Ton Derksen, *Lucia de B. : a Reconstruction of a Judicial Error,* 2006

Chapter 3: The Death of baby Amber

Introduction

The unexpected death of baby Amber is considered to provide the strongest proof against Lucia de B.. Allegedly, there is a poison (digoxin). The Court claims to calculate the time of the fatal administration of the digoxin, and in their view Lucia is strongly implicated. During the alleged administration the monitors were strangely silent. So the court maintains that Lucia, as the one responsible for these monitors, must have shut them off to hide something, something terrible. This cannot just be a coincidence. The court concludes that there is legal and convincing proof that the accused did commit the murder of baby Amber.[1] Since in the court's view this proof is very strong and independent of any other argument,[2] the court thinks to have found its first locomotive that should draw the cases which on their own would not make the station 'beyond reasonable doubt'.

My brief answer is: indeed, all this is not a coincidence. The data have been chosen and interpreted in such a way that they fit the accusation, and crucial exculpatory evidence is not mentioned.

Brief history of baby Amber

Baby Amber died in the early morning of 4 September 2001. She was almost six months. She was very unlucky with her constitution. She had a syndrome that no one could diagnose. She had a heart deviation, she had heightened tension in the blood vessels of the lungs. She had an oedema and fluid in her lungs. She had serious problems with her intestines. She had to be artificially fed. She often had constipation and stomach aches. Further there were periods of unexplained low levels of blood values. On the 25th of July she had a heart operation which was successful according to the heart specialist. But both pathologists who looked at the body, did not want to exclude that a failing heart had been the cause of her death.[3]

From the very beginning the girl had problems with the oxygen intake. After the operation there seemed to be some improvement. The hospital talked about the baby going home albeit with artificial feeding and extra oxygen. But during the last days before her death the need for oxygen increased again and increased rapidly. On August the 28th extra oxygen was needed. And in spite of this extra oxygen the saturation level dropped to 79% on September 1st (the values are usually between 95% and 100%).

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[1] Arrest, consideration 10.1.37.

[2] It does not lean on the statistical Coincidence Argument, or on the Compulsion Argument, or any relation with other cases.

[3] Maes, Verklaring 19 Febraury 2004, p. 11

On September the 2nd the medical files mention fever and a diarrhoea. On the 3rd, during the day shift, an increasing need of oxygen was noted. In the course of the evening the oxygen supply was increased from 0,3 to 0,4 liter. The baby seems to be in pain all evening. The mother is very worried. According to the trend graphs – the graphs which give a continuous presentation of the values of the monitors – the saturation level dropped below 90% in spite of the extra oxygen. Around 23:00 hr there is a further drop in saturation. Lucia is worried and she connects the monitor, which already gave the saturation value, to better monitor the functions of Amber's heart rate and breathing frequency.

4 September 2001

Around 0.15 hr on the 4th of September 2001 there are still low saturation levels, in spite of the extra oxygen. Lucia increases the oxygen to 0,5 liter. Somewhere around 1.00 hr two medical doctors, a paediatrician and her assistant-doctor, comply with Lucia's wish to visit Amber. Amber is troubled by diarrhoea, nausea and reflux of food. Lucia's worries about Amber's conditions are not shared by the two doctors. Amber was not okay, but she was not seriously ill, so they concluded from their examination. Amber is brought back to her room and is again connected to the monitors. The examination lasts some 20 minutes according to the assistant-doctor. The court notes that both Lucia and the paediatrician give 1.00 hr as the time of the examination. At 1.15 hr the trend graph shows new monitor activity. The court concludes that at that time the medical examination must have been finished.

At 2.10 hr blood is collected from the baby. It shows no special reasons for concern. The values for potassium and sodium are within the normal limits.

The trend tables indicate that the baby's crisis starts at 2.46 hr with a serious drop of heart frequency. At 2.45 hr the frequency was still 168 beats per minutes, at 2.16 hr there are only 116 beats per minutes. One minute later the values are critical: the heart beat has gone down to 68, and the breathing frequency has dropped to 50. At the moment of the crisis Lucia and a colleague of hers are in Amber's room. Both nurses see that within a minute the saturation level drops dangerously and they see Amber's face turn blue-grey.

The assistant-doctor is called and he is in Amber's room at 2:52 hr. At that moment Amber has a heart beat of 39. He calls the reanimation team. At 2.53 there is a cardiac arrest, the asystole. At 2.52 hr the monitor gave the last value for a heart beat, the last value for respiration already came at 2.50 hr. However, the trend graphs present a nearly simultaneous and abrupt drop of both heart rate and respiration.

In spite of all reanimation efforts Amber dies, according to the files, at 3.35 hr. At no moment however did any heart activity return. Both the paediatrician and the assistant-doctor were present at the reanimation. Afterwards a declaration of a natural death was signed.

5 September 2001
The next day the hospital retracts its declaration of a natural death, it now suspects an intoxication. What happened? Early in the morning a nurse goes to her superior and ventilates her suspicion that Lucia has killed the baby. Lucia had been present at several incidents during the last year. That was *too* coincidental! Soon a list of nine reanimations during which Lucia was present, circulates through the ward, and in the afternoon the hospital informs the police that a nurse may be involved in a murder. At the same time the hospital informs the police that the nurse had been present at five other suspicious deaths. (Before the 4th of September these deaths had all been given a declaration of natural death). Everybody believes that such a coïncidence cannot just be a matter of chance. Soon the assistance of a professional statistician[4] is called in, and on the basis of the data he received, he concludes: this is not a question of chance. And then everybody feels justified in believing that the nurse Lucia must be the murderer.

6 September and later
And then a search for the poison starts. The hospital obduction of the baby, which had been finished, is redone by the police pathologist. Neither of the pathologists finds anything suspicious. But 48 hours after the baby's death the second pathologist finds some mysterious gauzes in the body from which she manages to press a few drops of a bloody fluid. (It could not to be called blood, she states firmly). After a failed search for a potassium intoxication, labs in Holland find digoxin in the bloody fluid, and the digoxin expert of the judicial lab concludes that the baby must have died from a digoxin intoxication, as no digoxin was prescribed to the baby during the last two months of her brief life (6 months in all).

The prosecution is now convinced that the nurse Lucia killed the baby Amber by means of a fatal administration of digoxin. The court wants to know when this administration has taken place. The two Dutch toxicologists before the court gave a time indication of the alleged administration. The administration must have taken place some 60 to 90 minutes before the crisis. That is the time for digoxin to have its fatal impact.

The court then notes that during the period of 60 to 90 minutes before the crisis the nurse Lucia looked after the baby, and that during that time – miraculously – the monitor was not active. The court concludes that Lucia must have switched off the monitor to avoid being caught by an alarm.

The court is satisfied: there is a poison, there is a time of the fatal administration, and the nurse Lucia is implicated because the monitor she was responsible for, had been turned off during the time of that fatal administration. The court even knows how it must have happened: 'via the tap on the V.I.' Besides this there is the statistical evidence that the incident could not have been an accident. And thus it

[4] At the moment his professional status is questioned by all Dutch statisticians.

seems that the court have provided legal and convincing proof that Lucia is guilty of murder.

But almost everything is wrong with this. That is what I shall now argue!

Refutation I: time construction — during the period of the alleged administration of digoxin the medical doctors examine Amber. That is the reason why the monitor is off.

The courts calculates the time of the administration of the poison with great precision. It must be between 0.11 hr and 1.14 hr. And it points to the telling coincidence that exactly at that time the monitor in Amber's room was switched off, while Lucia had been in Amber's room quite often during that time. The court argues: if the monitor had been switched off *by accident*, Lucia should have noticed it and she would have switched it on again, just as she had done at the beginning of her night shift, to keep an eye on the vital values of Amber. So the fact that the monitor was not switched on, indicates that Lucia must have switched it off on purpose. And what could have been her reason for switching off the monitor (she denied to have switched it off) but some evil intention? The court concludes: Lucia did administer the fatal digoxin to Amber at that time. It was to hide this administration that she switched off the monitor.

