion. Hyponatraemia was not her presenting problem.[60]

(47) Dr. Maconochie considered the diagnosis of encephalitis/encephalopathy was made at an early stage and that of non-convulsive status epilepticus had a high probability given her past history of seizures. He did not comment on hyponatraemia as it was addressed by Dr. Bingham. He gave his opinion as to cause of death as I(a) cerebral oedema; (b)

[58] Ref: 090-003-004, 005
[59] Ref: 090-006-008, 011
[60] Ref: 091-006-021

encephalitis/encephalopathy and hyponatraemia and II status epilepticus.[61]

(48) The Inquest verdict gave as the cause of death 1(a) Cerebral Oedema due to (b) meningoencephalitis, hyponatraemia due to excess ADH production and Status Epilepticus.

(49) On 12th January 2012 we delivered to you the tissues, slides and paraffin blocks from Dr. Herron, the pathologist named on Claire's autopsy report dated 11th February 1997. We understand that Dr. Herron may have retained a small amount of tissue in a freezer. Please indicate whether you would require such material and we will investigate the position.

Requirements

(50) The Inquiry team requires your assistance with the following:

(a) To examine the tissues, slides and paraffin blocks, and if you so require, the frozen tissue, to set out your observations of the brain tissue and to comment thereon in your formal report both in medical terminology and also with an explanation which might be more easily understood by the general public.

(b) To answer the additional specific queries set out below in a formal report.

(c) Any other matters which you regard as relevant to the investigation of Claire's care, treatment and death.

(51) The most pressing matter is to receive your advice on the following issues.

Your analysis of tissues and slides

(52) We seek your general opinion on the tissues, slides, paraffin blocks and if you deem it necessary, the frozen tissue. In particular we would ask you to comment on:

(a) Your opinion on the presence/absence of:
- encephalitis, meningo-encephalitis or meningitis
- hyponatraemia,

[61] Ref: 091-007-028

- excess ADH production and
- status epilepticus

and the extent and/or severity of any such condition.

(b) Your opinion on whether any conditions at (i) above contributed to Claire's death, and if so, to what degree.

(c) Your opinion on the causes of Claire's death, and whether this accords with the Verdict on Inquest or with the original Death Certificate.

(d) The likely effect on the weight and appearance of Claire's brain of all that occurred between her respiratory arrest at approximately 02.30 on 23 October 1996 and the withdrawal of ventilator support, including the process of coning itself as well as the fluids and medication administered over that period.

Stages of a brain only Autopsy and accompanying autopsy documents

(53) Please explain the various stages of a brain only autopsy and in particular:

(a) What are the initial stages of the brain only autopsy, who carries them out, what is done and for what purpose or reason and what documents are produced at that time.

(b) Explain the process of fixation and what effect, if any, this process has on brain weight.

(c) When is the brain cut carried out, by whom, what does this entail and what documentation is produced at that stage ?

(d) When are histology slides created, by whom, how and by whom are they examined and analysed and where are the results of that examination recorded?

(e) When is the CSF sample taken, by whom, for what purpose, who analyses that CSF sample and when is the result of that analysis normally available ?

(f) We refer to the provisional anatomical summary[62].

[62] Ref: 090-005-007.

(i) Please confirm whether or not this document appears to be complete in Claire's case. If not, please identify the elements which are missing.
(ii) When would this provisional anatomical summary have been compiled in Claire's case, by whom, is this document normally signed and if so, by whom, what is the purpose of this document and what would have happened in Claire's autopsy at that stage?

(g) Who provides the clinical summary in the autopsy report and when and upon what basis is it compiled? What steps are taken to ensure that it is both complete and accurate and by whom?

(h) What medical notes would you have expected to have been provided to the neuropathologist for Claire's autopsy both initially and after fixation? We refer you specifically to Dr. Herron's answer at Question 17(b and c) on page 11 of his witness statement WS-224/1 and invite your comments on his statement insofar as they relate to Claire's case. What onus does the neuropathologist bear in reading those medical notes to ascertain the actual clinical history?

