



Neutral Citation Number: [2019] EWHC 1454 (QB)

Case No: HQ15C01680

IN THE HIGH COURT OF JUSTICE
QUEEN'S BENCH DIVISION

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 10/06/2019

Before :

MRS JUSTICE YIP DBE

Between :

AXO	<u>Claimant</u>
- and -	
SALISBURY NHS FOUNDATION TRUST	<u>Defendant</u>

Simeon Maskrey QC & Harry Trusted (instructed by **Price Slater Gawne Solicitors**) for the **Claimant**
David Pittaway QC (instructed by **DAC Beachcroft LLP**) for the **Defendant**

Hearing dates: 1, 2, 3, 7 May 2019

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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MRS JUSTICE YIP DBE

Mrs Justice Yip DBE :

1. This is a claim for damages brought on behalf of a boy born prematurely at Salisbury General Hospital in 2008. Shortly after birth, he received a tenfold overdose of pancuronium bromide (referred to hereafter as pancuronium), which is a muscle relaxant used to facilitate mechanical ventilation. It is alleged that this caused him to sustain significant brain damage which has resulted in cerebral palsy.
2. The defendant trust admit that the overdose was negligently administered so that breach of duty is not in issue. At the start of the trial, Mr Pittaway QC for the defendant repeated the apology previously given to the claimant's parents for that error. However, it is the defendant's case that the neurological injury is unrelated to the overdose. It therefore falls to me to determine the issue of causation.
3. At the start of the trial, I made an anonymity order protecting the identity of the claimant. He and his parents are not to be named in any report of the case. I shall therefore refer to him as AXO. Further, it is unnecessary to include his precise date of birth in this judgment and I shall refer to the day he was born as 'Day 1' and the subsequent day as 'Day 2'.

Factual background

4. AXO was born just before 30 weeks gestation. His mother had experienced premature rupture of the membranes four weeks earlier. That was appropriately managed. She was given a dose of steroids to aid foetal lung maturity and prescribed antibiotics prophylactically. Regular monitoring over the next four weeks showed no signs of infection or other complications.
5. On the day of his birth, AXO's mother was admitted to the hospital reporting regular uterine contractions. A CTG trace showed some reduced variability and early decelerations in the foetal heart rate. It is unnecessary to explore this further, since it was ultimately agreed that there is no evidence that AXO suffered any intra-uterine insult sufficient to cause neurological injury.
6. At 15.19, AXO was born by spontaneous vaginal delivery in reasonably good condition. His Apgar scores were 5 at 1 minute and 9 at 5 minutes, which would not be unexpected given his prematurity. He was intubated and ventilated prior to the second score. AXO was given Curosurf surfactant, a drug routinely given to premature neonates to enhance lung maturity. He was transferred to the neonatal unit, where he had a second dose of Curosurf. The first blood gas results were not indicative of any significant hypoxic-ischaemic insult prior to delivery. His mean arterial pressure ("MAP"), measured with a cuff at 16.00, was 32. This was within the normal range; it being generally accepted that the pressure should be maintained at or above the figure representing the number of weeks gestation (in AXO's case 29/30). Until about 20.00, AXO appeared to be doing well.
7. By 20.00, there was some concern for him, and a doctor (Dr Osoba) was called. His MAP had fallen to 25 and his oxygen requirements had increased. Dr Osoba saw AXO at 20.45. He decided to call the on-call consultant Dr Nick Brown, who came in from home to see AXO. Dr Brown's first note is timed 22.30.

8. Blood pressure improved, rising to 26 at 21.00, then 29 at 22.00 where it remained at 23.00. In the same period, AXO's oxygen requirements increased from 27% at 20.00 up to 100% at 23.00. Ventilator pressure had also been increased. Blood gas value was satisfactory at 19.27 but demonstrated mild respiratory acidosis at 21.42.
9. When Dr Brown attended, he concluded that it was likely that the endotracheal tube was blocked. He changed the tube and noted good air entry was achieved straightaway. The removed tube was noted to be "slightly clogged". A chest X-ray was interpreted as showing "bad RDS" (respiratory distress syndrome). AXO was given a saline bolus (to expand blood volume) and morphine and a plan was made to give a further dose of Curosurf at 12 hours of age. Dr Brown remained on the ward to care for AXO.
10. After 22.30 and until 01.00 there are significantly fewer recorded observations in the records. Dr Brown explained in evidence that there was real concern for AXO's condition (which he described as "a peri-arrest situation") during this period. The team was fully occupied in looking after him and Dr Brown said that the lack of entries in the notes reflects the intensity of the efforts to save AXO. The neonatology experts instructed in the case agree that such an explanation is a reasonable one.
11. Dr Brown made a retrospective note, headed 23 – 24.00 hours. There is some doubt as to when he actually made the note and there are disputed factual issues within this period, to which I will return. In particular, Dr Brown records in this note a MAP of 22 but it is disputed that such a fall occurred before midnight.
12. A statement was obtained from the neonatal nursing sister, Sister Aala. The defendant chose not to call her to give evidence, but the statement is before me in evidence. According to Sister Aala, AXO's blood pressure was 28 at 23.57.
13. At this time, a base deficit of -3.8 was recorded. This represents moderate acidosis. The neonatology experts agree that the blood gas results demonstrate a mixed acidosis where the metabolic component was relatively mild in comparison to the respiratory component. Dr Brown thought that AXO was 'fighting the ventilator'. In other words, his attempts to breathe were not synchronised with the ventilator and were impeding the control of ventilation.
14. Inotrope support (to increase blood pressure) was given by way of dopamine which was commenced at midnight at a rate of 5 mcg/kg/minute.
15. Given the concerns about AXO's ventilation and oxygenation around midnight, Dr Brown brought forward the time at which he was to receive Curosurf and prescribed pancuronium to paralyse AXO to stop him fighting the ventilator. This represented entirely appropriate treatment. The Curosurf was given at 00.20 and the pancuronium at 00.25.
16. Unfortunately, when the dose of pancuronium was prescribed, a decimal point was put in the wrong place, causing AXO to receive ten times the recommended dose. The prescription should have been cross-checked, but the error was not identified. It was not appreciated that AXO had received an overdose until after 08.00 on Day 2 when he remained unexpectedly 'flat'.

17. The next recorded blood pressure reading was at 01.00. MAP was then 22. This represents significant hypotension, particularly since AXO was by then receiving dopamine to raise his blood pressure.
18. The dopamine dose was increased to 10 mcg/kg/minute and AXO's blood pressure rose to 30 at 01.30. The oxygen requirement had reduced to 48% at 01.00 and was 21% at 02.00. Blood gas values demonstrated a mild metabolic acidosis with an increasing base deficit during the morning of Day 2.
19. That morning, AXO was transferred to Portsmouth to be cared for in the tertiary neonatal centre there. There was some dispute about the basis on which the decision to transfer him was taken. However, that is no longer material as it is now conceded on the claimant's behalf that the evidence does not establish (on a balance of probabilities) that he would not have been transferred but for the overdose. I entirely agree with that analysis and will therefore approach the issues I must decide on the basis that AXO would have been transferred in any event.
20. The transfer was effected by a specialist team from Portsmouth, led by Dr Groves, consultant neonatologist. While AXO was being transferred from the ward incubator to the transport incubator he was accidentally extubated. That is a recognised risk and does not represent any failing in AXO's care. Other than that, the transfer was uneventful. It is the claimant's case that the extubation caused a further insult, which he was unable to withstand as a result of the pancuronium overdose. He was hypotensive during the transfer and his arterial blood gas showed a significant increase in the base deficit, indicative of an increasing metabolic acidosis. By the time he arrived at Portsmouth, there was evidence of both renal and hepatic impairment.
21. AXO was handed over to the consultant neonatologist on the neonatal intensive care unit (NICU) in Portsmouth. The recorded admission time to the Portsmouth NICU is around 13.10 on Day 2. There is no suggestion that AXO received anything other than proper care at Portsmouth or that he sustained any neurological insult while there.
22. At 16.20 on Day 2, AXO received a further dose of Curosurf. It is documented that his blood pressure dropped to the low 20s after administration of that drug. His dopamine was increased, and blood pressure improved.
23. A cerebral ultrasound scan performed on Day 2 was reported to be normal, although the expert neuroradiologists instructed in this case noted that there may have been some "flares" (possible markers of damage) on retrospective review of the images. Thereafter, AXO's brain began to show the typical pattern associated with periventricular leukomalacia.
24. Periventricular leukomalacia ("PVL") describes a pattern of brain damage, usually sustained as a result of hypoxic-ischaemic insult at a particular stage of gestation (26 to 34 weeks), although the cause is not always fully understood. That damage may occur in utero or, in the case of a premature neonate, after birth. The evolving picture seen across the repeat scans demonstrates that AXO suffered damage around the time of his birth.

