FINAL 21.11.05

NEUROPATHOLOGY REPORT ON Robert HAMILL (deceased)

I have been asked by Ms Patricia Fitzmaurice, Deputy Solicitor to the Robert Hamill Inquiry, to provide an expert neuropathology report to assist Dr William Lawler to prepare a report and to address the following 2 main areas:-

1. To consider the exact nature of the brain damage caused to Mr Hamill, including my view as to whether the investigation and report of Professor Crane was comprehensive and accurate.
2. To indicate if any other factors in my opinion are significant to the investigation into the cause(s) of the death of Robert Hamill.

Documents

1. Report of Professor Jack Crane
2. Photographs of deceased taken at post mortem
3. Transcript of Professor Crane's evidence
4. Dr Lawler's draft report

From Dr Lawler's draft report I have noted the following time scale and a few of the clinical findings.

April 27th 1.20h	Deceased was kicked. Known to be unconscious Had abrasion on "side of head"
April 27th 2.05h	Unconscious and breathing noisily "Laceration" at "left side of head"
April 27th 2.15h	Glasgow Coma Scale (GCS) 5/15 Intubated
April 27th 6.30h	Now in RVI Belfast – "large abrasion left temple" Small wound approx 1cm in occiput "large grazed area on left hand side of head"
April 27th Noon	extubated
April 27th 18.00h	Making purposeful movements, but agitated
April 28th	Restless, not obeying commands. SEDATION started
April 29th	Apyrexial sedation stopped
April 29th 12.15h	Transferred from ITU to Ward 39 GCS 4-7/15 Prescribed chlorpromazine Nasogastric feeding started
April 30th	Had CT
May 1st	Agitated – need for increased sedation Decerebrate movements noted

May 2nd & 3rd	GCS 5-6/15
May 4th	Sweating
May 6th	Sweating profusely, temperature fluctuating Receiving chlorpromazine
May 7th	Pyrexia 40 degree C – blood culture taken
May 8th	BP 160/100, BP 190/105
May 8th 14.30h	Pyrexia >40 degree C, but hypotensive BP60/?
May 8th 17.03	He died

Relevant investigations – Full Blood Count showed normal white cell count
Creatine Kinase (CK) 924 (normal range 30-140 u/l)

PHOTOGRAPHS

I will restrict my comments to the photographs of the head and skull.

Photograph 3 – there is a healing laceration in the left temple region with a surrounding bruise
Photograph 4 – This is a blown up view of the healing laceration
Bruising seen in left upper eyelid
Photograph 5 – Full face seen again bruising of left upper eyelid present.
Probable graze at side of left nostril (but I think this is related to his care in hospital)
Photograph 15 – Haemorrhage seen in left temporal muscle but not in scalp
Photograph 16 – side view of head with scalp retracted and haemorrhage seen in inner surface of scalp.
Photograph 17 – there is a haemorrhagic area under the dura over the left supra-orbital plate. No obvious fracture of supra-orbital plate seen.
Photograph 18 – there appear to be 2 fractures present in the left sphenoiddal wing.

NEUROPATHOLOGICAL SLIDES

Slide 1 of temporal lobe and anterior hippocampus

There is mild hypoxaemic/ischaemic neuronal change in the anterior hippocampus. In the cortex it is difficult to assess hypoxaemic/ischaemic change as there is patchy vacuolation (as in swelling of the brain) is seen in the neuropil. There is no laminar cortical necrosis present. No haemorrhage is seen at all in this slide and the white matter shows no focal lesion.
On special staining, with an immunohistochemical technique, using an antibody to beta amyloid precursor (beta APP) there is no axon bulb formation in this slide. Using this technique with a different antibody, an antibody to glial fibrillary acidic protein (GFAP) there are reactive astrocytes present. A further stain using an antibody against macrophages (scavenger cells) shows increased numbers of those cells with some focal collections of macrophages. No significant deposits of iron are seen, only an occasional macrophage in the meninges contains some iron.

Slide 2 – similar area to slide 1

In the meninges overlying the brain tissue there is slight fibrosis with a few cells present within the fibrous tissue, but no evidence of acute meningitis is seen. There is no significant hypoxaemic/ischaemic neuronal change, but there is some vacuolation in one gyrus and an occasional hypoxaemic/ischaemic neurone in 2 gyri. No laminar cortical necrosis is seen. An occasional vessel with lymphocyte cuffing (lymphocytes are one of the white blood cells) is seen in the white matter, but no foci of necrosis are seen. There is a mild astrocytic response present on special staining but no staining is seen for beta amyloid precursor protein (beta APP).