(i) What further examination is carried out, by whom, when is this done, what document sets out the findings of that examination and who is usually the named author of that document?

(54) Please explain when the autopsy report dated 11 February 1997 [63]was likely compiled in Claire's case, who is usually responsible for compiling this type of report, who is usually the named author of this type of document and is this report normally signed by the author?

Dr Herron's report of the brain-only autopsy

(55) What information would you have expected to have been told in the "*Clinical Summary*" section of the autopsy in Claire's case?

(a) Please compare and contrast what information you would have expected to have been told and the information set out in the "*Clinical Summary*" of the autopsy report (Ref: 090-003-003)

(56) We refer you to the recently received autopsy request form which we understand was completed by Dr. Heather Steen, Paediatric Consultant.

[63] Ref: 090-005-007

(a) What information would you have expected to have been set out in that form in Claire's case? In particular please state whether you would have expected that form to have included specific information on the first serum sodium result on admission, nature and volume of the hypotonic fluid administered to Claire and the 2nd serum sodium result of 121mmol/L recorded at approximately 04.00 in the margin at Ref: 090-022-057 of the medical notes, and state the reasons for your answer.

(b) Please compare and contrast the information in that autopsy request form with the information you would have expected to have been included in that form.

(57) Claire was a 9½ year-old girl who weighed 24.1kg on admission to RBHSC. Explain the significance of the fixed brain weight of "*1606g*" found at the autopsy (Ref: 090-003-004) and explain what may have caused this weight.

(58) Explain the meaning of, and the significance of, the <u>presence</u> of each of the following during Claire's autopsy:

(a) "*Subacute inflammation meninges in perivascular space*" (Ref: 090-003-003)
(b) "*Neuronal migration disorder*" (Ref: 090-003-003)
(c) "*Symmetrical brain swelling*" (Ref: 090-003-004)
(d) "*Effacement of gyri*" (Ref: 090-003-004)
(e) "*Uncal prominence*" (Ref: 090-003-004)
(f) "*Diffuse brain swelling*" on sectioning of the brain (Ref: 090-003-004)
(g) "*White matter swelling with effacement of the IIIrd ventricle*" on sectioning of the brain (Ref: 090-003-004)
(h) "*Unremarkable*" cerellum. (Ref: 090-003-004)
(i) "*Focal meningeal thickening, and a cellular reaction in the meninges and perivascular space in the underlying cortex*" and "*in the deep white matter focal collections of neurones are present arranged in a haphazard manner*" in the histology of the cortex and white matter (Ref: 090-003-004)
(j) "*Generally good neuronal preservation*" in the histology of the basal ganglia (Ref: 090-003-004)
(k) "*Focal collections of neuroblasts in the subependymal zone suggestive of a migration problem... generally good neuronal preservation... in the periventricular grey matter and mammillary bodies... small foci of necrosis... in the periventricular grey matter which are probably a consequence of cerebral oedema*" in the histology of the perventricular grey matter, hypothalamus and mammillary bodies (Ref: 090-003-004)
(l) "*Some rarefaction and occasional ischaemic neurones ...in the pyramidal cell layer*" in the histology of the hippocampi (Ref: 090-003-004)

(m) "*Dentate nuclei are preserved*" in the histology of the cerebellum (Ref: 090-003-005)
(n) "*Focal haemorrhagic necrosis*" in the histology of the brain stem (Ref: 090-003-005)
(o) "*Neuronal migrational defect*" (Ref: 090-003-005)

(59) Explain the meaning and the significance of the absence of each of the following during Claire's autopsy:

(a) "*Cortical venous thrombosis*" (Ref:090-003-004)
(b) "*Meningeal exudate*" (Ref:090-003-004)
(c) "*Necrosis"* (Ref:090-003-004)
(d) "*Evidence of cortical necrosis, either laminar or focal*" on sectioning the brain (Ref: 090-003-004)
(e) "*Evidence of shift at the midline*" on sectioning the brain (Ref: 090-003-004)
(f) "*Evidence of necrosis*" in the "*paraventricular structures including the mammillary bodies*" on sectioning the brain (Ref: 090-003-004)
(g) "*Basal ganglia or diencephalon lesion"* on sectioning the brain(Ref: 090-003-004)
(h) "*Evidence of brain stem haemorrhage to suggest Leigh's disease*" on sectioning the brain stem (Ref: 090-003-004)
(i) "*Cortical necrosis*" in the histology of the cortex and white matter (Ref:090-003-004)
(j) "*Pigmentation or calcification*" in the histology of the basal ganglia (Ref: 090-003-004)
(k) "*Vascular proliferation... in the perventricular grey matter and mammillary bodies*" (Ref: 090-003-004)
(l) "*Displaced neurones or Ammon's horn sclerosis.."* in the histology of the hippocampi (Ref: 090-003-004)
(m) Identification of a tumour in the histology of the hippocampi (Ref: 090-003-004)
(n) "*Significant cell loss in Purkinje cell or granule cell layer...cerebellar cortical dysplasia"* in the histology of the cerebellum (Ref: 090-003-005)
(o) "*Myelinolysis*" in the histology of the brain stem (Ref: 090-003-005)
(p) "*Discrete lesion ...to explain epileptic seizures*" (Ref: 090-003-005)
(q) Identification of "*other structural lesion in the brain like corpus callosal or other malformations*" (Ref: 090-003-005)

(60) "*The reaction in the meninges and cortex is suggestive of a viral aetiology*" (Ref: 090-003-005)

(a) Explain how the "*reaction in the meninges and cortex*" could be "*suggestive of a viral aetiology*".

(61) *"...although a metabolic cause cannot be entirely excluded."* (Ref: 090-003-005)

(a) Explain whether you agree with Dr Herron's comment, and, if so, how "a *metabolic cause cannot be entirely excluded*" on the evidence of the autopsy. If you do not agree, state why. (Ref: 090-003-005).

(62) Had you been approached to perform an autopsy in Claire's case, explain whether you would have:
(a) asked for a full post-mortem
(b) considered a brain-only autopsy satisfactory.
Please explain the reasons for your answer. We have provided you with Claire's medical notes and records including her chest x-rays and report for information purposes.

CT scan

The image of the CT scan was taken at 05.30 on 23rd October 1996 (just over 3 hours after her respiratory arrest). Dr Peter Kennedy, Radiology Registrar, RBHSC, noted the results in Claire's clinical notes (Ref: 090-022-058) and at the back of the CT request form (attached). Dr Love, Radiology Registrar made a report of the scan results (Ref: 090-033-144).

On Thursday 12 January 2012 we delivered to you a CT scan relating to Claire Roberts. You have informed us that you will ask Dr. Kieran Hogarth, Consultant Neuroradiologist, for assistance in interpreting, and commenting generally, on the CT scan results and the CT scan documentation.

(63) We would also wish Dr. Hogarth to assist in answering the following questions:

(a) What degree of swelling can you observe on the CT scan image?

(b) Is the degree of swelling shown in the CT scan image (recorded in the medical notes at 05.30 on 23rd October 1996) and report (Ref: 090-033-114) consistent with: (i) the brain swelling described in the autopsy report and (ii) the entry in Claire's medical notes by P. Kennedy at Ref: 090-022-059 ?

(c) Claire had a history of moderate to severe learning difficulties and attentional difficulties (Ref: 090-013-018). She attended a special school. Could Claire's learning and/or attentional difficulties have affected her brain weight (or vice-versa), and if so, how?

(64) We would also ask Dr. Hogarth to consider the attached request for the CT brain scan made on a 2 sided radiology request form dated 23rd October 1996 and completed by Dr. Bartholome, the Paediatric medical Registrar on Allen ward. There are notes on the 2nd page of the form relating to the CT scan, which appear to have been signed by Dr. P. Kennedy. In particular:

(a) What information would you have expected to have been set out in that form in Claire's case?

(b) Please compare and contrast the information in that request for a CT brain scan with the information you would have expected to have been included in that form.