25. It is not in dispute that the PVL led to AXO's cerebral palsy. He has been left with significant neurodevelopmental impairment. All four limbs are affected in a diplegic pattern (his legs are more affected than his upper limbs). There is gross motor, fine motor, speech and language, social and cognitive impairment. AXO has sufficient insight to recognise his disabilities and differences with his peers. It is very sad to read of the distress this causes him.
26. Since quantum is not to be assessed at this stage, I will say no more about AXO's condition, but it is apparent that he and his parents face significant challenges. Although they all appear to be rising to those challenges, there can be no doubt that this claim is of great significance to them given the potential for a significant award of damages to ameliorate some of the difficulties they will face in the future.

Issues arising

27. For the purpose of this claim, the parties are agreed that PVL is an indivisible injury such that the test to be applied is whether the pancuronium overdose made a material contribution to the development of the condition (see *Bailey v Ministry of Defence* [2009] 1 WLR 1052).
28. The claimant must prove that the overdose did make a material contribution to the injury on a balance of probabilities. The claimant does not need to prove the mechanism by which the overdose caused damage, only that it did so. However, consideration of the respective opinions on the mechanism of damage is inevitably required before arriving at any conclusions. The balance of probabilities is just that. It does not require medical certainty, or indeed anything approaching that.
29. It is the claimant's case that he sustained two insults to his brain, both of which were contributed to by the overdose of pancuronium.
30. The expert neurologists, Dr Newton and Dr Smith, agree that the episodes of hypotension documented at 01.00 on Day 2 (after the pancuronium had been given) and during the process of transfer to Portsmouth did materially contribute to the PVL.
31. Therefore, the primary issue identified for me in opening was whether the overdose of pancuronium played a material part in either or both of those episodes of damaging hypotension.
32. In his closing submissions, Mr Pittaway QC highlighted evidence from Professor Mitchell, the consultant neonatologist instructed on behalf of the claimant, that the second episode was likely to have been responsible for "most if not all" of AXO's neurological injury. However, he then expressly confirmed that he agreed that it would be sufficient for the claimant to prove that the drop in blood pressure documented at 01.00 was caused by the overdose. On behalf of the defendant, he invited me to say that the claimant had not established that on the evidence before me.
33. The first issue then is whether I am satisfied, on the balance of probabilities, that AXO suffered hypotension as a result of the pancuronium overdose.
34. In resolving that main issue, I will have to decide whether AXO in fact sustained a significant fall in blood pressure after the administration of the overdose of

pancuronium. It is the defendant's case, supported by evidence from Dr Brown, that the fall in blood pressure to 22 occurred prior to midnight. If that is right, it cannot have been caused by the overdose which only occurred at 00.25. However, while a temporal relationship is a necessary requirement if causation is to be established, it cannot by itself establish a causal link.

35. As to the second insult, around the time of the transfer, the claimant's case has frankly shifted during the course of the litigation and at trial. That is not to be critical since it is only at trial that the evidence can be fully explored and the claimant's representatives have done no more than respond to that evidence, making sensible concessions to reflect the final evidential picture.
36. The claimant's position in closing submissions was that accidental extubation and reintubation caused a second "hit", which AXO's brain was unable to withstand because of the combined effect of the earlier insult and his ongoing paralysis as a result of the pancuronium overdose. It is claimed that, but for the overdose, AXO would have withstood any adverse effects of the accidental extubation.
37. One part of the claimant's pleaded case was that the transfer was itself caused by the overdose and that consequently the defendant was responsible for what occurred during the transfer including the extubation. However, that part of the case is not maintained given Professor Mitchell's acceptance in cross-examination that, on balance, AXO is likely to have been transferred in any event. Therefore, I must approach the question of causation in relation to the second insult on the basis that the extubation was not itself caused by any breach of duty. The issue is whether the overdose contributed to AXO's inability to withstand this event.

The evidence

38. The evidence of AXO's parents was put before me in writing. I have read it and take it into account. Their account of the difficulties AXO has and the impact upon the whole family is poignant. However, this evidence does not directly assist with the issues I must decide at this stage.
39. The defendant called Dr Brown and Dr Groves but chose not to call any other clinician involved with AXO's care. Having obtained a statement from Sister Aala, there was no explanation as to why she was not called. Her evidence has not therefore been tested in the witness box. However, where she has provided relevant evidence, particularly as to AXO's blood pressure before midnight, I see no reason not to rely on it.
40. Dr Groves was, as Mr Maskrey QC acknowledged, an extremely impressive witness. As he put it, "she knew exactly what she was doing". It was apparent that Dr Groves' reputation as a very skilled neonatologist was recognised by the experts, and her competence shone through when she gave her evidence. I find no difficulty in relying upon the evidence she gave. Mr Maskrey realistically accepted that her evidence could not sensibly be challenged.
41. Dr Brown plainly found the experience of giving evidence rather more difficult. He was clearly very troubled by AXO's case and deeply regretted what happened. I am confident that he was doing his best to be truthful and helpful to the court but consider

that his evidence was coloured by a natural human reaction to the suggestion that something for which he was responsible could have caused AXO serious long-term disability. In the circumstances, I did not find his attempted reconstructions from his notes to be entirely objective or reliable. There were inconsistencies in his evidence and Mr Pittaway accepted that some inroads had been made in cross-examination. However, he invited me to accept that Dr Brown had been clear throughout that the drop in MAP to 22 had occurred before the pancuronium was given.

42. It must be remembered that the overdose was not recognised until the following morning, after Dr Brown had been home. Therefore, his recollection that the drop in blood pressure came before the overdose is likely to have been based on reconstruction rather than direct recollection as the importance of the sequence of events will not have been fully apparent until much later.
43. Dr Brown was unable to remember exactly when he made his notes. He thought that he made the first note dealing with events at 22.30 between 22.45 and 23.00. Initially, he said that he made his second note dealing with events between 23.00 and 24.00 just after midnight. However, he later accepted that the note contained reference to dopamine being increased, which he accepted occurred after the recorded MAP reading of 22 at 01.00. He then suggested (apparently for the first time) that he wrote this note in sections, completing the later part well after midnight, although he could not say exactly when. He said he had reflected over the last few weeks and realised the note must have been written in sections (although he had not sought to correct his statement before cross-examination).
44. Dr Brown's evidence as to timings changed in the witness box. In his statement, he said that MAP had been 22 by 23.00. In cross-examination, he said that was wrong and that the blood pressure of 22 had in fact been observed at 23.45. There is no record of a reading of 22 until 01.00. Dr Brown had to accept his original evidence that such low blood pressure had been detected at 23.00 was wrong because that did not fit with the timing of the administration of dopamine. Further, if right, it would appear he was saying that AXO had suffered a prolonged period of significant hypotension with limited effort to correct it. In my view, this simply cannot be right. Dr Brown's evidence that MAP was 22 at 23.45 does not fit with Sister Aala's evidence.
45. I find that I am unable to rely on Dr Brown's recollections where not supported by the records and I approach his evidence with caution generally.
46. Having said that, I do accept Dr Brown's evidence that AXO was very poorly between 23.00 and 24.00. This, it seems to me, comes from direct recollection rather than reconstruction. Having heard his evidence, I accept that Dr Brown does have a recollection of treating AXO that night and of being seriously concerned that he might die. Dr Brown considered him to be in a very parlous state, close to peri-arrest. He said that anything worse would not have been compatible with survival.
47. I note that Dr Brown was also cross-examined about the adverse incident report. However, this focused upon the reason for transfer to Portsmouth and this issue has now fallen away, given the concession that AXO would have been transferred in any event. Having already identified that I have reservations about Dr Brown's reliability (although not credibility) and that I will approach his evidence with caution generally,

I do not think it is necessary to say more about his evidence about the adverse incident report.

