BRIEF FOR EXPERT ON PHARMACOLOGY

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 Q.C.

(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.

(3) That certification was subsequently called into question after a television documentary into the deaths of Adam Strain and two other children (Lucy Crawford and Raychel Ferguson). As a result an Inquest into Claire's death was carried out nearly 10 years after her death by John Leckey on 4th May 2006.

(4) The Verdict on Inquest found the cause of Claire's death to be: 1(a) Cerebral Oedema due to (b) Meningoencephalitis, Hyponatraemia due to excess ADH production and Status Epilepticus. The Coroner also made findings, principally that the degree of hyponatraemia that she suffered (fall in her serum sodium level to 121mmol/L) contributed to the development of the Cerebral Oedema that caused Claire's death, but that Meningoencephalitis and Status Epilepticus were also causes albeit that he could not determine the proportionate contribution of the three conditions to her death.

(5) The Coroner's findings gave rise to a new registration on 10th May 2006 of the cause of Claire's death so as to reflect the Verdict on Inquest.

Terms of Reference

(6) 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.

(7) 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:

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

(8) The Inquiry has appointed Inquiry 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]

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

Claire's history and case

Pre-1996 referral

(10) 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.

(11) 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

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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)

3 Ref: 090-018-033, 034

valproate (Epilim®) before discharge, while weaning her from her previously prescribed Tegretol[4].

(12) 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]

(13) In May 1996, she was seen by Dr. Colin Gaston, Consultant Community Paediatrician in relation to behavioural problems including inattention, being easily distracted, having obsessions and constant activity. Dr Gaston noted, in his letter to Claire's GP, that he had discussed with Mrs. Roberts the option of treating Claire with a stimulant medication, such as Ritalin, Pemoline or amphetamine[6].

(14) Dr. Gaston saw the family again on 1st August 1996 and suggested a trial of one week's placebo vs. one week's Ritalin, such that one parent administered medication to which the other was blind. He noted *'a very small risk of inducing seizures with Ritalin.'* A series of manuscript notes referred to telephone conversations. It was noted that the blind trial was not attempted but instead she had been treated with Ritalin 10 mg daily until October 2nd 1996. On that date, parent(s) were noted as reporting *'dry mouth, viscous, pacing, ?agitated/unsettled 30 minutes after Ritalin.'* She was also noted to have *'??greater social awareness.'* Dr Gaston noted 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].

1996 referral

(15) 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*"[10]. 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[11].

(16) 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 at the RBHSC of cerebral oedema with dilutional hyponatraemia and impaired cerebral

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

perfusion as contributory factors. The A&E note for Claire 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[12].

(17) The admission note (timed at 20.00) refers to Claire as vomiting at 15:00 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[13]. 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[14].

(18) The admission diagnoses were noted as: (1) Viral illness; (2) Encephalitis (but this was subsequently scored through)[15]. Treatment was noted as "*IV fluids, IV diazepam if seizure activity*". She was to be reassessed after fluids.

(19) Claire's weight was recorded as 24.1kg[16].

(20) An IV prescription chart was prepared, ordering 500 ml of 0.18% sodium chloride in 4% dextrose to be given at 64 ml/h (equivalent to 65 ml/kg/24 h).[17] The nursing care plan referred to administering *'IV fluids as prescribed by doctor, according to hospital policy.'*[18] The nursing record includes a fluid balance chart. This stated that treatment was started at 21:30 with 64 ml hourly of 5/N saline. By 07:00, Claire had received 536 ml [just under 57 ml hourly]. During those 9 ½ hours, she was noted by Nurse McRandal to have had 1 'medium' and 5 'small' vomits.[19] The nursing notes describe these vomits as bile-stained; this was a change from the A&E note, where vomits were described as 'non-bilious'.[20]

(21) A medical note at midnight stated that she was slightly more responsive and had no meningism.[21] It was noted that she would be observed and reassessed

