SUPPLEMENTAL QUESTIONS FOR REPORT OF DR WANEY SQUIER

CLAIRE ROBERTS

Decision not to report to the Coroner

1. Please describe the criteria governing referral of deaths such as Claire's to the Coroner. On what basis could the decision not to report Claire's death to the Coroner be justified?

   The requirements for Coronial intervention were not clear in 1996 and varied from one Coronial jurisdiction to another[1] (Start, Delargy-Aziz et al. 1993). The purpose of the Coronial autopsy is to determine unnatural or violent death and the role of the pathologist is to assist the clinician and the Coroner in determining the need for a Coronial autopsy.

2. In all the circumstances should Dr. Steen, Dr. Webb or the pathologist have properly considered the death of Claire Roberts to be:

   (a) An unexpected death? yes

   (b) An unexplained death? yes

   (c) Complicated by a care management issue? Possibly: the request form suggests IADHS which is not a management issue.

[1] The main confusion seemed to be in relation to deaths associated with medical treatment. Individual coroners may have differing requirements with respect to the types of deaths in hospital reported to them. Many coroners, including the coroner in this study, require all deaths that occur within 24 hours of emergency admission to be reported. This is not a legal requirement but a working rule established by many coroners based on the principle that a definite diagnosis often cannot be satisfactorily ascertained during the first day after admission. Clinicians seemed particularly uncertain of their responsibilities when the proposed clinical diagnosis had not been confirmed "beyond doubt" or if patients with established diseases died shortly after readmission.

(d) And on any of those bases reported it to the Coroner? yes

Decision to conduct a brain-only autopsy

3. In all the circumstances was there justification for the Autopsy to be limited to 'brain only'?

There were questions of systemic disease such as gastroenteritis and hyponatraemia. A full autopsy was indicated. Further, a paediatric pathologist should have been consulted regarding this autopsy, either to do it or to advise on it.

4. What information should have been conveyed to Claire's parents when obtaining consent for limited post mortem, and should the pathologist have played any part in this process?

The consent would usually be discussed by the treating physicians who would have had dealings with them in the clinical care of the child. The pathologist should be ready to participate in this process as he is able to offer advice on the relative merits of full or limited autopsy in the individual case. This information can be conveyed to parents who may have reasons for wanting a limited autopsy. In my experience this is the usual reason for limited autopsy.

5. Please provide any guidance extant in 1996-1997 in respect of gaining consent from next of kin for post mortem/ limited post mortem.

There was little guidance at this time (Start 1996). The 1993 RCPath guidelines(Royal College of Pathologists 1991; Pathologists 1993) are strangely silent on the matter but the Joint Working Party of 1991 gives guidance. Essentially this is the responsibility of the Consultant in charge of the case. This person should explain to the parents the benefits for them and for the medical staff and should allow the family to opt for full or restricted examination in accordance with the Human Tissue Act 1961.

Consent forms were usually prepared by individual departments rather than on the basis of formal recommendations. In 1996 Pathologists were generally rather concerned about consent for autopsies and tissue retention and indeed the matter came to a head with the "Alder Hey" matter in 1999-2000.After that time strict guidelines were drawn up and improved bereavement services put in place.

6. Should the reasons behind limiting the Autopsy have been entered into the medical notes or recorded in any other manner?

This may have been helpful but was not a requirement.

7. What are the potential investigative advantages/disadvantages of deciding to conduct a limited Autopsy?

There are no investigative advantages of limiting the extent of the examination. The usual reason is the request of the family or a hard pressed or inadequately staffed autopsy service.

The disadvantages are the inability to examine all systems. This is particularly relevant when a systemic infection was suspected as the cause of Claire's illness on admission. Indeed the author of Claire's autopsy report recognises the disadvantages in writing in the Comment "as this was a brain only autopsy it is not possible to comment on other systemic pathology"

8. Should Dr. Steen have held discussions with or sought advice from Drs. Webb or McKaigue in respect of coming to such a decision?

It would have been helpful if she had also discussed this with the pathologists, who could offer advice on the optimal examination.

Autopsy Request Form

9. Having regard to the Autopsy Request Form, and accompanying neuropathology documents, we would be grateful if you would comment on its quality and suitability.

Conduct of the Autopsy

10. Having regard to the 'clinical diagnoses' of Cerebral Oedema, Status Epilepticus and query underlying Encephalitis (Autopsy Request Form): What tests would you have expected would have been conducted before Claire's death and why?

This should also be addressed to a clinician. I would have expected an EEG to have been done as well as microbiological studies such as blood and urine cultures and lumbar puncture.

11. What information would you expect to have been provided to the pathologist before the Autopsy commenced, who would you expect to have been responsible for providing it and what form would you expect it (ie medical notes and records discussion with the clinicians)?

A summary of the clinical history and the clinical problems should be presented by the clinician requesting the examination. Guidance on request forms is provided in the report of the Joint Working Party of 1991 (para 2.3). Specifically case notes and results of investigations should be available at the time of autopsy.