Expert evidence

48. As is common in a case of this nature, evidence was obtained from experts in a range of disciplines. The most contentious expert evidence was that of the neonatologists, Professor Mitchell (called on behalf of the claimant) and Dr Hawdon (called by the defendant). I heard oral evidence from both, and they were subject to detailed cross-examination. Each party raises some criticisms of or challenges to the other party's neonatology evidence. Analysis of this evidence is central to the issues I must decide.
49. That does not depend upon an impressionistic view of the respective experts' evidence. Despite somewhat differing styles, I thought that both experts gave their evidence in a considered manner. Professor Mitchell made a number of significant concessions in cross-examination, which I shall have to consider. Further, he accepted that having seen evidence of a dramatic fall in blood pressure and a temporal relationship with the pancuronium he had then looked for a mechanism to explain that. It seems to me that that was the reverse of what Mr Maskrey is critical of Dr Hawdon for doing. He suggested that Dr Hawdon's approach was to start from the proposition that the pancuronium was not responsible. I note that Dr Hawdon also made some concessions under cross-examination.
50. Mr Maskrey submits that Dr Hawdon fell into error in the following ways:
 - i) In her report, she concluded that it was likely that there was an intrauterine insult which caused preterm labour and CTG abnormalities before delivery and that this was the cause of the PVL. We know however that the membranes ruptured a month before AXO's birth and the neuroradiologists agree that the insult occurred no earlier than a few days before birth. Dr Hawdon's theory therefore could not be right. She also accepted that she was not qualified to interpret the CTG. In cross-examination, Dr Hawdon accepted that there was no evidence of an intrauterine insult. Mr Maskrey suggests that her willingness to put that forward as an explanation when it was contrary to the evidence casts doubt on her opinions generally.
 - ii) Dr Hawdon said in her report that it was likely that AXO's blood pressure remained low, causing worsening hypoxia, as he deteriorated between 22.00 and 24.00. Mr Maskrey says that she has not reflected on the absence of any note of low blood pressure in this period or on Sister Aala's statement. Further, she has not expressly referenced the entry at 01.00 in the opinion section of her report.
 - iii) Mr Maskrey suggests that Dr Hawdon was wrong to say that had the therapeutic dose of pancuronium been given a further dose would have been required. He says this ignores the overall improvement in AXO's condition which she accepted in cross-examination.
 - iv) Dr Hawdon advanced the suggestion that the increase in base deficit between 11.05 and 11.56 on Day 2 was simply a continuum. However, she accepted in cross-examination that there was in fact a step-change. She was unable to

explain that. Mr Maskrey suggests that an objective expert would have highlighted that this was a feature that did not fit neatly with her theory.

- v) There was a complete absence of reference to literature in Dr Hawdon's report. Mr Maskrey made it clear that he would not criticise an expert for not relying on literature but did criticise her for apparently not doing a literature search before finalising her opinion. She was apparently not aware of a letter published in the Lancet or drug data sheets from Australia and New Zealand which were relevant when considering a possible link between pancuronium and hypotension.
51. It seems to me that these are matters I should have in mind when I analyse the competing views. However, I do not consider that they fundamentally undermine Dr Hawdon's evidence overall. Both experts have highlighted the evidence they rely upon as supporting their opinions. Both have made concessions under cross-examination. There are other aspects of the evidence that may be relied upon to challenge the opinions of each expert's evidence. However, I consider that any generalised criticism of either expert would be unwarranted. The parties acknowledge that this is a complex case and it seems to me that there is scope for some difference in opinion. I will have to approach the neonatology evidence by careful cross-referencing of the evidence and the findings I make.
52. The parties agreed that it was unnecessary for the expert pharmacologists and neuroradiologists to be called. Although those experts had not reached complete agreement, it was considered that the differences between them were not such as to require oral evidence. Their evidence was therefore presented in writing by way of their expert reports and joint statements.
53. This presents no difficulty in relation to the neuroradiology evidence where there was a very substantial measure of agreement between Dr Stoodley and Dr McConachie. They agree that the scans show that AXO is likely to have sustained the causative insult or insults within a timeframe of a few days of the first scan (Day 2). They did not consider that the quality of the images allowed for precision in defining the time of onset of the relevant insult(s). Dr McConachie thought there was some evidence to favour an insult having preceded the pancuronium overdose but accepted that, even if that was so, any reduction in cerebral perfusion related to the overdose could have exacerbated the effect of the preceding insult.
54. Given the way in which the claimant's case developed at trial, I consider that it might have been helpful for me to have heard from the pharmacologists. It seems to me that their reports contained material differences in opinion that had not been resolved by the joint statement, particularly as to any effects of a pancuronium overdose around the time of transfer. However, I must deal with the case on the basis of the evidence before me. In relation to the pharmacology evidence, I have done so by carefully considering the content of each expert's written evidence and considering that in the context of the other evidence in the case.
55. There had been some significant narrowing of issues between the expert neurologists, Dr Newton and Dr Smith. The claimant called Dr Newton to give evidence and he was cross-examined.

56. To some extent, I considered that Dr Newton strayed beyond his area of expertise. I fully accept that the care of a sick neonate inevitably involves a multi-disciplinary approach such that in practice the boundaries between experts in different disciplines are somewhat fluid. I acknowledge that Dr Newton's practice over the years has required him to understand and to explain multifactorial causes of neonatal brain injury to parents and others. It is often very helpful to have the input of experts from different disciplines to provide a complete picture on causation. However, Dr Newton acknowledged that parts of his evidence were based upon "undergraduate medicine" and his management of neonates as a junior doctor but no directly relevant experience for 20 years. The weight to be given to such evidence must inevitably be limited.
57. The agreement reached by the neurologists that the two periods of hypotension materially contributed to AXO's brain injury falls squarely within their field of expertise. However, Dr Newton's evidence as to the underlying cause of the hypotension can add very little, if anything, to the neonatology evidence.
58. Dr Smith accepted such matters fell outside his expertise. Although he attended court, Mr Maskrey decided that it was unnecessary to cross-examine him. As with the pharmacologists and neuroradiologists, I received his evidence in writing in the form of his report and the joint statement and I take it into account.

Findings of fact

59. The evidence demonstrates, on a balance of probabilities, that AXO was not damaged prior to his birth. Although early rupture of the membranes presents risks for the foetus, AXO did not develop infection. I accept Dr Hawdon's evidence that having had little liquor around him after the rupture, the risks to AXO's lungs were increased and he was very likely to have surfactant deficiency and breathing difficulties.
60. The absence of neurological damage but likelihood of problems with the lungs fits entirely with AXO's condition at birth and his early observations. AXO was therefore a vulnerable baby but neurologically intact and in relatively good condition given his gestational age.
61. I accept that, until 20.00, AXO appeared to be doing reasonably well and responding to treatment with surfactant. Dr Hawdon pointed to his first blood gases as demonstrating that his carbon dioxide levels were higher than would be expected in a healthy baby of 29-30 weeks gestation. The neonatology experts agree that he developed significant respiratory distress syndrome. His progress was consistent with worsening RDS; appropriate measures were taken to treat that, and the interventions were controlling any deterioration.
62. It is likely that the initial worsening of his condition from around 20.00 was caused by the blocked tube in the context of already worsening RDS.
63. There was a fall in blood pressure at 20.00 to 25, which was low but not critically so. There was sufficient concern about AXO that the nursing staff asked Dr Osoba to review him and Dr Osoba decided to call Dr Brown at home.

