Neutral Citation Number: [2025] EWCA Crim 795

Case No: 202100426 B5

IN THE COURT OF APPEAL (CRIMINAL DIVISION)
ON APPEAL FROM THE CROWN COURT AT NEWCASTLE UPON TYNE
Mr Justice Griffiths Williams
T20057640

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 26/06/2025

Before :

LADY JUSTICE MACUR DBE
SIR STEPHEN IRWIN
and
MR JUSTICE PICKEN

- -

Between :

COLIN CAMPBELL A.K.A NORRIS	**Appellant**
- and -	
THE KING	**Respondent**

- -
- -

Michael Mansfield KC and Nick Brown (instructed by **Birnberg Peirce**) for the **Appellant**
James Curtis KC and Sahil Sinha (instructed by **Crown Prosecution Service**) for the **Respondent**

Hearing dates: 6 to 9, 12 to 16, 20, 21 May; 3, 4 & 6 June 2025

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Approved Judgment

This judgment was handed down remotely at 10.30am on 26 June 2025 by circulation to the parties or their representatives by e-mail and by release to the National Archives.

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Macur LJ, Sir Stephen Irwin and Picken J:

Preamble:

We are aware that, in addition to Colin Campbell, his family and friends, and the families of Mrs Hall, Mrs Wilby, Mrs Ludlam, Mrs Bourke, Mrs Crookes and Mrs Dominique, and those patients who are referred to as 'extra' patients and identified only ever by initials herein, there will be other bystanders who have a general interest in the outcome of this appeal. Some observers have made clear in their applications to follow the proceedings by CVP that they seek to draw parallels between this case and other similar cases that may be ongoing. We make clear that we have each contributed to writing this judgment mindful of the necessity to explain the decision we reach, which has been dependent upon our view of an intricate debate between eminent scientists, by identifying the relevant issues and addressing them in terms of an appeal against conviction in the circumstances of this case. As we subsequently explain, we do not adjudicate upon the substance of medical disagreement by way of a civil judgment nor seek to substitute ourselves as members of a jury.

Introduction

1. On 3 March 2008, at the Crown Court sitting at Newcastle Upon Tyne (Mr Justice Griffith Williams and a jury), the appellant, then going by the name of Colin Norris, was convicted of four counts of murder and one of attempted murder. On 4 March 2008 he was sentenced in respect of the murders to life imprisonment with a minimum term of 30 years, less 166 days spent on remand and in respect of the attempted murder to a concurrent sentence of Imprisonment for Public Protection (IPP) with a minimum term of 20 years.

2. On 21 December 2009, this Court dismissed his appeal against conviction. (*R v Norris* [2009] EWCA Crim 2697). (See below.)

3. The appellant now goes by the name of Colin Campbell and appeals against conviction upon a reference by the Criminal Cases Review Commission ("the CCRC") pursuant to section 9 of the Criminal Appeal Act 1995. The decision to refer, supported by a statement of reasons, is dated 12 February 2021, and relied upon the expert reports of Professor Marks, instructed by the appellant, and Dr Croxson, instructed by the CCRC. That is, the reference was made based on 'new' evidence which is said to undermine the medical expert evidence led at trial on behalf of the prosecution. For reasons that will be explained below, Professor Marks is now replaced by Dr Hopkins as an expert witness for the appellant.

4. The appeal is opposed by the prosecution relying upon the further expert opinion they have received, including from witnesses who appeared at trial, Dr Kroker, Professor Ferner, Professor Hall and Professor Vanezis and additionally Professor Semple, Professor Heller, and Dr Cowling which has been led in rebuttal.

5. The appellant is represented by Mr Michael Mansfield KC and Mr Nick Brown. Mr James Curtis KC and Mr Sahil Sinha appear for the respondent prosecution. None of these counsel appeared at trial or the first appeal.

Delay

6. The substantial delay in listing this appeal has been unfortunate and despite the best efforts of this Court (Holroyde LJ, the Vice President presiding throughout the preliminary hearings to ensure continuity of case management), which has sought to give final directions for the substantive hearing of the appeal on several occasions since December 2022.

7. Draft Grounds of Appeal were prepared on 16 April 2021. The Respondent's Notice was filed on 30 June 2021, later supplemented by a further Respondent's Notice, dated 12 October 2022, in which the respondent challenged the proposed fresh evidence as meeting the criteria in section 23 of the Criminal Appeal 1968.

8. At a directions hearing on 15 December 2022, it became apparent that Professor Marks, the principal expert witness on whom the appellant wished to rely, was suffering from a terminal illness and would not be able to engage further in the appeal process. The hearing was adjourned to a date to be fixed in February 2023. Directions were given and the parties were urged to co-operate in relation to several matters which were not the subject of formal directions.

9. Further preliminary hearings were listed, sometimes adjourned and often frustrated by the necessity on the part of the appellant to identify an appropriate source of, and then commission, further expert evidence, the preparation of which was subsequently delayed.

10. Thereafter, the appellant made an application to amend the grounds of appeal against conviction pursuant to Criminal Procedure Rules 36.14(5), including to seek to include reference to other ("extra") patients in the Leeds teaching hospitals, who were not nursed by the appellant but who had been identified during the police investigation as suffering from hypoglycaemia, and for further disclosure of their medical records.

11. On 26 March 2024, the full Court (the Vice President, Picken J and Sir Stephen Irwin) heard the applications. The Court refused the application for disclosure which would occasion considerable further delay and which "as it seems to us, would serve no purpose." The ruling continued:

> "… We sympathise with the practical difficulties which have arisen on both sides, including, sadly, the deaths of an eminent expert witness on each side. But we have to balance that against the need to bring the appeal to a conclusion within a reasonable period of time. As we have previously observed, the appellant has a keen interest in knowing the outcome of his appeal; so, too, do the bereaved families of the victims."

12. Regrettably, further preliminary hearings were required and delay occasioned. In the three weeks preceding this hearing, which commenced on 6 May 2025, further applications were made by both the appellant and the respondent to adjourn the appeal which had been listed to hear evidence for three weeks and subsequent closing submissions over two days. It is unnecessary to detail the bases of those applications but only to record that this Court refused the applications. Suffice to say that, in the event, the appellant has continued to be represented by his counsel of choice, and the respondent's difficulty concerning the attendance of one of its expert witnesses has been accommodated.

Background facts in summary

13. The appellant qualified as a nurse in October 2001. On 8 June 2002 he took up a post on Ward 36 in Leeds General Infirmary ("LGI") and in September 2002 transferred to Ward 23 at St James' Hospital, Leeds ("SJH"). Ward 36 in LGI and Ward 23 in SJH were orthopaedic wards in which many elderly female patients had been admitted for, or were recovering from, surgery most commonly in relation to hip fractures and replacement.

14. On 11 December 2002, Mrs Ethel Hall ("EH"), a patient on Ward 36, died suddenly and unexpectedly of brain injury caused by hypoglycaemia. The death was determined to be suspicious. A retrospective review of other deaths on Ward 36 and Ward 23 revealed that four other elderly female patients had apparently suffered sudden, severe and unexplained hypoglycaemia that had been resistant to treatment by the administration of glucose or otherwise. These were Mrs Vera Wilby ("VW"), Mrs Doris Ludlam ("DL"), Mrs Bridget Bourke ("BB") and Mrs Irene Crookes ("IC").

15. Details of their relevant clinical history are referenced in greater detail below, but it is convenient to include a clinical pen picture of each at this stage which is derived from the summary of evidence given during the summing-up.

16. EH was 86 when admitted to LGI Ward 36 on 11 November 2002 after falling and fracturing her right hip. She had shown signs of mental confusion before and after her surgery. At approximately 5 am on 20 November 2002 she was found to be in a hypoglycaemic coma. She was treated with numerous doses of glucose until her blood sugar levels had returned to normal but remained in a coma and died three weeks later. An immunoassay and full forensic post-mortem examination ruled out all natural causes for hypoglycaemia or subsequent death. Ward records of pharmaceutical stores indicated that two vials of Actrapid insulin were in the fridge on Ward 36 "on the evening of 18 November 2002, which were missing at 6 am on 20 November 2002." The records could not explain their use in the meantime and the inference was drawn that someone on the night shift had used the insulin to inject EH.

17. VW was 90 on admission to Ward 36 for surgical repair of a fracture to the left hip. She was confused and incontinent. At approximately 10.30 pm on 17 May 2002, she was found in a hypoglycaemic state bordering on coma. VW's subsequent state was consistent with the administration of insulin by injection, or an anti-diabetic drug used for the control of diabetes. VW survived but died 8 months later of unrelated natural causes. Her body was cremated. (The appellant was charged with her attempted murder.)

18. DL was 80 on admission to Ward 36 on 14 April 2002 suffering from heart failure. She was discharged on 10 May 2002 but was re-admitted to hospital the following day. She was agitated and confused and was considered by staff to be a difficult and demanding patient. On 12 June 2002 she suffered a fall that caused a fracture to her left hip. She was transferred to Ward 36 at the LGI for surgery. At approximately 8 am on 25 June 2002 she was found in a hypoglycaemic coma. DL died on 27 June 2002. Her death was attributed to natural causes, stroke and cardiac failure, and her body was cremated.

19. BB was 88 on admission to Ward 36 on 16 June 2002 after falling and fracturing her right hip. She was in the ward at the same time as DL and VW. She was frail and

confused, with incoherent speech and incontinent. She had a history of strokes and of chronic subdural haemorrhage. On 1 July 2002 she was diagnosed with a serious and life-threatening bacterial infection which caused diarrhoea. She was prescribed a major tranquilliser and was noted to be agitated in the mornings. On 20 July 2002 she fell out of bed. At approximately 3 am on 21 July she was found to be in a hypoglycaemic coma from which she never recovered. She died just after midnight the following day. Her cause of death was certified as a stroke. Her body was buried but exhumed 14 months later for post-mortem examination.

20. IC was 79 on admission to Ward 23, SJS, after falling and fracturing her left hip. After surgery she was generally unwell. She had chronic obstructive pulmonary disease ("COPD") and was breathless on slight exertion and required oxygen. She could not walk unaided. She had a leaking surgical wound and was very thin and unkempt. At approximately 6 am on 19 October 2002 she was found to be deeply unconscious and in a hypoglycaemic coma. She died the following morning. Her death was attributed to natural causes, initially thought to be a stroke, but later certified as respiratory failure due to COPD. Her body was cremated.

21. The five patients shared certain common features in that: (i) they had been suffering from a number of chronic medical conditions and were in poor health; (ii) had nevertheless undergone surgery in respect of a fractured hip; (iii) had not suffered significant complications from the surgery; (iv) had presented with symptoms of dementia and confusion; and (v) did not have a history of diabetes mellitus or hypoglycaemia and had not been prescribed anti-diabetic drugs . All had been patients under the appellant's care.

Trial

22. The appellant was arrested. His subsequent trial lasted in the region of five months and included oral evidence from 132 live witnesses. Many other witness statements were read.

23. The prosecution case, which relied upon both scientific expert and circumstantial evidence, was unequivocally that there was no natural explanation for any of the five patients' hypoglycaemia and that they must have been given a massive exogenous administration of insulin or anti-diabetic agent. The brain damage caused by the hypoglycaemia was either the cause of, or a significant contribution to, the deaths of four of the patients, and but for the circumstances of VW as will be indicated below, would have led to her intended death.

24. It was said that the appellant was the common denominator in each incident and had been 'on shift' immediately before the critical time in each case. He had previously displayed a dislike and hostility towards elderly patients demonstrated by his insensitive and rude attitude towards them. He had predicted the collapse of EH in terms that "she might go off tonight at about 05:15" when speaking to his colleagues. The appellant had shown himself to be arrogant and manipulative. He was "over-confident" and did not heed advice despite his newly qualified status. He had been spoken to on several occasions by his supervisors in relation to incidents which had the potential to cause harm to patients, for example setting up saline drips that had infused too quickly. As part of his training, he would have administered insulin subcutaneously under supervision. Whilst working on Ward 36, he had prepared insulin for a diabetic patient

and had been aware of the different types of pharmaceutical insulin. However, in interview he had attempted to downplay this knowledge.

25. The appellant gave evidence and called evidence. He denied committing any unlawful or malicious act that was responsible for causing the five elderly women to enter hypoglycaemic coma. He said that he had provided proper nursing care to all. There were colleagues who, contrary to the prosecution case, described him as professional and competent with a nice manner with patients and that he taken criticism well. He could be outspoken but generally got along well with colleagues and patients of all ages. He denied that he had mentioned a dislike of nursing elderly patients, rather he had expressed a wish to do a greater variety of work. His knowledge of diabetes and insulin treatment remained basic, but he accepted that he had been trained in administering subcutaneous and intramuscular injections of morphine and insulin.

26. Defence experts suggested that there might be natural causes for the hypoglycaemia of VW, DL, BB and IC and that that hypoglycaemia might not have caused death or significantly contributed to it in the cases of DL, BB and IC. However, even if the prosecution proved an exogenous administration of a substance which caused hypoglycaemia and death or significantly contributed to it, the appellant denied that it was he who had administered it. There was another male nurse, JS, who could have been responsible for doing so. JS had personal knowledge of the effects of insulin for he was an insulin dependent diabetic and kept his own emergency supplies of Actrapid insulin and syringes at home. He (JS) had had mental health problems at the relevant time of the four deaths and one near death. JS only had an alibi for the relevant time concerning DL's death.

27. The judge identified and summarised the issues for the jury to be:

    i) Were they sure that in each case the victim had developed hypoglycaemia because of being injected with insulin;

    ii) In relation to EH, whether it was the appellant who had injected her with insulin;

    iii) Were they sure that hypoglycaemia caused or contributed significantly to the death of VW, DL, BB and IC;

    iv) If so, were they sure that it had been the appellant who had administered insulin or an anti-diabetic agent in each case, and, if so;

    v) Were they sure that he had intended to kill or cause really serious injury in the cases of EH; DL; BB and IC, and that in the case of VW he had intended to kill.

28. The appellant was convicted, by a majority of 11:1, on all counts.

First Appeal

29. An application for permission to appeal against conviction was referred to the full Court. There was a change of counsel for the appellant. Aikens LJ presided over the hearing. Leave to appeal was granted at the outset of the hearing. The perfected grounds of appeal raised three issues which centred upon cross-admissibility of evidence. It was argued that the judge failed adequately:

1. to direct the jury on the question of the cross-admissibility of the evidence of the separate deaths on the question of whether the deaths were proved to be as a result of the exogenous administration of insulin as opposed to a rare but recognised phenomenon of naturally occurring hypoglycaemia, and

2. to direct the jury on the question of the cross-admissibility of evidence on the issue of identity.