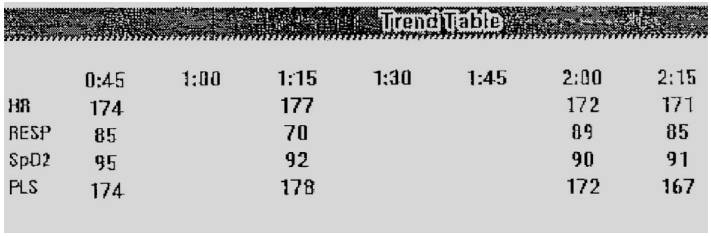
This reads like a detective story. There is one major problem: during the period that Lucia allegedly injected the poison, two medical doctors were active with Amber. This is not how the court sees it. According to the court the medical check-up took place at 1.00 hr. And the court supports this claim with references to what Lucia herself said, and what the paediatrician said. What better evidence could the court wish?

But first let us ask: what does an examination 'at 1.00 hr' mean in the language of the hospital? A quick search through the medical files, both of medical doctors and of nurses, teaches us, that – generally spoken - there are only two kinds of times: it is 1.00 hr, 2.00 hr, etc., or it is 1:30 hr, 2.30 hr, etc. So the time indication 1.00 hr in fact refers to a period from 0.45 hr to 1.15 hr. Fortunately, we can use the monitor print-outs to determine the precise time of the medical examination: Amber was not at her own room during this examination (she was in the examination room), so during that time her monitor was not connected.

Let us ask further: how much time did it take the doctors to examine Amber? In his first statement the assistant-doctor Pul, who was one of the two doctors present, speaks about '15 to 20 minutes'.[5] Later he adds: 'To insert an I.V. in a small child easily takes a quarter of an hour'. So a twenty minute examination is plausible. We have to add that Amber had to be taken from, and to be brought back, to her own room. So the period without monitor print-outs might well be closer to 25 than to 20 minutes. We therefore need a period of 20 to 25 minutes without monitor-activity to locate the medical examination.

[5] Declaration 13 February 2004.

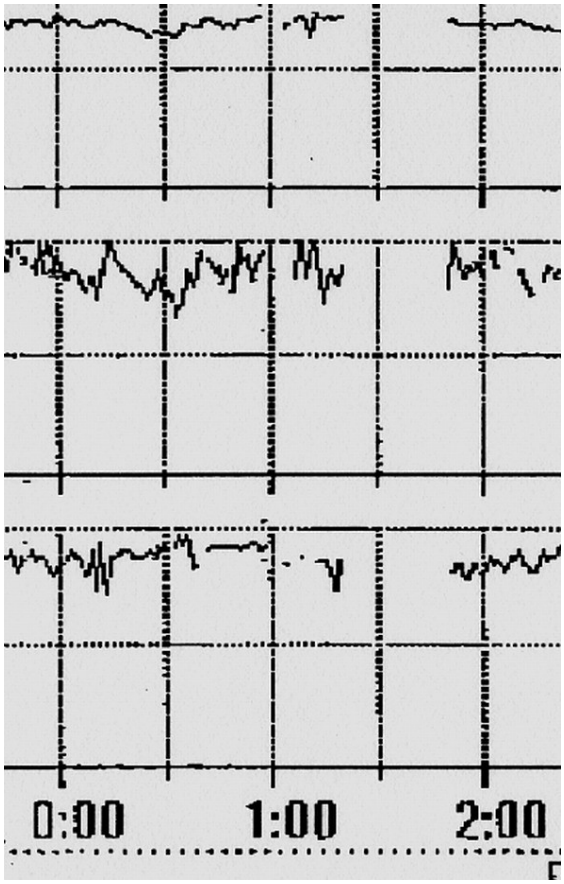
The court notices that the *trend table* (the table which gives the values of the monitors at specific pre-set intervals, in this case every 15 minutes) shows that at 1.00 hr, at 1.30 hr and at 1.45 hr the monitor did not measure any values. So at first sight this table, which is included below, shows a gap of 30 minutes with no monitor activity between 0.45 hr and 1.45 hr. It seems then that there is enough time for a physical examination around 1 o'clock.



	0:45	1:00	1:15	1:30	1:45	2:00	2:15
HR	174		177			172	171
RESP	85		70			89	85
SpO2	95		92			90	91
PLS	174		178			172	167

But thought it looks like a gap of 30 minutes, the table does not imply such a gap at all. That table *only* tells us the monitor values at the exact times mentioned; the table does *not* tell what happened between those times. So the table leaves open the possibility that the monitor was switched off for only a very brief period round 1 o'clock. In that case the medical examination of 20 to 25 minutes could not have taken place around 1 o'clock: the monitor would not have been switched off long enough.

Fortunately we need not remain in a state of ignorance: the *trend graphs* (the graphs which present the monitor values continuously instead of once every 15 minutes, presented below) give a precise answer to the question as to what actual period the monitor was inactive.



The trend graphs present, from top to bottom, the heart activity, the frequency of breathing, and the degree of saturation. The precise values are not relevant here. But what is crucial is that around 1 o'clock there is only a brief period during which there are no monitor values. Careful measurement brings out that around 1 o'clock there are some six minutes without monitor activity. That is, the continuous trend graphs show that around 1 o'clock there is not a 20 minutes gap without monitor-activity. And this implies: the medical examination cannot have taken place around 1 o'clock.

Let us look at the period between 1.15 hr and 2.00 hr. The trend graph tell us that between those times there is a large gap without monitor activity. I measure some 28 minutes, which is long enough for a medical examination of at least 20 minutes. So the medical examination must have happened during that period. Using the trend graphs a precise time for the medical examination can be calculated: from about 1.20 hr to 1.48 hr.[6]

This conclusion finds support in the declaration made by Smits, the managing-director of the Juliana Children's Hospital, before the police on the 17th of February 2001:

> *the relatively good medical condition of the child was established by medical doctors some 45 minutes before the reanimation.*

[6] Note that in that case that monitor will not display values at 1.30 hr and 1.45 hr, as the trend table indicates.

As this reanimation began around 2.50 hr, the medical examination is placed around 2.00 o'clock, rather than around 1.00 o'clock. That is, while Smith's declaration does not harmonize with the period claimed by the court, it does harmonize fairly well with the period which emerges from the trend graphs.

A medical examination from 1.20 hr to 1.48 hr also matches with the police statement that at 2.00 o'clock the I.V. was inserted. (After the medical examinations the medical doctors had ordered an I.V.).

Furthermore, the assistant-doctor present at the medical examination estimated that there were 45 minutes between the end of the medical examination and the reanimation. This reanimation started around 2.50 hr. Note that also this estimate conflicts with the court's claim of a medical examination around 1.00 hr, but that it accords fairly well with a medical examination which ended around 1:50 hr.

We have already seen that the trend graphs present a brief period without monitor activity around 1.00 hr, - some five minutes What happened at that time? The medical files mention much throwing up by Amber and diarrhoea. So the monitor might well have briefly switched off around 1 o' clock because of some changing of cloths and diapers.

Indeed, this time analysis does not suit the court's position: the period during which Lucia was supposed to have injected the poison, is exactly the period during which two medical doctors examined Amber. Moreover, any reason to charge Lucia for switching off the monitors to hide some terrible action, collapses. The coincidence of the alleged period of administration of the fatal poison and the non-operation of the monitors has not got the dramatic implication the court wants to attach to it. During that period no one injected any poison (we assume that the court would not now want to charge the doctors with an injection) and during that time the monitor was switched off simply because Amber was in another room being examined by two medical doctors.