64. I find that by the time Dr Brown arrived there was some real concern about AXO. Dr Brown's initial note is timed 22.30. His evidence was that this was the time he arrived, and that his note was made shortly later, after he had attended to AXO.
65. Dr Brown recognised the possibility of a blocked endotracheal tube and changed it. I accept Dr Brown's evidence that this did not bring about the sustained improvement that he had hoped for. I also accept that he called Portsmouth that night to arrange for AXO's transfer in the morning and that at least part of the reasoning for expressing that request as "provisional" was that he feared AXO might not survive the night. I accept that he regarded AXO as being in a critical condition. Dr Brown noted his impression that AXO's condition was caused by "Blocked ET tube plus shunting." A chest x-ray was interpreted as showing "bad RDS".
66. AXO's respiratory status continued to deteriorate. His oxygen requirements rose between 20.00 and 21.00 and markedly so thereafter. By 23.00, he required 100% oxygen. Despite receiving 100% oxygen, Dr Brown recorded that AXO's oxygen saturation was down at 73 to 80 between 23.00 and midnight. There was a need to increase the settings on the ventilator before midnight. Blood gas just before midnight showed significant respiratory acidosis. It was clear that good ventilation and oxygenation was not being achieved. However, there was no significant metabolic component to the acidosis at this stage.
67. I accept that the absence of any significant metabolic acidosis at midnight is an indicator that AXO had not suffered damage up to that point. However, there is clear evidence in the records (including the adverse incident report) of difficulty in ventilating and oxygenating AXO at midnight. This led to the decision to sedate and paralyse AXO.
68. I also accept Dr Brown's account that AXO was critically unwell by midnight. He described this as the "peak time of worry."
69. There is evidence within the records that there was concern about AXO's blood pressure before midnight. Dr Brown ordered a bolus of saline when he attended at 22.30, with a view to increasing blood volume and improving cardiac output. Further, dopamine was commenced at midnight. In order for the infusion to have commenced then, it is likely that the decision to prescribe dopamine was taken around 23.30 to 23.40. The dose given is recognised to be a low (starting) dose. Practice varies as to what dose will initially be given if a neonate has significantly low blood pressure. Professor Mitchell suggested that such a dose could be given because of concern about AXO's respiratory status but he did accept in cross-examination that there appeared to have been concern about AXO's blood pressure prior to midnight.
70. Overall, I find that AXO's condition deteriorated significantly after 20.00 and became critical in the period from 22.00 to midnight. The pattern was consistent with severe RDS and difficulties ventilating AXO, which had reached a peak of concern around midnight.
71. On the important issue of when the significant drop in blood pressure to a MAP of 22 occurred, I am unable to accept Dr Brown's evidence that this was observed before midnight. I have already set out concerns about Dr Brown's evidence and his attempts to reconstruct events from his notes. He was plainly confused about timings

and unclear as to when his notes were made, and I find his suggestion that his note should read “paralyse with pancuronium” rather than “paralysed with pancuronium” to be an unsatisfactory explanation. It is known that the dose of dopamine was increased between 01.00 and 02.00, after the recorded MAP of 22 at 01.00. Dr Brown makes no mention of the recorded blood pressure at 01.00 in his statement. The evidence in the records (including the chronology of treatment) and that of Sister Aala is much more consistent with a natural reading of Dr Brown’s note, which is that AXO was already paralysed with pancuronium at the time that a fall in blood pressure to 22 was first noted.

72. I accept Sister Aala’s written evidence that AXO’s blood pressure was 28 just before midnight. It seems to me that this is consistent with the evidence as a whole. I also find, contrary to Dr Brown’s evidence, that the drop in blood pressure to 22 was not observed before the pancuronium was given. Had it been, I would have expected there to be some note of that, since it was a significant finding. There are no recorded blood pressure readings between midnight and 01.00, when the reading of 22 was noted. Therefore, I find as a fact that AXO suffered a significant drop in blood pressure from 28 to 22 sometime between midnight and 01.00.
73. There is no direct evidence to narrow the timeframe further. Therefore, I shall have to approach the expert evidence on the basis that the factual evidence establishes that the significant fall in blood pressure occurred between midnight and 01.00. That leaves open the possibility of it occurring either side of the administration of the pancuronium overdose at 00.25.
74. AXO’s condition improved between 01.00 and 02.00. By then, he had received Curosurf (at 00.20) and the pancuronium (at 00.25) and the dopamine dose had been increased. His blood pressure was 30 at 1.30 and his oxygen requirement came down. During this period, it appears that effective ventilation had been achieved. During the morning of Day 2, a modest metabolic acidosis was developing. Creatinine and urea levels at 08.15 showed some evidence of evolving renal impairment (a marker of AXO having sustained damaging under-perfusion). AXO remained deeply paralysed (indeed this led to the recognition that he had received an overdose of pancuronium).
75. The expert evidence suggests that the observed rise in base deficit before AXO’s transfer was caused by ‘washout’ of tissue acidosis following the earlier insult (whatever its cause). This increasing deficit therefore should not be seen as evidence of further deterioration and is consistent with AXO being adequately ventilated on the morning of Day 2. Dr Hawdon accepted this in cross-examination.
76. At 10.00, AXO was noted to have “poor cardiac output”. Although highlighted in some of the expert evidence, that note did not receive a great deal of attention at trial. Dr Hawdon’s review of the notes suggests that at this time AXO was noted to be “stable”
77. I come then to events around the time of transfer. The transfer records contain some conflicting entries about the precise timings of the transfer process. The expert neurologists jointly considered the records and attempted a reconstruction in their joint statement. They noted that the last arterial blood gas result at Salisbury was at 11.05. It showed a base deficit of -7.4. I note there is a recorded blood pressure reading of 31 at 11.00. The first entries in the Portsmouth transfer records were made

