Friday, 25 November 2022

(10.27 am)

(In the presence of the jury)

MR JUSTICE GOSS: Mr Astbury.

MR ASTBURY: My Lord, Anna Milan, please.

DR ANNA MILAN (sworn)

Examination-in-chief by MR ASTBURY

MR ASTBURY: Thank you. Could we begin with your full name, please?

A. It's Anna Margaret Milan.

Q. Thank you. I understand it's Dr Milan?

A. It is, but Anna is fine.

Q. I know the temptation is, because I am asking the questions, to direct the answers at me, but if you could keep your voice up please and ensure that it is projected to the back of the court, we would be very grateful.

A. I apologise, I've had a cold, so if you can't hear me, do shout.

Q. I am sure someone will let us know if there is a problem.

Your occupation, please?

A. I am a consultant clinical biochemist at Liverpool Royal.

Q. Thank you. I think you worked specifically in the

clinical biochemistry unit at Liverpool University Foundation NHS Hospital Trust?

A. Yes, that's correct.

Q. You have been asked to comment on a blood sample that arrived at your laboratory, is that right --

A. It is, yes.

Q. -- in the name of [Baby F]? [Baby F] was born on 29 July 2015.

A. Correct.

Q. And you've had the opportunity to look at the records at the laboratory in that regard?

A. Yes, I have.

Q. Thank you. I think you were able to confirm, were you, that a blood sample taken from [Baby F] was received from the Countess of Chester Hospital at 4.15 in the afternoon of 6 August 2015?

A. Yes, that's correct.

Q. And that that sample was submitted to be tested for insulin and C-peptide levels?

A. It was, yes.

Q. Thank you. How are samples delivered, please, to your laboratory?

A. It very much depends on the nature of the test that's required. With insulin and C-peptide they have to be stored frozen, so that would have come via courier or

taxi in a bag that is temperature controlled to maintain that sample integrity.

Q. Thank you. Once the sample arrives, just so we understand -- where precisely is the laboratory?

A. We've just moved into a new building but it used to be in the Duncan Building as part of the Royal Hospital. The specimen reception, which is where the bag would have arrived, is on the ground floor and then it's brought up to the fourth floor.

Q. What happens, please, with the sample when it first arrives in its frozen form?

A. If it's a frozen sample it's treated as a priority to make sure that sample stays frozen, so every sample is taken individually with the request form to make sure that the patient name, date of birth and identifier, whether that's NHS or hospital number, match the details on the request form. If that happens then the sample is just refrozen with a bar code number on it.

Q. So on arrival, triage involves checking it has all the necessary detail --

A. Yes.

Q. -- to identify its origin and the purpose of the sampling?

A. Correct.

Q. And then it's placed in your own freezer?

A. Yes.

Q. Okay. How, once this process of checking and triaging the arrival of the sample is complete and it is placed in the freezer, what happens to the sample next and within what sort of time frame?

A. Again it very much depends on what tests are requested and also if it's stated as urgent. So at that time -- this was obviously 6/7 years ago -- insulin and C-peptides were measured in a batch; by that I mean they are not run in real time. And that's largely because we're an adult hospital, so we don't get urgent requests. So if it had been requested as urgent, we may have put it on the analyser that day, but at that stage this sample wasn't requested as an urgent, so it was frozen until we ran the batch the following week.

Q. So at that time, because of the nature of the bulk of the work that you received, insulin/C-peptide requests would be done together in batches?

A. Yes.

Q. And your recollection is that was the following week?

A. It was, yes.

Q. All right. Now, does the sample have to be defrosted before it is analysed?

A. It is, yes. So before we defrost anything, just so again to maintain sample integrity, we make sure all the

maintenance is done on that analyser and it passes all of its QC checks. By that I mean that it is fit to run before we defrost any samples.

Q. So in the context of this particular sample and insulin and C-peptide, is a specific machine used for that process?

A. It is. I know it doesn't mean a lot, but it is what we call a standalone machine. So it's in a separate room, so it has somebody dedicated to run it, and once that's -- it's routine, it's a routine analyser, but we have dedicated people to run it and make sure it's fit before anything goes on it.

Q. Again, in the context of insulin and C-peptide, that's a machine that would be gone to with a batch from time to time and before anything was analysed on it, it would be --

A. Yes.

Q. -- what, the maintenance would be checked?

A. All maintenance is done and there's various procedures, documented SOPs, as would be expected in a laboratory.

Q. Pausing there, sorry, SOPs?

A. Standard operating procedures. We are under accreditation by a governing body and to make sure our lab is fit for purpose we have to have very documented procedures in place to ensure that everything is

standardised, so machines are fit for purpose but are fit for purpose the same as they would be in any laboratory in the UK.

Q. Right. So you mentioned you're part of a standard?

A. Yes.

Q. Who sets that standard?

A. It's UKAS, UK Laboratory Accreditation Schemes.

Q. Do the manufacturers have any input on those maintenance procedures?

A. They do. So they dictate what maintenance they deem is necessary for that machine to be running. They're very standardised procedures. They have to be ticked before the machine can actually be used.

Q. Would any sample be placed within the machine before all of those maintenance checks were completed?

A. No.

Q. We've mentioned the manufacturer. Can you confirm who the manufacturer is and whether it's significant?

A. Our manufacturer for all of our analysers is Roche in the laboratory.

Q. How would you characterise Roche in your industry?

A. They're global. They are a massive business, UK, US, globally, and one of the largest suppliers of laboratory equipment in the UK and worldwide.

Q. And do they provide the additional equipment to go with

the machine that's required for the testing?

A. Yes, they provide all of the consumables that are needed, all of the reagents, all of the QC material -- and that's material that, once you have done your maintenance, then you have to test it to make sure it's performing, and all of the calibration standards as well.

Q. You mentioned QC, that stands for?

A. Quality control.

Q. Thank you.

A. Sorry, I talk in abbreviations.

Q. Forgive me for being pedantic.

A. No, no.

Q. The fact that this company, Roche, provide all the equipment, does that give rise to a particular term that you use for the collective?

A. In the sense of?

Q. Well, Roche assays. Could you explain what they are?

A. Yes. The term assay is -- so insulin is an assay, C-peptide is an assay. Everything that we run per analyte is deemed an assay. So overall Roche probably are responsible for about 400 to 500 assays that can be available.

Q. Right. You mentioned the standards that are maintained. Once the machine has been checked, quality assured, the

standard procedures have been run through and the analysis is completed, what happens then with the results?

A. Then we defrost the samples, ensuring they've been defrosted and mixed, and then they are placed on the analyser ready for analysis. They go through, depending on how long and which assay, they might take 20 minutes/half an hour for analysis, and then the results are held. So we always put QC through after as well to ensure that during that time window that machine was performing appropriately. And once those QCs, quality controls, at the end of that batch are analysed and are deemed appropriate, then all the results that were run between those two time points are then released on to a technical validation system.

Q. Can I just break that down a little bit? You told us you do more than one sample on each batch?

A. Yes.

Q. So, did I understand this correctly, that the results are held in a holding area almost --

A. Yes.

Q. -- whilst another quality assessment run is -- takes place?

A. Yes.

Q. What does that involve, please?

A. Again, that's just running through what we call quality control material. So they have assigned values for each of these analytes and we have a window of which deem them acceptable, so a range by which if it doesn't hit that range, then we'd have to reject that batch and re-run it. So we always put them through at the beginning and the end, particularly on a standalone analyser, which is one that's used in batches, to make sure during that time window everything is running appropriately. So they go through at the beginning and they have to pass before we put samples on. And they go through at the end to determined that during that time window, whether it be 3 hours or 4 hours, that everything was running appropriately.

Q. It's not until you're satisfied, at the start and the end, of the efficiency of the system that you then release from that holding --

A. Yes.

Q. -- position? Where do the results go from there?

A. Then they go -- that's what we call technical validation. So one of the lab staff will have looked at the results of the QC at the beginning, they'll have looked at the results of those quality controls at the end, and they will then what's called technically validate. And then they come on to a list for

a biochemist, which is myself and others, to then review clinically with whatever information we may have been given.

Q. So once everybody is satisfied that the machine is working accurately and that the results as produced are accurate, then they go on to a human analysis, if I can put it that way --

A. Yes.

Q. -- to consider what the numbers mean?

A. Yes.

Q. Would that be a fair way to put it?

A. That's correct.

MR JUSTICE GOSS: Interpretation?

A. Yes.

MR ASTBURY: A much quicker way to put it. Thank you.

So what happens at that stage then, please?

A. At that stage they are put on what we call a list, just for an easy term. We've got a technical term for it but it goes on to a list. Then, as a biochemist, we get a report that shows us the QC data so we can actually then confirm that technically they'd been validated, which I know is sort of -- makes it another level of checking. Then we start to look at them. If there's been information on the request form we can add an appropriate clinical comment. If the numbers themselves

speak, so what they say, we can also add a comment just based on the numbers as well.

Q. Once they've been through the human filter, if I can put it that way, what happens to the results then?

A. Depending on the nature of the comments that we might put on there, if it's something that we require or we deem that needs telephoning to the requester, whether that be an inpatient doctor or whether that's an external hospital, we will then phone that result through to the requesting location, especially back in -- when this was done we still required snail mail, it wasn't as electronically based as it currently is. So rather than wait for a paper report to get through to the requesting location, if it was deemed appropriate we would have phoned a result through.

Q. We'll come to that in a moment, but perhaps we should deal with the results of this particular sample next.

The sample was labelled, you checked, as having been taken at 17.56 on 5 August 2015; is that right?

A. That's correct.

Q. It was analysed within your laboratory and the results for this particular sample were -- and I think in fact you've provided a printout of the results; is that right?

A. Yes.

Q. If I can ask Mr Murphy to put AM1 on the screen, please.

Not something we've seen before. This is a document I'm sure you recognise from your professional life. Could you just please confirm for us what the results showed as a result of the analysis that you have described to us?

A. This screen obviously looks a bit alien because it's what we would see on our in-system -- what we call Telepath, which is how we interpret our results. But just to orientate you, the top left is the unique identifiers, that's the hospital number of the patient. Obviously at that stage, the name -- because when the request came in it might have been that they were referred to as twin 1, twin 2 without a first name, so we've kept with that with twin 2 on the request form.

Date of birth and the requesting location.

The specimen number is the unique identifier we'd have given that sample when it came into the laboratory once we had checked all the demographics, so that the name matched with the request form.

Obviously the collected time is the time it was collected at the referral location.

Then underneath you've got 6 August, 16.15. That is when we booked it into the system, so that time is when it was actually booked in.

Underneath you have three tests -- we'll, you've got two tests but two different units for insulin. So C-peptide is reported in picomoles per litre. And the value of less than 169 means it was undetectable on our system, so that's the lower report. We couldn't measure it in our assay.

Q. Sorry, pausing there, there comes a point where there is such a small amount that even your computer can't -- your testing equipment can't detect its presence?

A. Correct.

Q. And the threshold for that presumably is 169?

A. Yes, it is.

Q. So when it says less than 169, that could be zero, that could be 168 or anywhere in between?

A. Basically it means that we cannot accurately give it a number because it could be anything below that or it could be completely zero, but the assay itself can't distinguish anything below that number.

Q. Thank you.

A. Then the insulin it reported in two different units. But the important one with relation to the C-peptide is the one that's got SI in brackets next to it. That's the international reporting units. That puts it in the same units as the C-peptide, which is picomoles per litre. So it's only a factor different, it's not that

we've measured it twice. There's a multiplication factor involved. But the important one is the 4,657, because that's in the same units as the C-peptide, and obviously they come from the same molecule, so that's what gives you your indication.