It was, further, submitted that the combined failures on grounds 1 and 2 meant that there was a failure to address how the cross-admissibility of evidence could support the different counts. The failure adequately to direct the jury on this issue was fundamental and rendered the applicant's conviction unsafe. The assistance given to the judge before the summing-up, it was suggested, was inadequate and failed to address the question of bad character following the admission of evidence under section 101(1) (a) of the Criminal Justice Act 2003.

30. We quote from other parts of the 2009 appeal judgment below, however, at this stage it suffices to record that the Court of Appeal in 2009 found:

> "74. …It is clear that the judge was careful, both at the outset of his summing up and when summarising the evidence in relation to each victim, to emphasise to the jury that it had to reach separate conclusions in relation to each victim on the question of the cause of the hypoglycaemia. The judge said that the jury had to decide whether they rejected the possibility that the hypoglycaemia was the result, in the case of each victim, of natural causes … the judge neither explicitly nor implicitly directed the jury that if they found that in one case the hypoglycaemia was the result of non – natural causes they could use that as supportive of such a conclusion in another case.
>
> …
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> 76. Was there a danger that the jury might use the evidence of Professor Ferner and Dr Kroker on the extreme unlikelihood of five cases of naturally occurring hypoglycaemia (in so short a time in two nearby hospitals) as supporting a conclusion that the cause of the hypoglycaemia in each of the five cases must therefore have been non – natural? Would such a line of reasoning have been wrong, and should the judge have made a more specific warning against it?
>
> 77. Clearly it cannot follow, either as a matter of logic or probability, that because it would be "extraordinary" to have five cases of hypoglycaemia resulting from natural causes in so small an area and so short a space of time, therefore it is evidence to demonstrate that it is either certain or more likely that all of the five cases were the result of non – natural causes. Such a line of reasoning would be wrong in terms of legal analysis and, we suspect, must also wrong in terms of scientific or probability analysis. It was not the conclusion that Professor Ferner or Dr

> Kroker was suggesting by their evidence. We are satisfied that each was simply indicating that, based on their experience, it would be quite extraordinary to have five cases of naturally occurring hypoglycaemia in the circumstances postulated by the defence.
>
> 78. The judge might have given a direction that warned the jury against the line of false reasoning set out in the paragraph above. He did not specifically do so, but approached the matter in another way and, we think, in a way that was more likely to ensure the jury did not take such a line of false reasoning. He reiterated, time and again, that the jury must decide, separately in each case, whether the jury could exclude natural causes for the hypoglycaemia. Only if they could, were they to go on and consider the issue of who was the administrator of the insulin or anti – diabetic drugs. In our view, the judge was wise to do this and not to put the possibility of the forbidden line of thinking into the minds of the jury at all. If, as we must assume they did, the jury dutifully followed the judge's directions on the issue of proof of the cause of hypoglycaemia in each case, then they could not have considered the particular evidence of Professor Ferner and Dr Kroker we have highlighted as supporting a conclusion that it therefore followed that in all five cases the cause of the hypoglycaemia must have been non – natural."

31. The appeal was dismissed, the judgment concluding:

> "90. We wish to repeat our sincere admiration for the way in which Griffith Williams J dealt with all the complex issues in this case, in particular the vast amount of scientific evidence, in his summing up to the jury. It was a tour de force."

32. We echo that accolade.

The CCRC decision

33. The CCRC received an application made on the appellant's behalf on 21 October 2011, supported by advice from leading counsel who had appeared on appeal, and a report from Professor Vincent Marks. On 1 September 2016 the CCRC notified the appellant of its decision that there was no real possibility that his conviction would be overturned and he was given until 2 January 2017 to respond to the CCRC's provisional Statement of Reasons. The appellant's solicitors responded on 3 January 2017. On 2 August 2019, the CCRC issued a second provisional Statement of Reasons refusing to make a referral. On 7 January 2020, the CCRC received and considered the appellant's response to the same and subsequently decided that there was a real possibility that the appellant's convictions would not be upheld and that it would therefore refer the case.

34. The decision to refer the cases was summarised by the CCRC in a "Summary to assist the Registrar" in these terms:

"The case against [the appellant] was wholly circumstantial, and was heavily reliant on expert opinion evidence. There was very little evidence specifically inculpating him in the murder of Mrs Hall, except insofar as it could be argued that, taken together, the cluster of cases pointed towards his involvement. …

The CCRC has decided to refer [the appellant's] convictions based on fresh expert evidence from Professor Vincent Marks (who was instructed by [the appellant's] representatives) and Dr Simon Croxson (whom the CCRC instructed).

Professor Marks and Dr Croxson do not agree on every point, but they agree that insofar as each of the four patients exhibited hypoglycaemia, that condition may be accounted for by natural causes. (As noted above, it was and is agreed that the fifth patient, Mrs Hall, was murdered.)

The CCRC recognises that the new material from Professor Marks and Dr Croxson is not capable of proving that [the appellant] did not administer insulin to one or more of the five patients. However, it appears to the CCRC that the following features of the new expert evidence supports a reference to the Court:

• Hypoglycaemia in the elderly and frail is much more common than was recognised at trial.

• The range of conditions recognised as risk factors for hypoglycaemia is significantly greater than was appreciated at trial.

• All four patients had a range of co-morbidities known to cause or be a factor in the development of spontaneous hypoglycaemia.

• Professor Marks, broadly supported by Dr Croxson, says that insofar as any of the four patients had hypoglycaemia, it may have arisen as an epiphenomenon of various co-morbidities.

• Dr Croxson says that it is unsafe to rely upon Point of Care Testing of glucose levels in the elderly, due to a phenomenon known as peripheral shutdown. As a result, one of the patients may not have had hypoglycaemia at all.

The CCRC considers that there is a real possibility that the Court will conclude, based on the new expert evidence, that [the appellant's] conviction for the murder / attempted murder of one or more of the four patients is unsafe. Further, it appears to the CCRC that the safety of the appellant's conviction for the murder of the fifth patient, Mrs Hall, depends on support from the other four cases, and that insofar as the new expert evidence calls into question the safety of one or more of those four convictions, the

> prosecution's assertion that no-one other than [the appellant] could have been responsible for the murder of Mrs Hall may be correspondingly less secure."

35. The CCRC decision is explained in greater detail in the Statement of Reasons which was served. The revised grounds of appeal, as permitted by the full Court on 26 March 2024, do not expand beyond the pertinent issues indicated above, save in discursive articulation, and are summarised below rather than reproduced in the narrative form in which they appear.

The grounds of appeal

36. The grounds of appeal assert that:

i) There is 'new' evidence which posits a plausible natural cause for the occurrence of the hypoglycaemia, if indeed present at all, in the case of each of the index patients;

ii) In the alternative, the new evidence in relation to the onset of hypoglycaemia, if caused by exogenous insulin, undermines the prosecution case as to when the insulin was administered and exculpates the appellant;

iii) Insofar as the new expert evidence calls into question the safety of one of the convictions in relation to VW, DL, BB and IC, it undermines the reliability of the prosecution expert evidence in relation to the three other patients;

iv) Insofar as the new expert evidence calls into question the safety of the convictions in relation to VW, DL, BB and IC, it undermines the safety of the appellant's conviction of the murder of EH given that the prosecution case cast the appellant as a "common denominator".

37. The appeal is pursued in terms that the new evidence is at the "frontier" of scientific knowledge and is "groundbreaking". Acknowledging the summing-up to have been "meticulous", nevertheless Mr Mansfield KC stated that the jury had been "left empty handed" and deprived of the benefit of the "evolution of understanding and knowledge about hypoglycaemia" as now advanced by Dr Hopkins and Dr Croxson which calls for "a holistic approach" to the symptomology and explains the possibility of natural causes to account for the hypoglycaemia.

Preliminary issues in the extant appeal

38. As we indicate above, the appellant had made an application to amend the grounds of appeal against conviction pursuant to Criminal Procedure Rules 36.14(5) to include reference to other patients who were not the subject of charges and for the associated and further disclosure of their medical records.

39. The Court heard the application on 26 March 2024 and refused the application for disclosure. The Court interpreted this proposed new ground of appeal as portending a "cluster" argument by asserting the incidence of several cases of sudden and severe hypoglycaemia occurring in elderly patients which were established not to have been caused by exogenous insulin" and ruled:

> "Just as the respondent cannot rely on the rarity of deaths from sudden, severe and unexplained hypoglycaemia, to use statistics as a diagnostic tool in order to prove that the appellant must have been responsible for one or more deaths, so the appellant cannot point to any evidence of greater frequency of such deaths in order to prove by statistics that the appellant was not responsible.
>
> Further, if the expert evidence establishes that the present state of medical knowledge is such that convictions in 2008 must now be regarded as unsafe, then the proposed new line of inquiry is unnecessary. If the expert evidence does not achieve that end, the proposed further inquiry cannot assist the appellant. The important issue is the state of medical learning on this topic generally, not a consideration of a small number of [patients] in Leeds."

40. Upon receipt of documents which indicated the key points of evidence to be adduced in chief by the appellant, filed in compliance with directions given by this Court on 24 November 2024, the respondent took exception to what the respondent characterised as the "latest in a series of attempts to insert these issues [that is the 'extra' cases over and above the index cases] into the court's consideration of this appeal". In the respondent's view, the March 2024 ruling disposed of the issue and this was an attempt to deploy an impermissible 'cluster argument' which would undermine the careful timetabling of the appeal hearing. The respondent accepted that the Court had directed a joint expert meeting to consider the extra cases. The unanimous consensus of the respondent experts was that the material was irrelevant. Consequently, the respondent filed an application dated 8 April 2025 seeking to exclude any such evidence from the appeal.

41. The agreed record of the second experts' meeting established that there were six patients, including Mrs Belinda Dominique ("BD"), which the appellant's experts considered to bear "sufficient similarities" to the index patients "to support the argument that natural phenomena could have been responsible for [their] observed hypoglycaemia". The respondent's experts considered there to be "significant differences between the two groups in regard to clinical circumstances, duration of hypoglycaemia and treatment required to correct the hypoglycaemia".

42. We considered the application on the papers. It appeared to us that there was substance in the written submission made on behalf of the appellant that: "Whilst the Court refused the claimant's application to amend the substantive grounds of appeal so as to include …the 'cluster phenomenon' the court did not rule that the evidence relating to the extra Leeds case was inadmissible in relation to the remaining grounds of appeal."

43. Consequently, we gave a provisional indication, as follows:

> "This indication is given without prejudice to any further oral argument which either side may wish to advance on 6.5.25 upon the respondent's application to excise reference to any evidence relating to the 'extra patients'.
>
> The Court notes, and endorses, that the "appellant does not rely upon these additional six cases for mounting a statistical or

> cluster argument, or to argue how common or how rare the phenomenon of sudden severe spontaneous hypoglycaemia is". (See Appellant's skeleton argument dated 24 April 2025 at paragraph 48)
>
> Subject to the indications given below, the Court is minded to hear evidence *de bene esse* regarding the dispute between the experts briefed on behalf of the appellant and respondent "as to whether and to what extent the other Leeds cases (a) are truly comparable to the four deceased and the two patients involved in the cases of attempted murder and (b) are truly comparable to cases appearing in the world literature." (See Directions 21.11.24 at paragraph 1.)
>
> The evidence will be confined to the 'extra patients' [ML], [MH], [EW] and [JW].
>
> The evidence relating to [BD] was led at trial. [LR] is patently differentiated by the prior diagnosis of type 2 diabetes.
>
> There will be no further disclosure of medical records.
>
> The evidence will be accommodated within the agreed witness timetable."

44. Neither side wished to advance further argument at the outset of the appeal and, therefore, the direction was finalised. We have heard evidence relating to three of the other cases, ML, MH and EW, as we describe below and were able to do so comfortably within the time frame.

45. Associated with the issue of the 'extra' patients, and in response to a request made by the appellant, the Court consisting of Holroyde LJ, VP, Sir Stephen Irwin and Picken J was "provided with, and has reviewed, all the notes sent by members of the jury during the trial", which had previously been returned to the Crown Court by the Court of Appeal Office following the first appeal. Two notes were disclosed, the Court being aware that "the relevance of these notes is a matter in issue between the parties."

46. The first was a note which was sent by the jury on the morning of 12 February 2008, which read: "The jury would like to ask council (sic)– if there had been any further episodes of sudden and profound hypoglycaemia, resulting in coma in non-diabetic patients, after 2002 in any of the Leeds reaching hospitals?"

47. The second, a note sent on 13 February which read in its entirety and with emphasis in the original: "The medical history of BD shows that she <u>is</u> a diet-controlled diabetic".

48. We have no reason to think that the judge did other than to follow the usual procedure upon receipt of the notes; that is, to discuss them with counsel and thereafter to respond accordingly and appropriately to the jury. No transcripts have been obtained of this part of the trial, and we therefore do not know explicitly what the response of either trial counsel was in discussion with the judge, or the exact terms of the subsequent answer given by the judge to the jury at the time. However, we do note that in the

summing-up, which commenced on 21 February 2008, some nine or 10 days later, the judge said:

> "You will recall your written request of Counsel. Neither has called any evidence, and so this is a matter which you can put out of your minds to ensure that you do not run the risk of speculating as to what evidence may or may not have been called."

49. We make clear at this point that we absolutely reject any suggestion, as appeared to be being made in cross-examination of some of the witnesses called by the respondent, that there was any issue of non-disclosure or concealment of any material relating to other patients.

50. The appellant's solicitor at trial has given a comprehensive and unequivocal response to questions asked of her by the CCRC in this regard. She could not remember the names of the extra patients that had been researched at this remove, although some of the names put to her by the CCRC, namely JW, MH, HO, EW and ML were familiar "but our files will have the full notes."

> "We had 90,000 (ninety thousand) pages of medical records. I had a caseworker, and sometimes two, working on those records throughout the life of the case. They were checked and re-checked, and various tasks pertained to those records. As I say above, all tasks were recorded, both in advance, and when completed, with evidence gathered."

51. Having regard to that information, we find that, for whatever reason, the decision made by leading and junior counsel for the defence at the time not to introduce the evidence before the jury was informed and irreproachable.

Hearing of appeal

52. Neither the appellant nor the respondent has sought to place transcripts of the expert evidence adduced at trial before us. Apparently therefore both the appellant and the respondent are content that the summing-up accurately encompasses a summary of each of the relevant expert's evidence. Accordingly, we have been vigilant in policing questions posed by both Mr Mansfield KC and Mr Curtis KC to those witnesses who gave evidence at trial, namely Dr Kroker, Professor Ferner and Professor Hall, about what they could remember saying about certain issues or whether certain topics were raised during the trial. It seemed to us that this was unfair to the witness and that any answers garnered would be unreliable in that it called for a feat of memory in relation to events 17 years ago.