12 Ref: 090-012-014
13 Ref: 090-022-050
14 Ref: 090-022-051
15 Ref: 090-022-052
16 Ref: 090-041-142 (the Admission Sheet signed by SN Geraldine McRandall) and Ref: 090-021-049 (Treatment Form)
17 Ref: 090-038-134
18 Ref: 090-043-146
19 Ref: 090-038-133
20 Ref: 090-040-140, 090-012-014
21 Ref: 090-022-052

in the morning. Directly beneath that note is an entry for the blood biochemical and haematological results:[22]

"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.[23] Claire's white cell count results then dropped to 9.4 as recorded in the medical notes at 04:00 on 23rd October 1996[24] which appears to have the printed lab report result of 09.35.[25] There are also printed lab reports for white cell count results of 5.70 from a specimen on 23rd October 1996,[26] and of 5.54 from a specimen on 24th October 1996.[27]

(22) In the late morning of 22nd October 1996 Claire, who was described as 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.[28] She was described in the note of the ward 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.[29]

(23) The fluid chart for 22nd October 1996[30] does not note the solution given. However, an undated prescription chart[31] 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.

(24) At 15:10 Claire was reported as having a 5-minute strong seizure at 15:25. At 16:30, her teeth tightened slightly.[32] Dr. Webb saw Claire and noted a history of vomiting and listless followed by a prolonged period of poor responsiveness.[33] 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

22 Ref: 090-022-052
23 Ref: 090-022-052, 090-032-108
24 Ref: 090-022-057
25 Ref: 090-032-111
26 Ref: 090-032-112
27 Ref: 090-032-110
28 Ref: 090-040-141
29 Ref: 090-022-052, 053
30 Ref: 090-038-135
31 Ref: 090-038-136
32 Ref: 090-042-144
33 Ref: 090-022-055

and looking vacant, not obeying commands. She did not have papilloedema[34]. Dr. Webb's impression was that Claire's motor findings were 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.[35] 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.[36]

(25) 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.[37]

(26) Those doses were ordered on a prescription chart.[38] The nursing notes record a stat dose of phenytoin given at 14:45,[39] with a second dose at 23:00 following blood sampling for phenytoin levels[40].

(27) The next medical note (untimed) refers 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 (rather than 12mg) with the time of administration 15:25.[41] There is no signature on the drug chart to confirm that this stat dose was given[42] but the nursing notes record *'stat IV Hypnoval* [midazolam] *at 3.25pm.'*[43] No dosage was recorded against this entry. 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[44]. Also from 16.00, no 18 solution was continued with 452 ml given over 7 h to 23.00 (64 ml/h)[45].

(28) 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

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34 Ref: 090-022-053, 054
35 Ref: 090-022-054
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37 Ref: 090-022-054
38 Ref: 090-026-075
39 Ref: 090-040-141
40 Ref: 090-040-138, 090-038-135, 090-026-077
41 Ref: 090-040-141
42 Ref: 090-026-075
43 Ref: 090-040-141
44 Ref: 090-038-135, 136
45 Ref: 090-038-135

suggested an additional anticonvulsant intravenous infusion: sodium valproate 20 mg/kg as an initial dose, followed by 10 mg/kg over 12 h.[46] 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.[47] A further attack of *"teeth clenched and groaned"* for *"1 min[ute]"* is recorded at 19:15.

(29) 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.[48]

(30) 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 with registrar - ↓ fluids to ⅔ of present value – 41 ml/h. Send urine for osmolality.*'[49]

(31) 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.[50]

(32) A nursing note at 21:30 referred to Claire receiving midazolam at 3 ml/h, completed by 22:40.[51] At 23:00, 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.[52] 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.