Lucia's memory (after many months) was mistaken about the time of the medical examination, as was the memory of one of the doctors. They were not far off, though. The medical examination that started at 1.20 hr, almost fell within the period belonging to the hospital 1.00 hr-indication: from 0.45 hr till 0.15 hr.

Summarizing, there is no reason to think that there was any fatal injection with digoxin, and there is a good explanation why the monitors did not work from 1.20 hr till 1.48 hr: Amber was in another room for a medical examination. The only failure the court can ascribe to Lucia, is a slight memory failure after several months about the precise time of a medical examination.

So I conclude that the court's time indication is wrong. The court neglected the trend graphs which tell precisely which times the baby Amber was disconnected from the monitor. It turns out that during the

time that the nurse is supposed to have committed the crime, two medical doctors examined the girl. So there is no reason to believe in an alleged poisoning. Moreover there is no evidence to connect Lucia to the alleged intoxication.

Refutation II: digoxin intoxication — there was no digoxin-intoxication

In our view the defence was mistaken to accept the idea of an acute digoxin intoxication some 60 to 90 minutes before Amber's crisis. Here I will argue that there is no question of digoxin intoxication.

The medical literature cautions against the reliability of digoxin tests in forensic investigations. It is well-known that the test results may be false positive. That is, there may be a positive reading for digoxin in the blood, while there is no digoxin present. This outcome may be due to the presence of Digoxin Like Immunoreactive Substances, in short DLIS. The scientific article to which the experts before the court referred several times and which gave the court its reduction of 5 µg/L as a compensation for the postmortem redistribution, explicitly warns that during infancy the presence of DLIS may be responsible for unreliable digoxin test results.[7]

The literature explicitly warns against false positive readings in situations where one looks for a possible digoxin intoxication.

> Because of the magnitude of this interference, it is essential that methods be developed for measuring digoxin in the presence of DLIS. This is particularly important when such analysis are required in forensic science cases of suspected digoxin toxicity.[8]

In the *Arrest* (the written-out verdict of the court) there is no mention of these considerations. However, in the present case we should take the possibility of a false positive result very seriously. From the three different tests assays which were used during the trial, many experts consider the Emit 2000 Digoxin Assay and the Imx Digoxin Assay as too insensitive for making the difference between digoxin and DLIS. The more recent HPLC-MS test is more reliable here.

On the 5th of February 2004 the expert witness Lusthof told the court that only this latter method measured digoxin in contrast with DLIS. On the same day the expert De Wolff praised the "wonderful test developed by the NFI (Dutch Forensic Institute) that specifically measures digoxin". This is "the golden standard". This qualification was also used by the international digoxin specialist Dasgupta in his interview in the Dutch newspaper *Vrij Nederland*.[9].

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[7] G. Koren et alia," Interpretation of Elevated Postmortem Serum Concentrations of Digoxin in Infants and Children", *Arch.Pathol.Lab.Med.* vol. 113, juli 1989, p. 761.

[8] D.W. Seccombe, M.R. Pudek, K.H. Humphries (1987), "Minimizing analytical interferences from digoxin-like immunoreactive substances (DLIS) in cases of digoxin toxicity", *J. Forensic Sci.* 1987 May, 32 (3), pp. 650-7.

[9] Private communciation e-mail 17 April 2006: "In general immunoassay for digoxin is subjected to many interference including DLIS while more sophisticated analytical technique

The results of these three tests were:

digoxin concentration in the blood from the gauzes[10]			
5 September 2002 [11]	Emit 2000	IMx	HPLC-MS
blood from the gauzes	22 µg/L	25 µg/L	7 µgr/L

The most reliable method, the HPLC-MS, measures 7 µg/L as the digoxin concentration. One would think that after hearing the expert witnesses the court would conclude that the digoxin concentration in the blood is 7 µg/L. But it doesn't. Apparently it has so much confidence in the two other two tests, the Emit 2000-assay and IMx assay — even though these were sensitive to DLIS — that the court takes the average of the two readings 22 µg/L and 25 µg/L as its final judgement. Expert witness De Wolff (who had also advocated the Golden Standard) argues:

> the concentrations measured with the two different techniques are very close, and that in itself is a criterion for saying that it may be 100% certain that it is digoxin.[48]

This argument is called *consilience of inductions*. Two different methods give the same result. This shared result argues strongly in favour of the common reliability. There is however one condition: the methods should not be both subject to the same error. But that is exactly the case here: neither of the two tests can reliably make the distinction between digoxin and DLIS. So the consensus of the test results might just as well the result of similar percentages of DLIS which were measured in both tests. When there is DLIS in the blood, it will be measured as digoxin in both tests. Compare this with buying several newspapers of the same edition to make sure that your favourite soccer club won indeed.

I conclude that in this case corresponding results do not increase the reliability against false positives. In a court case with such charges (seven murders and three attempted murders) we need to take as our starting point the result given by the HPLC-MS test that does make a difference between digoxin and DLIS. This test gave a digoxin concentration of 7 µg/L digoxin in Amber's blood. Given the thera-

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such as HPLC/MS is free from such interference because digoxin molecule is identified by its mass spectral characteristics which is also the fingerprint of the molecule. In an American court of law most likely the Judge and Juries will be very much concerned regarding the discrepancy between digoxin results obtained by the Gold Standard, HPLC/MS and two immunoassays. Many references in the scientific literature including research by our group for last 18 years clearly show that both EMIT 2000 and IMX digoxin are subjected to DLIS and other interferences. Moreover, HPLC/MS where an extraction is necessary prior to analysis also eliminates any potential matrix effect where immunoassays are affected by matrix other than serum or plasma and hence may explain the discrepancy."

[10] In his "Toxologisch rapport naar aanleiding van aanvullende vragen" of 4 Match 2003 Lusthof presents the concentrations measured in the liver tissue. The same problems against Emit and IMx are valid here too.
5 March 2003Emit 2000IMx HPLC-MSliver tissue 19 µg/L19 µg/Lnothin showed up

[11] Lusthof, Rapport Toxologisch onderzoek naar aanleiding van een mogelijk niet natuurlijk overlijden, 5 september 2002.

peutic limits of 1-2 µg/L this would still indicate a (slight) digoxin intoxication, so one might think.

Before drawing this conclusion, however, we need to take into account that the blood sample tested was obtained some 50 hours after the death of the baby.[12] On the 5th of February 2004 expert witness De Wolff explained to the court that the digoxin concentration in the blood will be higher because of postmortem distribution after death. This post mortem elevation should be compensated for by subtracting 5,1 µg/L from the test result. De Wolff based his advice on "the most important handbook of clinical toxicology". In this book De Wolff found a reference that mentions "that in the case of deceased children whose digoxin levels were monitored before and after death an elevation of 5,1 µg/L occurred after 24 hours". The article referred to is G. Koren *et.al.* (1989), "Interpretation of elevated post mortem serial concentrations of digoxin in infants and children". (On the 11th of May 2004 De Wolff refers directly to this article). The court accepts the advice and subtracts 5 µg/L from the average result of the unreliable Emit and Imx tests. It thus obtains 24 µg/L minus 5 µ/L = 19 µg/L as the digoxin concentration of the blood.[51] I already indicated why we should take the most reliable test, the golden standard, as our starting point. We are talking about murder and a possible life sentence. Only the most reliable results are good enough. The measured digoxin concentration in 2002 was 7 µg/L. After a reduction with 5 µg/L for the post mortem redistribution, the concentration is 2 µ/L. This is, as the experts before the court themselves suggested, within the normal therapeutic range of 1 to 2 µg/L.