12. Would you have expected the pathologist to have a discussion with the clinician and/or neurologist at any time before the Autopsy Report was provided and if so when and why?

Yes. This is not always necessary. In this case, while two diagnostic conclusions had been reached in the Final Report there remained further uncertainties such as whether the history of diarrhoea and vomiting may have been associated with CNS infection or whether there was metabolic disease. These issues should have been investigated with the relevant clinicians prior to finalising the autopsy report.

13. Should the pathologist to have sought a specialist opinion from anyone prior to providing the Autopsy Report, for example:

(a) Consultant Chemical Pathologist as to the likely cause of Cerebral Oedema and/or the possible effect of the hyponatraemia

Yes

(b) Consultant Radiologist as to the CT scan carried out on 23rd October 1996 (Ref: 311-006-001) for any evidence of Status Epilepticus

Yes. Most radiologists would not be willing to attempt to identify features of status epilepticus but the scans should be reviewed to look for causes of status. Further review of the scans would be of great assistance in corroborating the pathological diagnosis of a neuronal migration disorder.

(b) Paediatric Neuropathologist or a Neuropathologist specialising in neurogenetics for any evidence of neuronal migrational defect

Yes. This is an unusual condition. In this brain the findings are so subtle that I consider them to be normal. In view of the history of "mental handicap" and epilepsy and the apparent absence of relevant hippocampal pathology it would have been advisable to ask for a further opinion to assist in answering some of the clinical questions which remained unclear in the final autopsy report. Review of the brain

scans and consultation with someone more experienced in interpretation of paediatric brain pathology would be best practice.

14. Was the length of time from necropsy to Report unusually long or appropriate?

It is long but this is not unusual for neuropathology reports. There is a period in which brain fixation and tissue processing are undertaken which is a minimum of about 3-6 weeks. This is very dependent on staff availability and priority given to diagnostic work on living patients. The 1993 RCPath guidelines indicate that a final report should be issued in 4-6 weeks. I doubt that this standard is often met, even today.

Autopsy Report

15. Comment generally on the quality and suitability of the Autopsy Report. In particular does it comply with the teaching and guidance in 1996/1997?

The report is consistent with the 1993 guidelines of the RCPath. Aspects of the conclusions are not in that there does not appear to have been an attempt to reconcile all of the clinical problems with the findings or to discuss inconsistencies with the clinicians.

Epilepsy is described as iatrogenic but this term was not used in the history as given in autopsy request from.

There has not been any attempt to confirm the observations made with additional studies. The autopsy report comment suggests a low grade meningo-encephalitis which is inconsistent with the clinical suggestion of acute fulminant encephalitis.

No Gram stains were done to look for a bacterial cause.

No special stains were done to look for subtle hippocampal pathology to explain the history of epilepsy or to confirm the findings thought to represent neuronal migration disorder. This is particularly surprising in the context of a consented autopsy, the purpose of which is to make a detailed diagnosis. This contrasts with the Coroners autopsy where the aim is primarily to establish the cause of death.

16. Having regard to the Autopsy Report, and the Provisional Anatomical Summary, we would be grateful if you could comment on the following specific issues:

(a) What is the purpose of such a Summary and what might it reasonably be expected to contain?

The 1993 guidelines indicate that anatomical summary appears should list the major findings and be the basis for coding the results of the autopsy.

(b) The fact that the Autopsy Report is unsigned, and that the Inquiry has not yet seen a signed version of this Autopsy Report whether to indicate authorship or signify finalisation;

This is most unusual. This is an official record of the autopsy and a part of the clinical record. It should be signed by the person responsible for it.

(c) The fact that there is no reference to any further evidence or documentation sought or received, no reference to any discussions or verbal communications in respect of the Autopsy process. Would you expect such a note?

I would expect such consultations to take place and, if written, that they should be filed with the autopsy report. If only verbal consultations took place the outcome of any discussions may be part of the final diagnosis but may not necessarily be recorded.

(d) Would you expect the pathologist to be informed as to the reasons for the limitation/restrictions on the Autopsy? Should he make any enquiry himself?

In the case of a child who has died suddenly with no clear clinical diagnosis I would expect a full autopsy to be done. I would expect a paediatric pathologist to be consulted or involved. The pathologist should have at least confirmed the reasons for a brain only examination.

(e) The fact that the pathologist is given as Dr. Herron and he gave evidence at the Inquest on that basis but yet it is now claimed not to be so.

This is most unusual. The pathologist taking responsibility for the autopsy should attend the Inquest. If that person is unavailable the Coroner may be asked if another person might attend.

(f) Should Dr Herron as Registrar should have had the Autopsy Report signed by Dr Mirakhur as his Consultant and/or as someone who contributed to the Autopsy/Autopsy Report.

A Consultant should sign the report of a trainee either as a supervisor or as someone who contributed to the report. Dr Herron writes at paragraph 23 (WS 224-4) that all reports are subject to scrutiny by the Consultant Neuropathologist.