(33) The neurological observation chart, started at 13:00 on 22nd October 1996, shows that at 13:00 she was noted as *opening her eyes to speech* and at 1430 as *opening eyes to pain*. Thereafter, hourly recordings until 02:00 on 23.10.96 all stated there was *no eye opening*. 'Best verbal response' was noted as *none* from 13:00 to 18:00 and thereafter as *incomprehensible sounds*. Her 'best motor response' was noted as *obey commands* at 13:00 and at 20:00, *localise pain* between those times and *flexion to pain* thereafter.[53]

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46 Ref: 090-022-055
47 Ref: 090-040-141, 090-142-144
48 Ref: 090-042-144
49 Ref: 090-022-056
50 Ref: 090-038-135
51 Ref: 090-040-138
52 Ref: 090-038-135
53 Ref: 090-039-137

(34) Her Glasgow Coma Scale (GCS) score was given as 9 on first checking and thereafter was 6 - 7, except recorded as 8 at 20:00. There was a rise in temperature from normal to between 37.5 C and 38 C from 19:00 and of pulse rate from <90 at 13:00 to 115 at 18:00, thereafter remaining at 100-105. There was no significant change recorded in blood pressure.[54]

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

(36) Claire was transferred to intensive care at 03:25'[55] 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 23:30 on 22nd October 1996.[56] 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 04:20 and vetted at 04:38.[57] The blood could therefore have been taken between 03:15 and 04:00.

(37) 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*"[58]

(38) The CT scan was reported as showing "*severe diffuse hemispheric swelling with complete effacement of the basal cisterns. No focal abnormality identified*".[59]

(39) 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.[60]

(40) An untimed note (possibly between 08:10 and 18:25) is made by Dr. Robert Taylor, Consultant Paediatric Anaesthetist. It refers to Claire becoming

54 Ref: 090-039-137
55 Ref: 090-040-138, 139
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57 Ref: 090-031-101
58 Ref: 090-022-057
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60 Ref: 090-022-059, 060

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)*".

(41) 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.[61]

Post-mortem findings

(42) 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.[62]

(43) 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*'.[63]

(44) 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.

(45) 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 cerebrospinal fluid*'. Dr. Herron could not rule out a metabolic cause.[64] There was no other discrete lesion identified to explain epileptic seizures.

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(46) 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.[65]

Inquest in 2006

(47) 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").

(48) 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.

(49) 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.[66]

(50) 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) encephalitis/encephalopathy and hyponatraemia and II status epilepticus.[67]

(51) The Verdict on Inquest verdict gives the cause of Claire's death as: 1(a) Cerebral Oedema due to (b) Meningoencephalitis, Hyponatraemia due to excess ADH production and Status Epilepticus.[68]

<u>Requirements</u>

(52) The Inquiry team requires your assistance with the issues and queries set out below. If you aware in addressing them of the applicable standards in 1996,

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66 Ref: 091-006-021
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please explain what they were and how (if at all) they differ from the applicable standards in 2012.

(53) ***Administration of IV drugs***

It would be useful for you to set out in your report an explanation of the 3 ways to give IV drugs, which we understand to be the following:-

(a) A bolus of the drug - a single dose of the drug administered intravenously by a syringe and is always carried out by a doctor. Please deal with the time it usually takes to administer and the extent to which any rate of administration is prescribed.

(b) A loading dose – given where the efficacy of the drug depends upon obtaining a certain level of that drug in the bloodstream. In an emergency situation a doctor will prescribe this rapid dose and the nurse administers the drug by a syringe driver which is attached to the cannula. Please explain how long a loading dose of phenytoin might take to administer in that way. In a non-emergency situation, the drug is given a number of times over a period of days to build up to the required level in the bloodstream.

(c) A maintenance dose - medication subsequently administered to maintain the required level of the drug in the bloodstream. Please explain how much of the drug is usually dissolved in an IV drip, and run over a 12 or 24 hour period.

(54) ***Rectal diazepam***

(a) Please explain whether Dr Sands' prescription of 5mg rectal diazepam at about 12:15 was appropriate or otherwise in October 1996.

(b) Please explain within what period of time you would expect rectal diazepam to take effect.

(c) Please explain how you consider that rectal diazepam can generally affect neurological assessment, including observations on the Glasgow Coma Scale, and in particular, Claire's neurological assessment.

(d) Explain whether, in light of Claire's condition, an EEG should be required before/following the administration of rectal diazepam in October 1996.