Cerebro-spinal fluid (CSF) analysis

(65) Explain the meaning and significance of the post-mortem cerebro-spinal fluid (CSF) analysis (Ref: 090-030-095), and, in particular, the following results:

(a) The cerebro-spinal fluid appeared "*bloodstained*"

(b) Protein of "*95.0*" g/L

(c) Leucocytes of "*4,000*" cells/uL

(a) Explain whether this result could be attributed to death related changes and explain the reasons why / why not.

(d) The ratio of erythrocytes to leucocytes (300,000:4,000)

(a) Explain whether this result is sufficient to warrant a diagnosis of meningo-encephalitis, and explain the reasons why / why not.

(66) State whether you agree with Dr. Herron's statement that when taking a CSF sample at autopsy contamination by blood, if the needle goes through a vessel or nicks brain tissue, may account for a high protein level (Question 8, WS-224/2), and state the reasons for your answer.

Status epilepticus

(67) Please identify the neuropathological sequelae of status epilepticus.

(68) The clinical diagnosis for Claire was non-convulsive status epilepticus (NCSE) from the morning of 22nd October 1996 until approximately 04.00 on 23rd October 1996. If Claire had been in non-convulsive status epilepticus for almost 24 hours:

(a) Would any neuropathological changes depend upon the underlying cause of NCSE?

(b) If the underlying cause of that state was encephalitis, would changes be inevitable given the time course?

(c) If the underlying cause of that state was some other form of encephalopathy (not clinically definable), then what would you expect to have seen?

(d) If the underlying cause of Claire's impaired conscious state and intermittent fits was gradually evolving cerebral oedema due to hyponatraemia *ab initio*, is it likely that would have caused changes in her brain histology? If so, please describe and explain those changes.

(e) Would you have expected the brain only post mortem that was performed by Dr. Herron to have demonstrated those changes, and if so, how?

(69) Claire had a history of epilepsy but she had been seizure-free for 3 years and off anti-convulsant drugs for 18 months prior to her admission to RBHSC on 21st October 1996. The Inquiry is not aware of diagnosis ever having been made of a defined epileptic syndrome. In those circumstances:

(a) Would you have expected to have observed neuropathological evidence of this past history of epilepsy (given that no diagnosis had ever been made of a defined epileptic syndrome)?

(b) If you would have expected neuropathological evidence, then what sort of evidence would you have expected to find?

(c) Did you find any such neuropathological evidence of a past history of epilepsy? If so, please describe it and explain its significance. If not, what is the significance of such an absence?

(70) If there was evidence that Claire might have had a brief convulsive epileptic event described by Dr. Webb as "*some focal seizures on Monday and right sided stiffening*" (Ref: 090-022-055) on the afternoon of 21st October 1996 and prior to her admission that evening:

(a) Would you have expected to have observed neuropathological evidence of this? If so, please describe and explain the evidence that you would have expected to find.

(b) Did you find this evidence? Please explain the significance of its presence or absence.

(71) In the circumstances, including the chest x-rays, would a full post-mortem likely have offered any further useful information as to the most likely underlying cause of Claire's illness and death? In your experience, would there be any reason for not carrying one out and if so please explain it. We also invite your comments on Dr. Herron's answer at Question 14(e) (Page 7, WS-224/1).

Encephalitis / Meningo-encephalitis / Meningitis

(72) Please comment as to whether, in your 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.

(73) If Claire had:

(a) Encephalitis

(b) Meningo-encephalitis (most likely viral)

(c) Meningitis
   (i) What evidence would you have expected the pathologist to have seen at autopsy of each condition?
   (ii) What evidence of each condition was present / absent according to Dr. Herron's report?
   (iii) What is the significance of the presence or absence of any evidence of each condition?
   (iv) What neuropathological evidence would you have <u>expected to see</u> in the sections and slides provided.

(74) Is it possible that if Claire's illness and death was precipitated by :

(a) Encephalitis,

(b) Meningo-encephalitis or

(c) Meningitis
   (i) There would have been evidence of the underlying disorder in some parts of the brain but not others?
   (ii) There might be no evidence thereof in Claire's brain?
   (iii) You would expectto find associated pathological abnormalities in organs other than the brain on post-mortem? If so, please identify those organs.