53. The appellant produced a free-standing bundle of 'advice files' in relation to the four additional patients, namely ML, MH, EW and JW, which comprised documents and prosecution expert witness statements prepared in 2004 and 2005, including those of Professor Ferner and Dr Kroker. The documents give details of individual patient's antecedents and brief medical history, pertinent hospital admissions and extracts from the relevant witness statements in relation to pharmacology, toxicology, orthogeriatrics, histopathology, biochemistry and pathology.

54. Despite the case management direction that both appellant and respondent should produce all expert evidence upon which they intended to rely well in advance of this hearing, we have received further written reports from the respective expert witnesses who have given evidence before us during the appeal. This 'additional' written opinion was either (i) tendered by Dr Hopkins after hearing certain opinion evidence of the respondent expert witnesses; (ii) tendered by the respondent expert witnesses in response to such further reports or (iii) made in response to questions posed by the court at the conclusion of the witnesses' evidence. We regarded it appropriate to receive these additional reports and statements so to ensure our full understanding of the respective cases. Both sets of experts have also supplemented their additional reports by references to medical literature which was not previously mentioned.

55. Over the course of 12 days we heard evidence from Dr Hopkins, consultant physician and diabetologist and Dr Croxson, consultant geriatrician with an interest in diabetes, in support of the appeal; and Professor Heller, professor of clinical diabetes, Professor Semple, professor of translational molecular medicine, Dr Kroker, consultant physician and geriatrician, Professor Ferner, honorary consultant in general medicine and clinical pharmacology and Professor Hall, professor of clinical cardiology.

56. Other experts prepared reports for the appeal but were not required to be called for cross examination: Dr Cowling, consultant in microbiology and infection control, Dr Lumb, forensic pathologist, Dr Morley, consultant clinical pathologist and forensic toxicologist, Professor Vanezis, forensic pathologist and Dr du Plessis, consultant neuropathologist.

57. We have accepted the contents of reports filed as the evidence-in-chief of their author, save as amended or clarified by the author when giving evidence or by filing supplemental reports, and subject to what we have determined to be successful challenge during cross-examination.

The law relating to new evidence

58. Section 23 of the Criminal Appeal Act 1968 provides that:

> "Evidence
>
> (1) For the purposes of an appeal, or an application for leave to appeal, under this Part of this Act the Court of Appeal may, if they think it necessary or expedient in the interests of justice—
> …
>
> (c) receive any evidence which was not adduced in the proceedings from which the appeal lies.
>
> (2) The Court of Appeal shall, in considering whether to receive any evidence, have regard in particular to—
>
> (a) whether the evidence appears to the Court to be capable of belief;
>
> (b) whether it appears to the Court that the evidence may afford any ground for allowing the appeal;

> (c) whether the evidence would have been admissible in the proceedings from which the appeal lies on an issue which is the subject of the appeal; and
>
> (d) whether there is a reasonable explanation for the failure to adduce the evidence in those proceedings."

59. The considerations listed in section 23 (2)(a) to (d) are neither exhaustive nor conclusive, but they require specific attention: see *In R v. Erskine; R v. Williams* [2009] EWCA Crim 1425; [2009] 2 Cr. App. R. 29 at [39].

60. There is no question in our minds but that all the witnesses who have given evidence before us have done so conscientiously and mindful of an expert's duty owed to the Court. The evidence of Dr Hopkins and Dr Croxson is certainly 'capable of belief'. As Professor Semple said in cross-examination: "I find my colleagues' evidence to be learned and interesting and physiological. Again, it is about the weights and the demarcation of probabilities." The evidence of Dr Hopkins and Dr Croxson would have been admissible at trial.

61. As indicated above, we are satisfied, and bear in mind, that the evidence relating to the 'extra' patients was available to the defence and was, it appears to us, deliberately not utilised at trial save for the case of BD, despite the prompt of the jury question to which we have made reference. Nevertheless, we are satisfied that our consideration of Dr Hopkins' hypothesis for the causation of the severe, sudden and profound glycaemia, which is supported by Dr Croxson, regenerates this evidence in a specific fashion; that is, in the reliance that Dr Hopkins and Dr Croxson place upon it as support for the hypothesis they postulate, and not by reason of any surreptitious "cluster argument".

62. Whether the combination of that evidence provides any ground for allowing the appeal is an issue that we address below. Prior to conducting that analysis, we concluded that the evidence of Dr Hopkins and Dr Croxson prima facie may afford a ground for allowing the appeal: see section 23(2)(b) and *Lundy v. The Queen* [2013] UKPC 28 at [120.]. We were not prepared to assume from our reading of their several reports, that the 'new' evidence was "analogous to a re-packaging of evidence that was before the jury and cannot be said to present a compelling new perspective.": see *R v Kai-Whitewind* [2005] EWCA Crim 1092; [2005] 2 Cr. App. R. 31 at [97]. Despite the urgings of Mr Curtis KC and Mr Sinha to refuse to receive the fresh evidence, we determine that it was just and expedient to have the expert opinion for and against the new hypothesis tested before us.

63. Equally, we have regarded it to be just and expedient to receive the evidence of the respondent's experts called in rebuttal. We reject the bland assertion made in an otherwise unparticularised closing submission in this regard, as made by Mr Mansfield KC and Mr Brown, that the respondent now seeks to advance an entirely new basis for a conviction which was never put before the jury: see *R v Fitzgerald (Mark Wayne)* [2006] EWCA Crim 1655 at [34] and [35]. Undoubtedly, the prosecution case at trial as summed up to the jury was that there was no natural cause to explain each of the relevant index patient's clinical presentation of hypoglycaemia; to the contrary, the course of the hypoglycaemia and its response to treatment mirrored that of known cases of exogenous insulin administration. It remained the same in the 2009 appeal as it did before us.

64. However, the admission of new evidence does not determine the appeal. It is for this Court to determine "whether the conviction is safe and not whether the accused is guilty": see *R v Pendleton* [2001] UKHL 66; [2002] 1 WLR 72 at [19]. The question is not what the effect of the new hypothesis may have had upon the jury. The responsibility for deciding whether the new evidence renders a conviction unsafe is for this Court: see *Dial and another v Trinidad and Tobago* [2005] UKPC 4; [2005] 1 WLR 1660 at [31]; *R v. Mushtaq Ahmed* [2010] EWCA Crim 2899 at [24]]; *R v Park* [2020] EWCA Crim 589 at [175].

Medical issues

65. The medical issue raised at trial, on appeal in 2009 and in 2025 can be stated quite simply: when and in what circumstances is it proper to infer poisoning by an overdose of injected insulin, as opposed to severe hypoglycaemia arising from natural causes?

66. All the experts are agreed that there is only one route to absolute certainty of insulin poisoning: where high levels of insulin are found in the bloodstream, with no corresponding levels of a substance known as c-peptide, then the insulin in that blood is manufactured (exogenous) rather than naturally arising (endogenous).

67. The relevant blood tests were not performed at a time which would establish conclusively whether VW, DL, BB, and IC had been victims of malpractice. Initially, the cause of their deaths was attributed to natural causes, and the issue was only revisited following the discovery of EH's predicament. In the three 'extra' cases of MH, EW and JW, the blood tests were conducted and showed that the insulin in their blood was endogenously produced.

68. As we have indicated above, the experts called by the appellant say that these 'extra' patients otherwise demonstrate a similar presentation, signs and symptoms to those of VW, DL, BB and IC which corroborates the hypothesis which they advance; namely, that frailty and self-neglect or lack of self-awareness in old age, in the context of a combination of comorbidities reflecting the bodies depleting hepatic, renal, pulmonary and cardiac reserves may give rise to sudden and severe hypoglycaemia.

69. The experts called by the respondent disagree that the 'extra' patients provide a genuine comparison with the index patients. They contend that the 'extra' patients all suffered from distinct conditions recognised to make them vulnerable to severe hypoglycaemia and all apparently responded to glucose therapy. Their presentation was entirely consistent with natural hypoglycaemia unlike that in the trial cases.

70. Regardless of the absence of immunoassay, the index patients presented with sudden, severe, profound hypoglycaemia which, significantly, was not responsive to glucose therapy. This was a critical and distinguishing feature. Their presentation mirrored that of known exogenous insulin overdose (whether accidental or deliberate). Naturally occurring hypoglycaemia which is recognised to occur in cases of self-neglect and inherently depleting bodily function in the old and frail, was easily countered, often by a cup of "milky tea and a biscuit".

Our approach to the evidence

71. As we indicate in the preamble to this judgment, this appeal is neither a civil dispute, nor a trial at first instance. There is no complaint that the summing-up failed to summarise the copious evidence, fairly and in considerable detail, to the jury. We do not attempt to recite or summarise all the thousand plus pages of reports, and numerous papers in the medical literature to which they refer and which we have read, or the very extensive oral evidence called before us. As we indicate below, the two joint expert meetings directed by this Court succeeded in narrowing the issues and clearly identifying the scientific debate. We focus only on the critical points, and on establishing the context necessary for comprehension of the critical points, to address this appeal and to render an accessible judgment.

The system in health

72. We begin by summarising the agreed evidence as to how insulin operates within the healthy body, to maintain an adequate supply of glucose to the tissues, without causing or permitting either excessively high blood glucose or excessively low blood glucose.

73. Glucose is the principal fuel of the body. The body regulates the delivery of glucose to the cells, so that there is enough for proper functioning, but not too much. Insulin is key to the maintenance of that balance.

74. The principal source of glucose in the body is the ingestion of food. The body absorbs carbohydrates, compounds of carbon, hydrogen and oxygen. Carbohydrates take many forms: sugars, starches and fibres. Digestion breaks down such foods and glucose is released into the bloodstream. The cells in the body require to utilise sufficient glucose but not too much; the need for glucose is continuous, whereas the ingestion of food is episodic. The circulation of blood delivers glucose to the cells. The body strives to achieve a balance between too little glucose in the bloodstream, and thus too little delivered to the cells (hypoglycaemia), or too much glucose in the bloodstream (hyperglycaemia).

75. Insulin is a hormone produced by specialised cells ('Beta' or islet cells) in the pancreas, a large organ located in the abdomen behind the stomach. When the level of glucose in the bloodstream rises to around 4/4.5 mmol/L (millimoles per litre), the pancreas secretes insulin. Naturally produced ('endogenous') insulin breaks down into two molecules, one molecule of insulin and one molecule of a different and inactive substance termed 'C-peptide'. Once released, insulin promotes the absorption of 'excess' glucose in the bloodstream into the cells of the liver, muscle and fat, storing the glucose for future use, but also preventing hyperglycaemia. The stored glucose in the liver and the muscles takes the form of a starch termed "glycogen".

76. The body releases stored glucose to raise the blood sugar when it is needed. The pancreas secretes glucagon, another hormone. However, the process of release of glucagon is inhibited by the presence of insulin in the bloodstream. When the glucose in the bloodstream falls below around 4/4.5 mmol/L, the secretion of insulin by the pancreas ceases. Glucose in the bloodstream is no longer 'pushed' into 'storage' by the insulin, and the release of glucose into the bloodstream from the 'stores' in the liver is no longer inhibited by the presence of insulin. Glucagon takes over to stimulate the liver to release its stores of glycogen. Thus, a natural balance is achieved, and the body avoids hypoglycaemia. As Dr Hopkins for the appellant put it in evidence before us, "glucose is kept in a very narrow physiological range throughout life … because the

human body has evolved to maintain this, glucose has a key role in metabolism of all the tissues in the body".

77. When required, in addition to the release of glycogen, the liver and to a lesser extent the kidneys, can operate to reconstitute and release glucose into the bloodstream by breaking down fat and, if necessary, muscle. This process is termed 'gluconeogenesis'. Thus, if need be, the body can call on reserves beyond the stored glycogen.

Injected insulin and diabetes

78. The body's self- regulatory system is disrupted in those with diabetes. Those suffering from the form of diabetes known as Type II diabetes, commonly arising in middle age or beyond, develop resistance to insulin. Hence even if the pancreas is producing what would otherwise be adequate quantities of insulin, it is not fully effective, and the result is a degree of hyperglycaemia. There is a natural variation in the extent of the disorder amongst those suffering with Type II diabetics.

79. Those suffering from the less common form of the disorder known as Type I diabetes have a pancreas which has ceased to produce insulin. This form of diabetes is thought to be an auto-immune disorder, commonly arising in younger people and arising more suddenly. Artificial or exogenous insulin is almost always required to treat Type 1 diabetics and may be required for sufferers of Type II. Injectable insulin is held routinely in hospitals (as in this case) because of the high prevalence of diabetes, especially amongst those in later life.

80. Inevitably, injecting exogenous insulin, even with care, and spread over a number of times a day, is a much less finely calibrated and responsive process than the natural system we have summarised above. Instead of a natural balance maintained by the sensitive, hormonally controlled system of the body, the decision as to how much insulin should be injected must be reached by considering how much glucose will be needed, what food is being consumed, how much energy is expended and so forth, and the room for error is considerable. All the experts agree that accidental insulin overdose in diabetics is commonplace, and the incidence of self-harm by the use of injectable insulin well-recognised.

The first experts' meeting: identifying the issues upon which the experts agree and disagree

81. After exchange of their initial reports, the experts, or as many of them as available, met on two occasions as directed by the Court.

82. On 24 September 2024 the experts discussed generic issues and the index Cases. The key points can be summarised as follows:

(1) VW, BB, IC and EH suffered "sudden severe hypoglycaemia". Dr Hopkins and Dr Croxson, doubted whether DL did so, challenging the Point of Contact ('POCT') method of testing the level of blood sugar (that is, obtaining a small quantity of blood usually by finger prick) in a patient with low blood pressure, peripheral oedema and peripheral shutdown. The other experts disagreed, citing the large number of consistent test results, not all of which were conducted when DL was subsisting under those conditions.

(2) Sudden severe hypoglycaemia was more widely recognized in 2024 than in 2008. Dr Hopkins and Dr Croxson considered that "there has been a greater recognition of the occurrence of hypoglycaemia outside of the context of diabetes, but it was noted that most epidemiological studies the observed hypoglycaemia has been mild rather than severe. There have been case reports of more severe hypoglycaemia in the context of comorbidities.". The other experts disagreed, saying that there was no wider recognition of such a phenomenon other than in patients treated with insulin or other drugs given to lower the blood glucose.

(3) All agreed that over the same period there has been a greater recognition of mild hypoglycaemia because of more frequent testing in hospital or care home settings and the increase in the prevalence of diabetes.

(4) All agreed that knowledge of sudden severe hypoglycaemia has not materially changed since 2008.

(5) All agreed that the analysis of the five index cases is not materially changed by the epidemiological studies of hypoglycaemia in frail and elderly patients referred to in their expert reports by the appellant's experts.