(55) ***IV Phenytoin***

The IV loading dose of phenytoin on 22nd October 1996 was calculated to be 632mg, rather than 432mg. The amount of phenytoin that is recorded as having been administered to Claire at 14:45 is 635mg.[69]

[69] Ref: 090-026-075

(a) Please explain in what form, and in what volume, IV phenytoin would have been available in a paediatric hospital in October 1996, e.g. if in ampoules, then their size or sizes. In particular, explain what would be involved in the administration of 635mg IV phenytoin from a practical standpoint, e.g. the likely number of ampoules required to administer 635mg of IV phenytoin.

(b) Please explain within what period of time you would expect IV phenytoin to take effect.

(c) Please explain whether the administration of either 432mg or 635mg IV phenytoin at 14:45 was appropriate or otherwise in October 1996.

(d) Please explain what effect on Claire you consider the administration of 635mg of IVphenytoin rather than 432mg would have had, particularly in terms of her level of consciousness and general condition.

(e) Please comment upon the extent to which any effect on Claire's presentation of such an overdose of phenytoin could have affected the assessment of her condition.

(f) Please explain what the toxic range for phenytoin would be for a 9 year old child weighing 24.1kg. In particular, state whether the amount of phenytoin administered to Claire meant that she was in a toxic range for this drug.

(g) Please explain whether Claire's phenytoin level of 23.4mg/L recorded at 23:30 on 22nd October 1996 (from a sample taken at approximately 21.30) is a high or toxic level.[70]

(h) Please comment on whether there may have been a correlation between the administration of an overdose of phenytoin at 14:45 and the subsequent attack at 15:10/15:25.

(i) Please comment on why the clinicians may have directed that the phenytoin levels be checked at 21:00, and whether in all the circumstances the clinicians ought to have measured the effect of phenytoin prior to 21:00.

(j) Please explain whether it was proper and appropriate to administer IV phenytoin to run for an hour at 23:00 on 22nd October 1996,[71] given the direction of Dr. Webb to follow the loading dose by "*2.5mg/kg 12 hrly*".[72]

(k) Please explain the significance of the phenytoin level returning to 19.2mg/L by 04:20 on 23rd October 1996.[73]

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(l) Please comment, in so far as you can, on why the drug prescription sheet[74] is ticked at intervals that do not tally with the medical and nursing notes e.g. Claire did not have prescribed and did not receive phenytoin at 08:30 on 22nd October 1996.

(m) Please explain how you consider that IV phenytoin can generally affect neurological assessment, including observations on the Glasgow Coma Scale, and in particular, Claire's neurological assessment.

(n) Please comment on whether, in the circumstances:

(i) an EEG

(ii) a heart rate monitor

should be required before/following the administration of IV phenytoin in October 1996.

(56) ***IV Midazolam***

(a) Please explain how midazolam would have been dispensed and recorded within the clinical ward in a paediatric hospital in October 1996.

(b) Please explain in what form, and in what volume, IV midazolam would have been available in a paediatric hospital in October 1996.

(i) Please state if in ampoules, then their size or sizes.

(ii) Please state what would be involved in the administration of 120mg IV midazolam from a practical standpoint e.g. the likely number of ampoules required to administer 120mg of IV midazolam and the length of time taken to administer.

(iii) Please state what would be involved in the administration of 12mg IV midazolam from a practical standpoint e.g. the likely number of ampoules required to administer 12mg of IV midazolam and the length of time taken to administer.

(c) Please state the rate of administration of the stat dose of midazolam.

(d) Please explain within what period of time you would expect IV midazolam to take effect.

(e) State whether midazolam is an anti-diuretic hormone stimulating drug, and if so, please explain the likely effect thereof on Claire.

(f) Please explain whether the once only administration of either 12 or 120mg IV midazolam at 15:25 was appropriate or otherwise in October 1996.

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73 Ref: 090-031-101, Ref: 090-022-057

74 Ref: 090-026-073, Ref: 090-026-075

(g) Explain whether it was proper for the IV infusion for midazolam to have been on the regular prescription chart[75] in October 1996.