Q. So just dealing with that briefly, so I understand it. In order to compare the two figures, please correct me if I'm wrong, they are expressed in exactly the same measurement or by means of the same measurement --

A. Yes.

Q. -- so that there's no, as it were, distortion between the comparison?

A. Yes. If you're looking for ratios, which is what you tend to look at for interpretation, you're looking at the SI units for insulin and then the C-peptide so you can calculate your ratio of C-peptide to insulin.

Q. You mentioned before that in some circumstances the hospital involved will be called, there's a telephone call takes place?

A. Mm-hm.

Q. You're able to confirm that happened in this particular case involving [Baby F]. If we can look, please, you provided, I think, a note of the telephone call; is that right?

A. Yes. We do try and -- obviously it's not always

possible but we do try and keep a complete audit trail end to end so that we can determine who a result was telephoned by.

Q. Thank you. If we could go to AM2, please. Can you confirm this is the document you were able to provide?

A. Correct.

Q. Please tell us or just explain to us briefly what this tells you, knowing the system that was in place?

A. Yes. Again, it's not a particularly attractive screen, but what it documents is the result that we telephoned, which was the C-peptide and insulin, who it was telephoned by, and where to. So it was telephoned to the Countess of Chester biochemist, which would be the equivalent of one of us at Chester, and where it was telephoned and what time. The advice we would have given them would also be the comment that was reported when they got the paper report as well.

Q. And we can see there:

"Advice information: low C-peptide to insulin."

A. Mm-hm.

Q. Is that, as you were telling us before, how you enter them in the same measurements --

A. Yes.

Q. -- so that a comparison can be made? Is that what you were alluding to there?

A. Yes. That's correct.

Q. You then have:

"[Question mark] exogenous"?

A. Yes. It's our shorthand way of putting "query exogenous". So while it might look as though it's a question mark, it's a shorthand we often use for query. So we're just basically saying, "Is this exogenous? It looks like it is".

Q. Okay. Very briefly, why does that stand out as exogenous?

A. The C-peptide is undetectable and in health C-peptide should be a lot higher than insulin because it's got a longer half-life and it's not active. So insulin is quickly cleared, so in health your ratio should be between 5 and 10 C-peptides to insulin.

Q. So it should be considerably higher than --

A. The insulin --

Q. -- (overspeaking) not considerably lower?

A. Yes.

Q. Then:

"Suggest send sample to Guildford for exogenous insulin."

Just explain that to us please.

A. It's not a standard comment and it's not something that most people take up. But in a case where there is

a suggestion of exogenous insulin, if people wanted to determine the type, Guildford is a specialist laboratory that can help. They have assays that can distinguish between the sources of the insulin. By that I mean is it human or -- because obviously some insulin supplements are bovine in origin or porcine, so they can help distinguish between that. But it's not something people tend to take up unless there's a real difficulty in trying to understand where that insulin came from.

Q. Right. Who is that a decision for?

A. That's for the requesting location to discuss with the clinical team.

Q. So it appears, on your note, on the basis -- that that's something that would have been raised with them rather than something you would have been considering --

A. Yes.

Q. -- from your perspective?

A. Yes, we wouldn't have sent a sample on unless there was a clinical demand for it. The results speak for themselves, so it's unlikely that it would be sent on. By putting that, it implied that we would keep the sample as well if they did want to send it on.

Q. Right, okay. And how long would the sample have been kept for whilst that decision was being made?

A. We would have kept it for at least 7 days because it

would have been refrozen after the assay.

Q. You mentioned Guildford and you told us about the type of quality assurance that takes place within your laboratory.

A. Mm-hm.

Q. Is there a quality assurance process from outwith the laboratory?

A. Yes. So every laboratory, as part of the UKAS accreditation, which was the governing body I mentioned earlier, we also have to participate in what's called external quality assessment. And this is a body that sends us anonymised samples every 4 weeks that we have to run through all of our assays as patients and then return the results, so you can see if your assay is performing in line with all the other Roche users in the UK.

Q. So you -- is this right, Guildford presumably is the HQ for your particular area of expertise; is that right?

A. Guildford is -- that's a separate laboratory, it's like our laboratory, but their specialism is insulin/C-peptide. But the external quality assurance is done by a body called Birmingham Quality. They basically cover all of the laboratories in the UK and send out these samples as part of their accreditation scheme. It's another level of checking.

Q. Another level of checking the efficiency of your laboratory, not internally but externally?

A. Yes.

Q. That happens on a regular basis?

A. Yes, on a regular basis. It is retrospective because obviously you have analysed them, the results have been reported, but it helps you try and identify if you've ever got any problems, whether it's a manufacturer-based issue, so if everybody performs badly, or whether it's an individual laboratory performance.

Q. Were there any problems at any time around the time of this sample in --

A. No.

Q. -- 2015?

A. No.

Q. Does that enable you to express any view as to the confidence you have in the results you have just explained to us?

A. Very confident in the results. I mean, the pattern is very clear-cut. It's not numbers that -- obviously the C-peptide is below the limit of quantification --

Q. Yes.

A. -- but the insulin is very much in the measuring range, so I have no doubts about the numbers that were produced. Every procedure was followed that we would

follow for any sample. There was nothing different about this sample.

MR ASTBURY: I have no more questions for you.

Cross-examination by MR MYERS

MR MYERS: Just a couple of questions please. You explained to us that the sample has to be frozen to maintain its integrity?

A. Mm-hm.

Q. If it's not frozen, does that undermine -- or does the sample deteriorate or is there a risk of the sample deteriorating?

A. So it very much depends on the time window of that. So we have procedures in the documentation that -- we've said about the SOPs -- that would say with what window we would accept a sample if it had arrived, say, in the post. But obviously this arrived frozen. But if it had come in the post and we didn't have any sort of questionable time window about how long that sample had been defrosted for --

Q. Right. If it had arrived unfrozen, what's the time window that you look at for a sample like this?

A. Again, it very much depends on the assay. So depending on what analyte, because some are more stable than others, but easily this insulin and C-peptide, because we have added them on -- and by that I mean if suddenly

somebody had said, I've got a reason to request it, we would add it on to a sample, so we would accept it within 12 to 24 hours.

Q. Okay. If it hasn't been frozen in the right way, is there a risk of that affecting the accuracy of results?

A. If it hasn't then, there is a risk but obviously with this we knew the time window from the time of the sample being taken to when we'd received it was within 24 hours anyway, even though it arrived frozen.

Q. The sample was taken at 17.56 on the 5th, wasn't it --

A. Yes.

Q. -- which is about 22 hours before you received it?

A. Yes.

Q. But as it happens, do you know at what point that sample was frozen in that process?

A. No, but obviously Chester's laboratory will have their procedures in place.

Q. Yes.

A. So that sample quality would have been checked before they'd have sent it to us. So they would have to have ensured that actually it's been stored appropriately and they are sending it to us appropriately as well.

Q. That's certainly what should happen, isn't it?

A. Yes.

Q. Can we just put up AM2 again, please, Mr Murphy.

This is a record, Dr Milan, of the communication between your laboratory and the Countess of Chester Hospital; is that correct?

A. It is correct, yes.

Q. And we can see that that communication took place on 12 August 2015 at 16.40?

A. Yes.

Q. And you've explained to us how it was that the timing worked out like that; I'm not asking any questions about that. I'm just going to ask you what it says at the bottom where it says:

"Low C-peptide to insulin. [Query] exogenous. Suggest sample to Guildford for exogenous insulin."

A. Mm-hm.

Q. Is that advice that is given to the Countess of Chester for them to follow up if they want to do so?

A. Yes. So that's then for the Countess of Chester to discuss with the clinical team. It's very rarely required because, as you say, the time window by the time the results is there, they've identified the cause and the patient -- the most important thing clinically is the patient. So in this case knowing what the source was probably wouldn't have aided it, but we've just given them the option to say: we've kept your sample, if you do not want to send it on, please get in touch and

we would forward it on.

Q. So the fact is at Guildford there's a specialist laboratory that looks at the nature of the insulin involved; is that correct?

A. Yes.

Q. And therefore if the unit who's requested this to be done have questions about what lies behind these readings, if they want they can follow that up?

A. Yes. And I mean, sometimes it happens when you've got sort of perhaps a bit more of a detectable C-peptide but it's still not in the right ratio, so could there be exogenous and endogenous? But in this case there's no endogenous present.

Q. No, but if there are any questions arising as to what lies behind these figures, the next step would be to send it to Guildford for specialist analysis?

A. If it was required, yes.

Q. If it was required, and that's something the hospital have to make a decision about, that's no duty on you to do that?

A. No.

Q. You keep the sample for a certain length of time afterwards, don't you?

A. Yes.

Q. And you stored the sample that was received from the

Countess of Chester for 7 days?

A. We did.

Q. And then it's disposed of?

A. Yes.

Q. So that means, were there any requirement to analyse that sample after that seven-day period, that couldn't be done because, as a matter of the procedure, it's been destroyed by them?

A. It has yes.

MR MYERS: All right. Thank you, Dr Milan.

Re-examination by MR ASTBURY

MR ASTBURY: Thank you. Just one matter arising, doctor, with regard to Guildford.

So I understand it, would Guildford assist with whether it was exogenous or not?

A. No. The results dictate that it's exogenous. They would just help, if you were unsure of the source, as in what is the -- is it mammalian exogenous insulin or is it bovine... It's generally used probably more in forensic cases where you need to determine --

Q. So those potential sources, can I just see if I have understood, so bovine insulin can be --

A. Or porcine, yes.

Q. -- obtained from a cow or from a pig?

A. Yes.

Q. That's the mammalian version that you discuss. Equally we've heard there are synthetic insulins.

A. Yes.

Q. So really, Guildford would have been deciding or assisting with exactly what type of exogenous insulin --

A. Yes.

Q. -- not whether it was exogenous or not?

A. Correct.

MR ASTBURY: Thank you. Does my Lord have any questions?

Questions from THE JUDGE

MR JUSTICE GOSS: Just one, yes. You say this arrived frozen. Is there a common way in which these samples are frozen in hospitals?

A. So once -- something for insulin/C-peptide, once it's been checked at the referral laboratory, so this would be Chester, it's spun, which basically means the serum is separated from the cells. That is frozen and it should be frozen at at least minus 20 degrees. And then obviously when it's sent to us, it'll be sent with ice blocks and dry ice to keep it frozen in the transport. But obviously Chester's only 30/40 minutes down the road, so it'll be in a cool bag, insulated box, with ice around it.

MR JUSTICE GOSS: So that will have happened some time in the 22 hours between the taking and its arrival --

A. Yes. They won't have taken it out. If it's how we do it and it's how most laboratories do it, they will not take it out of the freezer until everything is ready and the courier or the taxi driver is almost with them.

And obviously we transport samples like this frequently and most samples will stay frozen for a day in those conditions, if not longer. They are very well packed in.

MR JUSTICE GOSS: Right. Thank you very much indeed for coming and giving your evidence. It's complete and you are free to go.

MR ASTBURY: Dr Milan may be back.

MR JUSTICE GOSS: You may be back. Well, just in case then, I'll say this to you: don't speak to anyone about anything to do with this case, in particular your evidence, and don't seek out any information about what's going on in the trial from anyone or any source, be that over the various forms of media one can gather information now. So just keep your mind clear. Thank you very much anyway.

(The witness withdrew)

MR JOHNSON: Professor Peter Hindmarsh, please.

PROFESSOR PETER HINDMARSH (sworn)

Examination-in-chief by MR JOHNSON

MR JOHNSON: Would you start by giving us your full name,

please?