Slide 3

No significant hypoxaemic/ischaemic neuronal damage is seen and no laminar cortical necrosis is present. In the white matter there are several foci, 8 in number, of collections of macrophages. Also 4 vessels with increased numbers of cells around them are seen in the white matter, one of these vessels is thrombosed.
In the foci of macrophages there is loss of astrocytes. Although iron is present in some macrophages, it is not significant in amount. Occasional axon bulb formation is seen with the beta APP staining, but the main pattern with this antibody is a streaking type of pattern as seen in vascular type damage in cases of brain injuries.

Slide 4 – cortex

In the meninges there are a few red blood cells, macrophages and lymphocytes with mild fibrosis, but the vessels are normal. In the cortex there are spaces around the neuronal cell bodies and an occasional small vessel appears thrombosed. There is no laminar necrosis in the cortex, but there appears to be mild loss of neurones and mild hypoxaemic/ischaemic neuronal change in cortical layer 3 in one gyrus (it is difficult to assess this type of neuronal change in the other gyrus due to the swelling); there is mild hypoxaemic/ischaemic neuronal change in cortical layer 5 in 2 gyri.
In the white matter there are 4 foci of collections of macrophages with one microscopic focus of haemorrhage. There is gliosis around the focal areas of macrophages. A few axon bulbs are seen but the main staining with beta APP has a streak like pattern. Iron is seen in the macrophages in the white matter, but not those in the meninges

Slide 5 – ventricle and basal ganglia

Mild hypoxaemic/ischaemic neuronal cell change is seen. No focal collections of macrophages seen and no acute ventriculitis. No significant increase in gliosis is seen in the GFAP stain. Occasional scattered axon bulbs are seen. On special staining increased numbers of macrophages are seen.
There is no evidence of an infarct.

Slide 6 – optic tract, ventricle and basal ganglia

One collection of macrophages is seen below the ependymal that lines the ventricle. Special staining with beta APP has a vascular type pattern to it. The internal capsule shows no abnormality.

Slide 7 – cerebellum and dentate nucleus

There is no significant damage to the cerebellar cortex, but there is one focal area of macrophages. Only occasional scattered axonal bulbs are seen and no significant iron deposition is present. The large neurones in the cerebellar cortex (these are called Purkinje cells) are not reduced in number and show no significant hypoxaemic/ischaemic neuronal change.

Slide 8 – pons/midbrain

One focus of macrophages is seen and on special staining there is a small collection of swollen macrophages on one side with loss of GFAP on one side of the focus. No significant iron deposition is seen.

Slide 9 – deep gray matter ?thalamus

No collections of macrophages are seen. Also on special staining there is a little loss of glial cells from around vessels in the white matter. Occasional foci of axon bulbs are seen on beta APP staining. No significant iron deposition is present.

Slide 10 – white matter

Collections of cells seen around vessels, which do not stain for the macrophage marker. No significant axon bulb formation with beta APP is seen.

Slide 11 – corpus callosum

The meninges are within normal limits. There is no white matter damage and the corpus callosum is normal in the routine haematoxylin & eosin (H&E) stain. The adjacent cortex shows mild hypoxaemic/ischaemic neuronal loss and there appears to be slight neuronal loss. There is rarefaction (the tissue is less well stained) around vessels in the cortex. On special staining for beta APP there is no significant collection of axon bulbs, but some are seen in association with macrophages. No significant iron deposition is seen.

Slide 12 – pons

No obvious foci of macrophages are seen and there is no degeneration in the white matter tracts. A few scattered axon bulbs are seen in some of the tracts running from side to side in this section and there is a slight increase in macrophages. No significant iron deposition is seen.

COMMENTS

1. FRACTURED SKULL
The area of haematoma found on the left supra-orbital plate would indicate that there has been a fracture of this area of the skull. These can occur as part of head trauma with fractures elsewhere in the skull, but more often in association with a fall on or injury to the occiput, even without producing a fracture in the occipital bone.

This may have occurred in this case as well as the fracture to the left side of the skull as a result of direct impact in that area with the overlying abrasion/laceration and bruise as seen in the facial photographs.

2. CONTUSIONS
None of these slides showed evidence of contusions in the cortex. The changes seen in the white matter in one slide could be those of a gliding contusion, but these changes seem to be similar in all the areas of white matter with collections of macrophages and loss of glial cells around the vessels.

There were also no surface contusions seen as stated in the post mortem report.

Contusions are not always seen in cases who die after head injuries, in this case the movement of the brain within the intracranial cavity has caused acceleration/deceleration forces to occur leading to the axonal injuries that are present rather than to contusional damage, however the presence or absence of contusions is not commented on in the description of the coronal sections of the brain.