(h) The Intravenous Fluid prescription chart[76] states *"50mls N. Saline + 69mg midazolam"* at a rate of *"2mls/hr over 24 hrs"*. Please comment on the appropriateness of this and how the concentration ratio of midazolam is altered by the addition of 50mls of fluid.

(i) Please state the rate of infusion of midazolam.

(j) Please explain how you consider that IV midazolam can generally affect neurological assessment, including observations on the Glasgow Coma Scale

(k) Please comment on the effect that 12mg of midazolam may have had on Claire and her presentation at that time, in particular, the assessment of her neurological condition.

(l) Please comment on the effect that a dose of 120mg of midazolam would have had on Claire and her presentation at that time, and in particular:

(i) The extent to which 120mg of midazolam could have induced anaesthesia in Claire

(ii) The extent to which 120mg of midazolam may have affected the central nervous system observations and level of consciousness in Claire

(iii) Claire's symptoms that may have been attributable to the administration of 120mg of midazolam from 15:25 onwards

(iv) Claire's symptoms that would not have been attributable to that medication

(v) The effect that 120mg of midazolam may have had on Claire's fluid management, sodium level and SIADH

(vi) The effect that 120mg of midazolam may have had on Claire in combination with the other medications she was receiving

(m) Explain whether an EEG should be required before/following the administration of IV midazolam in October 1996.

(57) ***Sodium Valproate***

(a) State whether sodium valproate is an anti-diuretic hormone stimulating drug, and if so, please explain the effect thereof on Claire.

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75 Ref: 090-026-075

76 Ref: 090-022-055

(b) Please explain within what period of time you would expect sodium valproate to take effect.

(c) Please explain whether Dr Webb's request for the once only administration of an intravenous dose of 400mg sodium valproate administration at 17:15 was appropriate or otherwise in October 1996.

(d) Please explain how you consider that sodium valproate can generally affect neurological assessment, including observations on the Glasgow Coma Scale, and in particular, Claire's neurological assessment.

(e) Please comment on whether, in the circumstances, an EEG should be required before/following the administration of sodium valproate in October 1996.

(58) ***Effect of Administration of Combination of Drugs***

(a) Please explain the likely effect of the administration of the combination of the following drugs :

- 5mg rectal diazepam at about 12.15
- 635mg IV phenytoin once only administration at 14.45
- 12 or 120mg IV midazolam once only administration at 15.25. Please give a response separately for the combination of 12mg or 120mg.
- 400mg sodium valproate once only administration at 17.15
- IV phenytoin 60mg 12 hrly at 23.00 run over one hour
- IV midazolam 69mg/24 hrly increased to 3ml/hr between 21.30 and 22.40

on:

(i) Claire generally and in particular her level of consciousness (particularly on neurological assessment using the Glasgow Coma Scale)

(ii) the presentation of Claire's symptoms on 22nd and 23rd October 1996

(iii) any cerebral oedema

(iv) the other drugs

(b) Please also explain whether this combination of drugs was likely to have had any impact upon:

(i) Claire's fluid retention and/or

(ii) Claire's low serum sodium concentration

(iii) SIADH

particularly when combined with administration of IV fluids of NaCl 0.18%.

(c) Explain whether there is likely to be any correlation between the administration of drugs, whether individually or in combination, and:

(i) the *"attacks"* Claire suffered as recorded at Ref: 090-042-144 and

(ii) Claire's respiratory arrest at approximately 02.30 on 23rd October 1996

(d) Explain whether, in October 1996, the frequency of the nursing observations should have been increased after the administration of the various drugs during the day, and if so, at what time(s) the frequency should have been increased.

Other matters

(59) Please notify the Solicitor to the Inquiry if there are other issues that we have not identified but which you regard as relevant and important for you to discuss.

Documents

(60) You will need to consider all the documents in Claire Roberts' case to carry out a thorough review of the evidence and form an opinion on the issues. Please contact the Inquiry Secretary to discuss any other or further documents that would be helpful for you to have in forming your views and providing your Report

Conclusion

(61) It is of fundamental importance that the Inquiry receives a clear and fully reasoned opinion on these pharmacological issues.

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