- at 11.30. The first column records observations “on unit”. I heard from Dr Groves and she explained that these observations would be done virtually as soon as the team arrived on the unit. She therefore confirmed that she arrived just before 11.30. I accept that evidence.
78. Blood pressure measured non-invasively was 25 when the transfer team arrived. By then, dobutamine (a second-line inotrope) had been prescribed with infusion of that drug commencing at 11.25, just prior to the transfer team’s arrival.
 79. After the initial observations, Dr Groves inserted a radial arterial line, which provided more accurate monitoring of AXO’s arterial blood pressure. She noted a MAP of 24 and confirmed in evidence that this was the reading that she obtained immediately after insertion of the line. The dobutamine was continued. A note in the transfer records suggests that blood pressure was 21 prior to commencement of dobutamine, although that reading does not appear elsewhere.
 80. Once the arterial line was sited, AXO was transferred from the ward incubator to the transport incubator and was accidentally extubated in the process. I find that Dr Groves was alert and responded quickly, immediately re-intubating. AXO was ventilated via a bag and mask until the new tube was inserted. AXO remained paralysed by the pancuronium, which may have facilitated the reintubation, which Dr Groves told me was “very easy”. She said the whole process took “a couple of minutes”.
 81. Observations were maintained during the transfer. AXO’s blood pressure was 24 at 12.00, 26 at 12.30 and 34 at 13.00. Arterial blood gases at 11.56 showed a significant rise in the base excess from -7.4 at 11.05 to -13.8 at 11.56. The metabolic component had increased. Dr Groves’ evidence is that the 11.56 reading was taken following the transfer to the transport incubator and the subsequent reintubation. A further blood gas was performed during the transfer at 12.45, when the base deficit was -14.
 82. There was then a step-change in the base deficit between 11.05 and 11.56, consistent with a significant increase in acidosis. The neonatology experts are agreed (Dr Hawdon accepting this in cross-examination) that such a severe rise is usually consequent on an acute event.
 83. The neurologists agreed that AXO probably suffered hypotension during the transfer to Portsmouth and that this was a further insult which probably contributed to his PVL. The claimant’s case, as pleaded (paragraph 29 (vi) of the Amended Particulars of Claim), was that this period of hypotension was caused by, AXO’s accidental extubation during the transfer process.
 84. On the basis of Dr Groves’ evidence and, having cross-referenced what she said with the relevant entries in the notes, I find as a fact that AXO’s MAP, measured via an arterial line, was 24 before the accidental extubation and remained at 24 when the next reading was taken at 12.00. I find that dobutamine was commenced before the extubation occurred and was given in response to concerns about AXO’s blood pressure. The introduction of a second-line inotrope at that stage is consistent with a significant fall in blood pressure and I see no reason to doubt the entry in the transfer notes that a reading of 21 had been taken prior to the introduction of dobutamine. I find no evidence that AXO suffered a drop in blood pressure following the extubation.

It initially remained the same as it had been immediately before extubation, at 24, and then rose during the journey to Portsmouth.

85. I do, however, find that there was a significant rise in metabolic acidosis around the time of AXO's transfer, which was outside the expected trajectory.
86. It is an unchallenged fact that AXO suffered a further drop in his blood pressure to the low 20s after administration of Curosurf at 16.20 on Day 2. His blood pressure improved with an increased dose of dopamine. There is no evidence as to how long it took to do so.

Causation of the first episode of damaging hypotension

87. I must turn to consider the expert evidence on causation in light of my findings of fact. It is not in dispute that AXO suffered a damaging insult linked to the significant hypotension noted at 01.00 and that such insult materially contributed to his neurological damage. The issue is whether the hypotension was caused by the pancuronium overdose.
88. Professor Mitchell's opinion was that the overdose of pancuronium caused major destabilisation of AXO's blood pressure and was the major contributory factor to severe and sustained hypoperfusion. In his report, he advanced an explanation as to the mechanism by which this occurred as follows:

“... the effect of the pancuronium overdose will have been a profound, global loss of muscle tone which will be associated with a fall in systemic venous return and consequent fall in cardiac output with fall in systemic blood pressure.”
89. In response to questions from the defendant under CPR 35, Professor Mitchell provided clarification of that mechanism and made it clear that he considered hypotension to be a physiological, rather than pharmacological, effect of a large dose of pancuronium. In doing so, he suggested that a large dose of pancuronium would abolish resting muscle tone causing flaccid paralysis. He also cited literature (Fenton et al, 1992) suggesting that pancuronium may have a direct effect in compromising autoregulation of cerebral blood flow in ventilated preterm infants which might provide an additional way in which an overdose may have contributed to the neurological injury.
90. Professor Mitchell also identified that product information published in Australia and New Zealand cited significant hypotension and shock as a possible side-effect of an overdose of pancuronium bromide.
91. At trial, Professor Mitchell maintained his view that the hypotension observed at 01.00 was probably caused by the pancuronium overdose and that it would probably not have occurred had the correct therapeutic dose been given. However, he made some significant concessions during cross-examination.
92. First, he accepted that, in the majority of neonates, the administration of the therapeutic dose of pancuronium causes total paralysis (although a significant minority will not be completely paralysed). Therefore, for the majority of babies, the

effect of an overdose would be no greater than that of the therapeutic dose, but it will last longer. I note that this accords with the agreement of the pharmacology experts in their joint statement that the effect of the pancuronium on the contribution of the muscle pump to circulation would not be increased by an overdose, but it would last longer.

93. As I must resolve issues going to causation on a balance of probabilities, I must assume that AXO would have responded to a therapeutic dose as the majority of neonates do. On that basis, I am unable to find that the overdose caused a greater reduction in muscle tone than would have been caused by the therapeutic dose.
94. Next, Professor Mitchell acknowledged the recorded drop in blood pressure “to the low 20’s” following the administration of Curosurf at 16.20 on Day 2 (at Portsmouth). In cross-examination, he accepted that, as Curosurf was given five minutes before the pancuronium overdose, he could not say whether the drop in blood pressure recorded at 01.00 was caused by one drug or the other or by the combination of both. He went on to say that such a significant fall would not generally be recognised with the administration of Curosurf. However, he acknowledged that the evidence of what occurred at 16.20 on Day 2 could not be ignored.
95. In re-examination, Professor Mitchell confirmed that he would not expect such a significant fall following the administration of Curosurf and a therapeutic dose of pancuronium. Accordingly, he affirmed his view that the overdose was the likely explanation for the fall in blood pressure at 01.00.
96. Professor Mitchell acknowledged that, in reaching his opinion, he had relied on the contemporaneous association between the fall in blood pressure and the administration of pancuronium. He had then looked for a mechanism to explain that. He recognised that there was no pharmacological mechanism, therefore it must be physiological. His theory was that the mechanism was increased venous pooling and he had found some support for this in the literature in the form a letter to the Lancet (McIntosh, 1985). McIntosh reported the case of a neonate born at 29 weeks who was observed to suffer a significant fall in blood pressure following 12 out of 14 repeated therapeutic doses of pancuronium, administered for restlessness. He noted that he had found no previous reports of this but that

“ most paediatricians using pancuronium in the neonatal period seem to have occasional experiences of this sort.”

McIntosh theorised that, in an infant with only marginally adequate circulating volume, the abolition of muscle activity will cause a fall in venous return and cardiac output with an associated fall in blood pressure.

97. Dr Newton also thought that “the hypotension at the time of pancuronium administration is probably more than coincidence” (see his response to the Part 35 questions). In cross-examination, he admitted that he did not really know the mechanism by which pancuronium would cause hypotension and that he had not administered the drug for about 20 years. It seemed to me that his evidence on this issue relied on Professor Mitchell’s opinion and did not carry any significant independent weight.