3. TRAUMATIC DIFFUSE AXONAL INJURY
There are perivascular collections of macrophages in the white matter with a few axonal bulbs around them, these are shown up in the slides using an antibody to beta amyloid precursor protein and are also seen to some extent on H & E sections. Although there are some axonal bulbs around these areas, I do not think there is extensive axonal bulb formation as there were only a few in the corpus callosum, as well as a few in the upper brain stem, but these in the brain stem were not near to the aqueduct, they were seen more towards the anterior part of the brain stem (slide 8).

The perivascular collections of macrophages represent areas of repair after haemorrhage. These could be a result of diffuse vascular injury or traumatic diffuse axonal injury. In my opinion if they were a result of traumatic diffuse axonal injury (TDAI) I do not think they were extensive in the corpus callosum or around the aqueduct in the midbrain.
Traumatic diffuse axonal injury can be graded according to their site and severity (references 1 & 2). However in this case as there are no photographs of the brain and in the descriptions of the brain cut there are no focal lesions

seen in the corpus callosum. As I do not think there are haemorrhages with axon bulb formation in the corpus callosum and around the aqueduct of the midbrain I would not classify this as severe TDAI.

GRADING OF TRAUMATIC DIFFUSE AXONAL INJURY

GRADE I - diffuse axonal bulb formation only seen microscopically
GRADE II - focal lesion with axon bulbs involving corpus callosum and diffuse axonal bulb formation seen microscopically
GRADE III – focally in the corpus callosum and the posterior-lateral area of the brain stem.

Grades II & III can be said to be severe if the focal lesions are apparent macroscopically

Therefore if they were as in traumatic diffuse axonal injury they would be Grade II as defined by Adams et al (reference 1), but it is not severe.

If there is a gliding contusion in the white matter rather than axonal injury around a vessel this suggests that the diffuse axonal injury was of a greater severity, but I think there is only Grade II TDAI in this case.

However diffuse vascular injury is also described and again it is also thought to be due to acceleration/deceleration within the brain. Here numerous haemorrhages are seen in the white matter and brain stem with no focal areas. If they are present in the brain stem they are thought to be incompatible with life (reference 3). These rarely occur in the caudal pons or medulla. These lesions are not well described and although they would fit with this case I would be more inclined to call the lesions in this brain traumatic diffuse axonal injury.

3. HYPOXAEMIC/ISCHAEMIC CHANGES
I agree there is no cortical laminar necrosis, the hypoxaemic/ischaemic neuronal changes are difficult to age because they can occur after 30 minutes of the insult occurring and remain for a few weeks.

In ischaemic brain damage the neuropathology changes are-
Cerebral infarcts of varying sizes
Cerebral infarcts affecting watershed areas where the tissue is supplied by 2 or 3 cerebral arteries
Laminar necrosis of the cortex where neurones are lost and there is a line of necrosis where they should have been.
Neuronal cell changes:-

- in the larger neurones of the cortex in layers 3 & 5
- larger neurones in the basal ganglia and/or thalamus
- larger neurones in the hippocampus in an area known as CA1
- the larger neurones in the cerebellum

In total ischaemia of the cerebrum of only 2 minutes, neuronal necrosis occurs; but arterial hypoxia without cardiac arrest or hypotension is

inadequate to cause brain necrosis. Coma can persist for about 2 weeks in cases where there has been respiratory arrest without cardiac arrest in young people and they can recover (reference 4).

In hypoxic lesions without ischaemia there are usually no neuropathological changes (reference 5).

In this case there is no description of a macroscopic infarct of any type and no infarcts are present in the sections. There is some hypoxaemic/ischaemic neuronal damage, that is pink neurones are seen and if this is graded as in the reference from Graham et al (reference 6) it is diffuse and mild. This change can occur within an hour of hypoxic/ischaemic damage. It can also be due to other insults than the original episode when he was assaulted. Hyperthermia itself can also cause hypoxic/ischaemic neuronal damage

As far as I am aware hyperthermia gives rise to fits, but does not usually give rise to active breakdown of muscle fibres (this process is called rhabdomyolysis) on its own without there being a disorder of mitochondria. I also do not know of any specific brain changes that occur in malignant hyperthermia (reference 7).