(6) All agreed that exogenous insulin brought about the death of EH.

(7) All agreed the clinical data in the five cases (although there were some later adjustments to the detail).

(8) All agreed that all five index patients were elderly and frail women who had fractured the neck of a femur and had co-morbidities of various kinds. Despite their age and frailty, it was proper to proceed to surgery, since the risks of conservative treatment in such a case were very high. Dr Hopkins and Dr Croxson emphasised that these patients would not have been regarded as fit for any elective surgery. All agreed that all these patients were at risk of many complications in the post-operative period.

(9) All agreed that the onset of severe hypoglycaemia was sudden and without prior warning in all these cases, save in respect of VW where Dr Hopkins and Dr Croxson questioned the timing of the onset of hypoglycaemia.

(10) In a specific answer in relation to all five index cases the following was recorded: "All the experts …agree that the hypoglycaemia was refractory, returning over many hours, despite frequent, substantial and repeated doses of glucose, intravenously and by infusion. By contrast, spontaneous hypoglycaemia in non-diabetic patients is usually reversed by a single dose of glucose followed, if necessary, by intravenous glucose infusion." An 'Agreed Record' was prepared and signed by the participants. For logistical reasons Professor Semple was unable to sign the record of the first meeting but later agreed the contents. However, when cross-examined on this section and despite his signed agreement, Dr Hopkins expressed his dissent from this passage.

(11) All agreed that sudden severe hypoglycaemia, requiring prolonged resuscitation including multiple doses of concentrated intravenous glucose, in elderly ladies following operative repair of fractured necks of femur, in the context of frailty and various co-morbidities, are recognised in patients who have received insulin or insulin

inducing drugs, and in patients with fulminant liver failure or in patients with cardiogenic shock.

The second experts' meeting: the 'extra' cases

83. On 5 December 2024, the experts, other than Dr Kroker, met again by video link to discuss the cases of 23 patients who had been diagnosed as suffering from hypoglycaemia at or near the point of their death and which cohort had previously been identified by the police investigation for analysis by the prosecution experts before the trial. All experts agreed that there was sufficient documentation available to make valid judgements on the facts and to enable comparison with the index cases. Following discussion, Dr Hopkins and Dr Croxson considered that there were six 'extra' patients whose cases were comparable to those of the index patients. These were significant in that they were patients who had not been nursed by the appellant, and, in some cases, whose hypoglycaemia was conclusively established to have been hypoglycaemic due to natural causes.

84. We indicated above the ruling we made in relation to this additional cohort of patients. In fact, we need only summarise the discussion in relation to three 'extra' cases, namely MH, ML and EW as Mr Mansfield KC and Mr Brown no longer maintain that JW presents a valid comparison.

85. The experts agreed that MH suffered severe hypoglycaemia of sudden onset. It was also agreed she had severely abnormal liver enzymes, a marker of liver dysfunction. The respondent's experts noted her severe liver impairment as the likely cause of her hypoglycaemia and noted her rapid response to glucose treatment. Dr Hopkins and Dr Croxson argue that since MH died 3 hours after the hypoglycaemic episode it "makes it impossible to know if the initial glucose treatment would have been sufficient had she lived longer" and thus that her case merits comparison with the trial cases.

86. It was agreed that ML was hypoglycaemic on admission to hospital and had a further, more severe episode of hypoglycaemia in hospital. She had a history of gastric surgery, use of high dose corticosteroids and chronic liver damage, which it was agreed were potential causes or contributions to hypoglycaemia. The experts called by the respondent noted also that, when the low blood sugar recurred, it was relatively easy to correct. Drs Hopkins and Croxson agreed with the "potential causes" of hypoglycaemia but maintained their view that this case forms a valid comparison with the trial cases.

87. In the case of EW, she too had been hypoglycaemic on admission and experienced a further episode in hospital. The experts called by the respondent considered that the amount of glucose required to correct hypoglycaemia on each of these occasions was significantly less than in the trial cases and was not comparable. Dr Hopkins and Dr Croxson maintained that the case is comparable as "part of a spectrum including some of the trial cases".

The accepted causes of hypoglycaemia, other than poisoning

88. It is agreed that there are well established causes of severe hypoglycaemia: diseases or disorders which affect the functioning of the liver or the kidneys, including cardiogenic shock (a very serious heart failure) leading to such poor circulation that the liver or the kidneys become congested or otherwise cannot function; primary failure of liver or

kidney function; widespread cancer in its final stages as it "hoover[s] up" glucose; septicaemia, or blood borne infection. These are all persisting conditions. Hypoglycaemia is a product of these conditions, rather than the cause.

89. Insulinoma, Insulin Auto- immune Syndrome ("IAS") and tumours secreting 'IGF' (insulin growth factor) which gives rise to hypoglycaemia are exceedingly rare and out with the clinical experience of any of the experts who gave evidence before us. There is no direct evidence suggesting that any of the index patients suffered from one of these disorders.

90. Other than the very rare conditions (insulinoma, IAS and IGF) where the problem is caused by additional insulin being released into the bloodstream other than from the pancreas, the problem in all these cases is not excessive insulin, but a failure to release glucose. In the opinion of the experts called by the respondent, the consequential hypoglycaemia is relatively easily resolved by treating with glucose, although the underlying conditions will continue, and it follows logically, may give rise to further episodes.

Severe hypoglycaemia as an effect of age, frailty and the 'co-morbidities': the appellant's proposition

91. Notably, Dr Hopkins and Dr Croxson agree that EH did develop, and that all four of the other index cases may have developed, hypoglycaemia because of injected insulin. The questions they were asked by the CCRC require them to do no more than question that conclusion, which they do with some difference of emphasis across the four cases.

92. Dr Croxson and Dr Hopkins both accept that sudden, severe hypoglycaemia in elderly/frail people, in the absence of either exogenous insulin (or, theoretically, insulin inducing drugs) or the specific illnesses identified as leading to such, is rare. However, as indicated above, their proposition is that severe hypoglycaemia can arise in elderly patients, in the absence of those specific conditions, from a combination of general frailty and some of the range of disorders or diseases of age: termed the 'co-morbidities' as shorthand deployed during the hearing of the appeal. The proposition is that age and frailty can lead gradually to a 'tipping point' where the body's control of glucose and insulin fails. There is a spectrum of such a situation, and in the absence of a confirmatory immunoassay, there is room for doubt as to cause by exogenous administration of insulin.

93. In their closing submissions, Mr Mansfield KC and Mr Brown summarised the proposition in this way:

> "78 In the elderly and frail and those who are unwell and have particular co-morbidities, the automatic counter-regulatory systems which each of us have can be affected in a number of ways:
>
> (a) As a result of the ageing process, all of the organs which play in the automatic counter-regulatory systems which prevent hypoglycaemia become gradually impaired until the point when, as a result of the aging process and increasing frailty, multiple systems may be failing in an individual patient.

(b) Impairment of the liver may affect and reduce the ability of the liver to produce and store glucose.

(c) Impairment of the kidney may affect and reduce the ability of the kidney to produce and store glucose.

(d) Impairment of the kidney may affect and reduce the ability of the kidney to clear endogenous insulin.

(e) If the patient has longstanding poor nutrition, their ability to produce and store glucose may be substantially reduced.

(f) There is likely to be some attenuation of the normal hormonal responses to low blood glucose levels.

(g) Particular co-morbidities, for instance, infection falling short of sepsis, will increase the individual's body's demand for glucose.

(h) Particular co-morbidities, such as hypotension and heart failure will reduce the blood flow through the liver and the kidney and reduce liver and kidney function."

The respondent's rebuttal

94. The experts called by the respondent reject the hypothesis advanced by Dr Hopkins and Dr Croxson to account for the nature of the hypoglycaemia observed in the index patients. They have no clinical experience of such a case. They have never seen it documented. They do not accept that it arises in the literature. They do not see why it should be so. With some small differences of emphasis, they find nothing in the analysis of the index cases or the extra cases to persuade them that it exists.

95. The respondent's experts do accept that frail, elderly people can sometimes develop hypoglycaemia, because of the gradual decline of the body with age, through a number of causes. But, in the absence of the known conditions radically disrupting the functions of the pancreas, the liver and the kidneys (the organs critical to maintaining an adequate supply of glucose to the tissues), their view is that such hypoglycaemia will be of gradual onset, usually mild and will not be profound (in that it will not usually impact on consciousness) and that the hypoglycaemia (as distinct from any underlying condition) will be responsive rather than refractory to treatment. Even where severe hypoglycaemia does develop from acute liver or kidney failure, from septicaemia, from advanced tumour, or from serious heart failure leading to congestion of the liver, the hypoglycaemia is readily, or fairly readily, corrected.

96. Conversely, the pattern of 'sudden' (spontaneous/ unexpected/without obvious natural cause), 'severe' (blood glucose reading below 2 mmol: L) and 'profound' hypoglycaemia (associated with unconsciousness or reduced consciousness), and 'refractory' to treatment (requiring large and repeated infusions of glucose), is the typical pattern observed and anticipated in cases of insulin poisoning. These elements were termed the 'phenomena' as shorthand deployed during the hearing of the appeal.

97. One passage in Dr Kroker's evidence captures the rejection of the appellant's proposition most vividly.

> "Q. All right. The scenario is, … an approach which combines ageing, frailty, dementia, eating, nutrition, with comorbidities as a scenario to explain severe hypoglycaemia. Have you understood that...Do you accept that possibility?
>
> A. No.
>
> Q. No?
>
> A. I know that's a very sharp 'No', but … I believe all physiological phenomena will have an explanation. And for the carbohydrate metabolism, we have been for 120 years, worked out virtually all little details of this particular thing. So, the moment you basically depart from this path, you have to follow the same principle. If you tell me that frailty causes hypoglycaemia then I would like to know, why? What is the cause? It is not so that you can use a very fuzzy term which describes a group of people, patients, and link it to something with a specific link. You have to explain why this vulnerable group of elderly patients who we call frail is prone to some type of hypoglycaemia. That I would accept. But I would not accept to say frailty causes hypoglycaemia."

98. There are two critical issues which arise from the evidence on this key issue. Firstly, the degree of rarity of such cases as the appellant proposes would arise in the geriatric community. Secondly, the patterns of presentation which arise, and would logically be expected to arise, in natural cause hypoglycaemia on the one hand, and insulin poisoning on the other.

Rarity?

99. Developing their submissions in their opening and closing addresses, Mr Mansfield KC and Mr Brown have suggested that the prosecution relied upon the 'rarity' of the cases of such hypoglycaemia at trial, and that the experts called on their behalf continue to do so, contrary to the judgment of this Court in 2009 and the ruling made on 26 March 2024 as indicated above; the "forbidden fallacy".

100. We reject this argument, as did this Court in 2009: see paragraphs [77] and [78] of the 2009 judgment reproduced in [30] herein.

101. It was that point which was reinforced in the ruling of 26 March 2024. There is nothing illogical or improper in considering whether the scenario advanced by the appellant is commonplace, rare or vanishingly rare.

Rarity – expert experience

102. Dr Hopkins is a consultant in general medicine. He sees a broad range of medical emergencies. He is not a specialist in 'orthogeriatrics', care of those elderly patients with a series orthopaedic problem of which a classic example is a broken neck of the

femur. He has a special interest in diabetes. He has specialised in diabetes since 1991 in Liverpool, London and now, Jersey. He agrees that cases whereby frail elderly patients acquire severe hypoglycaemia that is "unexpected, severe, coma associated and refractory" arise "very infrequently". He could call to mind "[an] example from my own experience of hypoglycaemia, which are difficult to explain exact causes, but are associated with multiple morbidity. Most recent case I have seen was a blood glucose of 1.9 millimole per litre, associated with altered consciousness in a person with underlying heart failure and no relevant treatment with further episodes of glucose that were on the low side to a lesser degree, [that is], around the three mark. But with subsequent recovery after effective treatment for heart failure. Again, a situation which where there are parallels in terms of the presence of a very low blood glucose would clearly impact on cognition."

103. In oral evidence he suggested that cases of "severe" hypoglycaemia were "not regularly seen, but not unknown in routine clinical practice, to the extent that most practitioners with an interest will see an occasional case of hypoglycaemia that would fit the definition of "'severe' … these cases do occur and probably occur more frequently than is actually recognised."

104. In another passage, Dr Hopkins gave an example where he linked the underlying cause of hypoglycaemia to the need for extended treatment:

> "Certainly, in the context of certain specific natural phenomena that defines the cause of hypoglycaemia, it is not uncommon to give quite significant and prolonged courses of glucose. One specific example, if I may give it, in the context of adrenaline sufficiency – this is patients whose adrenal gland and(?) steroid hormones fail for natural reasons in some cases. These patients can occasionally present with hypoglycaemia that can be profound and meet the definition of 'severity' – and indeed I've seen that. But even after treating the underlying cause, which is a deficiency of steroid hormone, by giving steroid, it may take 12 hours or more of continuous glucose infusion to maintain steady state glucose, without support. So, there are many circumstances where there is underlying physiological defence, where ongoing support with glucose is required. Thus, this concept of refractory by needing more prolonged treatment is not a specific indicator of any one pathology."

105. Dr Croxson has had a longstanding interest in the elderly diabetic person, and in addition to his clinical experience he has been awarded an MD for his work and writing in that field. From 1994 to 2016 when he left clinical practice, he was a consultant physician in Bristol, with a special interest in general, geriatric and diabetic medicine. He was "very much a hands-on clinician" focussed on the frail elderly.

106. In his report, dated May/June 2017 he stated:

> "Perhaps my clinical experience might be useful; I worked for 36 years on NHS medical wards and have a good memory for interesting patients and have always been interested in the glucose levels. I have seen several people with mild

> hypoglycaemia not due to anti-diabetic drugs, but we are not really interested in them. I saw one patient in 1980 in Weymouth with severe hypoglycaemia masquerading as loss of consciousness due to a stroke, who had hypoglycaemia due to a malignant tumour. I saw a second person in Merthyr Tydfil with the same problem. I may have seen a third person since then, but I cannot recall a third person; but for the sake of argument, say there was. In 36 years, I saw 3 people with significant hypoglycaemia, giving me a chance each year of 1 in 12 of seeing such a case …".

107. Significantly, we note that Dr Hopkins and Dr Croxson do not appear to have experience of cases fulfilling the phenomena and arising from a combination of the general 'co-morbidities' of age. Dr Hopkins has provided examples of heart failure, albeit which responded to treatment, and kidney failure (adrenal insufficiency). Severe heart failure is one of the identified causes of severe hypoglycaemia, as is kidney failure. Nor does Dr Hopkins indicate that the hypoglycaemia (as opposed to the underlying disease) was difficult to correct. In both definite examples given by Dr Croxson, the hypoglycaemia arose from malignancy. None of the examples provided by either Dr Hopkins or Dr Croxson was 'sudden' (see [97] above).

