DR. HARVEY MARCOVITCH

[redacted]

Phone
Mobile
e-mail [redacted]

Memo to Senior Counsel, IHRDNI

This memo arises from reading the reports of Prof. Rating and responses from Dr Squier and Prof. Kirkham

1.In the advisers' consolidated report regarding Adam Strain, we declined to speculate on the likely cause(s) of death, given the disagreements voiced between Prof. Kirkham on the one hand and Dr Coulthard & Prof Gross on the other, while taking into account the uncertainties raised by Dr Squier.

2. While I do not resile from that opinion, the above reports have raised issues which are pertinent not just to Adam's case but also to the other cases being examined by the Inquiry.

3. Dilute saline infusates were in use for more than 50 years with only occasional alarms being raised (such as the paper by Arieff et al). Many millions of children will have received maintenance fluids with infusates such as No 18 solution. Undoubtedly, many would have received what is now regarded as an excess volume or been administered the IV fluid at an excess rate. Many of these children will have had risk factors for inappropriate secretion of ADH - such as being postoperative or having an acute neurological illness.

4. Despite the above, the overwhelming majority came to no harm. While recent studies have shown that the use of No 18 solution leads to lower mean serum sodium values than the use of 0.45% or 0.9% saline, the incidence of symptomatic hyponatraemia leading to cerebral oedema is very low, to the extent that most of the medically qualified factual witnesses to the Inquiry have rarely or never encountered a case. Similarly, in my own experience it is vanishingly rare, despite many decades of using dilute IV maintenance fluids. There can be no doubt this explains why paediatricians went on using dilute solutions for some years after concerns had been raised.

5. Logically, this leads to the inference that children who develop symptomatic dilutional hyponatraemia after receiving excess IV water are in some way distinct from the much larger number who do not develop symptoms. In other words (to use a contextually unfortunate phrase used by the Deputy CMO when she initially tried to explain some of the deaths) the children who succumbed may have done so because of an 'idiosyncratic reaction.' I assume she meant by this that they had some hitherto unrecognised predisposing condition, which in itself was asymptomatic.

6. This is not biologically implausible. There are children who have inherited disorders of mitochondrial function or who are unable to handle certain metabolites which can be produced within the body intermittently. Such children are apparently 'normal' only to develop sudden, sometimes life-threatening illness in response to acute infection or a change in diet.

7. The possibility of occult predisposing factors was raised by Prof Kirkham, in her report on Adam, when she postulated a number of potential aggravating factors she believed likely to be responsible for Adam's death, while accepting he received an excessive volume of water over a relatively short time period.

8. Other experts have raised the possibility of contributory factors (such as cerebral venous obstruction), without going so far as Prof. Kirkham in terms of causation.

9. Prof. Kirkham's caveats about causation are consistent with the view expressed in 5) above. While maintaining my opinion that I do not have the expertise to advise the Inquiry into all possible aspects of causation, I believe it is reasonable for the Inquiry to consider the concept of 'idiosyncracy.'

10.This is even more pertinent in the case of Claire. Here, the experts, witnesses and advisers are all unable to provide the Inquiry with a clear narrative as to the initially provocative pathological event that brought her to hospital, albeit the final common pathway (as with Adam) was through hyponatraemia, raised intracranial pressure and cerebral oedema. It will be apparent to the Inquiry that the nature of Claire's acute illness, variously described as *encephalitis*, *encephalopathy* and *viral infection* cannot be precisely defined, given the inconsistency between her clinical progress and the neuropathological findings (and to some extent the CSF cellular analysis). Furthermore, she had an ill-defined past (or chronic) neurological diagnosis and disagreement remains as to whether or not she had a seizure disorder. The biochemical analyses are inadequate to offer retrospective proof of ADH excess, albeit all experts consider this was likely. It would not be unreasonable to hypothesise that Claire, whose infusion rate and volume was not so dramatically abnormal as Adam's, might have been predisposed to hyponatraemia if fluid therapy and monitoring were anything less than scrupulous.

11. A similar hypothesis could be raised in Raychel's case. Here it is not difficult to understand the mechanism of hyponatraemia, in that vomitus (which is equivalent to 0.9% saline) was replaced by 0.18% saline. Nonetheless, the apparently rapid progression of symptomatic hyponatraemia is somewhat surprising and one could reasonably speculate that many other children, (mis)treated similarly would have come to no harm.

12. It remains a key feature of the children involved that there were iatrogenic causes which led to their profound electrolyte disturbances and it is unquestionable that there are lessons to be learned by doctors, nurses and health service managers in preventing and in dealing with such tragic consequences of what the Inquiry might conclude amounts to substandard care.

13. However, Prof Kirkham's stated hypotheses raise the issue as to whether there might be wider lessons for medical researchers to learn about the relationship between fluid balance and neuronal function.

14. In this context, I am reminded of possibly analogous cases, previously considered by the advisers but which did not fall within the Inquiry's Terms of Reference. These were children who suffered cerebral oedema due to diabetic ketoacidosis (DKA), in whom the issue of IV fluid management is of prime importance. To my knowledge there is a wider corpus of scientific literature on this topic than on hyponatraemia alone (probably because it is more common) but the mechanisms remain obscure and the reasons why some children with DKA have rapidly developing cerebral oedema but most do not is still an open question, in particular how it might relate to IV fluid administration.

Harvey Marcovitch FRCP FRCPCH
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