We conclude that, even if we follow all the approximations of the court, there is no question of a digoxin *intoxication.*

This argumentation was accepted by Prof. G. Koren,[13] the first author of the aforementioned article, when the problem of the post mortem elevation of the digoxin concentration after death is at issue.

> *A 48 hr post mortum level of 7 µg/L by HPLC can well be within the therapeutic range during life, because post mortem redistribution can be of several folds. G.Koren MD.*[14]

Also another internationally renowned digoxin specialist prof. A. Dasgupta accepts this conclusion.[15] In fact he takes a further step:

> *Even if you do not subtract 5 microgram/L from the HPLC/MS digoxin value of 7 microgram/L, a digoxin value of 7 microgram/L*

[12] Depending on the history of the gauzes the time is 56 hours or 49 hours. (It is 48 hours if they were placed in the body at the end of the first section. During the second section (48 hours after the first one) the blood was squeezed from the gauzes. Or so it is said).

[13] Professor at the Clinical Pharmacology Department, Developmental Pharmacology and Toxicology, Toronto,Ontario.

[14] Private communication e-mail 16 April 2006.

[15] Professor clinical chemistry, Department of Pathology and Laboratory Medicine (DPALM), Houston Health Sciences Center, University of Texas.

although toxic may not be fatal. It should show symptoms of digoxin toxicity without killing the child immediately.[16]

When we take a closer look at the literature we see that there is even less of a reason to suspect a digoxin toxicity. First, the NFI gives as a normal digoxin concentration: 0,8 - 2,2 µg/L. Secondly, the court was informed by De Wolff that the necessary reduction was 5,1 µg/l. That leaves us with a 1,9 µg/L. Thirdly, the reduction of 5,1 µg/L applies to blood from gauzes obtained 24 hours after death. However the blood was obtained some 50 hours after death.

In his first deposition before the court on the 5th of Februari 2004 De Wolff mentions a reduction of 5,1 µg/L for blood obtained after 24 hours, but still referring to the same article by G. Koren he states on the 11th of May 2004 that the same reduction applies to blood obtained after a period of 48 hours. But this article states, as De Wolff mentions correctly on the 5th of February 2004:

Our analysis reveals that, when measured within the first 24 hours after death, digoxin concentration is likely to be 5.3 to 8.3 nmol/L higher than at death.[17]

Koren's article tells us as well: the longer the time after death the higher the level of post mortem reduction,[18] and the more we should deduct to get a reliable guess about that the digoxin concentration at the time of death. He writes:

After 48 hr the elevation can be much higher than after 24hr, because more digoxin is released from tissues (where it was in high concentrations) into the blood (where concentrations are low). Also, this is an AVERAGE of many observations, so the elevation in particular case can be much higher.[19]

This draws our attention to the fact that in 75% of the cases the digoxin elevation within the first 24 hrs measured by G. Koren *et al*. varies from 4.2 to 6.6 µg/L.[20] In other words, the court should take into account that it is possible that the digoxin concentration in Amber's blood at the time of her death was not more than (7 - 6,6 =) 0.4 µg/L. (And we didn't even take into account the 50 hours instead of the 24 hours.)

Using Koren's article we can actually make an informed guess about the average increase in digoxin after 48 hours. His graphs show that the average increase of the digoxin level from 24 ours to 48 hours is: 10.4 µg/L – 8.1 µg/L = 2,3 µg/L. This has to be added to 5.1 yielding 7.4 µg/L. Further we have to take into account that the 5.1 µg/L

[16] Privé communicatie per email: maandag 17 april 2006, 19:19 uur.

[17] Gideon Koren et al. (1989) op. cit., p. 761. The 5,1 µg/L is calculated on the basis of the average of 6.5 nmol/L (given in the summary of the article). That gives: 6,5 x 0,798 µg/L = 5,187 µg/L.

[18] Gideon Koren et al. (1989) op. cit., p. 761.

[19] Privé communication by email: 22 April 2006.

[20]

nmol/L 5,36,5 (mean)8,3µg/L4,22945,1876,6234

increase is the average increase *within 24 hours,* not *at* 24 hours. That makes for a further average increase of 1,2 µg/L[21] *at* 48 hours. The total average increase is thus: 8.6 µg/L.[22] However we have to deduct a possible increase in the test result due to DLIS-increase, as Koren *et al.* did not use a HPLC-MS method.[23]. Koren *et al.* find an average DLIS-increase after death of 0.78 µg/L.[24] The total average increase, deducting the average DLIS-increase, is then: 8.6 – 0.78 = 7.82 µg/L. So taken into account the 50 hour interval after death, the digoxin concentration of 7.1 µg/L which the HPLC-method found, may well completely be the result of post mortem redistribution.

In short, in the judgement that there is a digoxin *intoxication* the following points were not taken into account:

(1) it is only the golden standard HPLC-MS method that can reliably distinguish between digoxin and DLIS.
(2) post mortem reduction should be based on some 50 hours after death, not the 24 hours.
(3) in this calculation one should be aware of the possibility of higher than average elevations.

In view of these shortcomings we understand Koren's reaction:

> *The post mortem level in this case, based on the HPLC method you mentioned - could well be within the therapeutic range during life. If the verdict of murder was based on this level - there is a risk of major injustice and terrible violation of human rights here. GK.*[25]

In conclusion: there is *no reason* to conclude to a digoxin *intoxication*. Moreover, there are different clinical data that strongly contra-indicate such an acute digoxin intoxication.

Five clinical data which plead against an acute digoxine intoxication

(1) The coroner (pathologist) Spaander ascertained that after death Amber's heart was not contracted. But an acute digoxin intoxication makes the heart contract as expert witness De Wolff told the court.[26] So a non-contracted heart is a strong indication of the absence of an acute digoxin intoxication.

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[21] This is ½ of the increase during the first 24 hours, which was 2,3 µg/L.

[22] This is lower than the highest digoxin increase measured: 9.44 µg/L.

[23] As in his (1989) Koren *et al* did not use a HPLC-MS method, there is the possibility of a DLIS-increase which is hidden within the digoxin increase. This potential DLIS-increase has to be deducted from the average postmortem digoxin increase to get the average increase of digoxin pure.

[24] Koren calculates the possible extra-DLIS using the digoxin concentration of babies who did not get any therapeutic digoxin before their deaths, measured before and after their death. This amount of extra DLIS is 0.78 µg/L on an average. This very low figure fits with results found by Bentur et al (1999) ('Postmortem digoxin-like immuno-reactive substances (DLIS) in patients not treated with digoxin, *Hum. Exp.Toxicol.* 18 (2): 60-70)

[25] Private communication by email: zaterdag 22 april 2006, 03:23 uur . Onze cursivering.

[26] Statement before the court, 5 February 2004, p. 53. This has been confirmed by a well-known Dutch children pathologist, and by the pathologist who di the obduction of the girl.

(2) On the 4th of September at 2.10 hour a blood sample was taken from the baby Amber. The potassium level was 3,8 mmol/L. In his deposition of March 16th 2004 De Wolff indicates that the potassium-concentration measured in serum (blood) is at the low-normal range (between 3,7- 4,9 mmol/L). This expert witness tells the court that, in contrast with a chronic administration of digoxin, an acute digoxin intoxication will lead to a high potassium-concentration (a little over 5mmol/L).[27] The court recognizes the problem and asks De Wolff whether a low potassium-concentration found is compatible with a digoxin intoxication. De Wolff answers that the low-normal potassium concentration is not incompatible with an acute digoxin concentration. But this only implies: it is possible. However, when collecting evidence in a murder case we need plausibility and not just pure possibility. And vis-à-vis plausibility the hypothesis of the court does badly: there remains a severe tension between the low-normal potassium concentration measured and the idea that there is an acute digoxin intoxication.