108. The experts called by the respondent have never encountered such a 'co-morbidity' case.

109. Professor Heller is in full time clinical practice and holds a chair in clinical diabetes. He too has a special interest in hypoglycaemia. His clearly expressed view is that he would not expect a case of sudden severe hypoglycaemia without a sudden dramatic cause, and he has not seen it.

110. Professor Semple has more than 20 years' experience of caring for the elderly as well as a specialist interest in diabetes, endocrinology and the mechanisms of glucose regulation in the body. He has served as deputy chief editor of the European Journal of Endocrinology for the last six years. His evidence on this point was: "I have thought very hard and trawled my memory banks, as it were, and outside the context of treatment for diabetes I have never seen that constellation of sudden onset profundity and above all requirement for a sustained treatment with very high doses of glucose."

111. Dr Kroker has been a consultant physician at the Chelsea and Westminster Hospital since 1997, seeing all patients arriving on the ward and with a very high number of elderly orthopaedic patients such as the index and 'extra' cases. He sees around 200 elderly hip fracture patients a year. He has only seen blood sugars as low as those we are considering in "patients who are riddled with metastases, have large cancers. But otherwise, … in patients who have been on insulin for diabetes. Otherwise, I have never seen that." He has never seen the combination of phenomena in a patient with natural causes:

> "… I mean, there's one important thing to realise. If you have a patient who is incredibly unwell, in intensive care and I have been in intensive care myself for two years as a doctor then you need approximately 3 to 5 gms of glucose in someone's whose liver and whose kidney and whose lungs are severely

> diseased and basically hardly function to maintain normal glucose levels. So approximately 120 gms in these very, very unwell patients are sufficient to maintain their glucose and to maintain their neurological integrity.
>
> If you have a circumstance in which you need now suddenly very much more in the way of glucose substitution, then the only physiological explanation I'm aware of is that the cells are taking glucose in a way that it is not physiological. That means there is a constant effect of insulin opening the cell gates to take in glucose. So, this circumstance in which you see a huge amount of glucose which you need to restore blood glucose levels, that is only something in these cases I can explain with maximum effect of insulin.
>
> And the real issue is here that our physiology is very robust. If our blood sugar level goes low, our endogenous insulin secretion stops. So, if you then have a situation in which you give far more glucose than you actually need normally in a patient who is very severely ill and can't produce their own endogenous glucose as a reserve, then the only explanation from my physiological understanding of the process is that there's on going insulin effect. And that's the problem I have with these four index cases. This particular pattern is not something I have either seen before or after in any of my orthopaedic patients."

112. Professor Ferner was a consultant physician and professor of clinical pharmacology, in position as a consultant on the ward from 1990 until 2020. He cared for many known exogenous insulin poisoned patients, but none where there were the five phenomena arising from the negative bodily effects of old age and frailty.

113. Professor Hall has been a consultant cardiologist and consultant physician in practice for more than 40 years. He has dealt with many cases of sepsis, renal failure and liver failure, as well as cardiac failure and cardiogenic shock. He defers to the experts in hypoglycaemia as to the causes of 'spontaneous hypoglycaemia', but he cannot "recall seeing in the clinical context" a case of severe spontaneous hypoglycaemia sufficient to cause "marked symptoms".

Rarity – the literature

114. Early in his evidence, Dr Hopkins accepted that changes in recognition that severe hypoglycaemia can occur outside the context of diabetes, was not new:

> ".. as I said, there are case reports in the literature that predate the time of the trial. There have been occasional cases reported since. Certainly, in terms of the epidemiological aspects of this and recognition of hypoglycaemia in the elderly, there has been more publication since. So, it's a continuum, basically. As time goes on, the amount of evidence increases and has gradually increased since the time of the original trial."

Nevertheless, all the medical literature to which he referred us in this regard, except for one case study, pre-date the trial in 2008.

115. A paper published by Hedayati and another in 1977 reported upon 11 cases of spontaneous hypoglycaemia in congestive heart failure in adults, ranging from 15 to 65 years old treated in Iran. There was a range of causes for the heart failure. The mechanism of hypoglycaemia was discussed and was "thought to be a combination of liver dysfunction, low calorie intake, malabsorption, and increased glucose utilization by ischaemic tissues, including the heart". In each case the hypoglycaemia was associated with congestive heart failure. All the patients "had symptoms and signs of advanced congestive heart failure, longstanding passive liver congestion, possible cardiac cirrhosis and malnutrition".

116. In 1992 a letter published by Drah and Ghose reported upon a single case of an elderly patient who was admitted to hospital with longstanding heart failure due to ischaemic heart disease, with atrial fibrillation and comatose. He was peripherally cyanosed, with extremely low blood pressure (60/40mmHg). He was also significantly hypoglycaemic, and he remained hypoglycaemic for four days before he died, despite active treatment. He showed signs of poor nutrition. On autopsy he was found to have an enlarged heart with widespread coronary atheroma. His liver showed severe congestion and central necrosis (dead tissue). The authors linked their findings to an earlier paper (Mellinkoff and Tumulty 1952) where the cause of hypoglycaemia was said to be chronic liver congestion due to heart failure

117. Shilo and others published their paper in 1988 in the Journal of the American Geriatrics Society. The paper looked at 63 patients above the age of 65 who developed hypoglycaemia, comparing them with a control group of 83 older patients, sex and age matched, in all cases undergoing corrective surgery for hip fracture. These groups of patients were identified retrospectively from a search of 11,686 patients' records. The results of the study were that around 40% of the patients' showed signs of hypoglycaemia. Hypoglycaemia was identified by a reading of below 2.77mmol/L. However, "Symptoms and signs of hypoglycaemia were noted [clinically] in only 23 [out of 63] patients of whom 16 developed neuroglycopenic symptoms, and 7 presented with adrenergic symptoms". Analysed, the results showed that "low plasma albumin levels, liver disease, malignancy and congestive heart failure were significant predictors of hypoglycaemia." All but two of the patients who developed hypoglycaemia had risk factors. The authors considered that acute food deprivation was a major risk factor for developing hypoglycaemia. 43% of the patients who developed hypoglycaemia had liver disease. The authors concluded "...it is reasonable to assume that the combination of liver disease with other risk factors, especially malnutrition, led to the development of hypoglycaemia". The authors also concluded that the other risk factors included "heart failure, sepsis and malignancy. The causes of hypoglycaemia in patients with heart failure are not related directly to the heart disease but rather to the complications accompanying this condition, such as liver congestion, low caloric intake, malabsorption, and increased glucose uptake by ischemic tissues." The authors assumed that the combination of malignancy and malnutrition led to hypoglycaemia. Importantly, in none of these cases was hypoglycaemia "the apparent immediate cause of death".

118. Mannucci and others published in 2006. This was again a retrospective study of patients over 65 in a hospital in Florence. Patients with a diagnosis of diabetes were

excluded. The standard adopted for hypoglycaemia was 3.3mmol/L, and so the study covered the whole range of those so defined, from mild to more severe. The study found that 8.6% of the group (58 patients out of 678) showed hypoglycaemia on at least one occasion in hospital, in three cases whilst undergoing insulin/glucose treatment for malnutrition. The authors confirm that "most of the cases of hypoglycaemia that we identified were relatively mild and did not require any specific treatment". On page 448 of the report, it is recorded that 10 subjects, or 1.7% of the group, showed severe hypoglycaemia with blood glucose of 2.2mmol/L or less. There is an inconsistency however in that on p449 the authors look at outcomes and they write "Of the seven patients with blood glucose <2.2mmol/L. five died during in-hospital stay, and the other two in the following year". No single death was attributable to hypoglycaemia. The researchers looked through the clinical notes for signs and symptoms of hypoglycaemia, described in the study as "sweating, tremor, tachycardia or worsening of cognitive function". The hypoglycaemia was asymptomatic in about 25% of cases, but the paper does not correlate the severity of hypoglycaemia with the lack of signs and symptoms. In these patients the authors found "hypoglycaemia was associated with pulmonary failure, dementia and pressure ulcers, and with CHF [congestive heart failure], renal failure, malignancies and lower tract urinary infections".

119. Abdelhafiz and others published in 2012. Hypoglycaemia in their study was defined to be "less or equal to 3.9mmol/L", thus a relatively liberal definition. 41% of the hypoglycaemic patients in the study were diabetics. In 78% of these patients the hypoglycaemia was asymptomatic. The conclusion of the paper was that:

> "Hypoglycaemia in hospitalised older people tends to be associated with sepsis, organ dysfunction or polypharmacy. The development of hypoglycaemia in hospitalized older people appears to be a risk factor for adverse outcomes. The association of hypoglycaemia and adverse outcome is likely due to the coexisting multiples comorbidities and frailty rather than a direct causal link. Hypoglycaemia and other biochemical markers such as low albumin and low cholesterol should alert clinicians to the frailty of older patients and every effort should be exerted for maintaining nutrition and physical activities." (Emphasis provided)

120. In the course of his evidence, we asked Dr Hopkins if he was aware of any literature where [1] there was no question of exogenous insulin or sulfonylurea administration, [2] where the onset of hypoglycaemia was sudden and severe, [3] where the hypoglycaemic episode was refractory to treatment with glucose, but [4] where once the hypoglycaemia was overcome, there was no further episode of hypoglycaemia. Dr Hopkins helpfully considered the matter overnight, and he referred us to a paper by Khoury and others (1998).

121. The paper deals with a single case of a man of 72 who suffered 'spontaneous' hypoglycaemia associated with congestive heart failure. The patient was admitted to hospital for treatment of severe congestive heart failure. He had difficulty breathing, bilateral pleural effusions and peripheral oedema. He was clearly severely ill. The onset of hypoglycaemia took place on the third day after admission when the patient became confused and was found to have significantly low blood sugar, (approximately 1.2 mmol/L.) The symptoms of hypoglycaemia resolved after "aggressive intravenous

infusion of glucose" but recurred over the next six days. The hypoglycaemia resolved once the congestive heart failure was corrected. The patient left hospital with normal blood glucose and died of a cardiac arrest some six months later; his blood glucose levels were normal.

122. The authors noted that "To the best of our knowledge, this is the first reported case of hyperinsulinism during hypoglycaemia in a patient with CHF." They considered the mechanism "poorly understood" but considered it was likely to be "impaired insulin degradation and shunting of portal blood into the systemic circulation". This would mean reduced blood supply to the liver.

123. In evidence Dr Hopkins said that:

> "In my mind this case highlights the fact that spontaneous, severe and prolonged hypoglycaemia can occur as a natural phenomenon and the prolonged normal glycaemic can resume following improvement in the underlying health issues that led to hypoglycaemia. It also highlights the fact that an unusual natural mechanism in this case. It is well recognised in the literature that hypoglycaemia occurs in the context of heart failure. Interestingly the observations here show that abnormal processing in the body of insulin may have been partly responsible. I think this highlights the fact how little we still know about the control mechanisms and how they can break down in disease processes."

124. The experts called by the respondents are generally sceptical of the utility and, sometimes, the quality of the medical literature advanced by the appellant. They note that the studies are necessarily retrospective. They dismiss the proposition that there would be any brake or inhibition on publication of case reports or studies suggesting or confirming the incidence of severe refractory hypoglycaemia arising from the very common "co-morbidities" found in the elderly patient population. Precisely because such cases would be rare, they would be of interest and would be publishable. The respondent's experts do not accept that profound hypoglycaemia in the circumstances proposed by Dr Hopkins and Dr Croxson is more recognised either in the reputable medical literature, or in practice since the trial.

125. From our own independent review, we find that the medical literature does not authenticate Dr Hopkins' hypothesis. We do not consider that Hedayati takes the issues in this appeal any further, save that it confirms that congestive heart failure is one of the established cause of hypoglycaemia. Similarly, Drah confirms the incidence of hypoglycaemia in chronic liver failure associated with heart congestion. The Shilo paper is of interest, but in our view, it is questionable if it does more than confirm the established list of disorders and conditions leading to significant hypoglycaemia. Mannucci confirms the pattern of generally mild hypoglycaemia in the elderly population and does not deal with refractory hypoglycaemia. Abdelhafiz recites the work of Mannucci and others and does not appear to add anything to those previous papers.

126. The Khoury paper is interesting in several respects. It does seem to be a case where the authors indicate that excessively high insulin, rather than low glucose, was the cause.

The authors record that: "In our patient, an inverse relationship was found between the serum insulin and C peptide and the serum glucose, an indication that hyperinsulinism was the cause of the hypoglycaemia. The mechanism of hyperinsulinism is unknown ...". However, as the authors make clear, although the mechanism was "unknown" or "poorly understood", the cause was well-known, namely congestive heart failure, and in this instance really serious congestive heart failure. The symptoms of hypoglycaemia resolved after "aggressive intravenous infusion of glucose" but recurred over the next six days. The hypoglycaemia resolved once the congestive heart failure was corrected. The patient left hospital with normal blood glucose although he died of a cardiac arrest some six months later, then still with normal blood glucose levels." Finally, the authors note that this was the first such reported case, consequently confirming the rarity of this reported cause of hypoglycaemia in the literature.

127. In his closing submissions Mr Mansfield KC effectively conceded that the hypothesis advanced by Dr Hopkins and Dr Croxson is not assisted by the medical literature, referring to the literature as "sporadic" and necessarily "retrospective". In these circumstances, he emphasised the importance of the analysis of the 'extra' cases for the corroboration that they afford to the hypothesis advanced.

128. Prior to reviewing the evidence regarding the 'extra' cases, it is convenient to address submissions made by Mr Mansfield KC and Mr Brown regarding the "backwash" created by the jury question sent on 12 February 2008. They submit that the question is pertinent and called for the jury to have been told about the 'extra' cases. They argue that it is a matter for the jury whether the 'extra' cases were 'out of scope' or if they "match in every way the parameters" of the phenomena upon which the prosecution case relies.

129. We have already made plain our view in relation to certain aspersions cast as regards the position of the prosecution, the expert witnesses called at trial and the previous defence team. It is also inevitable that we should comment that submissions made on behalf of the appellant on this issue have tended to slip into the territory of 'what would the jury have made of all this?', however quickly self-corrected.

130. We agree with Mr Mansfield KC that the notes sent on 12 and 13 February 2008 indicate that, even after five months of hearing complex evidence, the jury were still engaged in the trial process and conversant with the evidence and several of the issues arising. Notably, however, prior to the summing-up, the note on 12 February only mentioned two of the five phenomena upon which the prosecution relied. Accordingly, even leaving to one side the fact that the appellant's then legal team made the decision not to rely upon the 'extra' cases (in addition to BD), we find that the notes do not, in any event, advance the appellant's case on the significance of the 'extra' cases in the appeal.