THE EXACT NATURE OF THE BRAIN DAMAGE

In my opinion he had sustained blows to his head, which resulted in the fractured left sphenoidal wing and the haematoma over the left supra-orbital plate. The latter is more likely to have been due to an occipital injury than to the injury causing the left sphenoidal wing fracture. During these injuries he had acceleration/deceleration damage to his brain resulting in traumatic diffuse axonal injury of Grade II microscopically. Most of the traumatic diffuse axonal injury was in the white matter, the areas were seen as collections of macrophages and all appeared to be of the same age with no large areas of white matter rarefaction around them so they were not getting larger.

There was some evidence of hypoxaemic/ischaemic change with pink neurones in some areas of the cortex also mild loss of neurones was present as well. There was no evidence in the slides or the macroscopic description of the brain from the post mortem report of infarction, so the hypoxaemic/ ischaemic change was mild. This change could well be related to the initial assault, but some may have been due to the hyperthermia he had. Also the amount of white matter damage may have been increased by the hypoxaemia/ischaemia, but I do not think this has increased the damage by more than one third and it is probably much less.

CONCLUSIONS

1. The neuropathology in this case has been hampered by no photographs of the brain and the macroscopic description is brief with no indication if there were any areas of infarction; although mention of

no focal lesion being seen in the corpus callosum was given, none was given of the brain stem other than 'diffuse punctuate haemorrhage' and no description of the cortex was given. The number of slides is also small and if they are representative of the lesions, miss out some of the areas of the brain which are important to take in cases of diffuse axonal injury, for example sections of the posterior part of the corpus callosum and further sections of the upper brain stem. Looking for ischaemic changes in the brain, sections of both hippocampi with the dentate line should have been taken

FROM THE INFORMATION AND SLIDES AVAILABLE

a. I do not agree that there is severe traumatic diffuse axonal injury in this case. the grade of DAI is II with scattered white matter damage.

b. The lesions seen histologically showing a macrophage response with little in the way of ongoing damage are not, in my opinion, enough to cause his sudden death. The probability of his death through Neuroleptic Malignant Syndrome is one, which I would agree with.

c. The white matter damage may have been made worse by hypoxaemia/ischaemia, but these lesions in the white matter are not enlarging with more recent changes in the surrounding white matter.

d. There is hypoxaemic/ischaemic neuronal change, which is diffuse but mild as it involves several gyri in several slides, but there are no cerebral infarcts nor evidence of laminar necrosis in the cortex. I therefore consider the hypoxaemic/ischaemic changes not to have been a significant effect in this case, but they did have an effect in worsening his initial brain insult of the order of less than one third

REFERENCES

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2. Blumbergs PC, Jones NR, North JB. Diffuse axonal injury in head trauma. J Neurol Neurosurg Psychiat 1989; 52 838-41
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4. Cole G, Vowie VA. Long survival after cardiac arrest: case report and neuropathological findings. Clin Neuropathol 1987; 6: 104-9
5. Rie MA, Bernad PG. Prolonged hypoxia in man without circulatory compromise fails to demonstrate cerebral pathology. Neurology 1980; 30: 443

6. Graham DI,Gennarelli TA, McIntosh TK. Trauma. Chapter 14 First Volume of Greenfield's Neuropathology 2002. (Editors Graham DI, Lantos PL.) pages 870-873.
7. Gurrera RJ. Sympathoadrenal Hyperactivity and the Etiology of Neuroleptic Malignant Syndrome 1999; 156: 169-180.

Declaration

The facts as stated in this report are true to the best of my knowledge and belief. I understand that this report and any oral testimony in relation to my findings and opinions may be used in court proceedings arising out of this case. I make it knowing that I shall be liable to prosecution if I have wilfully stated in it anything which I know to be false or that I do not believe to be true.

I understand that, as an expert witness, I have an overriding duty to assist the Court with matters within my expertise, and to advise independently of whoever has instructed me. I believe that I have complied with that duty.

PERSONAL BACKGROUND

I am a consultant neuropathologist for the Salford Royal Hospitals NHS Trust based at Hope Hospital, Salford. My degree is Medical Bachelor and Bachelor of Surgery from Newcastle University in 1969, my main postgraduate diploma was gained from the Royal College of Pathologists in 1977 and I was elected as a fellow of the Royal College of Pathologists in 1989

I gained the diploma of Obstetrics, Royal College of Obstetrics and Gynaecology in May 1971 and diploma of Child Health in November 1972.

I became a consultant neuropathologist in 1980 and worked at Manchester Royal Infirmary until I moved to Hope Hospital in 2001. I have performed over 900 coroner's postmortems on head injury cases and give neuropathological opinions on criminal cases to the Forensic Pathologists in Greater Manchester.

Dr Helen Reid, MBBS, FRCPath

November 21st 2005