(3) The court claims that the injection of the digoxin took place at approximately 1.30 hr. In that case the effects should have been clearly visible on the monitor. In the case of small children serious consequences should occur within 5 to 20 minutes after intravenous injection. As other medical doctors have told us, it would lead to hearth rhythm problems. However, the trend tables and the trend graphes do not show any problems. The action of the hart and the pulse are relatively constant till just before the crisis started at 2.46. The absence of such effects casts doubt on the idea of an acute digoxin administration.

(4) Moreover, an acute crisis such as that of Amber, does not accord with a digoxin intoxication. There should be a gradual deterioration, again according to the medical specialists who I consulted.

(5) The assistant doctor Pul claimed to have seen a "broad hart complex" on the monitor. Later during the trial he was asked to draw this image. It was generally considered to be a good representation of a potassium intoxication. This would fit the initial hypothesis of a potassium intoxication. However, expert witness Uges indicates that the drawing doesn't comply with the idea of a digoxin intoxication. The so-called moustache of Dali is missing.

We have already concluded that the golden standard method did not show an acute digoxin *intoxication*. We have now seen that there are five clinical facts which further undercut the idea of an acute digoxin *intoxication.*

The Strasbourg results: the miracle requested failed to occur

[27] He writes: "Usually, at a digoxin intoxication, one sees an increased potassium concentration above 5.0 mmol/L" (p. 11).

In the spring of 2004 the court of appeal asked the NFI (the Dutch toxicological institute) to re-examine the remaining bloody fluid and the remaining tissues with its HPLC-MS method. These tests did not yield any results. So the NFI requested the renowned 'Institut de Médicine Légale et de Médicine Sociale' at Strasbourg to use its modern LC-MS/MS-method to test tissue, blood and eye fluid. Much was at stake. In the accompanying letter the NFO wrote:

> *There is also a sample of femoral blood. The concentration in this sample would be very important, as it is the only sample that could show recent administration of digoxin before death. However, the sample consists of only some drops of blood, which have dried up during storage. But maybe you can do a miracle on this sample![28]*

In view of this letter it is somewhat puzzling that before the court the NFI expert Lusthof was very flippant about the absence of the Strasbourg results at the end of the trial.[29] Asked what the relevance of these outcomes were for his conclusions he answered:

> *I do not think that these outcomes are of crucial importance to my conclusions.[30]*

Apparently it is not relevant whether there is not a demonstration for the recent administration of digoxin! Given a charge of murder with a possible life sentence more care would not have out of place.

In June 2006, after the publication of the first edition of my book, the NFI finally revealed the Strasbourg test results. The NFI had received these results on the 22nd of June 2004.

blood (from gauzes)	7.4 ng/ml
vitreous fluid	0.2 ng/ml
brain tissue	4.7 ng/mg
liver tissue	0 ng/mg, nothing in 2 separate analyses
kidney tissue	10.2 ng/mg

What do the Strasbourg results tell us about a possible digoxin intoxication?[31]

First we note that the digoxin concentration of 7.4 ng/ml in the blood may completely be the result of post mortem redistribution. So if one wants to demonstrate a digoxin intoxication, it should be done on the

[28] E-mail 26 maart 2004. Compare also the cry for help in the e-mail of 23 March 2004 about the 'remaining vitreous fluid': [it] is the last chance to demonstrate recent administration of digoxin before death".

[29] The NFI expert Lusthof admitted after the revelation of the Strasbourg-results that one could not any longer rely on the older methods. 'With such an (old) test one does not know what one measures' (Television prorgamma NOVA3 June 2006)

[30] Declaration 5 February 2004, p. 14.

[31] To be precise: the alleged blood is not blood but a bloody fluid, as the second pathologist remarked. This has an interesting consequence: the 7,4 µg/L does not measure the digoxin concentration in the blood, but the digoxin concentration of the fluid that diffused from the organs.

basis of the test results of digoxin concentrations in the organs. However, to determine whether the digoxin concentration measured do demonstrate an acute and recent digoxin intoxication we need to know how and how quickly digoxin distributes from the blood (after injection) to the organs. Internationally there is a consensus that there is no formula for such a diffusion.[32] So the quickest way to remove the claim of a digoxin intoxication is to point out that there is no reliable way to demonstrate such an intoxication.

However, I will not follow this easy way here, however valid it is in itself, as there is a quick and dirty method which makes possible a well-informed and careful guess.

It is known that (on the average) after 30 minutes half of the digoxin injected in the blood has disappeared from the blood. After 60 minutes there is only 25%, and after yet another 30 minutes there is only 12.5 % left. After six hours only 1% of the digoxin injected is still in the blood. Reversely, (assuming a rough two-compartment model) we may guess that, from the digoxin which is in the organs after six hours, after 30 minutes about 50% will be in the organs. After 60 minutes that will be about 75% and after 90 minutes that will be approximately 87.5%. This is not precise, of course, and not quite reliable, but it is the best guess we can make. Hastreiter and Vander Horst (1983) follow this line.[33]

The next question is: how much digoxin will be in the different organs of small children such as Amber (6 months) after a therapeutic treatment and after an acute intoxication? We do not know, of course, but the numbers in the literature, though differing greatly, are all very high.

I realize that the answer depends on the amount of digoxin administered to the baby. As neither I nor any of the experts before the court know this, I have collected all the data which I could find. The following table is the result of my research. I realise too that most of the data have been collected with assays which could not distinguish between digoxin and DLIS. Polish research from 2003 is promising, however. They also find extremely high values with the modern HPLC/MS method.

	Kim 1975[34]	Andersson 1975[35]	Selesky 1977[36]	Lang 1978[37]	Hardle 1983[38]	Hastreiter 1983[39]	Hastreiter 1984[40]	Grellner 1997[41]	Scislowski (2003)[42]

[32] Prof. Michael hall (Halle) confirmed this recently: 'Unfortunately, there is no 'formula' to calculate tissue concentration after a single dose',

[33] Hastreiter & Van der Horst (1983, p. 5):[Because half of the digoxin will disappear from the blood in 30 minutes] 'one would expect, after intravenous dose, that 50% of the maximal concentration would occur in the tissue bu 0,5m 75% by 1, and 94% by 32 hours'. ('Postmortem digoxin tissue concentrations and organ content in infancy and childhood', *Am.J. Cardiology* 52 (3), pp. 330-335)

[34] P.W. Kim, R.W.Krasula, L.F. Soyka en A.R. Hastreiter (1975), 'Post-mortem Tissue Digoxin Concentrations in Infants and Children', Circulation (1975), 52; 1128-1131.[The results are for 'full-term' neonates and older children (from 3 years on) For Amber I took the average.].

nieren	213-251	165-217	130	635	500	291-688	130– 1683	520	362
lever	44,5	40-96	35	193	250	75-151	35 – 501	222	457,3
hart	128,5			630/553	400	250-450	200 – 1252	255	
herse nen	21-33	23-54				32-57			

Selesky (1977), Hastreiter & van der Horst (1984), Grellner (1997) and Scislowski (2003) measure intoxications, the other papers specify the concentration after therapeutic usage. There is a wide range in the numbers. I propose to do my calculations using the whole range.