The 'extra' cases: how comparable are they?

131. Although we have already referred in brief to these patients in [86] to [88] above, it is convenient to summarise some of the relevant features here for the point of comparison with the index patients.

132. ML was hypoglycaemic on admission to hospital, thereafter experiencing a further, more significant, episode of hypoglycaemia during her hospital admission. The rate of

onset of her first hypoglycaemic episode is unknown. She was a frail older woman and showed signs of a severe systemic inflammatory response to hip infection, had a history of gastric surgery, had previously used high-dose corticosteroid, had adrenal insufficiency identified at autopsy and had chronic liver damage. Significantly, her hypoglycaemia was relatively easy to correct and, as such, was not refractory unlike the index cases.

133. MH had severely abnormal liver enzymes, which is a marker of liver dysfunction. She too responded to glucose treatment relatively swiftly.

134. EW was also hypoglycaemic on her admission to hospital, experiencing a further episode of hypoglycaemia in hospital. The amount of glucose required to correct her hypoglycaemia on each occasion was significantly less than in the index cases.

135. The circumstances appertaining to BD had already been considered by the jury, most probably at the behest of the defence, since she had not been nursed by the appellant. In July 2001 she suffered a sudden, severe and unexplained hypoglycaemia. There was extensive reference to her circumstances and clinical presentation in the summing-up. She was elderly and a patient at the LGI where she underwent surgery to repair a hip fracture. The experts called on behalf of the respondent noted that she had suffered a definite and catastrophic heart attack leading to cardiogenic shock. The hypoglycaemia recurred on three occasions despite the administration of glucose. However, there was evidence that she was a diet controlled diabetic and, as agreed by all experts at the second expert's joint meeting: "… this case was different from those considered at the trial in as much as BD had been treated therapeutically with insulin before becoming hypoglycaemic. In addition, the documents may not have reflected accurately the insulin administration."

136. We note that at paragraph 251 of the Statement of Reasons, this is stated:

> "The CCRC asked Dr Croxson to consider whether any clear cases of severe hypoglycaemia had occurred in circumstances in which [the appellant] could not have been responsible, and whether any such cases might support the theory that naturally occurring hypoglycaemia was more common than the prosecution had suggested. Four potential cases were identified [EW, ML, MH and another not subsequently considered by either Dr Hopkins or Dr Croxson to be comparable to the index cases) They were elderly women, with co-morbidities known to be associated with spontaneous hypoglycaemia."

137. Dr Croxson reviewed the available material relating to these four patients in 2017/18. He did not consider that they matched the five trial cases in terms of manifesting severe hypoglycaemia that had occurred not on admission but later during the hospital stay and that was difficult to correct. In Dr Croxson's opinion, the important points was that the description of 'severe' rather than 'mild' differentiated the majority of the cases under consideration at [the appellant's] trial from the additional cases

138. Asked by the Court during his oral evidence, why he had changed his view, Dr Croxson explained that "stepping back", he was able to bring a different perspective to the cases. That is, Dr Croxson now supports Dr Hopkins view that, whilst there are differences between the 'extra' cases and the index cases, nonetheless they are all on what could be described as a "spectrum". However, he maintained that he had not changed his view

that there were differences, as he had previously stated, between the index and 'extra' cases.

139. The experts called by the respondent agree that some features of the 'extra' cases are comparable with the index cases, but to quote from the record of the second joint meeting of experts:

> "The Crown experts consider that there are significant differences between the two groups of cases in regard to clinical circumstances, duration of hypoglycaemia, and treatment required to correct the hypoglycaemia … The experts agreed that the additional Leeds cases confirm the rare but well-established propensity of some natural phenomena to induce severe hypoglycaemia. The Crown experts noted that those natural phenomena, which in the patients considered were liver failure and cardiogenic shock, had been discussed at trial. There was nothing to suggest that severe, refractory, hypoglycaemia occurred more commonly in these additional patients than anticipated from reports in the medical literature".

140. Our objective appraisal of the agreed clinical presentation in the case of the index cases confirms this assessment, as we have compared the details of the index patients below.

Mrs Wilby

141. VW was 90 years old when she was admitted to Leeds General Infirmary on 2 May 2002 having fallen and broken her left hip. She lived in warden-controlled housing. She was small: in July 1990 she was 4 feet 8¾ inches (144 cm) tall and weighed 42.6 kg (6 st 9 lbs). She had been noted to have a raised serum calcium concentration since 1990; a pelvic mass, first identified in 1990, and likely to be formed of calcified lymph nodes; and a heart attack in 1993, when her blood glucose concentration was raised.

142. On admission on 2 May 2002, VW was pale, shivering, feverish, and confused. She was treated with antibiotics and underwent hip surgery on 5 May 2002. After the operation, she developed atrial fibrillation (a fast irregular heartbeat), which resolved within a few hours. The next morning, VW was sitting in a chair, awake and talking. A laboratory blood glucose result of 12.4mmol/L suggested that she had diabetes. By 16 May 2002, she was able to stand and walk one step with support.

143. On the morning of 17 May 2002, she appeared drowsy but was "Arousable. Not confused, talking. Slow speech.? Dehydrated". She was given an injection of morphine 5mg at 7.30 pm that evening. At 10.40 pm, a doctor saw her because she was "not as responsive as earlier today". The point-of-care blood glucose reading was 1.8mmol/L. A Glasgow coma score was reduced at 8/15. She was treated with intravenous glucose.

144. The next morning, the blood glucose concentration was 3.6 mmol/L, and the Glasgow coma score was 13/15. The blood glucose concentration fluctuated over the next day. By 22 May 2002, the blood glucose was 20.7 mmol/L, and Mrs Wilby was subsequently treated as a diabetic.

145. Mrs Wilby remained in hospital for some months, before discharge to a nursing home. She died on 30 January 2003 from pneumonia.

Mrs Ludlam

146. DL was 80 years old. She suffered from heart disease and was in controlled atrial fibrillation. She had suffered a heart attack in or around 1993 and had a permanent pacemaker.

147. DL had been admitted to hospital in April 2002 with severe heart failure and a chest infection, and was discharged on 10 May 2002, only to be re-admitted the next day. Whilst an in-patient in Chapel Allerton Hospital, she had fallen causing damage to the bones of the right hip, but by relatively soon after was moving about, and quite independent until the second fall. She broke her left hip in another fall on 12 June 2002.

148. After admission to Leeds General Infirmary, her operation was delayed because she was anti-coagulated, and then further delayed by an episode of fast heart rate, a high serum potassium result, and presumed chest and urinary tract infections, treated with the antibiotic ciprofloxacin. She also was given insulin and glucose to treat the presumed high potassium concentration.

149. DL underwent surgery for the broken hip on 21 June 2002. She was made to fast overnight on various occasions prior to that operation. After the operation, she developed a rapid heartbeat treated with digoxin but was clinically stable.

150. DL was given morphine (5mg) on the morning of 25 June 2002. Later, she was extremely short of breath and unresponsive, with a fast heart rate and widespread peripheral oedema. Naloxone, a morphine antidote, was partially effective. By 9.15 am, she was "extremely unwell". She had fast atrial fibrillation, congestive cardiac failure and hypoglycaemia.

151. Although conscious by 26 June 2002, DL remained very unwell, with abnormal blood tests, signs of infection and persistent heart failure. She then developed signs of a stroke affecting the right side.

152. She had received repeated and significant doses of glucose administered as both boluses and infusions. In total some 372.5g of glucose was administered to correct diagnosed hypoglycaemia. Despite continued ill-health, her blood glucose had seemingly improved when compared to the position on 25 June 2002 at the start of the episode, despite no further glucose being administered.

153. DL died at 4.30 pm on the afternoon of 27 June 2002. Death was certified as due to stroke, cardiac failure, ischaemic heart disease and atrial fibrillation.

Mrs Bourke

154. BB was 88 years old when she was admitted to Leeds General Infirmary with a broken hip after a fall at home.

155. Her past medical history included a hysterectomy, a heart murmur noted in 1994, and breast cancer treated by mastectomy in 1999.

156. She was admitted to hospital on 21 February 2002 with acute confusion from a chest infection and found to have bilateral chronic subdural blood clots and an old stroke. She was re-admitted on 14 April 2002 with fits, a brain scan revealing the chronic subdural blood clots and the old stroke.

157. After rehabilitation, she was discharged on 20 May 2002.

158. BB underwent hip surgery on 17 June 2002 and was beginning to mobilise the next day. Her recovery was complicated by an episode of incoherent speech and by rabid Clostridium Difficile diarrhoea.

159. She was less well by 19 July 2002, when she had swelling of both legs. At 3.30 am on 21 July 2002, a doctor recorded that she had left-sided weakness, and a point-of-care glucose result of "LO". The blood glucose concentration improved with intravenous glucose.

160. The blood glucose concentration repeatedly rose above normal with oral or intravenous glucose and then fell below normal. During that day, however, BB's condition deteriorated, and at 00.30 am on 22 July 2002 she was noted to have stopped breathing. Her death was certified as being the result of a left-sided stroke.

Mrs Crookes

161. IC was 78 years old when she fell and broke her hip and was admitted to St James' Hospital on 10 October 2002.

162. She had undergone a hysterectomy in 1959, investigations for epigastric pain in 1968, cataract operations in 1988, an episode of wheezy bronchitis in 1996, and urinary tract infections in 1999 and 2001, but was in generally good health.

163. On the morning of 11 October 2002, after fasting overnight, she underwent surgery with insertion of a dynamic hip screw. She was seen post-operatively because she had not passed urine. She required supplemental oxygen, and was deficient in vitamin B12 and folic acid, and possibly also vitamin C. Her wound was leaking fluid.

164. On 18 October 2002 she had a fever, but the white cell count was normal, and her temperature settled.

165. On the morning of 19 October 2002 IC was seen urgently because she was unresponsive, her Glasgow coma score was 3/15, the point-of-care blood glucose concentration was 1.6 mmol/L at 7.30 am, and 50 mL glucose 50% was given intravenously. The blood glucose concentration rose to 18.7mmol/L.

166. The white cell count had risen from 9.1 ×109 /L when IC was first seen that morning to 19.8 ×109 /L about 9 hours after her collapse. Antibiotics appropriate for the treatment of aspiration pneumonia were given, but IC did not recover.

167. IC died at 1.20 am on 20 October 2002, the cause of death being certified as: respiratory failure, chronic obstructive pulmonary disease and osteoporotic fracture neck of femur.

Conclusion

168. Whilst, undoubtedly, the four elderly women patients in the index cases were in parlous physical, and in some instances, mental health just as were the three elderly women patients in the 'extra' cases, it appears to us that they are certainly differentiated in the identification of the underlying pathology and particularly so in the refractory nature of the hypoglycaemic episodes recorded.

169. On our own analysis, the 'extra' cases serve to underline rather than undermine this aspect of the phenomena that are said to be distinctive in those cases of administration of exogenous insulin.

Analysis of the patterns of response to insulin, to glucose treatment and the implications

170. Professor Heller, who has a particular interest and expertise in the impact and absorption of insulin gave evidence that up to half of the insulin produced by the pancreas does not escape into the blood stream because it is absorbed by the liver whilst the remainder circulates. The model of the mild hypoglycaemia which it is accepted can arise from the effects of ageing is not an excess of insulin but rather a lack of capacity to absorb, store or regenerate glucose. Lack of nutrition, perhaps accompanied by very low body weight, and thus loss of muscle and fat, means that there is less glucose (or the carbohydrates which the body converts into glucose) available in the bloodstream, to be utilised or stored, as well as a reduced storage capacity. As the body ages gradually, so these processes decline gradually, and hypoglycaemia may develop. However, it is common ground that the process of decline is gradual, and that commonly any hypoglycaemia is mild, and relatively easily corrected.

171. Professor Heller emphasised that even in the circumstances of severe underlying pathology, taking the example of liver damage, "you would not expect the insulin levels to be high, in fact you would expect them to be low, and you would expect [that] just a normal IV infusion should maintain glucose levels". In the severe cancers, the glucose is rapidly consumed or "hoovered up". In liver or kidney failure, whether from primary disease or because of severe heart failure, it is a failure to mobilise glucose adequately. In severe malnutrition, or in the starving or extremely cachexic patient, there is no excess of insulin, but rather no reserves of glucose. Thus, it would be logical to expect that the immediate problem of acute hypoglycaemia would be readily resolved by moderate delivery of glucose; the risk of recurrence does not displace that expectation.

172. When giving evidence on this point, Dr Hopkins said:

> "So, this concept of refractory hypoglycaemia –… in the context of other health issues that are sufficient to cause severe hypoglycaemia, if they are not corrected in themselves – in other words, the underlying path of physiology is still present, then the requirement for glucose to treat may persist, and this may give the impression that the glucose appears more refractory to treatment."

Later he said:

> " … There are cases, other cases that were seen in Leeds in which there was clear profound hypoglycaemia. My own experience is also that albeit uncommon but does occur. There is no doubt that

> prolonged hypoglycaemia, which may appear refractory, does occur by natural causes. Not only in these cases, but you know, although, I mean the kind of scenarios that we have described, but also more generally, if there is an underlying severe pathology that can impact on normal regulatory processes, the degree that severe hypoglycaemia, excuse me, occurs then that in itself may make the hypoglycaemia refractory. It is not … in the context of somebody being given insulin it is the ongoing action of insulin. If, for example, the hypoglycaemia is being caused by impairing kidney or liver function or absence of corticosteroid, any of the things that we have described, that means that while that failure remains, the hypoglycaemia will tend to continue and may require ongoing continuous treatment. So, it is not specific to any one cause."

173. We harbour the concern that Dr Hopkins may have been at cross-purposes about what the experts called by the respondent meant by "refractory to treatment". Firstly, the discussion here is of a "underlying severe pathology", not a general collection of 'co-morbidities'. Secondly, although Dr Hopkins is obviously correct that whilst such underlying pathology persists, hypoglycaemia may continue to arise, that is not the point. The critical point being made by the respondent is that the acute hypoglycaemia seen in the index patients was refractory to administration of glucose even in large bolus doses, not that it was recurrent requiring ongoing infusion.

174. Professor Ferner produced graphs in respect of each of the index cases which showed the various readings of blood glucose post-diagnosis of hypoglycaemia throughout their treatment with glucose therapy.

175. At the experts joint meeting on 24 September 2024, all the experts including Dr Hopkins and Dr Croxson agreed that these graphs accurately depicted the data to be derived from the available clinical notes. In fact, it subsequently became apparent to Professor Ferner that the graphs did not include all relevant infusions. Thereafter he produced revised graphs also detailing the ascertainable total amounts of glucose administered in each of the cases – whether through infusion or as boluses or, in the form of Hypostop gel that would be administered orally.