98. Dr Hawdon's opinion is that there was no causal link between the pancuronium overdose and the hypotension recorded at 01.00. In the joint statement, she noted that three different mechanisms had been proposed in the course of the case as to the effect of the pancuronium on blood pressure. She did not accept the mechanism put forward by Professor Mitchell and rejected the suggestion that a larger dose could cause "deeper" paralysis so affecting venous return. In the joint statement, Dr Hawdon said:
- "there is no mechanism by which the overdose of pancuronium caused acute or prolonged hypotension and there are other more plausible candidate causes for hypotension."
99. Dr Hawdon accepted that there was no evidence to indicate that AXO had been compromised or damaged before delivery. However, she explained that AXO was vulnerable. He was born at 30 weeks, the membranes having ruptured about a month earlier. It was to be expected that he would have surfactant deficiency. She also agreed that he appeared to be responding to surfactant initially and that there had been a degree of stabilisation. However, the first blood gas values were not normal. Despite intervention, the carbon dioxide level was higher than would be expected in a healthy baby born at this gestation. AXO's blood pressure fell at around 20.00. His requirement for oxygen rose between 20.00 and 21.00 and by 23.00 he was requiring 100% oxygen. Her view was that he had had surfactant deficient respiratory distress syndrome and that this compromised the heart. The interventions AXO was receiving were probably ameliorating the deterioration in his condition but there was evidence that his lungs were difficult to inflate after the endotracheal tube was changed around 22.30. Gas exchange was not being achieved and the settings on the ventilator showed that more pressure was required to inflate the lungs. The drop in blood pressure at 01.00 could just reflect the fact that AXO was very unwell before he turned a corner.
100. Dr Hawdon accepted that there was an insult, something was causing reduced cardiac output for a time, but did not accept that it was a sudden event. Her evidence was that that AXO's general condition leading up to midnight to 01.00 was sufficient to cause poor perfusion. Dr Hawdon said that babies with respiratory distress syndrome are at high risk of developing peri-ventricular leukomalacia without there being a single moment insult. The low blood pressure was likely to be part of the overall condition where AXO had severe RDS, poor oxygenation and high levels of carbon dioxide.
101. In the joint statement, Dr Hawdon opined that it was more likely that the drop in blood pressure was due to the administration of Curosurf than pancuronium, given the documented fall in blood pressure following Curosurf the following afternoon. In cross-examination, she accepted she had not said that in her report. She frankly admitted that she had overlooked the significance of the entry in the Portsmouth records until the discussion with Professor Mitchell and the pharmacologists for the purpose of their joint statements. She said that Curosurf can cause a fall in blood pressure by allowing blood to flow through the lungs more easily, causing a transient drop in the systemic circulation. If that happens, the effect will be quick, and it can be ameliorated by giving a saline bolus and/or dopamine. The blood gas at 01.00 indicates an improvement in lung compliance, which would support this. The same thing appeared to have happened the following day. She accepted that a fall in blood pressure was a rare occurrence (although it was not vanishingly rare – she had

observed it in practice). By contrast, she had never observed a fall in blood pressure following the administration in pancuronium. I felt that she dealt with this well and I would not be critical of her for not identifying the point earlier.

102. Overall, having heard both experts, I found Dr Hawdon's evidence to be more compelling than Professor Mitchell's. Once Professor Mitchell had acknowledged that the majority of babies would be fully paralysed by a therapeutic dose of pancuronium, it seemed to me that the mechanism he put forward could not explain why the overdose had caused an effect that would not, on balance, have arisen with the correct therapeutic dose. I also have in mind his significant concession in cross-examination that he could not say whether it was the Curosurf or the pancuronium or a combination of both that caused the hypotension.
103. Having said this, I recognise that Professor Mitchell gave his evidence in a considered way and that he maintained his view that the pancuronium had caused the hypotension noted at 01.00. I fully accept that medical science cannot always explain every step in a chain of causation and that this is not required in order to prove a causal link on a balance of probabilities. All that the claimant is required to prove is that the overdose is likely to have made a material contribution to the outcome. The fact that it may not be possible to prove exactly how it did so is not fatal to establishing causation.
104. The fundamental point relied upon by Professor Mitchell is that there was a temporal link between the highly unusual event of a tenfold drug overdose and a significant episode of hypotension.
105. In his closing submissions, Mr Maskrey developed this point further. In doing so, he referred to the product data from Australia and New Zealand, which had received very little attention in the trial up to that point. The following points were highlighted:
 - i) "Neonates are particularly sensitive to pancuronium ... Dosage must be individualised ... and further reductions may be necessary in prematurity, acidosis, hypothermia and during antibiotic therapy."
 - ii) "Hypersensitivity reactions occur rarely. Bradycardia, bronchospasm, hypotension and cardiovascular collapse have been reported."
 - iii) "Symptoms of overdose are prolonged apnoea, respiratory depression and/or muscle weakness, significant hypotension and shock."
106. I consider this to be an important piece of evidence which must be put into the balance. Setting aside Professor Mitchell's evidence as to the mechanism by which the overdose led to hypotension, there is evidence that neonates are particularly sensitive to pancuronium; that significant hypotension has been recognised as a side effect of an overdose and that AXO suffered significant hypotension at least broadly around the time that he received the overdose.
107. It is perhaps unfortunate that the Australia / New Zealand product data did not have greater prominence before the end of trial. It was not referred to in the claimant's opening nor was it explored with the experts. I suspect that it assumed greater importance given the concessions made by Professor Mitchell in the witness box and

the way in which the claimant's case evolved with the evidence. I am not critical of the claimant's representatives for dealing with this evidence in the way that they did. Further, I make it clear that I do not consider the fact that the significance of the evidence was only highlighted at the end of the trial should be held against the claimant in any way. It is material that is before me and which must be given appropriate weight. I note that Professor Mitchell had highlighted the Australia / New Zealand product data in his written evidence (in answer to the Part 35 questions) and that it was open to the defendant's representatives to obtain evidence to respond to this and/or to cross-examine Professor Mitchell about it.

108. I do note though that Dr Hawdon said in her report [p.267]:

“Hypotension is only a recorded side effect of pancuronium overdose in standard texts if anaphylactic reaction occurs”.

She explained that immaturity of the immune system in a neonate, particularly a preterm neonate, would make that very unlikely. She was not cross-examined on this.

109. AXO had no other symptoms of an anaphylactoid reaction (see such as flushing, hives, bronchospasm and/or swelling of the lips, face and tongue), making it very unlikely that he suffered anaphylaxis.

110. Professor Ferner's evidence as set out in his report [p.292] was that:

“Pancuronium has little effect on blood-pressure in most newborn infants, although there is some evidence that it sometimes causes a rise in blood pressure, and a single case report suggesting that it can cause a fall in blood pressure.”

111. The single case he refers to is that reported by McIntosh. A subsequent study (Miall-Allen, 1987) of 16 infants given pancuronium and 16 given pethidine showed a tendency for heart rate to rise in those given pancuronium but no significant changes in MAP. Blood pressure became more stable after pancuronium. A further study (Greenough, 1989) of 18 ventilated infants given pancuronium compared to 11 not given pancuronium found no difference in mean daily blood pressure, variability of blood pressure, or number of episodes of hypo- or hyper-tension. Professor Ferner's evidence was that the effects of a pancuronium overdose are an unlikely explanation for the episode of low blood pressure at 01.00, although that could not be excluded. He was not subject to cross-examination.

112. Although Dr Cockbill had maintained that the drop in blood pressure was consequent on the overdose, her response to the defendant's CPR 35 questions made it clear that she relied upon Professor Mitchell's evidence and was not providing an independent opinion in this area.

113. Having taken account of all the evidence, including the data from Australia and New Zealand, I am not persuaded that the claimant is able to establish a causal link between the overdose and the hypotension recorded at 01.00. Mr Maskrey accepted (as he was bound to on the evidence) that blood pressure can fall for a variety of reasons.