A. I'm Peter Christopher Hindmarsh, and I'm a professor, emeritus professor, of paediatric endocrinology at University College London and also a consultant paediatric endocrinologist at University College London Hospitals.

Q. Thank you. Do those hospitals include Great Ormond Street or not?

A. That's a separate entity, but yes.

Q. Are you a professor of paediatric endocrinology there as well?

A. No, that title is merely conferred by University College London.

Q. Thank you. Are you an honorary consultant at Great Ormond Street though?

A. Yes. At that stage, yes.

Q. Thank you. A paediatric endocrinologist, what does that mean in terms that I can understand, please, professor?

A. So what we deal with are the hormones in the body that regulate a number of areas, such as overall metabolism, glucose, or perhaps in layman's terms sugar, metabolism, fat metabolism, growth and development, and air response to stress.

Q. Thank you. Were you consulted by Cheshire Police in relation to the case of [Baby F]?

A. I was.

Q. And did the concerns of Cheshire Police relate to a hypoglycaemic episode that [Baby F] had had on 5 August 2015?

A. That's correct.

Q. Were you given a quantity of material which included the following: some maternity records for [Baby F]'s mother? The Countess of Chester's medical records for [Baby F]? Specimen result, a specimen result sheet for [Baby F]? A prescription for [Baby F]? And witness statements made by a number of other experts, who included Dr Dewi Evans and Dr Sandie Bohin?

A. That's correct.

Q. Were you told that the suspicion was that [Baby F] had been given synthetic insulin?

A. Yes. I think the terminology used was "extraneous insulin injection/infusion", but yes.

MR JUSTICE GOSS: "Extraneous" meaning that what insulin had not been manufactured or made by the baby?

A. Correct, yes. I prefer, my Lord, the term "exogenous" if we can use that.

MR JUSTICE GOSS: As long as we all understand what exogenous is.

MR JOHNSON: Exogenous means, what, please, professor?

A. It means something that's not been produced within the

body.

Q. Thank you. With that question in mind, did you consider the information that you had been given?

A. I did.

Q. And did the issues that you considered include the following: was [Baby F] given exogenous insulin, when was he given it, and how was he given it?

A. In considering the episode of hypoglycaemia, I did conclude that the cause of the hypoglycaemia was not due to any endogenous production of insulin and that it was -- that the findings, the biochemical findings, were compatible with the administration of exogenous insulin.

Q. Yes. Right. I just want to deal with the circumstances that led you to your conclusions, if I may. Can I start with your report, with your section 1, which is page 3 of the report, I believe.

Did you, in your report, set out the circumstances in which [Baby F] had been born in the 29th week of -- sorry, the 30th week of gestation?

A. Yes. I made a note about that, about the birth weight and about the subsequent progress within the first 12/24 hours of life, when focus rightly centred on breathing, the use of artificial surfactant to help in terms of ventilation and breathing, a noted blood glucose concentration of 2.7 millimoles per litre.

Which -- it's lower, when repeated at 1.9 millimoles per litre, but corrected very rapidly with a standard infusion of 10% dextrose, delivering a glucose infusion rate of 4.2 milligrams per kilogram per minute, which is a normal rate for a newborn.

Q. What I'd like to do, if we can, professor, is just take the chronology reasonably slowly for all our benefits, really, not least my own. If Mr Murphy would help by putting up tile 5, please, just to refresh your memories as to the way things progressed.

Here is the medical record to which you have just referred, I believe, professor; is that right?

A. Yes, that's correct.

Q. You record the surfactant, you record a blood sugar reading at the bottom of the page, and then, as we scroll down to 2918, we see that repeat gas about half a dozen lines down and the glucose reading of 1.9, which is what you have just referred to?

A. That's correct, yes.

Q. That, as you have told us, was treated with 10% dextrose on an infusion?

A. Correct.

Q. And that simple treatment rectified the problem at that stage; is that right?

A. That is correct, yes.

Q. Thank you. Was there then an episode on the 30th through to 31 July, where [Baby F]'s blood sugar rose beyond the normal range?

A. That's correct as well.

Q. Was that treated with a very small dose of insulin?

A. It was.

Q. And did that have the required effect of reducing [Baby F]'s blood sugar within a relatively short period of time?

A. It reduced the blood glucose and it returned the blood glucose towards the normal range.

Q. Thank you. Moving on, if we may, to 5 August, the jury has heard a body of evidence relating to the fact that, shortly after midnight, in the early hours of the 5th, a bag of total parenteral nutrition was set up on an infusion at or about 00.25.

Could we put up the chart at J3191, please? Thank you.

I think you referred to this in your report, professor, and in particular you referred to the increase in heart rate that we can see charted there in the top third of the document on the screen; is that right?

A. That's correct.

Q. You refer also to -- well, you refer specifically to the

rise in heart rate at 1 o'clock. Then a further increase at 2, 3 and 4 o'clock. And you refer retrospectively to the fact that prior to the TPN infusion being administered to [Baby F], his, that is [Baby F]'s, heart rate had been running consistently at a rate of about 150 beats per minute?

A. Yes.

Q. If we go to tile 163, please, and scroll down so we get the reading in the early hours of the 5th.

Do we see there, professor, at 01.54 hours a reading, a blood sugar reading, for [Baby F] of 0.8?

A. That's correct.

Q. What does that reading mean?

A. Well, it represents a very significant change from the value recorded on 4 August at 23.32 hours, which was 5.5, and a value of 0.8 millimoles per litre is extremely low.

Q. We'll deal later with the potential consequences of such low blood sugar, but in general terms at this stage, is that low reading a cause for concern?

A. Absolutely.

Q. Rather than us going to and from a number of documents, you helpfully produced, as appendix 1 to your report, a table of blood glucose measurements; is that right?

A. That is correct, yes.

Q. I wonder whether Mr Murphy could put up that table. For the lawyers' benefit, this is in the witness statements at page I4261.

Just to be entirely clear about this, professor, all the black script on the page is your script, isn't it?

A. Yes, that is correct.

Q. What we have done is I have added into your document the T numbers, which are the tile numbers in the digital sequence of events presentation, so that if anybody wants to cross-reference the information in your table to the material that the jury has, there's a ready cross-reference there. All right?

A. Mm.

Q. So looking at that table, first of all, do we see at the top on 4 August at 23.32 the same material that we saw on the blood gas chart that we just had on the screen?

A. Yes, that's correct.

Q. Followed by the 0.8 reading at 01.54 in the morning?

A. Yes.

Q. Is that right?

A. That is correct.

Q. Thank you. Looking at that series of readings, first of all, and then we'll break it down a little, what does that tell you?

A. What it tells us is that the hypoglycaemia is persistent

from that first measurement of 01.54 hours, right through. There are some intermittent points where there's been an interruption of the infusion system, for example at 12.00 hours on 5 August, but once that's reinstated, the hypoglycaemia continues until cessation of the total parenteral nutrition at 18.55 hours on 5 August.

Q. You've already told us that the very first reading at 23.32 of 5.5 is a normal, in inverted commas, reading; is that right?

A. Absolutely, yes.

Q. The final reading at 21.17, would that be classified as normal?

A. It would, yes, absolutely.

Q. There is a reading at 5 in the morning of 2.9. We've heard from the staff at the Countess of Chester that that's above 2.6, which generally speaking they would take as their cut-off. Would you agree with that as a matter of principle?

A. That's conventionally the value used. I think, for the purposes of the court, we should continue with that.

Q. Yes, thank you. We can see there that that particular reading is on tile 200. I'd just like the jury to see the document that lies behind tile 200, from where that reading derives.

If Mr Murphy would zoom in on the 5 o'clock reading to include the initials of the person that recorded that reading -- 5 am, sorry.

Of course, you don't know who that person is, but I'm just doing that for the court's benefit at the moment.

Now, returning to -- if we could remove that, please. Could we go back to Professor Hindmarsh's table, please? It's the document I4261.

Did you look at the medical records to see what treatment had been given to [Baby F] over the period of time covered by the readings which you replicate in your table?

A. Yes, and I've tried as best I can to make notes down the right-hand column of what I think was happening with fluid administration anyway.

MR JUSTICE GOSS: There's a note from the jury.

(Pause)

MR JUSTICE GOSS: I'll tell you what the note says:

"Can the jury have a printout of the table?"

MR JOHNSON: Oh yes.

MR JUSTICE GOSS: I was going to raise that at an appropriate moment. I didn't want to interrupt the professor's evidence.

MR JOHNSON: Would they like that now?

MR JUSTICE GOSS: You put it up on the screen each time, don't you, but on the other hand if they have it on paper they can write on it or make any notes. I was going to say they should get it in any event because I want it, and you want it.

MR JOHNSON: I've got it.

MR JUSTICE GOSS: All right. We'll press on then. Sorry to interrupt you.

MR JOHNSON: Not at all. It is, of course, because it's been shown, available digitally. But if a paper copy is required there's no problem at all.

Sorry, professor. Just going back to your table, I think you compared, and I'm looking midway down your page 4 now, I think you compared that chronology, as you have produced it, to events that were going on with the treatment of [Baby F] at the time; is that right?

A. That's correct, yes.

Q. You looked in particular at boluses and infusions of sugar that were being given to [Baby F] and compared that information with the readings that were being obtained by the various blood tests that were being conducted?

A. That's correct, yes.

Q. And what did you notice so far as the interrelationship between the figures as reproduced on the screen and the

treatment that was being undertaken at the time?

A. Well, over this period of time we can see documented ongoing hypoglycaemia, which has taken place despite five bolus injections of 10% dextrose and the ongoing glucose delivery from the 10% dextrose infusion that was running concomitantly and the glucose that is also contained within the total parenteral nutrition.

Putting the infusion information together then that would give us a glucose infusion rate of somewhere in the region of 12 milligrams per kilogram per minute, which is twice the normal requirement of an infant -- of a baby.

What is more difficult for me to quantitate and add to that is the contribution essentially from the five bolus injections of 10% dextrose. So although I'm quoting an infusion rate delivering the 12 milligrams per kilogram per minute, it is likely that more glucose was being delivered because of the additional amounts coming from the bolus injections.

So in terms of the amount of glucose being administered, we're talking a minimum of twice the normal daily requirement, but probably more than that.

Q. From your examination of the records, did you identify -- and I'm midway down your page 4, professor -- three events of note that day after the TPN

started to run at 00.25 in the morning?

A. So I've commented already on the prolonged period of hypoglycaemia that appears to be associated with the introduction of that infusion. And then there is an episode commencing around 10.00 hours on 5 August when there were problems with the cannula, the infusion of TPN and fluids, which meant that this needed to be attended to, re-sited, and as a result of that, fluids were discontinued. And following that discontinuation, you can see there are two further glucose measurements, one at 11.46 hours at 1.4 millimoles per litre, so not too much different from the one at 10.00 hours, but then a further value at 12.00 hours of 2.4 millimoles per litre, which would imply that the blood glucose had started to increase spontaneously because at that stage there was no contribution from the intravenous route.

Q. So on the face of it, [Baby F] was a child who was receiving double the normal requirement of sugar as a result of the combination of TPN and dextrose, and yet when he was taken off that double quantity of sugar, his blood sugar actually increased?

A. That's how I see it and I believe that is correct.

Q. Yes.

MR JUSTICE GOSS: We'll pause there, I think, and distribute those at this stage.

MR JOHNSON: Thank you.

(Handed)

If we go, now the jury has the paper version, to tile 259, please, Mr Murphy. Could you expand it for us, please?

Professor, did you identify -- it's not the clearest screen, but did you identify that the TPN or some TPN was recommenced at about midday, according to that chart?

A. Yes. It looks as though the intravenous infusion problems were resolved and the infusion was commenced around 12 midday.