176. Dr Hopkins then reviewed the graphs himself by reference to the underlying source data available in the various medical notes and suggested slight amendments to some. These amendments were accepted by Professor Ferner but, he said, did not undermine the point which he was making. The graphs of each of the index patients disclosed similar 'oscillations' demonstrative of the refractory nature of their hypoglycaemia as would be expected in exogenous insulin administration.

177. We consider the graphs present a potent visual demonstration of Professor Ferner's evidence on this issue. Similar graphs were utilised at trial. We found Professor Ferner's evidence of the response to treatment of natural cause or minor hypoglycaemia, as opposed to that relating to the established and accepted pattern observable in the cases of known insulin poisoning, to be compelling.

178. The starting point relevant to this scenario, is of one large overdose of injected insulin. This will act to drive the glucose in the blood into the tissues and to be unavailable in

the circulation, causing swift severe hypoglycaemia and neuroglycopenia (the state in which the brain cells have insufficient glucose to function normally), neuroglycopenia's characteristic symptoms and signs, including confusion, weakness or fatigue, severe cognitive failure, seizure and coma.

179. The exact pattern will depend upon the delivery of the insulin and consequent effect. Insulins come in various forms, with various speeds of absorption into the blood stream. For present purposes the insulin missing from the relevant hospital wards in 2002 was Actrapid, a short acting insulin. Once in the bloodstream, the half-life of insulin is only a few minutes. Thus every 3 to 5 minutes the concentration falls by half. If the concentration is 10 at reaching the bloodstream, it will be five at 3/5 minutes, 2.5 at 6/10 minutes, 1.25 at 12/20 minutes and so forth exponentially. Thus, the effect of insulin injected intravenously would be expected to "wane rapidly".

180. However, insulin is normally injected subcutaneously, resulting in a depot or reservoir that forms under the skin; particularly if there is a large injection of insulin. In the case of elderly emaciated females with little body mass or musculature, Professor Ferner told us that it was more likely that the depot or reservoir would be slow to absorb because of their lax skin. As he put it:

> "If you assume the reservoir to be a sphere, the surface of the reservoir is the site at which absorption takes place. So, if you have one big injection, the absorption is really quite slow because most of the insulin is on the inside."

181. In his report of 12 June 2024, Professor Ferner described research conducted by himself and a colleague, Dr Moyns into the duration of glucose infusion and concluded that, even with Actrapid soluble insulin, the "median infusion time was 14 hours and, in some patients, much longer".

182. Both Professor Semple and Dr Kroker emphasised the same point. Dr Kroker referred us to the paper by Stapczynski and others (1984), the headnote of which reads in part:

> "We conclude that prolonged aggressive IV glucose infusion and serial monitoring of serum glucose levels is required in insulin overdoses. These patients may become hypoglycaemic much later than predicted from the conventional duration of action of the various insulin preparations".

183. For the purposes of this appeal, we find that if insulin poisoning was the primary cause of the hypoglycaemia observed in the four index cases (in addition to EH), it would be a one-off event. But such poisoning is an acute event, not a continuing long-term cause of hypoglycaemia. It would be rational, accordingly, to predict that [1] the hypoglycaemia would be sudden and severe [2], that it would be difficult to treat in the short term because of the scale of the oversupply of insulin, [3] that it would likely last for some hours before the absorption from a sub-cutaneous reservoir and then clearance of the insulin from the bloodstream is complete and [4] that thereafter there would normally be no further excessive insulin continuing to drive down the blood sugar. Thus, if the individual survives the acute phase of hypoglycaemia, at least without secondary damage to the organs responsible for maintaining an acceptable supply of

glucose to the brain and body, then the individual should not require further significant glucose treatment.

Applying the "holistic approach" to the index patients

Mrs Wilby

184. Mr Mansfield KC and Mr Brown submit that VW had dementia and was underweight at the time of admission, as well as having poor kidney function. The fact that she had an infection on 18 May 2002 might indicate that it had been brewing the day before. Alternatively, it is suggested that VW's episode of hypoglycaemia was attributable to an insulinoma.

185. Without prejudice to those issues, it is said that the fact that VW had been drowsy during the day on 17 May 2002, before the appellant is alleged to have injected her with insulin, points to the hypoglycaemia being the result of natural causes since drowsiness is a neuroglycopenic symptom of hypoglycaemia. This, it is said, "drives a coach and horses through" the prosecution case that the only possible explanation for VW's hypoglycaemia episode in May is exogenous insulin or sulfonylureas administered at some point that evening. Finally, it is suggested that the reasons why VW did not respond more quickly to treatment on 18 May 2002 is that she was suffering from the infection previously mentioned and/or because she was administered glucose only intermittently and at a relatively low rate when she was initially treated.

186. However, VW did not have any significant or major organ failure, including any adrenal failure. She did not have severe chronic kidney disease since, as Professor Ferner confirmed, her creatinine levels were normal and, although the appellant's experts both referred to her having low eGFR levels, as Professor Hall explained, eGFR is not accurate in patients such as VW.

187. Nor, as again Professor Hall confirmed, is there any evidence that there was a cardiac cause for VW's hypoglycaemia, or indeed for the change in consciousness that she experienced given that the blood pressure and oxygen saturation readings were adequately maintained at a time when her state of consciousness was disturbed.

188. Although alkaline phosphatase ('ALP') levels were raised, this may have resulted from bone trauma; both Dr Hopkins and Dr Croxson accepted that these levels could be consistent with a patient that had undergone hip surgery as opposed to indicating any particular liver dysfunction.

189. Whilst Dr Hopkins postulated a chest infection, the respondent's experts (in particular, Dr Cowling) exclude infection from being operative prior to the hypoglycaemic episode, reliant upon the CRP and white blood counts.

190. Weight loss, some 4kg in 6 weeks, occurred within a short period, rather than reflecting the long-term and serious examples reflecting anorexia nervosa. We find no merit in the 'malnutrition' point raised.

191. Dr Croxson accepted that the presence of an insulinoma was unlikely owing to its non-recurrence. Dr Hopkins considered that it remained a possibility since an insulinoma is by its nature intermittent. However, there was no prior diagnosis or sign of its presence

in VW's medical history and nor was there any recurrence after the hypoglycaemic episode in May 2002 and her subsequent discharge. We find the presence of an insulinoma is not supported by the clinical evidence.

192. More significantly, accepting for the sake of argument, the 'tipping point' theory as the cause of the severe, sudden, profound hypoglycaemia we find that it does not begin to describe or explain the refractory nature of the hypoglycaemia indicated in Professor Ferner's graph. Repeated and significant doses of glucose were administered as both boluses and infusions. The 'oscillating' glucose level pattern which the graph depicts, and the nature of the drop after administration of glucose, points to the presence of exogenous insulin. The same pattern is reflected in the graph produced by Professor Ferner in relation to EH, who was administered non-therapeutic exogenous insulin, and is not what would be expected if the hypoglycaemia was the result of natural causes.

193. The clinical presentation of VW is significant in that she survived the severe, profound hypoglycaemic episode and, once her blood glucose was stabilised, it is known that hypoglycaemia did not recur until August, and when it did it was mild and needed no more than a cup of tea to resolve. If Dr Hopkins is correct that hypoglycaemia will appear refractive until the underlying cause is treated, then if it did arise from a constellation of 'co-morbidities', the hypoglycaemia would require ongoing blood glucose infusion.

194. Although we note the point regarding the onset of VW's profound hypoglycaemia, this goes to identity of perpetrator and not causation. We deal with this issue in the case of EH below.

Mrs Ludlam

195. Mr Mansfield KC and Mr Brown highlight that, on admission, DL was already gravely unwell with advanced heart failure, low body weight and significant impairment of kidney function. Following surgery, she remained unwell. She had persistent low blood pressure. At the time of her hypoglycaemic episode, her oxygen saturations had fallen to 88% indicating significant respiratory failure. She was noted to be in severe heart failure. She had extensive swelling of her legs. Her blood pressure was low. Her blood became acidic with a pH of 7.2, which is consistent with hypoperfusion of her organ. Her kidney function was significantly impaired. There was evidence of liver impairment. There was evidence of infection. She remained gravely unwell with low blood pressure and her chest signs deteriorated, which was consistent with worsening pulmonary oedema or infection.

196. The appellant's position, in short, is that Mrs Ludlam's age, frailty and 'co-morbidities' provide a clearly plausible explanation for developing severe hypoglycaemia and her hypoglycaemia being an epiphenomenon of her underlying illnesses.

197. Whilst superficially these arguments have some force, our objective analysis of the facts in the context of the expert evidence we heard produces a different picture.

198. First, although DL is the only one of the index patients with substantial organ failure on admission, her clinical records show that her cardiac failure was nevertheless stable. Post-operation, she was diagnosed with tachycardia and irregular heartbeat (atrial fibrillation), however Professor Hall's review of the ECGs did not indicate to him that

either had resulted in myocardial infarction (heart attack) or cardiogenic shock which might give rise to impairment of the liver and the restriction of gluconeogenesis. Specifically, Professor Hall was clear that cardiac failure was not a cause of DL's hypoglycaemia contrary to the appellant's closing submissions.

199. Secondly, contrary to the assertion by Mr Mansfield KC and Mr Brown in closing submissions that Professor Ferner had previously expressed the view that liver damage associated with congestive heart failure could amount to a potential cause of DL's hypoglycaemia, he in fact indicated in his report that "when hypoglycaemia does occur in association with congestive heart failure, the medical literature indicates that it is expected to respond to the injection of relatively small doses of intravenous glucose, and does not recur". As he confirmed in his oral evidence, he rejects the notion that liver damage was a cause of the severe and refractory hypoglycaemia in Mrs Ludlam's case. Further, as to this, whilst Dr Croxson maintained that DL's raised liver enzymes suggested liver dysfunction from hepatic congestion (related to heart failure), he agreed that this represented impaired function rather than failure.

200. Thirdly, although Dr Hopkins considered that DL's kidney function was significantly impaired (with an eGFR at a level he said normally required dialysis), Dr Croxson noted that the elderly are affected differently such that dialysis might be considered unnecessary. The respondent's experts were agreed that DL's impaired kidney function did not amount to a failure that would, in and of itself, account for the hypoglycaemic episode.

201. Fourthly, accepting for the sake of argument, that any one or combination of the medical issues in DL's case (including heart failure or liver or kidney dysfunction) had resulted in severe, profound hypoglycaemia, the overwhelming view of the expert witnesses and medical literature is that it would have been easily corrected by a small or moderate dose of glucose and, even if theoretically persisting because of the underlying conditions, that blood glucose levels could be maintained by low quantities of glucose. However, as previously noted, in total some 372.5g of glucose was administered to DL in repeated and significant doses both by boluses and infusion. This is far more than the quantity of glucose expected to be required in hypoglycaemia from natural causes.

202. We do not ignore the point raised by Dr Croxson regarding the accuracy of the POCT in DL's case. This was not a matter raised at trial.

203. In any event, Dr Kroker's expressed opinion was characteristically straightforward:

> "This lady had a huge amount of glucose. She had altogether, according to my calculations, 325 gms of glucose given as bolus. Now as I said, 5 g/h are enough to keep a very, very ill patient in a normal BM range. But nevertheless, here you had to give repeatedly this high dose, and you get again an oscillating pattern, where you see that the blood sugar comes up after bolus administration of insulin and then falls back again. And again, the only explanation I have for that is that there was on going insulin effects in the system which allowed the glucose to move into the cells. So, I would disagree here with Dr Croxson's suspicion or hypothesis that these readings were inaccurate,

> because the hypotension, the shutdown, was not such that it consistently created a low blood sugar reading. Occasionally the blood sugar went up into the normal range. It would be very unusual if such systems consistently, if more than ten measurements fail. And then secondly, the massive amount of glucose which is needed to bring it up. So again, it's the same pattern: it is profound hypoglycaemia, difficult to control, you need amounts of glucose which are far beyond what you would need even in the very ill patient in ITU."

204. If called upon to decide this issue, we would find that the consistency of the large number of POCT results at the time when DL's blood pressure was not compromised would allay any doubt. However, we need not make a finding on that secondary issue since the judge's extensive summary of the evidence regarding DL left the jury in no doubt as to her very poor clinical presentation, in which context they were directed that the first step in their route to verdict was that they must be sure that she was suffering from hypoglycaemia.

Mrs Bourke

205. Mr Mansfield KC and Mr Brown submit that BB was very unwell with many 'co-morbidities' and established coronary heart disease as well as a recent myocardial infarction, dementia, low body weight, poor kidney function and, on 19 July 2002, new generalised oedema consistent with congestive heart failure and evidence of infection.

206. Although Dr Hopkins suggested the development of heart failure, postulating the existence of extensive heart failure at the same time as the hypoglycaemic episode, nonetheless he did not challenge Professor Vanezis's conclusion that, on post-mortem examination, there had been no cardiovascular event causing myocardial infarction as cause of death, and that there was no evidence of stroke. Furthermore, Professor Hall could not see any evidence of a cardiovascular cause for the fall in sugar levels, noting also that she did not have significant renal failure and that what small amount of information there was regarding her liver function suggested that it was normal. Nor was Dr Croxson's suggestion that BB's eGFR reading was suggestive of severe renal impairment borne out by the post-mortem performed by Professor Vanezis: there was no evidence of acute liver or kidney failure, of insulinoma or any tumours in the pancreas. BB's BMI was 16.8 on post-mortem examination (and may have been higher before decomposition), which indicated that she was underweight but did not indicate malnourishment or starvation.

207. Accepting, again for the sake of argument, the 'tipping point' hypothesis, any hypoglycaemic episode so caused would be expected to have been easily rectified and managed by low or moderate doses of glucose. However, yet again, as demonstrated by Professor Ferner's graph, BB's's severe hypoglycaemia was refractory; it resisted treatment throughout 21 July 2002 and as such is inconsistent with hypoglycaemia resulting from natural causes. On this point Dr Kroker said:

> "I think the oscillation is again something which I cannot explain, other than that there is ongoing insulin action, and that would indicate there is insulin in the system which is not controlled by the normal feedback mechanism. For example,

> that, if it's from the pancreas, the pancreas should at that point in time switch off all insulin secretion, but that is not the case; you see here on-going insulin action."

Mrs Crookes

208. IC had a low body weight suggestive of longstanding nutritional deficiency, and on admission had low oxygen levels and been diagnosed with and treated for chronic obstructive pulmonary disease. She had severe chronic kidney disease and, before the onset of hypoglycaemia, had severe respiratory failure, was markedly hypotensive and had an infection.

209. Although not maintained in the course of closing submissions, Dr Hopkins and Dr Croxson had both suggested that sepsis may have been operative in IC's case. Professor Ferner regarded the negative blood cultures as making sepsis unlikely and the agreed report of Dr Cowling concludes that IC did not have any serious sepsis, either on admission, before the episode of hypoglycaemia, or during it.