Starting from these data I make a very rough estimate of the digoxin concentration in the kidney and liver at 60 minutes after administration of the digoxin. (Since the case is alleged to be a case of *one* fatal administration of digoxin I need not worry about digoxin that has already been stored in the organs).

	digoxin concentration after 60 minutes		digoxin concentration found in Strasbourg
kidney	75% of 130 - 600 µg/L =	98 - 450 µg/L	10µ/L
liver	75% of 35 – 360 µg/L =	26 - 240 µg/L	0 µg/l
brain	75% of 21 – 57 µg/L =	15 – 43 µg/L	4.7 µg/L

The *crucial question* now is: are the different concentrations of digoxin found in Strasbourg compatible with an administration of digoxin 90

[35] Andersson, K-E, A. Bertler & G. Wettrell, 'Post-mortem distribution and tissue concentrations of digoxin in infants and adults', *Acta Paediatr Scand* 64, 497-504.[I tookthe concentrations of three children which had an age similar to that of Amber (3,5,4,5 and 8 months). Including the small babies the averages are: kidney 167, liver 82, brain 30 ng/g]

[36] M. Selesky *et al.*(1977), 'Digoxin concentrations in fatal cases'. *Journal of Forensic Sciences* (22), 409-417. [This is a case of an overdose of a 3 days old neonate of 2.2 kg].

[37] D. Lang, R. Hofstetter, G. von Bernuth (1978), 'Post-mortem tissue and plasma concentrations of digoxin in newborns and infants', *Eur J Pediatr*. 128(3):151-61. The numbers concern infants. For babies the concentrations are twice as high].

[38] W. Hardle & R. Aderjan (1983) Zeitschrift für Rechtmedizin (91 (1): 1-15), 'Classification of digoxin concentrations in blood and tissues in cases under suspicion of poisoning'. [They calculate the dividing line between the therapeutic patients and the toxic patients in a group of 45 adult patients which got therapeutic doeses and 13 cases of fatal intoxciation. In the case of children the dividing line is higher].

[39] A.R. Hastreiter & R.L. van der Horst (1983) [I treat Amber here as belonging to the adults. On average neonates had 450 µg/L in the tissue of their hearts].

[40] Hastreiter, A.R. Van der Horst (1984), 'Tissue Concentrations at Autopsy in Infants and Children Receiving Therapeutic Digoxin', *Journal of Forensic Sciences*, 29, no. 1, Jan 1984, pp. 139-146.

[41] W. Grellner, H. Kaferstein, G. Sticht, Combination of fatal digoxin poisoning with endocardial fibroelastosis. Forensic-science-international 1997 Oct 6; 89(3): 211-6. [The research examined digoxin concentrations in the case of digoxin intoxication, in this case a child of 3 years. The digoxin concentrations of Amber are comparable].

[42] M. Scislowski, S. Rojek, M. Klys, K. Wozniak, F. Trela,'Application of HPLC/MS for evaluation of fatal poisoning with digoxin in the aspect of medico-legal evidence', *Arch Med Sadowej Kryminol*. 2003 Jan-Mar;53(1):19-31. [They used the HPLC-MS method in the case of a suicide intoxication].

minutes (or 60 minutes or 30 minutes) before the girl's death.[43] In this context the following statement by Hastreiter an Van der Horst (1983) is highly relevant: *Liver tissue is another useful marker of digoxin toxicity.*[44] Also relevant is the information from the literature that digoxin starts to accumulate in the heart, the kidney and the liver fairly rapidly.

It seem to me that the discrepancy between the digoxin concentrations calculated and the concentrations found is so large that it is nearly impossible to see in the Strasbourg-results an indication of an acute digoxin intoxication. Even a therapeutic dosis would have yielded a much higher digoxin concentration in the kidney and the liver.

These calculations fit nicely with the results of Arnold and Puschel.[45] They discuss a case of an adult woman who died of an overdose of digoxin 80 minutes after the administration of that overdose. In her liver the digoxin concentratie was 100-110 µg/kg. In the kidney they found 130-145 µg/kg. In the case of children we may expect even higher concentrations (double the size), as for example Hardle & Aderjan (1983) teach us.

One could ask whether these data are reliable because most of research referred to did not use the modern HPLC-MS method. My answer is twofold: (1) all international digoxin experts whom I have consulted, refer to the research I quote.[46] Apparently the scientific community of digoxin specialists judge these data sufficiently reliable for a rough estimate. And recent Polist research (Scislowski *et al.* 2003) which *does* use the HPLC-MS method, also found extreme high concentrations in the organ tissues.

The conclusion is therefore: we have every reason to think that Amber did not die from a fatal digoxin intoxication. Next to (1) the trend graphs which exclude an administration between 1.15 hr and 1.45 (as the court claimed); next to (2) the fact that Aber's heart was not contracted (this being a strong contra-indication against an acute digoxin intoxication); next to (3) a potassium concentration which was too low for an acute digoxin intoxciation; next to (4) the absence of effects of an acute digoxin administration on the monitor; next to (5) the fact that the abruptness of the crisis does accord with an acute digoxin intoxication, next to (6) Pul's drawing which does not fit with an acute digoxin intoxication, we have now (7) the Strasburg results which more or less exclude the possibility of an acute and recent digoxin intoxication. (Also if we take a rigid line and reject every inference of the data as unreliable, the court's inference to an acute digoxin intoxication has to be rejected).

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[43] The Court of Appeal opted for an administration between 90-60 minutes before the girl's death, some experts preferred 30 minutes).

[44] p.5.

[45] W. Arnhold, K. Puschel (1979), 'Toxikologische und morphologische Befunde bei Digosinvergiftung in forensischer Sicht', *Z Rechtsmed.* 1979; 83(3):265-72

[46] Also the Dutch expert before the court, De Wolff uses articles from 1977 to empirically support his story about digoxin concentrations in the liver. See his Rapport 16 maart 2004, p. 9.

Where does the digoxin measured come from?
The thought may arise: Even if there is no a digoxin intoxication, there is dixogin. Where does that come from? Perhaps Lucia did administer it! Perhaps Amber died from that digoxin? Both Dutch digoxin experts made calculations to show that on the 4th of September 2001, the day of Amber's death, there should not have beeen any digoxin in Amber's body. Amber had had therapeutic digoxin, but that therapy stopped 50 days before her death. In those 50 days all (measurable) digoxin must have left the body.

To calculate this we have to know two things: how much digoxin was in the organs at the time of death and what is the half life of digoxin in the organs? Both numbers are unknown. So we have to put up with the best informed guesses.

The Dutch expert De Wolff starts with what he takes the maximal digoxin concentration in the heart (50 µg/kg) and in the liver (25 µg/kg). The half-life of digoxin in the blood is known (some 36 – 48 hours in healthy people), but the half-life in the heart and the liver are unknown as both De Wolff and Lusthof stress.[47] Also the international expert Dasgupta underwrites this: '*no one knows the half life of digoxin in the heart*'.[48] De Wolff assumes that the half-life of digoxin in the liver will be much longer than in the blood. After all, proportionally the organs store much more digoxin than the blood. So probably they discharge it more slowly. De Wolff guesses at a half-life of 7 days.[49] Taking these numbers as his starting points he calculates that after 50 days there will be no measurable amount of digoxin left in the body. Since digoxin is found in the body, De Wolff claims that the digoxin found in the body cannot derive from the digoxin therapy. The digoxin must be administered recently!

However, we should note (1) that the period is 49 days and that (2) that according to the scientific literature there may well be a realistic concentration of 500 µg/kg in the kidney. If we take a half-life value of 8 days (which is just one day more than the one chosen by De Wolff), there will be a concentration of 8 g/kg in the liver after 48 days.[50]

This is an interesting possibility. Assuming a half-life value of 8 days and given a realistic starting concentration of 500 g/kg, some digoxin remains in the kidney, and that concentration comes close to the one measured (8 versus 10) So this is a possible scenario: at the time of Amber's death the digoxin concentration was around 500 g/kg in the kidneys and assuming a half/life of 8 days, the theoretically remaining concentration of digoxin in the kidney is close to the one measured in Strasbourg. For the brains we have to assume a somewhat longer half/life.[51]

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[47] De Wolff, declaration 5 February 2004, p. 60: Lusthof, declaration 5 February 2004, p. 16
[48] Personal communication email 22 April 2006.
[49] De Wolff, Rapport 16 March 2004, p. 9.
[50] After 8 days 250 g/kg, after 16 days 125 g/kg, after 24 days 63 g/kg, after 32 days 31 g/kg, after 42 days 16 g/kg, after 48 days 8 g/kg.
[51] Starting from a concentration of 50 µg/kg a half/life of 12 days has to be assumed.