Q. And if we look at the paper version of your chart, if I can just hand to you --

A. I've got one actually.

MR JUSTICE GOSS: You can hand it back. You have two now, it doesn't matter.

MR JOHNSON: Sorry, my mistake.

If we look at your chart, do we see that at midday the blood glucose level was 2.4?

A. It was, yes. That's absolutely correct.

Q. But that by 2 hours later, at 14.00 hours, again that was heading in the wrong direction, back down to 1.9?

A. That's correct, yes, and remained there until later in the afternoon.

Q. Yes, by which time the infusions had been stopped again; is that right?

A. They'd been stopped at 18.55, I think, is the time, yes.

Q. So again, factually, is there, on the face of it, the paradox between a child being given more sugar but the blood sugar level dropping?

A. Correct.

Q. At 17.56, I'm still on page 4 of your report, did you record the fact that at that time the medical team took a blood sample for analysis from [Baby F]?

A. That is correct.

Q. And are the results of -- well, you set out the results of that sample, they are set out in our tile 292, please, Mr Murphy.

Do we see there a blood glucose level from the lab at Chester of 1.3?

A. That's correct.

Q. There is, on the face of it, a disparity between that result and the one we can see on your chart at 18.00 hours, which is 4 minutes later, which, if anybody wanted to look at it, is at 295. What's the explanation for that apparent, if any, for that apparent disparity?

A. So we have here the glucose measurement in the laboratory, which is a plasma glucose measurement, and we have a near-patient blood glucose measurement, so

there's a slight difference between the two. According to the International Organisation on Standardisation, a discrepancy of anything up to 0.8 millimoles per litre between a laboratory plasma glucose measurement and a near-patient blood glucose measurement is acceptable, so they aren't quite the same as -- there's a whole host of reasons why that is the case, but the discrepancy between the 1.3 and the 1.9, as I say, under the International Organisation On Standardisation, that would be within their acceptable range for potential discrepancies.

Q. Whichever is the more accurate, what we have here is an unacceptably low level; is that the essence of it?

A. The essence of it is, whether it's 1.3 or 1.9, it is very low.

Q. I just want to check my reference before I ask you the next question. You refer in your report, in the same paragraph that we've just dealt with, to the results that were obtained by Dr Milan's laboratory at the Royal Liverpool University Hospital. If Mr Murphy could put that on the screen, please. It's J26407, I think.

This is what Dr Milan spoke of about an hour ago or so. What do we see there, please, professor?

A. So we've got the sample, along with its timestamp of collection, at 17.56 hours on 5 April (sic). It's

a serum sample. And depicted below the dashed line are the results of the analysis undertaken and verified and released on 6 August at 16.15 hours. They show the measurement of C-peptide, which is quoted there at less than 169. The units aren't stated but we know that that is in picomoles per litre.

MR JUSTICE GOSS: We know, we've heard evidence of the fact that they don't -- the machine cannot detect anything less than 169. It could be between zero and 169. That's in evidence now.

A. Correct, yes.

You also have the insulin concentrations measured at the same time, 671 milliunits per litre and then in the -- in molar terms, that is the SI units, 4,657 picomoles per litre.

MR JOHNSON: Dr Milan told us that comparing the 4,657 figure for insulin with the C-peptide figure in the same units, the C-peptide figure should be anything between 5 and 10 times the size of the insulin figure; is that correct?

A. I certainly said that in my documentation. I'm not entirely sure I heard her say that, but I may have missed it.

MR JUSTICE GOSS: She did say it.

A. Fine. She is correct as well.

MR JOHNSON: You're both correct.

A. We're both correct.

Q. Very good. Can we deal next with your page 5, professor, and with the dangers of very low insulin. Can you explain to the jury the effect of a depressed level of insulin -- sorry, I said the dangers of very low insulin, what I meant to say was the dangers of very low blood sugar. Could you tell then jury what are the dangers of very low blood sugar, please?

A. The brain is reliant on a constant supply of glucose for function, and it does not store any glucose in reserve to any significant degree. It has some -- it can store glucose as glycogen, but that will only last 20 minutes. After that, there is no other energy available for functioning of the brain.

Now, fortunately, there is a slight way out of this problem and that is during hypoglycaemia, you can generate ketones and they're the breakdown products from fat. So you can break down fat as a source of energy and the brain will utilise the ketone bodies that are from that breakdown of fat as a substitute for the glucose that's missing. That's absolutely brilliant, it serves all of us very well indeed, and babies in particular, apart from one situation.

That is if your low blood glucose, hypoglycaemia, is

caused by an excess of insulin. Insulin will do two things. The first thing it will do is it will reduce blood glucose, as we've been talking about already. So you've lost your glucose, you have lost that source of energy. Can you fall back on ketone bodies? The answer is no. So the second problem with a high amount of insulin is that it will switch off ketone body formation. So in the situation of hyperinsulinaemic hypoglycaemia -- I apologise for the terminologies but that's what we're talking about, lots of insulin producing a low blood glucose -- the brain is now in a very, very susceptible state to incurring damage. That damage depends a little bit on the duration of hypoglycaemia and also the depth of the hypoglycaemia.

Now, initially, if you go down to a blood glucose of 2.6 or 3, then you'll have mild confusion and if you are involved in any cognitive process, such as reading and writing, then there will be a deterioration in that. But as we progress further down in terms of the blood glucose delivered to the brain, and that's not much, then it can lead on to seizures, death of brain cells, coma and, on occasions, death.

Q. So thus far, we have your opinion that the insulin in [Baby F]’s system was exogenous. You've just told us about the dangers -- well, you've told us also that the

depression in blood sugar coincided with the administration of fluids and you've told us of the potential consequences of administering exogenous insulin to anybody and, in particular, to a baby.

What I'd like to move on to, if we may, professor, is page 8 of your report, the means by which, in your opinion, the evidence suggests that this insulin was administered to [Baby F].

So it may be of some assistance to the jury to have one eye at least on the chart that you have -- the table that you have produced for us. Can you talk us through your conclusions so far as how it was this insulin was administered to [Baby F]? And can we start, please, with your understanding of the type of insulin that was available at the Countess of Chester Hospital?

A. The insulin in use, and has been in use for the last 20/25 years or so, possibly more, is synthetic insulin. We do not have stocks of what were the animal insulins, that's the pig and cow insulins, they would not be held as regular stocks, either on wards or in the hospital pharmacy, they would have to be requested in their own right. So we're talking about the synthetic human insulins.

These split into two groupings. One is the short-acting insulins, which, as their name suggests,

act quite quickly within 30 minutes, 60 minutes, if given by the under-the-skin injection route, and tend to last, in terms of their duration of action, for something between 4 and 6 hours.

There are two types. One is where the chemists have created an insulin that looks identical to human insulin, and that's the commonest ward stock, known as Actrapid. There are other insulins that you may hear about, such as NovoRapid Aspart or Humalog, and these are synthetic, but they have a modification made to one of the amino acids, one of the building blocks of the insulin molecule, to alter their onset of action.

We don't tend to use those as ward stock for any intravenous infusions if we need them. So on the ward, the most likely insulin available for use in any situation would be Actrapid insulin, synthetic human insulin.

Q. I would like to just show you --

MR JUSTICE GOSS: Sorry, before we do that, you said there are two groupings, a short-acting one, and then did you run on to describe the second one?

A. I did not, my Lord. Thank you for picking me up on that.

The other type is long-acting insulins, which currently are modified in a way to prolong the duration

of action up to 12 or 24 hours. They're predominantly given by the subcutaneous, under the skin, route.

MR JUSTICE GOSS: Right.

A. I have never seen any information on them being given intravenously.

MR JUSTICE GOSS: Thank you.

MR JOHNSON: You're familiar with these substances from your working life, I've assumed. Can I produce to you a vial of Actrapid insulin that was obtained from the Countess of Chester Hospital?

(Handed)

A. Yes.

Q. I'd quite like to hand it round the jury in a moment, please, my Lord. That on its face, I think, appears to be a 10ml bottle; is that right?

A. Yes. It's 100 units in 1ml and these are the standard 10ml vials.

Q. And just so the jury can have this in mind when they look at it, normally the bottle would be capped with what is within the bag as an orange -- yellowy-orange cap; is that right?

A. That's correct. It's in the bag itself, it's not attached.

Q. The reason it's been removed is because if one looks under the cap, one sees in effect a self-sealing cap;

is that right?

A. Yes. It's a latex bung, essentially.

Q. And if a medical professional wanting to extract -- how would a medical professional extract insulin from that bottle?

A. You would need a needle and syringe, and if you're using it therapeutically you would use an insulin -- a syringe graded to allow for an accurate dose, the drawing up of the insulin, because this is quite concentrated, this is 100 units per ml and we would probably -- we would be talking perhaps in ourselves of perhaps using no more than about 2 or 3 units given subcutaneously, or 5 units perhaps.

So you'd need a very accurate insulin syringe to -- if you wished to dose therapeutically. Then you would have to add a needle to that, put the needle through the resealable latex bung, draw up the desired amount, and withdraw the needle and syringe.

Q. When you say using it therapeutically, do you mean using it legitimately for legitimate treatment?

A. Yes, a prescribed insulin dose.

Q. Yes. And that would have to be measured very, very carefully?

A. It would.

MR JOHNSON: I wonder whether the jury could see the bottle,

please.

MR MYERS: I wonder if I could take a look first, my Lord. Thank you.

(Pause)

MR JOHNSON: Professor, what I'm going to do now, if I may, is deal with how this exogenous insulin was administered and then I will ask you ultimately how much of this went into the liquid that was being administered, so the jury know where I'm going.

Before I do that, can I formally exhibit this bottle and packaging, my Lord, please?

MR JUSTICE GOSS: Yes.

MR JOHNSON: I'm told I didn't make it entirely clear through you, professor. The needle attached to the syringe goes through the latex bung, and when it's withdrawn the bottle self-seals in effect; is that the position?

A. That's correct, yes.

Q. We can see for ourselves how much liquid is in there and we'll turn in due course to how much was removed.

Did you consider, in the light of the evidence that was available, how insulin was administered to [Baby F]?

A. I did. I think probably what we should say right at the outset is that it is not possible to give insulin by mouth, by the oral route, because it's a large molecule,

so it can't be absorbed very easily. And the second thing is that it is -- because it's a protein, it would be broken down or damaged by the acid in the stomach. So we're not talking about any form of oral administration or administration through a nasogastric tube, for example. We are talking about the administration of insulin either by the intravenous route or by subcutaneous administration, under the skin.

I'll deal with the subcutaneous route, if I may, first of all. In my report, and also in one of the exhibits I provided, I give the time course of insulin. That's figure 2, my Lord, in my report. But the point about the subcutaneous route is that with a duration of action of 4 to 6 hours, and over the period that we've documented of some 17 hours of hypoglycaemia, that would require multiple subcutaneous injections, as I say roughly every 4 to 6 hours.

Q. And the first one would have been at what time?

A. To get that effect you'd probably have to do that almost at the same time as you set up the total parenteral nutrition bag. The argument against that is there would be quite few injections and also it would be then difficult to start to explain why you had such a quick return towards normal blood glucose, particularly as you can see in the chart that was sent round that when the

TPN, the total parenteral nutrition, stopped at 18.55, we almost had an almost instantaneous rise to 2.5. But by 21.17 hours we had achieved normoglycaemia, whereas if we had been relying on subcutaneous injections, we wouldn't have seen such a rapid response in terms of the blood glucose, which would imply that probably an intravenous route is the most likely explanation.

Q. So for that reason, dealing with the intravenous route as being, in your opinion, the route by which this insulin was administered, how was it done?