210. Dr Cowling's unchallenged evidence was that, although there was some derangement of her liver function tests, IC did not have any serious organ dysfunction prior to the episode of hypoglycaemia. Professor Ferner similarly concluded that IC did not have chronic kidney disease of a severity likely to cause hypoglycaemia.

211. Professor Hall said that there was no cardiac cause for IC's loss of consciousness. Although she clearly had significant circulatory and respiratory problems, she became unconscious at a time when neither her levels of blood pressure nor oxygen saturation would result in any significant change in consciousness. Her ECG changes were non-specific at the time that she had become unconscious and there was no indication of an acute cardiovascular event that could explain IC's clinical situation. The possibility of a stroke or cerebrovascular accident was excluded by the CT scan which was performed.

212. Other possible natural causes raised by Dr Hopkins or Dr Croxson, such as hepatic dysfunction and adrenal insufficiency, were not pressed on the appellant's behalf either in cross-examination of the experts called by the respondent or in closing submissions. A speculation that IC was significantly malnourished was not maintained by Dr Hopkins.

213. In IC's case, Mr Mansfield KC and Mr Brown argue that there is no clear evidence that her hypoglycaemia was refractory to treatment. That is, she was administered, what was thought to be, a necessary therapeutic dose of insulin for about an hour at about 12 noon on 19 October 2002 to counter the very steep rise in her blood glucose readings following administration of bolus glucose and when she would have been extremely sensitive to the effect of even a small amount of insulin. However, Professor Ferner explained that, whilst the effect of this dose may have been to reduce the blood glucose somewhat, it would not have lasted until 3 pm and certainly not until 8 pm. In his view, this was a small dose of insulin which would have made "very little difference because if you have a high dose of insulin a little extra will not materially add to it".

214. Dr Kroker considered that Professor Ferner's graph did not show the oscillation seen in others but nonetheless was only consistent with exogenous insulin administration. He said in evidence:

> "With a running insulin, with a running dextrose glucose drip…. [12.5 gms… that just did not make any difference; she remained hypoglycaemic. And then at 18:00 hours her bedside glucose started to shoot up, but that was probably because she was given shortly before also again a bolus of 25 gms of glucose intravenously. So, you don't see here an oscillating pattern; you just see two spikes, two peaks. But again, the situation is such that, with a running glucose infusion of 12.5 g/h, I cannot really understand how she can go so low, because as I said, 5 g/h would be more than enough to keep her in a normal range. So again, I have to assume that the only way to explain that would be insulin action.
>
> …
>
> It is the only physiological explanation I can give. I try to explain this situation physiologically, based on the knowledge we have about our carbohydrate metabolism, how insulin works, how the feedback mechanism works. And the circumstance I see here is profound hypoglycaemia, very difficult to control, and an amount of glucose is needed which is well unknown to me in other circumstances, because, as I said, in severely ill patients far less glucose would be sufficient to keep them going. So again, I mean, I cannot give you another physiological explanation…."

Mrs Hall

215. Perhaps understandably, scant reference has been made so far to the case of EH. There is no doubt that she, a non-diabetic patient, was administered exogenous insulin. The CCRC refer the appellant's conviction in her regard, and the appellant submits, that this conviction would be rendered unsafe if we were to determine that any, or all, of the convictions in respect of the other four index cases were unsafe. That is, it is submitted that the atmosphere of the case created by the spectre and unlikelihood of four other patients experiencing sudden hypoglycaemia leading to death, or short-lived grave illness in the case of VW, would be dispelled.

216. We reject this submission. If the jury had acquitted the appellant in respect of the cases of VW, DL, BB and IC it is fanciful to imagine that there would be any prospect of a successful appeal against his conviction in respect of EH on the basis that is now pursued.

217. There is every likelihood that the jury followed the judge's suggestion to consider the case of EH first. The jury were directed to consider the evidence for and against the appellant, then defendant, on each count separately. There was a wealth of circumstantial evidence which would entitle the jury to be sure that the appellant was the perpetrator: the appellant's access to EH and the Actrapid insulin, missing from the ward store, at the relevant time; his alleged dislike and hostility towards elderly

patients; his expressed reluctance to complete the necessary paperwork if EH died; his prediction of the time of her collapse; his alleged tardiness in seeking the attendance of a doctor and then acting upon the doctor's instructions; and his subsequent telephone call to the ward asking after her condition.

218. However, it should not be overlooked that the jury's decision that the appellant had administered insulin to EH has a more far-reaching effect. In his oral evidence, Dr Hopkins volunteered that his opinion of a possible natural cause for the hypoglycaemic episodes witnessed in the cases of VW, DL, BB and IC was reached on a case-by-case basis. That is, his opinion was based on an analysis of the individual clinical facts. However, the jury were directed that they were entitled, if they determined that EH had been administered exogenous insulin to treat this as relevant and probative evidence, not only of the identity of the perpetrator, but also in their consideration of whether they were sure that the other four index patients had been poisoned or developed hypoglycaemia as a result of a rare medical phenomenon. This is not to resurrect any question of 'the forbidden fallacy'. Leading counsel for the appellant in 2009 accepted this general proposition, and this Court proceeded to confirm that "the judge's directions on 'cross admissibility' of evidence concerning the cause of the hypoglycaemia in each of the five victims" cannot validly be criticised.

Conclusions

219. Both the appellant and respondent submitted lengthy written closing submissions. Mr Mansfield KC and Mr Curtis KC spoke to the documents, which they both fairly attributed to the prodigious industry of junior counsel, Mr Brown and Mr Sinha.

220. Both were invited to provide copies of the written submissions to members of the press who had been present throughout the hearing, in the interests of transparency. Since, to our knowledge, these documents have entered the public domain, we find it necessary to observe that many of the paragraphs in the appellant's document which seek to reproduce certain extracts of the oral and written evidence of expert witnesses called by the respondent said to "support" the hypothesis presented by Dr Hopkins and Dr Croxson are highly selective and omit their strident caveats to the extent that they are unrepresentative of the witness's own reasoned and conclusive opinions.

221. As we indicate above, we reject the submission that the respondent seeks to uphold the convictions on a fundamentally different basis to that considered by the jury at trial. Reciting just one of the passages in the summing-up that represents the prosecution case advanced at trial will suffice:

> "Before I remind you of the evidence of Dr. Peter Kroker which was directly relevant to the cause of death in Mrs. Hall's case, I need to remind you of his evidence which was general to the cases of all five patients. He detailed the work he has done monitoring over a period of some a years, a total of 800 cases of elderly patients who have undergone hip fracture repair surgery. He said that he now has a very good idea of the sort of problems which are likely to be encountered in such patients. Postoperatively the majority of these problems would be heart problem or serious infections, and he made the point that they are a very vulnerable patient group. He said he has never seen a

> single case of serious hypoglycaemia in a patient who is not on some anti-diabetic treatment, either insulin or sulphonylurea. Although he has seen cases of serious hypoglycaemia in patients who had septicaemia the hypoglycaemia has not resulted in a catastrophic event. He said he has never seen a serious case which came without warning, although he has seen hypoglycaemia which has come on rapidly in patients with adrenal problems or in patient exhibiting pituitary pathology. However, the main feature of those cases was that a small amount of glucose was sufficient to correct the hypoglycaemia and none of those patients were in a vulnerable age group. He said that there are a number of conditions which can cause hypoglycaemia, but small amounts of glucose will control or stabilise the patient's blood sugar levels and he has not seen any patient who was not on anti-diabetic treatment who has not responded after a single treatment. With that experience he examined the clinical history of all five patients in this case. After examining their clinical histories, he came to the conclusion that there was in each case a constellation of clinical circumstances. These are, first all the patients were elderly females with a number of chronic medical conditions who had suffered typical medical complications after hip fracture repair, but in whom the surgical procedure of without significant complications, or any complications. If there had been complications, they had been dealt with successfully. Secondly, none of the patients had a history of diabetes mellitus or was prescribed anti-diabetic drugs. Thirdly, 4 to 12 days after the repair of the hip fracture the patients developed suddenly severe hypoglycaemia without warning and with no indication it was going to happen, and that hypoglycaemia resulted in coma. Fourthly, the four patients died as the result of severe hypoglycaemia. The medical practitioners recorded neurological signs which suggested brain stem damage in four of the cases. No neurological symptoms were reported in Mrs. Wilby's case, and she survived the hypoglycaemic episode. Fifthly, in all five cases huge amounts of intravenous glucose were required to bring the sugar levels back to their proper concentration and once that was done the blood glucose levels dropped repeatedly back into the hypoglycaemic range even though considerable amounts of glucose had been administered. In two cases, Mrs. Hall and Mrs. Wilby, who survived for longer than 48 hours no further hypoglycaemia was recorded after 24 to 36 hours. Sixthly, all these cases occurred within a time frame of 6 months on orthopaedic wards. Dr. Kroker said that he had no clinical experience of any such case and no colleague of his has ever seen such a combination of circumstances." (Summing Up P 249 – 252).

222. We agree that the summing-up indicates that the defence did not specifically and explicitly explore the 'tipping point' occurring in the 'constellation' of age, frailty and

consequent comorbidities as causative of the hypoglycaemia, but it is clear that the defence did interrogate at some length the impact of the four index patients' pre-existing medical conditions, age and frailty as potentially causative of their respective deaths, or, in the case of VW, the symptoms of what has been diagnosed as a profound hypoglycaemic episode. The judge directed the jury in terms:

> "You must look at the medical and scientific evidence, both for the Prosecution and the Defence, in the context of the evidence as a whole and decide whether the sure conclusion is that the hypoglycaemia was the cause or a significant contribution in the death of the patient whose case you are considering. It follows you must consider whether in each case of the three cases death was caused by any one or more of the pre-morbid conditions the patient had or a supervening stroke, and if it was whether the hypoglycaemia contributed significantly to that cause of death in the sense that the patient would not otherwise have died at or around the time that she did die had she not suffered the hypoglycaemia in the first place." (Summing Up P18, lines 14 to P19, line 2).

223. The summing-up referenced, as agreed by the experts in their first joint meeting, 11 'natural causes' which were known to lead to the development of hypoglycaemia. These included not only the rare insulinoma, IAS and IGF, but also those conditions which had perhaps greater relevance to the index patients albeit to a lesser degree, namely: Addisons disease, heart disease, severe kidney failure, severe liver failure, severe sepsis and starvation or anorexia nervosa. We note that the judge also referred to "malnutrition" which is not suggestive of either of the extremes of starvation or anorexia.

224. We also note the treatment in the summing-up of the prosecution case relating to BD:

> "But the real burden of the Prosecution submissions on this aspect of the case was that BD's hypoglycaemia is explained either by an accidental administration or by her clinical condition. They accept the 8.5 units of insulin cannot by itself explain her hypoglycaemia, but they submitted her hypoglycaemia is explained by delayed absorption and/or her congestive cardiac failure, which can itself on the evidence cause hypoglycaemia <u>as can multi-organ failure</u>. The Prosecution rely upon the differences between BD's case on the one hand and each of the five patients on the other. The five patients have not all had a heart attack or organ failure or congestive cardiac failure, around BD unlike the five patients was close to death." (Emphasis provided).

225. We reject the implicit submission that the jury were not directed that they must be sure that the respective cases of hypoglycaemia were not due to natural causes, even if incapable of precise identification. The judge's directions to the jury on this issue are clear and repeated throughout the summing-up.

226. We agree with Professor Semple that Dr Hopkins' evidence is "learned and interesting and physiological" but conclude that the hypothesis which he advances is inconsistent with, and fails to address, the phenomena evidenced in the case of the index patients. We arrive at that conclusion satisfied that the expert witnesses called by the respondent have, without misunderstanding the facts or the science and within the legitimate parameters of their respective expertise, responsibly interrogated the hypothesis against the facts with an open mind and understanding of their obligation to inform the Court of any change of opinion. In so far as they have conceded a theoretical possibility, this does not advance the appeal.

227. Realistically, the hypothesis cannot be ethically tested, but neither is it established by any clinical experience and nor has it been subject to peer review and publication.

228. By contrast, Professor Ferner's evidence regarding the comparison to be made between the clinical presentation of those known to have suffered exogenous insulin overdose, including in the case of EH, and those who have been established to have developed hypoglycaemia through natural causes, is corroborated by vast clinical experience and peer reviewed medical literature. Mr Mansfield KC and Mr Brown submit that "there are too many variables to draw any meaningful conclusions from the patterns of blood glucose levels which we see in each of the index cases". We disagree – in particular, that the jury were unable to draw appropriate comparisons and reach conclusions based on the graphs.

229. As the judge correctly directed the jury:

> "You have heard a number of scientific and medical witnesses saying that nothing is certain or that they cannot be one hundred percent sure about a test or diagnosis or raising their various alternative possible explanations. Professor Forrest, the biochemist, said a scientific hypothesis can never be proved, you can only find something is inconsistent with the hypothesis or disprove it. He said the only certainty in medicine is death. I mention that to make the point that when you are deciding on guilt you are not looking for scientific certainty. You judge so you feel sure. Of course, you must take into account, if it is the case, that there cannot be medical or scientific certainty about something, and also the undoubted fact that the boundaries of medical science are forever being extended. You will also take into account that some possibilities have not been excluded by the expert witnesses, but the fact there is or may be another explanation does not mean that you cannot be sure about something. When considering a possible alternative explanation, you should look to see if it has any basis in fact, if it is based on speculation, you should reject it, because speculation is guesswork and so it will not help you in reaching your conclusions of fact. If there is a factual basis for any possible alternative medical or scientific explanation what you must then do is look at all the evidence and decide on all the evidence whether the case has been proved so that you can be sure of guilt. You judge the case on all the evidence and ask yourselves the simple question, upon the whole of the evidence do I feel sure."

230. In the written closing submissions prepared by Mr Brown, he notes at paragraph 56 that:

> "In short, the weight of the evidence at the original trial that each of the women in the prosecution cases had been administered exogenous cases had been administered exogenous insulin or sulphonylureas was overwhelming. The Defence was left in the position of saying that the Prosecution had to prove their case on this issue, but they could not offer any alternative explanation as to how any of these patients had developed hypoglycaemia as a consequence of natural causes."

We agree. However, we do not agree with the submission in paragraph 76 of that same document that:

> "The fresh expert evidence of Dr Hopkins and Dr Croxson completely changes the landscape of the evidence on the crucial issue of whether the jury could be sure that, in each of the four prosecution cases the patient had developed hypoglycaemia as a consequence of being injected with insulin or the administration of sulphonylureas."

Outcome

231. We have no doubt about the safety of any of the five convictions. The appeals are dismissed.