How about the concentration of 0 g/L found in the liver? Research shows that the digoxin concentration in the liver is usually much less than in the kidney. So it is quite well possible that after 49 days there is no measarable digoxin in the liver left. Actually De Wolff himself sketches such a scenario.

I do not, of course, claim here that the half-life of digoxin in the organs is 8 days. I do note however that DeWolff's conclusion is based on a much too low estimate of the digoxin in the organs (in the heart 50 µg/kg rather than some 500 µg/kg).

So one answer to the question 'Where does the digoxin found in the body come from?' is: the digoxin in the bloody fluid is there due to post-mortem redistribution and the digoxin in the kidneys and the brains is the remnant of therapeutic digoxin.

There are still some other possibilities:

(2) the digoxin therapy may have lasted longer, so the period without digoxin would not be 49 days but only some 20 days
This is explicitly denied by the hospital. However, there is a mysterious message 'digoxin follows' from the laboratory twenty days before the baby's death, and one should not exclude the possibility of mistakes and of lying. (The records show that some people did make mistakes and that some *did* lie).

(3) the digoxin may have been administered during the reanimation
This option fits with the 10 µg/kg in kidney. But in the medical records about the reanimations there is no mention of any digoxin. (But no one was explicitly asked!). It does not accord with no digoxin in the liver

(4) a medication error might have been made so that the digoxin free period is much smaller than 49 days.
The records show that the hospital made a number of serious medication errors in other cases.

These are the main options I can think of. But whatever the proper explanation, the Strasbourg results demonstrate that there cannot — so it seems to me — have been an acute digoxin intoxication 60 to 90 minutes before death.

Was the health of the baby as good as was claimed by the hosptital?
The court claimed that Amber's health on the 4th of September was good. So her death is unexpected and non-natural. It is true that her health seemed to improve after the operation, 50 days before her death. But the medical files indicate that from the end of August her health deteriorated.

Many doctors and nurses mention her increasing need of extra oxygin. There were increasing problems with the blood values. Some nurse said that the night before the 4th of September 'Amber was very ill'.

Her heartbeat was much higher than usual (180 instead of 140). Amber threw up, she had diarrhoea, people talked about an infection. Assistant-doctor Kollen told the police that there were problems with the lungs, there are clots of slime in both lungs. There was also fluid in the lungs. He was not surprised that she died. *'There were so many unanswered question about her disease. That the cause of her death is unknown, fit in the overall picture'*.[52]

The children's cardiologist who was quite content about the state of the heart, also mentioned that Amber '*suffered from unexplained hypoglycaemias. We did not know the cause'*. [53]

So at the beginning of September 2001 the prospects for Amber were not as rosy as some people at the hospital claimed and the prosecution and the court repeated. True, her death could not be explained by the doctors of the hospital, but no reason is given that her death was unnatural. Actually, as we have seen, there is no reason whatsoever to think so.

Conclusion

Amber's life was tragic, but there is no reason to think that there was any murder.

The monitor was off from 0.20 hr to 1.48 hr, but Lucia had not anything to do with that. Two medical doctors examined Amber.

The golden standard, the HPLC-MS method, the only method which could distinguish DLIS from digoxin, (even both Dutch experts stressed this), measures a digoxin concentration in the bloody fluid of about 7 mg/L which, after reduction because of the postmortem redistribution, is much too low to speak of a digoxin intoxication. And the 2004 results of the Strasbourg tests yielded digoxin concentrations in the organs which are actually incompatble with an acute, recent digoxin intoxication.

There were also five clinical reasons against believing in an acute dixoxin intoxication.

We have also observed that in the night from 3 to 4 September 2001 the physical condition of the child was not as good as the court pretended. Many things were not understood about Amber's physical constitution. We have no reason whatsoever to claim that her death, however unexplicable to the doctors present, was non-natural.

Rather than claiming that Lucia had evil intents we should follow the judgement of the assistant-doctor Kollen, namely that Lucia had fought for the life of Amber.

Appendix with more detailed data

[52] PV 15 september 2001
[53] PV 15 september 2001

What are the digoxin concentrations in the different organs of 6-months-old babies after six hours? The answer will of course depend on the amount of digoxin administered. Nobody knows that amount. So I can only start from the range of concentrations that occurs in the scientific literature.

The numbers differ, but they agree on one point: they are all much higher than the numbers the Dutch experts took for granted in their arguments.

The following are the concentrations I have found. Where possible, I counted only the relevant cases (babies of around 6 months).

(I) therapeutic treatment: more than 3 days						
digoxin µg/kg	Andersson 1975[54]	Lang 1978[55]	Hastreiter 1983[56]	Hastreiter 1984[57]	range digoxin concen-trations	mean
number	n = 3	n = 5	n = 5	n = 2 en 3		
age	3½ , 4½ , 8 months	2, 2½, 6, 9 and 14 months	mean 12 months	1½, 3 en 12 months		
kidney	165, 217, 337	mean 635	mean 291 + 397	152, 884	152 - 844	353
liver	40, 55, 96	mean 193	mean 75, + 151	42, 189	40 - 193	289
heart	95,161,476	mean 630	mean 127, + 94	78, 181, 226	78 - 630	297
brain	23, 36, 54		mean 32, + 25	30, 57	23 - 57	36

(II) therapeutic treatment: one dose					
µg/kg	Kim 1975[58]	Andersson 1975	Hastreiter 1984[59]	range digoxin concentrations	mean
number	n = 2	n = 2	n = 3		
age	2 and 4 days	5 days	± 3,5 days		
kidney	228, 277	126, 304	139, 207, 277	139 – 304	223
liver	38, 61	80, 86	15, 60, 56	15 – 86	57
heart	168, 247	227, 374	231	168 - 374	249
brain	14, 29	9, 44	2, 5, 6	2 - 29	17

(III) overdose digoxin (poisoning through suicide or medication error)[60]

[54] Andersson et al. (1975). I have taken the concentrations of three children who came close to the baby A's age (3½, 4½ and 8 months). If the small babies are included, the mean is: kidney 167, liver 82, brain 30 µg/kg. There was a minimum of 5 days of therapeutic digoxin.

[55] Lang, Hofstetter, Von Bernuth (1978). The concentrations of infants were measured. For the babies the concentrations are twice as high.

[56] Hastreiter & Van der Horst (1983). The neonates had 450 µg/kg in the heart tissue.

[57] Hastreiter & Van der Horst (1984).

[58] Kim et al. (1975). I selected the data from two full-term neonates with one dose.

[59] Hastreiter & Van der Horst (1984)

[60] Summarizing five articles (of which I could get hold of just one, to wit Selenky 1977) Hastreiter & Van der Horst (1984) find the following digoxin concentrations of van 'six infants who died following accidental massive overdose of intravenous digoxin' (p. 144). Note that Selenky (1977) gives the lowest numbers for kidney and liver. The other concentrations are all much higher.