Underlying cause

(75) What is/are the most likely underlying cause(s) of Claire's condition given your findings and the post mortem findings?

(a) If Claire's condition resulted from cerebral oedema due to SIADH with hyponatraemia, would you have been able to see that in the pathology?

(b) What "*specific findings*" or "*structural changes*" in an autopsy would lead to being able to make a diagnosis of hyponatraemia? (Ref: 097-003-004).

(c) In particular, if one precipitating cause was SIADH, could examination of the lungs or any organ other than the brain have assisted and, if so, how?

(d) If SIADH was expressed as part of the diagnosis in the autopsy request form, state whether you would have expected the neuropathologist to inquire about carrying out a full autopsy in order to identify in other organs the cause of that syndrome, and state the reasons for your answer.

Author of Autopsy Report dated 11 February 1997

(76) We refer you to Dr. Herron's witness statements dated 19th and 23rd December 2011 in which we are informed for the first time that:

- Dr. Herron was only involved in the initial stages of the autopsy, the "*original autopsy*", the brain cut and took samples of CSF (Questions 14(a), 19 and 25(d), WS-224/1).

- Dr. Herron was not the author of the final autopsy report dated 11 February 1997 (Question 7(a), WS- 224/1) Dr. Herron's work was supervised by a Consultant Neuropathologist at the relevant time. Dr. Herron had assumed until he retrieved the documents to prepare his witness statement that he had also written Claire Roberts' final autopsy report. Dr. Herron alleges that it now seems to him that this is not the case, and that it was written by Dr. M. Mirakhur, a Consultant in the Department at the time (Question 25(d), WS-224/1; WS-224/2).

    (a) If Dr. Herron's involvement was limited to the initial brain cut and taking of CSF samples, state whether it was appropriate for the autopsy report dated 11 February 1997 to identify Dr. Herron as the sole author thereof, and state the reasons why.

    (b) If Dr. M. Mirakhur in fact carried out the examination of the brain after fixation, identify who you would have expected to have been identified as the author of that autopsy report.

    (c) Identify what systems, procedures and protocols you would have expected to have been in place at the time of Claire's death to ensure that autopsy reports identified the correct author thereof.

- "*There is no recording of the brain weight before fixation. Paediatric brains are extremely fragile at the time of autopsy and easily damaged by handling. They are often transferred directly into fixative without any further analysis in order to protect their structure.*" (Question 11(b), WS-224/1).

    (a) State whether it would have been normal practice to weigh the unfixed brain in Claire's case,

    (b) State in what circumstances it would not be appropriate to weigh an unfixed brain.

    (c) Please comment on Dr Herron's statement quoted above.

Dr. Herron's evidence as author of the Autopsy Report dated 11 February 1997 to and at Claire Roberts' Inquest on 25 April 2006 by deposition and orally on 4 May 2006

(77) Dr. Herron gave a deposition to the Coroner on 25 April 2006 and oral evidence at Claire Roberts' Inquest on 4 May 2006 as the purported author of the autopsy report.

(a) State whether you would have expected Dr. Herron to have read the notes on Claire's autopsy prior to:
(i) providing his deposition to the Coroner on 25 April 2006
(ii) giving oral evidence at the Inquest on 4 May 2006

(b) Identify the neuropathologist who ought to have given a deposition and oral evidence to the Coroner in relation to Claire's autopsy and state the reasons why.

Conclusion

(78) It is of fundamental importance that the Inquiry receives a clear and fully reasoned opinion on these neurological issues. To assist you we have attached an index of key documents together with a file of the documents that appear to be of particular significance. Please request any other documents that you consider to be relevant for the preparation of your report.

(79) If you regard any matters raised as outwith your area of expertise, please advise us of this as soon as possible.

(80) If you have any other relevant observations other than the issues we have raised, please also include these observations in your report.

(81) Your assistance on the Inquiry's requirements should be provided in the form of a fully referenced Expert's Report.