A. So intravenously there's two ways of doing it. The first would be to give bolus injections of insulin. And we know. When we do this in certain tests that we do in endocrinology. That hypoglycaemia will occur 20 to 30 minutes after the bolus injection. If you don't do anything else, the blood glucose will then start to rise back up again and be normal some 60 to 90 minutes after the bolus injection. So what you would need to do in this situation to maintain hypoglycaemia over such a protracted period of time is that you'd have to undertake multiple intravenous injections roughly every 2 hours.

Might I continue, my Lord?

MR JUSTICE GOSS: Please do, yes. Don't worry about watching my pen because I'm taking notes, but I'm

listening as well. Just carry on. If I ask you to pause -- if I need you to pause, I'll ask you to pause. Otherwise you carry on. You're speaking slowly and clearly and we're all picking this up, I'm sure.

A. So the second way of administering insulin intravenously is through an infusion. I think that this is probably the most likely way of achieving the blood glucose effects that we've observed. It would be a continuous infusion, using the bags of fluid that were available. It would fit nicely with the time course of events when the fluids were discontinued for re-siting the cannula at 10.00 hours on 5 August and would also be consistent with the events or measurements that took place after the total parenteral nutrition was stopped at 18.55 hours.

Those two points, but particularly the 18.55 hours one, fit from calculations I undertook. Assuming that the insulin was present in a steady state, at discontinuation of the TPN, for example at 18.55, that would be consistent with the disappearance of insulin from the circulation.

So if you had a concentration of 4,657 picomoles per litre at 18.55, when your total parenteral nutrition is switched off, then 32 minutes later -- sorry about the numbers because that's because of the half-life of

insulin, which is 4 minutes -- 32 minutes later there would only be 18 picomoles per litre, which is a normal fasting plasma insulin concentration. So that we could be sure that by the time we got to 19.30 hours, after the discontinuation of the infusions at 18.55, there would be almost no insulin in the circulation -- perhaps I should qualify that: there would be no exogenous insulin present in the circulation by 19.30 hours.

And because of the way in which insulin is removed so quickly from the circulation, it also means that the effect of the insulin on the cells to produce hypoglycaemia would be terminated fairly rapidly after that, so the rise of the blood glucose to 4.1 at 21.17 hours is entirely consistent with that -- with the pharmacology.

Q. Did you calculate from the blood sugar results the rate at which insulin was being -- exogenous insulin was being administered to [Baby F]?

A. I did, and to maintain a steady state insulin concentration of 4,657 picomoles per litre, we would need an insulin infusion rate of approximately 1.18 or 1.2 units per hour. And from that, we could add on some slight amounts to deal with adhesiveness of insulin to plastic in the infusion bags or in the giving sets, the

cannulas, but that's only going to be about 10% or 15%.

If we say 1.2 units per hour would be the infusion rate you would need to deliver to get a plasma insulin concentration of 4,657 picomoles per litre then it's going to be in the region of about 1.2 milliunits -- units per hour.

Q. So that from your -- 1.2 units per hour is what he was receiving from your calculations.

What I'd like to do is just look at J3151, please, which is the prescription of insulin to [Baby F] between 03.40 and 06.20 hours on 31 July. So comparing what he was given as treatment to what he was receiving on 5 August.

If you look on the screen, professor, you see there under the "dose" row, the prescription for insulin, which lasted 5 hours and 40 minutes, was of 0.05 units/kg/hour. Is that right?

A. That's correct. So that would be -- I can't do this in my head, so... So that's 0.07 units per hour, given he was 1.45 kilograms at that stage.

Q. So in general terms, 1.2 is about 18 times or so the prescribed amount, give or take?

A. Give or take, yes.

Q. Well, 20 times would be 1.4, wouldn't it?

A. Yes.

Q. Seventeen times, give or take.

A. I should point out, my Lord, that the infusion rates that you see on that chart are totally appropriate and exactly what we would use in standard care.

Q. Yes. So what we see on the screen now?

A. Yes. So that idea of 0.05 units per kilogram body weight per -- is the sort of number we would be going for.

MR JUSTICE GOSS: So that's the appropriate therapeutic dose?

A. Yes, to maintain a normal blood glucose.

MR JOHNSON: I'll come to in a moment the change in the bag, but just so that the jury know I'm going to deal with that point.

So having worked out how much [Baby F] was receiving, did that enable you to calculate the amount of insulin that must have been put into the TPN bag from which he was being treated?

A. Yes. I mean, that is -- it has been possible to do that. I came out for a -- for a bag lasting 24 hours, that would be about 28 units. Then I adjusted a little bit for the adhesiveness of insulin to plastic and allowed myself another 10 or 15%, which I think came out at then approximately 30 units. That would be the sort of amount that might be added.

Q. For a two-day bag, we have heard these bags are designed to run for 2 days --

A. Yes, then I would double that to 60.

Q. So 60. In terms of quantity, so that's units, we've heard that 10ml is 1,000 units. How much liquid needs to go into the bag to equate to the 60-odd units which was the concentration of the fluid being administered to [Baby F]?

A. So you'd need 0.6ml.

Q. So just over one half of 1 millilitre of liquid needs to be added to the TPN bag to deliver the rate of insulin that you have calculated [Baby F] was receiving?

A. Mm.

Q. We've seen for ourselves what Actrapid insulin looks like. It's a clear fluid. Going into a bag of TPN, would it be visible to the naked eye?

A. No, not at all, and I'd say clearly with those volumes you wouldn't notice a change in the shape or size of the bag.

Q. Drawing a line across your table as to when the fluids were stopped, we have heard evidence that a stock bag was taken and used once the long line was re-sited. Just so that you understand the evidence, the initial bag hung just after midnight was a bespoke bag in the name of [Baby F]. And the evidence suggests that

once the line was re-sited, to maintain the sterility of the process, a stock bag was taken.

Looking at the readings on your table, would it follow that the stock bag must have been contaminated as well?

A. Yes, it looks -- yes, it would imply that, yes, if that was the sequence of events.

Q. Yes. And if that was the case, looking at the blood glucose measurements, would it also follow that the stock bag was contaminated to more or less the same degree as the bespoke bag?

A. I think that is not an unreasonable comment to make. We know that there is a reasonable dose response curve between insulin dose and effect. And with the exception of the 2.9 millimoles per litre that we had our attention drawn to at 05.00 hours, the glucose concentrations are not much different in the period of time from the 01.54 hours through to 10.00 hours when things were changed compared to that period of time from 12.00 hours through to the last measurement, which was undertaken at 18.00 hours.

So I think it's probably reasonable to say that they are -- the contents are probably about the same.

Q. The level of contamination is?

A. Sorry, yes.

Q. And thus did you conclude that the explanation for [Baby F]'s clinical presentation from just after midnight on 5 August to the early evening of the same day was explicable, and only reasonably explicable, by the fact that the fluid he was receiving had been contaminated with insulin?

A. Yes, I do.

MR JOHNSON: Thank you. It may be that there are some further questions for you, professor.

MR JUSTICE GOSS: Yes.

MR MYERS: There are further questions. It's been quite dense. That's not meant to be rude to Professor Hindmarsh at all, I just wonder whether -- of course I forget the timings we're working to.

MR JUSTICE GOSS: I don't know how long you think you are likely to be, Mr Myers, but you'll recall I was planning on breaking off at half past, having an appropriate length of break, depending on how long you are likely to be, because there is no witness after Professor Hindmarsh -- well, there's one. How long will that witness be?

MR ASTBURY: Not very long: 25/30 minutes, we anticipate.

MR MYERS: I wonder whether that would be an appropriate time to take a break. We would be stopping in about 15 minutes in any event. Then we can go through to the

conclusion. I will probably be about 40 minutes, 45 minutes, maybe a little more, with Professor Hindmarsh, but I wouldn't expect to be much more than that.

MR JUSTICE GOSS: Can we have a half-hour break then?

MR MYERS: I'm fine with that then if your Lordship and everybody else is.

MR JUSTICE GOSS: I know this is really messing around with the formal arrangements but --

MR MYERS: It seems, if I may say, the natural place to take the break now (overspeaking) --

MR JUSTICE GOSS: Absolutely. No, I'm not against the principle of it.

MR MYERS: Thank you.

MR JUSTICE GOSS: I'm just trying to ensure that by 2.30 we have completed what we are scheduled to do.

MR MYERS: We'll certainly --

MR JUSTICE GOSS: That will give you an hour and three-quarters between you.

MR MYERS: We'll certainly have completed Professor Hindmarsh by then, I anticipate.

MR JUSTICE GOSS: All right. Sorry about this, normally we'd go on to 1 o'clock, but circumstances are different today. I apologise to everyone for the shortness of the break to get some refreshment and then we'll continue at

12.45.

Thank you very much indeed.

(In the absence of the jury)

MR MYERS: My Lord, I wonder if Ms Letby could be shown the exhibit that we looked at.

MR JUSTICE GOSS: Certainly. She has a copy, I think.

MR MYERS: No, the vial.

MR JUSTICE GOSS: Sorry, I beg your pardon.

MR MYERS: If it could be handed over through the glass maybe.

MR JUSTICE GOSS: Yes.

(Pause)

Mr Johnson, I didn't say anything to Professor Hindmarsh about not speaking to anyone about his evidence. I didn't think that in the 30 minutes available -- and it's essentially unique, it's self-contained evidence, but if someone -- I don't know who's looking after him.

MR JOHNSON: I don't think anyone is going to be giving him lessons on endocrinology.

MR JUSTICE GOSS: No, exactly. That's why I didn't do it. All right, thank you.

Is that all right? Have you seen it now, Ms Letby? Good, thank you very much.

(12.16 pm)

(The short adjournment)

(12.45 pm)

MR MYERS: My Lord, it should be a little swifter than I anticipated. As ever, having time normally leads to being able to save time.

MR JUSTICE GOSS: Not a problem, Mr Myers. You're under no pressure of time and if we don't complete the other witness this afternoon, so be it.

MR MYERS: Very well, thank you.

(In the presence of the jury).

Cross-examination by MR MYERS

MR MYERS: Professor Hindmarsh, could I just ask you a couple of questions about insulin in general before I go to some of the detail you have given us.

If a quantity of insulin in the form of Actrapid was introduced into a clear solution, would that be visible or would it not be visible?

A. It would not be visible.

Q. Does insulin, and I'm thinking about the form of Actrapid at the moment, have quite a distinctive smell if it's spilt or exposed to the air?

A. It does, because of the preservatives that are within it, which is -- it is usually the cresol component that gives it the distinctive smell.

Q. Thank you. I'm just going to ask you something about

the effects of a high concentration of insulin, something you that told us about in your evidence. You explained, Professor Hindmarsh, that in high concentrations, over a period of time, there can be very serious consequences if the body is dealing with an artificially high level of insulin; that's correct, isn't it?

A. That's correct, yes.

Q. You described once one moves beyond the initial cognitive impact, there can be seizures, there can be the death of brain cells, it could induce coma or indeed there could be death?

A. That's correct.

Q. I hope I have understood this: to reach its full effect, you can calculate the half-life to see when the insulin in effect is having a full effect on the system that it is being introduced into; is that correct? I might have simplified that rather than a lot.

A. You've done a good job, but not quite. The half-life describes how quickly the body removes a drug or something from the body, whereas I think what you're alluding to is how quickly does it get into the circulation and have an effect --

Q. Right.

A. -- which is more about the absorption characteristics

from whatever site you choose to use to administer.

Q. And how quick would that be?

A. So if you give a bolus intravenously, you can see an effect on blood glucose within 10 minutes and then you would register a blood glucose below 2.6/2.5 millimoles per litre 20 to 30 minutes after the bolus injection was administered.