	Selesky 1977[61]	Grellner 1997[62]	Scislowski (2003)[63]	range digoxin concentrations	mean
number	n = 1	n = 1	n = 1		
age	3 days	3 year	52 year		
kidney	130	520	362	130 - 520	337
liver	35	222	457,3	35 – 457,3	238
heart		255		255	255

summary of all three categories				
µg/kg	therapy (more than 3 days)	therapy: one dose	overdose	mean
kidney	353 (152 – 844)	223 (139 – 304)	337 (152-688)	304
liver	289 (40 – 193)	57 (15 – 86)	238 (35 – 457,3)	274
heart	297 (78 – 630)	249 (168 – 374)	255 (255)	267
brain	36 (23 – 57)	17 (2 – 29)		27

Clearly, the range is wide. Further, the literature tells us that digoxin concentrations in the organs of babies up to six months are generally much higher than the concentrations in the organs of children (above two years old) and adults. This is in line with the toxic concentrations for digoxin as given by Hastreiter and Van der Horst (1984):

Hastreiter & van der Horst (1984)	heart	liver
neonates	450 µg/kg	200 µg/kg
children under 2 years	300 µg/kg	200 µg/kg
older children and adults	250 µg/kg	100 µg/kg

Hardle *et al.* (1983)[64] give yet higher values after studying 58 adults.

Hardle *et al* (1983)	border of toxicity for adults
kidney	500 µg/kg
liver	250 µg/kg
heart	400 µg/kg

We are now in a position to make a rough estimate of the digoxin concentrations after 60 minutes. I calculate concentrations which correspond both to the smallest and to the highest values (For extra safety, I will even include the concentrations after one therapeutic dose rather than only cases of a fatal overdose). For comparison I add the digoxin concentrations in the organs of the baby in question as these were found in Strasbourg (2004).

	mean and smallest and highest concentration	75% after 60 minutes	Strasbourg results
kidney	(304) 139 — 844 µg/kg	(228) 98 — 633 µg/kg	10,2
liver	(274) 15 — 457 µg/kg	(206) 10 — 434 µg/kg	0
brains	(27) 2 — 57 µg/kg	(20) 1,5 — 43 µg/kg	4,4

kidneyliverheartlungsnumber of casesn = 4n = 3n = 2n = 3digoxin µg/kg130 – 168535 - 501200 – 1252 45 - 278

[61] Selesky *et al.* (1977). This is a case of an overdose given to a 3 days old neonate of 2,2 kg.

[62] Grellner et al. (1997). This is a case of digoxin poisoning of a three year old child. *If* baby A. would have died of an acute digoxin intoxication, then her concentrations would have been much higher, because digoxin concentrations in babies are much higher than in older children.

[63] Scislowski et al (2003). They used a HPLC-MS method in the case of a suicide poisoning.

[64] Hardle & Aderjan (1983). For small children the numbers will be even higher.

The concentrations found in baby A's kidney and liver are very much smaller than even the lowest concentrations found in the literature. Only the Strasbourg-concentration in the brain is not smaller than the smallest concentration found in the literature. But taking the mean concentration as our reference point, which is 27 µg/L, then the concentration measured in Strasbourg (4,4 µg/kg) is again much too small: 75 % of 27 = 20 µg/kg.[65]

So it seems nearly impossible to see an acute digoxin intoxication in the Strasbourg results. Even a therapeutic dose would yield more digoxin in the kidney, the liver and the brain after 60 minutes. This would seem to refute the charge that the nurse killed the baby by administering some fatal digoxin dose 60 to 90 minutes before the baby's death.

The hypothesis that a fatal administration took place thirty minutes before the baby's death, falters too:

	smallest and highest concentration	50% after 30 minutes
kidney	139 — 844 µg/kg	70 — 422 µg/kg
liver	15 – 457 µg/kg	7 — 228 µg/kg
brains	27 µg/kg (mean)	13 µg/kg

(A calculation shows that after 2 to 3 minutes the digoxin concentration of 10 µg/kg in the kidney is reached).

The concentrations that emerge form these calculations, correspond with the results of the research of Arnold en Puschel.[66] They discuss a case of an adult woman who died after 80 minutes due to an overdose. The digoxin concentration in her liver was 100-110 µg/kg. In the kidney a concentration of 130-145 µg/kg was measured. In babies we may expect higher (double) concentrations, according to Hardle en Aderjan (1983).

Appendix II: why Koren *et al.* results are not compromised by their not using the HPLC-MS method

The committee Grimbergen that approached you for advice, told me that the Dutch digoxin experts claim that a postmortem reduction is not necessary in the case of Amber because the "Koren-increase" of 5,1 µg/L was measured by an old method which could not distinguish between digoxin and DLIS.

They argue: Koren has measured a postmortem "digoxine" increase, but this increase is in fact an increase of digoxine + DLIS. So it is *theoretically* possible that the total increase (or a large part of it) is due to increase of DLIS after death. So in that case a digoxin concentration which is measured by an HPLC-MS assay (that is free of DLIS) need not be reduced.

[65] Note that Hastreiter & Van der Horst (1983) write explicitly: 'Liver tissue is another useful marker of digoxin toxicity', p. 5.
[66] Arnhold &. Puschel (1979).

My answer is: this is only a *theoretical possibility, but it has been empirically refuted.* Research by, among other, Bentur *et al*. (1999)[67] demonstrates this. They found in their empirical research that

> [the concentration of DLIS] does not increase *postmortem*. (p.67)

And:

> Our findings do not attest redistribution of DLIS (p.69).

That is, the theoretical possibility of De Wolf and Lusthof has already been refuted.

A careful reading of Koren *et al.* (1989) gives the same result. Koren *et al*. has measured "digoxine" concentrations before and after death, in children who had not got therapeutic digoxine. Because these children had not had therapeutic digoxin and because digoxin is not made by the body (this in contrast with DLIS), *Koren et al.* actually measured in these cases DLIS and post mortem DLIS-increase. This is what they write:

> *No effect for time after death on levels of endogenous digoxinlike substance(s) could be found'* (p. 759).

From their text we can even derive how small the average increase is which they found, namely 1,5 nmol/L – 0,5 nmol/L = 1,0 nmol/L = 0,78 µg/L.[68]

In conclusion, theoretically it could have been the case that the measured postmortem "digoxin" increase was mainly due to a postmortem DLIS increase. But empirically it turned out that is not the case. The two Dutch digoxin experts are mistaken in their argument.

Appendix III:

There is one more case in which the court manages to mention some possible intoxication (chloralhydrate). The boy fell into coma and the hospital discovered that the level of the chloralhydrate was very high. What the hospital did not tell was that it had prescribed the boy three times the allowed daily dose to quiet him down (1 x 626 mg daily, if necessary extra 2 x 625 mg) and that it had messed up by given two different medications while they intended to give only one.

Appendix IV:

In the other eight cases there was an incident during the service of the nurse, there were no indication of her involvement at all, but the court

[67] Y. Bentur, A. Tsipiniuk, U. Taitelman (1999), '*Postmortem* digoxine-like immuno-reactive substances (DLIS) in patients not treated with digoxin", *Hum. Exp. Toxicol* 18 (2): 67-70.

[68] In mijn artikel 'Ontbrekende wetenschappelijke inzichten over de Straatsburg uitslagen' van 19 maart 2007 zit een hinderlijke schrijffout in noot 103. Het gaat om de DLIS concentratie van 1,5 nmol/L na de dood en 0,5 nmol/L vóór de dood. De berekening maakt dit duidelijk, maar het is verwarrend dat de tekst de lezer hier op het verkeerde been zet.

uses a kind of statistical argument that it could not be a coincidence that all those incidents happened during her services. The statistics is faulty in a terrible way. I have recently got the support from two international statisticians, and English professor in the Netherlands and a very bright young logician-mathematician.

Appendix V:

Further there is a terrible misuse of experts by the court: they choose the one which fits the accusation. As soon as a favourite expert says something which is favourable for the nurse, the expert loses his credibility and some other experts arguing against the nurse is favoured. In three cases the court rejects the judgement of all six experts because none of them said something that discredits the nurse, so the court makes up its own medical story. It is just unbelievable, and I had not thought it possible that this would happen in the Netherlands. But now it turns out that this kind of travesty of justice is spoken at many more occasions.