114. I accept the evidence of Dr Hawdon that unstable respiratory status and a requirement for treatment of hypotension is characteristic of severe lung disease of prematurity.
115. The factual evidence establishes only that AXO's blood pressure was 28 shortly before midnight and 22 at 01.00. There are no recordings of blood pressure between midnight and 01.00, when the team are said to have been working hard to save AXO's life. The possibility that blood pressure had fallen or was falling shortly before the pancuronium (and Curosurf) was given cannot be excluded. This accords with the evidence of Dr Smith (as set out in the joint statement) that it was entirely possible that blood pressure was steadily falling in the context of worsening RDS. Professor Mitchell accepts that AXO's initial progress was consistent with worsening RDS.
116. I consider that the evidence in the records is consistent with Dr Hawdon's opinion that it is likely that AXO's lungs collapsed while the tube was blocked and that after the tube was changed the lungs proved difficult to reinflate, leading to difficulty ventilating him. Adequate gas exchange was not being achieved and the settings on the ventilator had to be increased. Further, Dr Brown's contemporaneous impression that there was "shunting" is consistent with Dr Hawdon's opinion that AXO is likely to have developed pulmonary hypertension causing flow of de-oxygenated blood from the lungs to the circulation of the body. She explains that this occurs with severe RDS, which the contemporaneous evidence demonstrates AXO had.
117. AXO had undoubtedly suffered a significant deterioration in his condition prior to the administration of the pancuronium. He was critically ill by midnight, although I acknowledge that he had not developed any significant metabolic acidosis at that time. I have found that he had severe RDS and that it was difficult to ventilate him.
118. Given the absence of a significant metabolic component at 23.57, Professor Mitchell said in the joint statement that there is no evidence of impaired systemic perfusion giving rise to reduced cardiac output at this time, as the resulting tissue hypoxia would give rise to a significant metabolic acidosis. However, in his report he had noted that blood pressure was already starting to fall as AXO's respiratory status deteriorated. In cross-examination, he said that anyone looking after this baby would have been concerned about him at midnight.
119. Blood gas values and oxygenation were improving from 30 minutes after administration of pancuronium. Professor Mitchell accepted that, relatively speaking, AXO improved during the night, after the administration of the pancuronium.
120. Whatever the cause of the insult producing the blood pressure reading at 01.00, a significant metabolic acidosis did not develop until later that morning. Professor Mitchell's opinion is that any damage done in the first insult is likely to have been relatively mild and that the majority of the damage was done in the second insult. In cross-examination, his evidence was that "there could have been some brain injury at the time of the original fall in blood pressure."
121. I do not consider that the absence of a significant metabolic acidosis at midnight precludes Dr Hawdon's opinion that AXO's condition was sufficient to cause poor perfusion. The neurologists agree that hypotension is often associated with poor tissue perfusion which contributes to poor outcome. It is the cause of this hypotension that I am concerned with. While I acknowledge that the absence of a significant

metabolic acidosis is something to be put into the balance, and I have done so, it cannot itself prove the cause of the hypotension.

122. It is relevant that there are also other episodes of AXO's blood pressure falling both before and after the pancuronium overdose. It had dropped to 25 at 20.00 (at which time his respiratory status was less concerning). AXO had required treatment with a saline bolus and dopamine. I note that Dr Newton said in the joint statement that AXO clearly had a tendency to low blood pressure, albeit he considered it had stabilised.
123. AXO's blood pressure dropped again on the morning of Day 2, prior to the accidental extubation and without any obvious precipitating cause then. Further, it is a known fact that AXO suffered a fall in blood pressure to the low 20's following the administration of Curosurf on the afternoon of Day 2. Of course, it must be remembered that AXO continued to be paralysed due to the pancuronium overdose on Day 2. Mr Maskrey points out, and I accept, that there had been no reported fall in blood pressure following the administration of the first two doses of Curosurf. However, the clear evidence of Professor Ferner is that the overdose could not explain a fall in blood pressure at this later time.
124. In my judgment, Professor Mitchell has relied too heavily on the temporal link when the evidence only establishes that these events occurred around the same time, not necessarily that the fall immediately followed the overdose. His proposed mechanism does not stand up to analysis. It is clear from the expert evidence as a whole that there is uncertainty as to precisely how a premature neonate will respond and as to the pathogenesis of PVL. What is known is that severe RDS is a significant risk factor and that AXO was very sick before the administration of the pancuronium. It is also known that he received Curosurf at around the same time and that this drug was later observed to cause a drop in his blood pressure.
125. Even if the administration of pancuronium did play a part, there is no sufficient evidential basis to find that the overdose caused something that would not have occurred with a therapeutic dose, given the probability that the correct dose would also have brought about total paralysis. In so far as the Fenton paper is relied on as evidence of pancuronium having a possible influence on cerebrovascular regulation, that research suggested that if there was an effect (which required further investigation) it was seen with the therapeutic dose.
126. While superficially it may be attractive to assume a link between the pancuronium overdose and the drop in blood pressure between midnight and 01.00, weighing all the evidence in the balance, I am unable to say that this episode of hypotension was probably caused or materially contributed to by the overdose.

The second episode

127. The claimant's case was opened to me on the basis that the second episode was a consequence of the transfer and accidental extubation. At that stage, it was claimed that the transfer would not have occurred but for the overdose. However, as I have indicated, that is no longer maintained. In the alternative, it was contended that the low blood pressure during the transfer and/or the metabolic acidosis developing during that time were materially contributed to by the pancuronium overdose.

128. As set out above, Mr Maskrey contended during his closing submissions that the accidental extubation caused a second “hit”, which AXO would have been able to withstand but for the pancuronium overdose.
129. The neurologists agree that AXO suffered hypotension during the transfer to Portsmouth and that this materially contributed to the PVL. However, Dr Smith made it clear that he did not agree that such period of hypotension was caused by the accidental extubation.
130. The cause of the brain damage is clearly a matter falling within the expertise of the neurologists. It is important to be clear that their agreement is that it was the hypotension that materially contributed to the PVL.
131. I note that Dr Newton’s opinion was predicated on AXO having suffered a period of hypotension following, and as a result of, the accidental extubation. Dr Smith accepted that AXO suffered hypotension during the transfer, albeit not that it was caused by the extubation. I have found as a fact that the drop in blood pressure occurred before the transfer commenced and that it did not drop further after the accidental extubation.
132. Professor Mitchell said that “something must have happened” to give rise to the significant increase in base deficit between 11.05 and 11.56. He conceded that there was evidence of some evolving renal impairment and deterioration in the base deficit before extubation occurred but said that the rapid increase in metabolic acidosis in this hour was outside the prior trajectory and not explained by the RDS. I note that he said in re-examination that the global insult causing the increase in metabolic acidosis did not necessarily have to be associated with a fall in MAP. However, the starting point must be the agreement of the neurologists that the damage was caused by the hypotension. I must therefore consider whether the pancuronium overdose caused or contributed to that hypotension.
133. Professor Mitchell’s evidence was that AXO had suffered poor perfusion and probably some brain injury as a result of the overdose and subsequent events. What happened during his transfer led to further brain injury in a baby who was pre-disposed to injury by the previous events. None of this would have occurred but for the overdose. He considered that the events during transfer were the major cause of AXO’s injury. He said (in cross-examination) that any brain injury sustained at the time of the original drop in blood pressure and AXO’s general condition would predispose him to injury so that injury or further injury could result from a relatively minor event. This second episode was therefore likely to be the more damaging epoch.
134. Professor Mitchell said that the insult was caused by cardio-respiratory instability due to the extubation. The lungs and chest muscles would have collapsed. That would not have happened if he had not been paralysed at that point. If not paralysed he would have been expected to tolerate extubation reasonably well. His theory is that, as AXO remained paralysed, systemic venous return was impaired.
135. Dr Hawdon accepted that the rapid rise in base deficit from -7.4 at 11.05 to -13.8 at 11.56 is exactly what one would expect to see if there had been a hypoxic event in that timeframe. She did not accept that such a rise could only be consequent on an

acute event but did agree that this would usually be the case in the absence of any other explanation. Dr Hawdon agreed that she would not be surprised if the lungs of a baby with respiratory distress syndrome were not fully reinflated following reintubation. However, she believed that AXO was kept adequately ventilated through the use of a bag and mask as demonstrated by his blood gas readings and his oxygen requirements afterwards. She thought it unlikely that the accidental extubation was the cause of an insult sufficient to result in PVL. Dr Hawdon pointed to there being no change in heart rate or blood pressure (MAP was 24 before extubation and remained at 24 afterwards).