Q. We know that in the case of [Baby F] -- sorry?

A. Do you want me to elaborate further on what you might see if you give it as an infusion or are you happy with that?

Q. By all means do because that's the way you regard this to have taken effect.

A. Yes. If you are going to infuse insulin then you have to allow for six half-lives to pass and the half-life of insulin is 4 minutes. So you would reach a steady state after 24 minutes. So it's not too dissimilar from an intravenous bolus, in fact.

Q. Probably rather clumsily, that was where I was going to. It would be about 25 minutes, or something like that, to begin to have its effect, would that be right?

A. It's probably having an effect but it's probably starting to have its maximum effect at about 25 minutes later, yes.

Q. We know that in the period before [Baby F] was first

given any dextrose to deal with what had happened, he was recorded as having a vomit and an increased heart rate, he became tachycardic. As matters followed in the hours that come after that, fortunately no further adverse physical effects were identified. So what I'm asking, and it's something that comes to mind given what you have said, is whether that is consistent with such a huge dose of insulin or whether one might have expected there to be more powerful physical consequences with the concentration you're telling us about?

A. What has been recorded was the rise in heart rate and I think that is consistent with the secretion or release of adrenaline, which is your first line of defence against a low blood glucose. So the hierarchy is you start off with adrenaline, then glucagon. That gets you sorted out hopefully in the space of minutes to hours. And then your next line of defence is called solon(?) growth hormone, which would probably not be having much of an effect until about a couple of hours into the event.

The vomiting, I think, would be consistent with what we do see occasionally -- well, not occasionally -- we do see in young people who become hypoglycaemic because they have got diabetes. Vomiting isn't an unusual feature of that.

In terms of the magnitude of the responses, I think what we would then be predominantly observing -- because the heart rate is probably at its maximal, it probably can't go much more than that. What you're then going to see are probably more the effects of glucose itself on brain function rather than any other peripheral manifestations.

So normally, if we reduced our blood glucose, we'd have that increase in heart rate, we'd feel a bit clammy, we might be sweating. Those would be the kind of cardinal features that we would see. They are not as easy to pick up in the newborn and even less easy to pick up in a preterm individual.

So those kind of classic responses to that, to a change of glucose, are not so easy to define -- neurologically, that's different.

Q. But looking at the physical manifestations, as he presented clinically, if it is the case that there was such a high concentration over a seventeen-hour period, is that in any way inconsistent with the physical presentation not being any more extreme given what can happen with high doses of insulin?

A. I think it is extremely variable, the responses that you get to hypoglycaemia. The first presentation could well be and often is collapse and seizure. What we don't

know very well is what is the duration between this event starting and you manifesting with neurological changes. We simply don't understand that.

What appears to be as important, at least from -- if I may use the results from animal studies, is that duration of hypoglycaemia, not necessarily the severity, is an important factor in determining (a) how you manifest and (b) what the neurological outcome will be in the longer term.

Q. We know that the allegation here, the way it is presented, is this is over a seventeen-hour period, maybe with a break part-way through it between 11 and 12 o'clock, but a seventeen-hour period of exposure to a very high level of insulin. So as one would look at this generally, Professor Hindmarsh, is it not surprising there wasn't a more profound physical impact at that time given what we know follows from high levels of insulin?

A. I don't think so. I think we can see such high levels of insulin in babies who are born with congenital hyperinsulinism, who may appear to be well up until the point of collapse.

Q. In terms of assessing the level of insulin that was present, we know that was done by means of an analysis conducted at a laboratory away from the hospital.

Blood glucose alone can't tell us what the level of insulin is, it can't give us the picomole figure, can it?

A. No.

Q. Nor can blood glucose alone give us the ratio of insulin to C-peptide, can it?

A. No, that's correct. Blood glucose can tell us what we might expect the insulin-producing cells in the pancreas to be doing in response to a changing blood glucose, but you're right in the sense that it doesn't give us a measure of what's happening.

Q. All right. I just want to, with your assistance, to look at another issue that arose during the course of your evidence, Professor Hindmarsh. I'm going to be making reference to the table that you prepared and we've all got copies of, with one or two items on the screens.

You were asked to take a look at the intensive care chart that we've got at slide 200, so I'll ask to put that up. We've got the tables to hand, but let's look at the screens, at the intensive care chart at slide 200. And if we go behind that, please.

Let's look at the chart. It was that reading that we've got in your table for 05.00. We'll just remind ourselves what we have there. I'll ask for Mr Murphy's

assistance.

We can see there at 05.00, it's quite visible, the reading of 2.9 for blood sugar. Do you see that?

A. Yes.

Q. Your attention was simply drawn, or our attention was drawn, to the initials that go with that. So I just remind us of what was raised with you.

Of course, 2.9 would place the blood glucose in the normal range, wouldn't it? Would it? I say it would, you tell us.

A. The normal range for blood glucose is 3.5 to 7.

Q. So this is still low in fact but it's higher than it had been; that's the point?

A. Yes.

Q. All right. Not in the normal range, but higher. Well, can we come out of that, please, and just looking at your table, I want to look at a couple of other items. Forgive me for using your assistance to simply go through what we can see here, but just to remind ourselves, we can see at 01.54 a reading of 0.8, which is very low, isn't it, Professor Hindmarsh?

A. It is.

Q. All right. Then at 02.55, we've got a reading of 2.3, which is a significant increase --

A. Yes.

Q. -- from 0.8, isn't it?

A. It is.

Q. I'm going to ask if we could have a look at the blood gas chart at slide 139, just to see that figure recorded.

I apologise for doing this through you, Professor Hindmarsh, it's really looking at the tables rather than asking for your expertise, but since we did this with you beforehand let's just follow this through.

If we scroll down, please, to the bottom of that chart we can see there on the bottom row a figure of 2.3 at 02.55.

A. Yes.

Q. You can see that, Professor Hindmarsh?

A. Yes.

Q. And we can note the initials there, which are not the same as the initials with the 2.9 figure, are they? We can all see that; I don't ask you to comment on it.

MR JUSTICE GOSS: You're not a handwriting expert, but you don't have to be to see it.

MR MYERS: No, thank you. I won't say more about the initials but there we are, I've drawn attention to that.

We can see there, Professor Hindmarsh, within just over an hour there's been an increase of 1.5 in those -- in fact in about 50 minutes, hasn't there?

A. That's right, yes.

Q. So an increase of 1.5. Now, I'd just like to look at something that happens in that period. Can we look at the intravenous infusion chart, please, at slide 191.

Ladies and gentlemen, we're looking in between 01.54 and 02.55 on the table.

We're going to go to the intravenous infusion chart at slide 191, please, Mr Murphy.

I would like us to, about four lines down, just enlarge what we can see for an entry timed 02.05. It's about the fourth line down. If we could highlight that, that would be helpful, so we all know we're looking at exactly the same thing.

This is 5 August, 10% dextrose, reading across, intravenous, and then there are some signatures. Can you see that, Professor Hindmarsh?

A. Yes, I can see that.

Q. We can see for "time and date started", it's got 02.05.

A. Yes.

Q. And a date of 5/8/15?

A. Yes.

Q. I'm not going to ask you to try to interpret those signatures.

If we hold that in our minds and look back at the table, that means between 1.54 and 2.55, in fact at

02.05, there has been a 10% dextrose given, hasn't there, intravenously?

A. That's what's charted, that's right.

Q. If anyone wants to make a record of that between those two readings on the table, between 01.54 and 02.55 we have 10% dextrose at 02.05 at slide 191.

We can certainly see, if that's correct, Professor Hindmarsh, that the reading at 02.55 of 2.3 has followed, by about 50 minutes, the 10% dextrose being given, hasn't it?

A. That's right.

Q. All right. If we carry on down that chart in a similar way, we can see on your table first that 04.02 -- keep the infusion chart on the screens. In your table at 04.02, of course insulin -- glucose, blood glucose, has begun to drop again, hasn't it?

A. That's right.

Q. It's down to 1.9 then?

A. Yes.

Q. We've had attention drawn to the reading at 05.00 of 2.9. But I wonder if you could pull out on the infusion chart, Mr Murphy, and drop a few lines down from where we are at the moment. Just where it's got the second up from the bottom as we have it at the moment, that's the one. Just enlarge that.

Again, I appreciate I'm simply asking you to read what it is we can see on the screen, Professor Hindmarsh, but we then have on 5 August, timed 04.20, with two signatures, a 10% bolus of dextrose, don't we?

A. Yes, same as before.

Q. Same as before. So I simply identify, it can be marked on our tables if you find it helpful, ladies and gentlemen, that between 04.02 and 05.00 there is 10% dextrose at 04.20 and that's on slide 191.

None of that, professor, is to cast any further challenge or question upon what you say, but it's so we have those additional figures on your chart.

A. Mm-hm.

Q. Thank you.

We can see therefore that between the reading of 1.9 on your table at 04.02 and the increase of a factor of 1 to 5 o'clock there's been a 10% dextrose bolus administered.

A. Yes.

Q. All right, thank you. We can take that down, Mr Murphy, thank you.

I'd just like to turn to the issue of the level of contamination across the period that we are looking at, Professor Hindmarsh, which was the last matter you dealt

with in cross-examination.

Working on the sample taken at 17.56, with the insulin reading of 4,657 picomoles per litre, if that applies across the whole period, was it your view that there must have been a half a millilitre of insulin added to the TPN bag or bags that were used, 0.6ml?

A. It depends whether the bags are going for 24 hours or 48 hours. So I think we concluded that it would be 0.6ml if it was for 48 hours.

Q. All right. Again, just starting from a fixed point, we know the sample was taken at 17.56 on 5 August; that's correct, isn't it?

A. Yes, that's the date stamp.

Q. Which is, as we know, nearly 17 hours after the first bag was put up at 00.25 hours. Simple maths.

A. Mm.

Q. Yes. Now, in fact, pausing there, that reading of 4,657 picomoles in fact only applies to the second bag, doesn't it, if there are in fact two bags, which appears to be the case? That reading came from the second bag, didn't it?

A. It did, yes.

Q. And the analysis is on that. That won't tell us in fact what the insulin level was in a bag that was put up -- a separate bag put up at 00.25, will it?

A. No, it won't, because we didn't measure that.

Q. No. And nor will it tell us what the insulin/C-peptide rate was -- ratio was, for any bag that was put up at 00.25, will it?

A. Well, we haven't measured that, so, no, it won't.

MR MYERS: Those are my questions, my Lord. Thank you, Professor Hindmarsh.

Re-examination by MR JOHNSON

MR JOHNSON: Just on that final issue, professor, would it be reasonable to assume that the rates of insulin in the body of a single person taken within 17 hours or 17.5 hours -- I'm probably coming at this the wrong way. Can we start with your chart, sorry? It might make my question a bit easier to understand.

So the question you were being asked, as I understand it, was that the insulin level measured by the lab of 4,657 was taken at just before 6 pm when we know from the on-ward blood glucose levels that [Baby F]'s, according to their measurements, blood glucose measurement was 1.9?

A. Yes.

Q. Am I right so far?

A. Yes.

Q. Would it be reasonable to infer that, given that we're dealing with the same person, in other words

[Baby F], and dealing with him within the same period of time, ie within the same day, that if he had similar blood glucose levels he's likely to have had similar insulin levels? In other words, looking at your chart, if one draws a line across the middle of it, which is when the bag was changed, given that the average blood glucose level before the change is about 1.9 and the average after is about that, give or take?

A. Yes, I think we've got -- the caveat is that there have been some attempts to raise the blood glucose during this period of time. What we know is that overall, the glucose infusion rate has essentially stayed the same throughout the course of this event of the 12 milligrams per kilogram per minute calculated from the TPN and the infusion. As I said earlier on, I can't be absolutely sure because it's not so easy to do it, the contribution from the boluses. But I think we could be safe to assume that the glucose infusion rate did not change, which would imply from the insulin/glucose dose-response curves that the amount of insulin around would be similar throughout the seventeen-hour period, allowing for the breaks from when infusions were discontinued.

Q. So even though the lab blood measurement was taken after the line was re-sited, given the readings taken before and after the re-site, it would be reasonable to infer

that the glucose level -- that the insulin level remained generally the same?

A. I think that would be my conclusion, yes.

MR JOHNSON: Thank you. Does your Lordship have any questions?

MR JUSTICE GOSS: No, I don't, thank you very much.

That completes your evidence, Professor Hindmarsh. Thank you very much for coming and giving it. You are free to go.

A. Thank you, my Lord.

MR JOHNSON: Professor Hindmarsh will return for [Baby L].

MR JUSTICE GOSS: Yes, you'll be coming back some time later. I'm not sure whether that will be this year or next year.

MR MYERS: My Lord, there is one -- I appreciate my cross-examination has finished. One apparent matter I would like to confirm in light of an earlier answer that Professor Hindmarsh gave and what he's just said in answer to questions.

MR JUSTICE GOSS: By all means.

Further cross-examination by MR MYERS

MR MYERS: I asked you early in my questioning whether blood glucose is a measurement for insulin or the ratio of insulin and C-peptide and you said it wasn't. So my

question is: if all we have is blood glucose before 12.00, because it's not the sample, how can you rely upon that to say the rate is the same?

A. So there are two components there, if I may take them. The first is, you are correct, that a measurement of blood glucose is not a measurement of insulin or C-peptide. That's kind of a given and that's what I was rather implying.

What we do know, though, is that there are clear dose-response relationships between the amount of insulin around and what the blood glucose might be expected to be. That's the point I was making just now.

So you are correct, yes, it doesn't -- it's not that if you've got a glucose of 2 that means that insulin must be whatever. It doesn't do -- that's not the situation because glucose is different from insulin. What we're talking about, and perhaps I didn't make that absolutely clear in my response, was that we're dealing with the relationship between insulin and glucose in terms of the dose response rather than glucose being an absolute reflection of what the plasma insulin or C-peptide concentration is. I hope that's not made it more unclear than perhaps it was.

Q. Can I just ask this to confirm it so it's absolutely clear on this? Can we work out what the level of

insulin was or the relationship, the ratio, between insulin and C-peptide at, let us say, 3 o'clock in the morning from the analysis that was taken from the sample from a different bag at 17.56?

A. I think we probably can in the sense -- because the glucose delivery throughout the period of time that we're discussing, the seventeen-hour period, in terms of the infusion, is a dose of 12 milligrams per kilogram per minute, and that would imply that that was obtained by a certain ambient plasma insulin concentration. And we know that in the afternoon it was 4,657, and it would be reasonable to assume that given that nothing had changed in terms of the glucose infusion rate, the actual amount of insulin was similar at that time period.

MR MYERS: Thank you for letting me ask those questions, my Lord.

MR JUSTICE GOSS: Not at all.

MR MYERS: Thank you, Professor Hindmarsh.

MR JUSTICE GOSS: Thank you. That is the end of your evidence at this stage. But as I have just said, you will be returning, so please do not talk to anyone about anything to do with this case so far as the evidence is concerned.

A. Yes.

MR JUSTICE GOSS: Don't seek out any evidence that is given between now and the next time you come to give evidence. You probably have enough things to be getting on with without reading about this in any source --

A. Yes.

MR JUSTICE GOSS: -- but please don't. Thank you very much indeed.

A. Thank you very much, my Lord.

(The witness withdrew)

MR ASTBURY: My Lord, may I recall Dr David Harkness, please?

MR JUSTICE GOSS: Yes, certainly.

DR DAVID HARKNESS (recalled)

Examination-in-chief by MR ASTBURY

MR ASTBURY: Could we begin by you stating your name for the record, please.

A. It's Dr David Ian Harkness.

Q. Dr Harkness, we've heard from you before, we know you were employed during the summer of 2015 at the Countess of Chester Hospital as a paediatric registrar and we heard last week about a night shift that you completed between the 3rd into 4 August 2015 and the death of [Baby E].

I would like to ask you, please, about your following night, the 4th into the 5th, and your

treatment of [Baby E]'s twin brother, [Baby F]. Were you accompanied on that night shift, as you were the night before, by Dr Wood?

A. I believe so, yes.

Q. The notes suggest that you saw [Baby E] on three occasions -- sorry, [Baby F], I do apologise. I wonder if we could go straight, please, to tile 161. Scroll down.

We can see a note dated 5 August 2015, timed at 01.30. Correct me if I'm wrong, I don't think that's your handwriting, is it?

A. No.

Q. Whose handwriting will that be?

A. I think that's Dr Chris Wood's.

Q. Could we go through the note, please. "RV"?

A. That's review.

Q. Your name?

A. And myself, yes.

Q. If we can see the note in its entirety, please, scroll down a little more so you can familiarise yourself with it, please, doctor.

A. Yes.

Q. If we can go to the top again. It begins:

"Multiple small milky vomits."

Is that right?

A. Yes.

Q. "Plus 9ml milky aspirate."

Do you recall whether that's something you saw or something you were told?

A. I can't remember.

Q. Okay. There's a note that [Baby F] was tachycardic at -- is that around --

A. Yes, 200 beats per minute, yes.

Q. And he was settled and there are ticks, correct me if I'm wrong, next to "bowels opened" and "passed urine"?

A. Yes.

Q. We then have what we're becoming used to, a diagram of a stomach (inaudible: coughing). Tell us please what's noted there?

A. "SNT", soft and not tender. "Not distended", so looks like a normal tummy. His bowel sounds were present, so his bowels are working.

Q. Okay. Does that suggest an examination?

A. Yes.

Q. By you or Dr Wood can you remember?

A. By myself that will be.

Q. Again another diagram that we're becoming used to -- I think they're lungs on the right?

A. Yes.

Q. And the arrow tells us?

A. That tells us that there's no problems on the lungs, that the air entry is good, both sides, with no crackles or wheeze or anything like that.

Q. It indicates the chest is clear; is that right?

A. Yes.

Q. Are you able to read the next line to us, please?

A. "Soft continuous murmur."

Q. What does that mean, please?

A. That's a whooshing sound that you get in the heart that is very common in premature babies. The most common cause is just what we call an innocent murmur, which changes as they get older. It is to do with increased blood flow through different parts of the heart. It can mean there's a hole in the heart or it can mean there's a little tube that's meant to close when you're born that hasn't, which if it's continuous it tends to be, but in most cases of one of those the close by themselves spontaneously over time.

But what I have then written is "femorals ++" which is the femoral pulses. If there's a problem with this little tube that stays open the pulses are really, really strong and quite different to what you'd expect so if I thought that that was significant I would have written what we call "bounding" or "cannonball" pulses, which I have not written. And then I have put

"fontanelle soft", which is again the soft spot on the skull.

Q. The plan, please?

A. The plan I have put:

"Re-screen and second line antibiotics."

So screening is a term we use when we look for infection. So what that entails is taking bloods to look for infection, putting in a cannula and giving antibiotics. He was already on antibiotics and so if you are worried at all about any possibility of infection when you're on antibiotics, you change to a different antibiotic, so second line antibiotics, which were -- cefotaxime and teicoplanin were the ones we would go for next.

So that was based on the fact that he was vomiting more and concerns around that heart rate being a bit high as well as concerns for the fact that his brother had, sadly, passed away the evening before.

Q. I was about to ask you on what basis did you reach that plan, but you have told us it's really the first two entries on your note?

A. Yes.

Q. We can go next, please, to note 177. Same shift?

A. Yes.

Q. About an hour later, 2.30. More familiar handwriting

this time.

A. Yes. That's mine, my atrocious handwriting, yes.

Q. Could you take us through the entry you have made on that occasion?

A. I have put "ATSP", which is "asked to see patient", so that is what we put if the nurses ask us to see them, regarding his tachycardia, which was 200 to 210 beats per minute as well as having large milky aspirates, so the milk coming up through the tube, and for --

MR JUSTICE GOSS: Sorry to interrupt you, does it say aspirate or aspirates?

A. Aspirate, sorry. With -- and being quieter than normal -- sorry, quieter than usual. His heart rate on the monitor showed a rate of 200 to 210 beats with what we call narrow complexes. So if you look at an ECG normally what you have is a small bump, a big tall inverse V shape and then another small little bump. A narrow complex is what it should be, there should be quite a big -- a spike that's quite rapidly up and down with a very narrow spike.

If it's abnormal, it can either be that you have lots and lots of those narrow spikes or you can have problems with a different part of your heart which are wide spikes, and they look quite different.

So what I was initially thinking at this point is

that these narrow -- so what I'm looking at there is the narrow suggests this is either normal or. Something which I'm sure you'll ask me about, the SVT.

I have put:

"Unable to clearly see P waves due to size of complexes."

So the P wave is the little bump that you get before you get this V -- inverse V shape. If that's there, it's normal. If it's not there, it suggests something called a supraventricular tachycardia or SVT. If it happened to an adult your heart rate normally is slower, so even if it's going faster you'd be able to work it out. Whereas with babies when it's that fast they're so close together that you can't actually see these little -- very clearly on the monitor.

Q. Just pausing there then, this is something you're seeing in real time?

A. Yes, this is on the monitors at this point in time.

Q. Okay. What was it, it might be obvious from your answer, that was troubling you most about what you could see at this stage?

A. So with infection, heart rates can go a bit quickly. Stress and pain can make their heart rates go quicker. But more often than not, they're sitting around 180, 190. It's rare for them to go to 200 and stay around

the 200, 200-plus mark. So that's my main concern: why is this fast and staying fast. If it was pain, if it was when I did a cannula, it might go up to 200 for a few seconds or a minute and come back down, but this being quite persistent over the hour or so from what I remember and from looking through the notes.

Q. It moves on to septic screen.

A. "So septic screen undertaken. Bloods sent for FBC [full blood count], CRP [C-reactive protein], U&Es (inaudible) bilirubin and lactate."

And then I have also sent a sample for blood culture and I have also sent that for a blood gas as well.

Q. The initial -- are these the abbreviations --

A. These are the abbreviations at the end.

Q. -- at the end of the sentence?

A. Yes, yes.

Q. Okay.

A. Then on the blood gas which is the test that we do to look at the amount of acid in the blood, to suggest whether there's infection or to suggest if there's any problems with getting oxygen around the body, it also shows us the blood sugar, or glucose, which was 0.8, which is very low.

Q. Does the blood gas indicate any other difficulties from recollection?

A. Not from recollection, no.

Q. You've examined him again. On examination, I think we have O/E.

A. Yes. I have put he handles well, so he's acting like a baby would act normally. He's pink, so's getting blood supply around his body and is well-perfused and his cap refill time -- so when you push on his chest for 5 seconds and take it off -- is less than 2 seconds, which is normal as well, so I am happy with everything at that point.

His heart sounds were normal, still has this murmur, but very quiet, his heart rate was still 200, and he still have good pulses which was reassuring. His chest was still clear, his abdomen was still soft and non-tender with good bowel sounds and no masses and his --

Q. I am just going to ask to you pause there. We've moved on, but the word systolic appears in your earlier entry.

A. Sorry. In your heart, you have two different sounds. You have your sounds where things are beating, so the top part of your heart beats and then it retracts so you have boom-boom. The systolic sounds is that first sound so a systolic murmur would kind of be a boom-shhhh sound in between.