136. The evidence of renal and hepatic impairment when AXO arrived at Portsmouth is consistent with a global hypoxic-ischaemic insult prior to his admission to Portsmouth.
137. AXO had been stable during the night. However, his blood pressure had dropped significantly before the transfer. Dr Groves, a highly experienced and respected neonatologist, regarded the extubation as relatively uneventful. Apart from the increasing metabolic acidosis, AXO's observations were relatively stable either side of the extubation.
138. Mr Maskrey argued in closing that the extubation was not sufficiently prolonged as to give rise to an increase in oxygen requirements but did cause a fall in blood pressure, or continuation of the fall in blood pressure, which was sufficiently prolonged as to cause further neurological injury. This seems to be an attempt to get around the difficulty that the neurologists have agreed that the hypotension caused the damage when the evidence is clear that the onset of the hypotension was before the extubation. He asked why there was a fall in blood pressure capable of causing neurological injury unless an event occurred at that time. He then argued that a baby would have been expected to withstand extubation and that the reason he did not was that he was paralysed. With respect, and admirable as Mr Maskrey's efforts were, this argument is circular. It assumes that the extubation was causative of the injury and then relies on that assumption to prove that there was an unexpected reaction to extubation.
139. The reality is that the evidence does not establish that there was an unexpected reaction to the extubation. Rather, there had already been a significant drop in blood pressure, requiring the introduction of dobutamine before the extubation occurred. The neurologists have agreed that this episode of hypotension caused damage to AXO's brain. The evidence at trial does not prove a causal link to the pancuronium overdose.
140. Having regard to the step-change in metabolic acidosis during the transfer, I do accept that, on a balance of probabilities, there was a second damaging event around this time. However, I reject the notion that it was due to the accidental extubation. The hypotension, which the neurologists have agreed was causative of damage, had commenced before, and was not caused by, the extubation.
141. I note also Dr Ferner's clear opinion (upon which the claimant's representatives chose not to cross-examine), that the effects of the overdose explain the prolonged paralysis but cannot explain the hypotension during the transfer. See, in particular paragraph 65 of his report [p.303]:

“It is not expected that the presence of declining concentrations of pancuronium bromide will cause a sudden fall in blood pressure after several hours.”

142. On the facts as I have found them to be, the claimant has not established that the second damaging episode was causally linked to the pancuronium overdose.

Overall comments on causation

143. Although PVL is rare, it is clear from a review of all the expert evidence that it is a condition that can occur in premature neonates without any failing in care.

144. RDS is a recognised risk factor for the development of PVL. Dr Smith notes in the joint statement that:

“In babies of this gestation who develop CP they are more likely to have had significant complications such as respiratory distress syndrome.”

Dr Smith’s view (upon which he was not cross-examined) was that AXO’s deterioration was “due to the evolution of respiratory distress syndrome” and that it was more likely than not that he would have developed cerebral palsy even if the overdose of pancuronium had not occurred.

145. The claimant’s pharmacology expert, Dr Cockbill, also confirmed this known risk when describing the use of Curosurf [p.247]:

“RDS is a major cause of acute mortality and morbidity in the preterm baby and may also be responsible for long term respiratory and neurologic sequelae.”

146. Dr Newton also acknowledged that the literature (including Hatzidali et al, 2009) showed an association between the need for ventilation for respiratory distress syndrome and attendant vascular instability and PVL. Further, he advised (at paragraph 87 of his report):

“It must be stated, however, that many babies (probably at least a third) have no identifiable risk factors so clearly there is more for us to learn about the mechanisms underlying the generation of PVL.”

147. All of this supports the view expressed by Dr Hawdon in the joint statement that AXO’s prematurity and perinatal course are sufficient to explain his neurological injury. She said that neonatologists are likely to have experienced the development of PVL in infants of this prematurity and perinatal condition “many times in their careers”.

148. It follows that the fact of AXO’s PVL and the associated adverse outcome is not something wholly unexpected that can only be explained by the overdose. On the findings I have made, it appears that his PVL is more likely to be linked to the general complications associated with his premature delivery.

Conclusions

149. It is natural to suspect a link between the significant overdose of pancuronium and AXO's severe neurological injury. I have the greatest of sympathy for AXO's parents who have witnessed their son suffer an adverse outcome after a significant medical error. However, a close analysis of the evidence does not establish the necessary causal connection between the two.
150. AXO was very sick at midnight. There were real difficulties ventilating him and I have accepted that Dr Brown feared that he might die that night. This was before the pancuronium was administered as a response to his critical condition. It is not clear whether the drop in blood pressure occurred shortly before or shortly after the overdose. AXO also received Curosurf around the same time. That drug caused his blood pressure to drop the following afternoon. In cross-examination, Professor Mitchell acknowledged the difficulty in attributing the fall to one drug rather than the other.
151. Professor Mitchell's explanation as to the mechanism by which an overdose of pancuronium would cause the rapid onset of hypotension did not withstand cross-examination. Having accepted that the majority of neonates would be fully paralysed by a therapeutic dose of the drug, his explanation that the overdose caused a greater loss of muscle tone cannot be maintained.
152. Although the claimant need not prove the mechanism by which harm was done in order to establish causation, once Professor Mitchell's theory has been discounted, all that is left is the temporal connection between the overdose and the hypotension. However, it is not possible to say more from the factual evidence than that the onset of significant hypotension was between midnight and 01.00. By itself, this is not sufficient to establish a causal link as a matter of probability, particularly in a baby who had a tendency to low blood pressure (per Dr Newton) and who suffered documented hypotension following the administration of Curosurf.
153. I have reflected carefully on the product data from Australia and New Zealand, which describes significant hypotension as one of the symptoms of pancuronium overdose. This, coupled with the temporal connection, might suggest a causative link. However, Dr Hawdon's unchallenged evidence was that hypotension is only a recorded side effect where anaphylaxis occurs. It is highly improbable that AXO suffered an anaphylactic reaction.
154. I have also had regard to the pharmacology evidence. Dr Cockbill propounded no pharmacological explanation for a link between the overdose and the hypotension. Professor Ferner's evidence (upon which he was not cross-examined) was that it is unlikely that the fall in blood pressure was caused by the pancuronium.
155. The evidence does not establish that the hypotension recorded at 01.00 was probably caused by the overdose. Having seen the neonatologists give evidence and after cross-referencing all the other evidence in the case, I prefer the evidence of Dr Hawdon that AXO's hypotension at 01.00 was probably part of his overall condition, flowing from his prematurity, severe RDS and the difficulty in ventilating him.

156. Although I have found that a second insult occurred around the time of AXO's transfer, this was not caused by his accidental extubation. Reintubation was carried out quickly and skilfully and the observations before and after the extubation show no change in blood pressure, heart rate or oxygen requirements. There had already been a significant drop in blood pressure before the transport team arrived, which led to the introduction of the second-line inotrope, dobutamine.
157. The neurology experts agree that this episode of hypotension was causative of neurological damage. However, there is no evidential basis for a link to the earlier overdose. Dr Newton's opinion was clearly predicated on the basis that the fall in blood pressure followed the extubation but that does not reflect the facts as I have found them. Professor Ferner's unchallenged evidence is that the effects of the overdose could not explain this episode of low blood pressure.
158. There is no alternative basis for finding that the overdose contributed towards a hypoxic-ischaemic episode around the time of transfer. On Professor Mitchell's evidence, AXO was predisposed to neurological injury at this time. He suffered a further significant drop in blood pressure before the extubation. That (according to the agreed evidence of the neurologists) contributed to his PVL. Professor Mitchell's evidence that he was unable to withstand the extubation because of the effects of the pancuronium overdose is not supported by the chronology.
159. Overall, I find that AXO's neurological injury is explained by his prematurity and perinatal course. Although he was born in relatively good condition, he was a vulnerable baby by reason of his prematurity and the early rupture of the membranes. He developed severe respiratory distress syndrome, leading to significant deterioration in his condition by midnight. The mechanisms underlying the development of PVL are not always clear. It is known though that babies of this gestation who develop cerebral palsy are more likely to have had significant complications such as respiratory distress syndrome.
160. I fully recognise the importance of my decision to AXO and his parents. It may be of little comfort to them, but I have looked very closely at all the evidence before reaching my conclusions. Having done so, I find that causation is not established. I must therefore dismiss this claim.