There are different types. A continuous one would

literally just be a whoosh-whoosh-whoosh sound in between the two different beats of the heart that you hear, the two different noises.

So systolic murmurs are a lot more quiet and those tend to be the ones that are either innocent or some holes in the heart or this duct, the PDA which is this little extra tube, so those tend to fit with those, and are relatively common, particularly in a stressed baby as well.

Q. Moving on, AF again?

A. So AF is the anterior fontanelle, the soft spot, which was normotensive, so as it should be normally.

Q. Right. And if we move down the page again, please, you have identified things that were troubling you; is that right?

A. Yes. Number 1 was hypoglycaemia, so low blood sugar. Number 2 was the tachycardia, the fast heart rate, where I have put:

"[Query] SVT [the supraventricular tachycardia] or [query] second to sepsis."

Q. Pausing there, we heard a little bit about SVT from Dr Gibbs, but just in a nutshell, please remind us what SVT is.

A. So SVT or supraventricular tachycardia -- essentially you have got the pacemaker of the heart, which is in the

top chambers of the right, that sends a message to the rest of your heart to beat. Sometimes what happens is either there's a problem with feedback, and it keeps on firing, or somewhere else nearby fires that messages (sic). So what happens is rather than having a nice regular beat, it fires so many messages that your heart just keeps on beating faster and faster and faster. We see that not too uncommonly and that tends to be -- with heart rates in the 200s to 300s that we tend to suspect that.

Q. Is the question mark a query?

A. Yes.

Q. So you query SVT?

A. Query SVT.

Q. And you also query --

A. "[Query] second to sepsis."

Q. So they were the two things running through your mind at the time?

A. Yes.

Q. You then set out a plan.

A. Yes. I have put:

"2ml per kg dextrose bolus."

So the dextrose being a different type of sugar that will help bring the sugar level up. I have put:

"10ml per kilogram of 0.9% saline [so salt water]

bolus."

So -- because if the heart rate's going faster we think, is he dehydrated, is there extra stress on his body, is this infection that is driving it, so giving some fluids can help reduce some of that pressure on the heart and help to reduce it. I have put:

"Started on second line antibiotics."

The cefotaxime and teicoplanin. He had a long line in place so the other thing we look for is if there's infection in the line, and if there's infection in the line you'd start a different type of antibiotic, which is teicoplanin. That's one that you use especially when you're looking for that. So that was why that choice was.

Then a 12-lead ECG. So an ECG looks at those little squiggles of the heart, a 12-lead looks at it from different angles and there's a much more sophisticated way of picking up problems with the heart better than the monitor, so we asked for one of those as well.

Then "consider adenosine". Adenosine is a medication which will slow the heart down -- very rapidly will bring it down. It will bring it down incredibly low and can cause problems in itself, it can go too low and potentially stop the heart. So we only use that if we're really convinced this is an SVT, hence

why it wasn't something we jumped for.

Q. And finally, please?

A. That was it, sorry. "Consider adenosine", that was the last one.

Q. Sorry, okay. And we can see your signature there?

A. Yes.

Q. Next tile, please. A third entry on your behalf, Dr Harkness, at 187. Same handwriting, so this is you?

A. Yes.

Q. It's 3.30 now?

A. Yes.

Q. So another hour passes. Is that the 12-lead ECG you're telling us about?

A. Yes. That shows the heart rate of 204. It shows narrow complexes -- so like I'd said, these very narrow inverse V shapes, and I still couldn't see these P waves, these little lumps that come before this V shape. What 25 millimetres per second or 50 millimetres per second is -- you can slow down how fast the paper moves through the machine. So if you halve the speed it's going through it makes everything look broader and makes it easier to try and see these little bumps that are called the P waves. And I still at that couldn't see it.

QTC is a corrected -- I've completely forgotten what I'm doing now -- is the corrected QT, which is -- your

Q wave is part of the large V that comes up and comes down, and your T wave is the bump that comes afterwards which is when the electricity goes back to where it should be. And we measure that time and if that's long that can make you go into these SVTs essentially.

So 0.44/0.45, tends to be around the upper limit of where we would say -- 0.44 is normally the figure we'd say, so around that upper limit.

Q. So having had the results of that ECG, you then discuss, do you, with Dr Gibbs?

A. Yes.

Q. And can you tell us what the outcome of that discussion was, please?

A. So Dr Gibbs felt this was unlikely SVT as the rate would likely be closer to 300 rather than 200. So like I said before, when the baby's heart rate goes faster anyway, you expect it to be faster, and 250 to 300 tends to be more of what we'd see with SVT rather than just over the 200 mark. So his suggestion was to repeat the fluid bolus of another 10ml per kilogram of saline and continue to monitor and only to give the adenosine, this medicine that slows the heart, if the heart rate goes up to around the 300 point.

Q. That's because of the risks that you described to us a moment or two ago?

A. Yes.

Q. Scroll down again, please. Some more results there.

A. So what I put there is "full blood count" at the top. There's "HB", which is the red blood cells of 140, which is normal. White cells, normal range. And platelets, normal range. The only thing that was slightly abnormal was the creatine, which is there as "creat" of 94. You'd normally expect that to be in the 30s/40s, and 94 would suggest he's possibly a little bit dehydrated.

I've put "awaiting calcium". Calcium is something that can cause -- if it's abnormal can cause irregularities in the way that the heart beats, essentially. So my impression from that point was: is this dehydration that's making his heart go fast because he needs more fluid? Is this sepsis? But we were happy that the heart rate wasn't fast enough for this to be an SVT, so I've then put "unlikely SVT". So the plan at that point otherwise was to continue to monitor his sugars. I've not mentioned his sugars in that note there, but they were on the -- recorded on the charts.

Q. Right, okay. Just dealing with sugar, can we go next, please, Mr Murphy, to tile 191, and the form behind it. Intravenous and subcutaneous infusion prescription chart. Are you familiar with that --

A. Yes.

Q. Can I ask you please to look initially -- if we go please to the entry on 5 August timed at 3.50. 3.50 am.

A. Yes.

Q. I'm going to ask Mr Murphy to highlight it so we're sure it's the one we're talking about.

So there are a series of entries there in the early hours of 5 August. By your reaction, do you recognise the entry at 03.50?

A. Yes. So what I would have done at that point is because we were thinking of dehydration, if we want to give more fluids rather than giving TPN, which we were already on, we also then will add on 10% dextrose on top to give extra fluids and extra sugar as well.

Q. Given the title of the chart, do we -- is that being given as an infusion rather than as a bolus?

A. Yes, that's an infusion, that one, so that's a rate of 50ml per kilo per day, so we would have increased from whatever his daily amount was on TPN and then, because we needed more, it would have gone up on the sugar instead. So I don't know from there how much he was on, but that would be in addition as well as having the boluses either side.

Q. Forgive me, but why the extra sugar?

A. So the sugar in that was more because that's the fluids we always use regardless -- will be 10% dextrose. The

dextrose, 3ml of which -- there are several, those were a bolus, so those are given over a couple of minutes and those are to correct the sugar as soon as possible, whereas the infusion is there as additional. It's primarily there to give additional water and hydrate as well as giving the sugar as well. So that one's more for his hydration as opposed to sugar at that point in time, but he'd had multiple sugar boluses as well.

Q. Is that your signature beneath the "prescribed by" --

A. Yes.

Q. We can see your signature on a number of entries; is that right?

A. Yes.

Q. Just going down the page to the 4.20. I think you were just telling us about a bolus to boost the sugar levels. Can we go to that, please? Is that another one of your prescriptions?

A. Yes.

Q. And for the reason that you have just set out for us.

As far as you recall, did any of these measures to boost the sugar have an effect on [Baby F]?

A. I'd need to look at the exact chart. I think all of them had an effect to bring it close to the regular range that we wanted, but they kept drifting up and down, which is why we needed to keep giving them.

MR ASTBURY: Thank you. I have no more questions for you, Dr Harkness. I'm not sure there are any --

MR MYERS: No, my Lord, Dr Harkness wasn't a witness we required on this count and we have no questions for him.

MR ASTBURY: Unless my Lord has any questions?

MR JUSTICE GOSS: I don't.

That completes your evidence at this stage. But coming back?

MR ASTBURY: Yes.

MR JUSTICE GOSS: So as before, what I said to you before still applies.

A. Yes.

MR JUSTICE GOSS: No discussion, no reading of any reports or research into what's been said during the course of trial. Thank you very much, doctor.

There we are. At least I'm consistent in not knowing how long sessions are going to take. You heard it yourselves, what was said, so I'm not in any way critical, I'm sorry you've had a shortened break now, but it does mean you begin the afternoon earlier and you're free to go.

It is difficult to know precisely how long witnesses are going to take. So another weekend. You well know, because you're into the routine now of this case and you well know your responsibilities.

It does occur to me, actually, Mr Astbury, it's helpful to have the occasional document. I'm not suggesting we have a lot of documents, but I am thinking that some of these neonatal charts, in particular one or two charts that are being regularly referred to and appear again and again and again at various times in the chronology -- to have a paper copy would be very helpful rather than having to look at the screen each time.

MR ASTBURY: I can see enthusiastic nods. So nobody's going to complain if we do.

MR JUSTICE GOSS: If you don't do it, when I come to sum up, I will do it and hand them out then. I think it'll be much more helpful to have them as working documents during the trial. I'm seeing a lot of nods.

All right, thank you very much indeed. I know it's a digital age, but it doesn't always work for every situation.

10.30 on Monday. It'll always be 10.30 unless I raise it and I'm not planning on raising it. Thank you very much indeed.

(In the absence of the jury)

MR JOHNSON: Shall I take that back so we can keep tabs on where it is?

MR JUSTICE GOSS: I think so, and it is exhibited. It should be exhibited and we will just retain the exhibit

reference number. I don't know whether you can see what that is on the --

MR JOHNSON: Yes.

MR JUSTICE GOSS: So it can go on the record.

MR JOHNSON: For the record --

MR JUSTICE GOSS: Is it on the label?

MR JOHNSON: It is. It's X815 on the police system. It hasn't been attributed the normal sort of NJ1, that sort of thing, it just says X815.

MR JUSTICE GOSS: That's all right. X815 will do, and the description of it, an example of 10ml of --

MR JOHNSON: And it now has the court label on it as well.

MR JUSTICE GOSS: -- yes. Dextrose. Thank you very much.

It's occurred to me during the course of the trial as well, the use of clock times. When I come to sum up, I am going to use the 24-hour clock to avoid any difficulties, so I'm converting all the times to 24 hours. So if we're dealing with, say, 7 pm, it's 19.00 hours. So I will be working from that and I'm going to use the word "tile" rather than "slide" or "tile" or whatever it is, so that there is consistency. I'm not being critical, but people at different stages are referring to them by different names.

MR JOHNSON: Yes, a bit like glucose and sugar.

MR JUSTICE GOSS: Well, obviously, the experts refer to it

as different things, we all know that. We can't standardise that, I'm afraid.

Thank you very much.

MR MYERS: We'd like a brief visit with Ms Letby if we may, please, my Lord.

MR JUSTICE GOSS: Thank you very much.

We have this loose at the moment, but if you can discuss with Mr Myers just about what paper documents it would be felt are helpful.

MR MYERS: There is a jury bundle, in fact, so it may be we can develop that.

MR JUSTICE GOSS: There is a jury bundle, a paper bundle, and we just have it in a section there. I suggest we have them all in a section there with a sub-index, perhaps. Right. Thank you very much.

(1.47 pm)

(The court adjourned until 10.30 am on Monday, 28 November 2022)

I N D E X