(g) Is it appropriate that the Autopsy Report was not filed with the medical records of Claire Roberts?

No. the report should inform the clinician and the GP and should be filed in the case records.

(h) Is it appropriate that the Autopsy Report is not sent to the GP and/or Mr. and Mrs. Roberts?

The 1991 guidance indicates that the post-mortem results should be communicated and explained to the patient's relatives as soon as possible. This is usually done by the clinician or GP and clearly depends on the report being sent in a timely manner to the clinician and GP.

(i) Would it have been appropriate to present the Autopsy Report at a mortality meeting/ audit or review meeting?

Yes but in addition to preparing and sending out to the clinician a written and signed document. It is often helpful if feedback from such a meeting is used in preparing the final report as it may assist in reconciling clinical and pathological findings.

(j) Apparent inaccuracies and inconsistencies with the medical notes and records, namely:

(i) Time of death – in fact the first brain stem death test was at 06:00 on Wednesday 23rd October 1996 and the second at 18:25 that evening;

(ii) Age at death (no date of birth given); This should be part of every report.

(iii) The history from the parents did not disclose that Claire:

- had no *"history of recent diarrhoea"*;

- did not have *"history of epileptic seizures since 10 months of age"*;
- was not *"well until 72 hours before admission"*, as she went to church on the Sunday and school on the Monday (the day of her admission)
- did not have *"similar symptoms"* to her cousin;
- did not start to vomit *"24 hours prior to admission"*

(iv) Claire's fluids were not, in fact, restricted – the restriction was confined to Solution no.18;

i, iii and iv contain errors some of which were transcribed from the autopsy request form.

(v) Her epilepsy was not *"iatrogenic"*. This appears to have been a completely new suggestion and is misleading. The source of this suggestion is unclear.

(k) Whether the Anatomical Summary is sufficient/accurate/ appropriate in light of the medical notes and records?

No, it does not reflect the complete clinical problem or pathological findings. There was no brainstem necrosis and the vessels which have been photographed and submitted to illustrate inflammation are not from the meninges, so the diagnosis of subacute inflammation in the meninges is not supported.

(l) Does the Autopsy Report comply with the contemporaneous Guidelines for Post Mortem Reports (Royal College of Pathologists, August 1993)?

The form of the report itself is adequate and complies with this guidance but the content and timing are not, nor is the failure to sign it and submit it to the clinician.

(m) Is it correct to interpret the Autopsy Report as neither confirming nor rejecting viral infection, epilepsy or metabolic cause as a cause of death, and that it adds nothing to the previously understood facts surrounding her death namely cerebral oedema?

The report concludes that there is a neuronal migration defect to explain epilepsy and a low grade meningoencephalitis to explain the admission illness and collapse. Drs Herron and Mirakhur have

both denied that they made a diagnosis of acute fulminant encephalitis although this was part of the clinical differential diagnosis suggested by Professor Cartwright and cited by Dr Herron (Dr Herron WS 224/4 page 14). There is no explanation for the cerebral oedema. It is surprising that there was no further discussion of the cause of the brain swelling when the clinical deterioration was so fast and the pathology thought to represent inflammation was so mild "mild subacute encephalitis" (page 13, statement of Dr Herron WS 224/4).

(n) The Report comments "*the features here are those of...*" How do you interpret this? Does it mean "*findings consistent with but not proof of*"? Are there conventions governing the phrasing employed in such reports?

My interpretation would be that these terms indicate that the existence of these conditions is established.

(o) Was it appropriate, in all the circumstances, and given the information available to omit all reference to hyponatraemia? What importance should have been attached to the history given on "*serum sodium dropping to 121,? inappropriate ADH secretion, cerebral oedema and respiratory arrest*"?

The neuropathologist cannot distinguish between causes of brain swelling not due to primary brain pathology eg from metabolic causes. The suggestion of inappropriate ADH secretion would be a reasonable explanation and further determination of the cause of swelling may be more appropriately dealt with by clinicians.

(p) What do the CODES of T-A0100, M-01000, M-40000, D4-00000 and D4-41720 that were on an earlier version of the Autopsy Report mean and should they have been removed from the one that is being presented as the final Autopsy Report?

These are codes used for filing and retrieval of data. They were regarded as important in 1996 before more universal introduction of systems allowing word searches for retrieving cases. They are used in pathology systems and are not required by the clinician. Separate codes are used for clinical disease recording.

(q) Was the purpose of Autopsy undermined in any way by limitation of post mortem to the brain alone?

Yes as systemic infection for example could not recognised.

(r) Do you agree with Dr. Steen's interpretation of the Autopsy Report given to the GP on 6th March 1997 (Ref: 090-002-002)?

(s) Do you agree with the synopsis of the Autopsy Report given by Dr. Webb by letter to Mr. and Mrs. Roberts (dictated 28th February 1997/ typed 21st March 1997) (Ref: 090-001-001)?

These letters us the autopsy diagnoses to explain Claire's terminal illness and death and appear to interpret the diagnosis appropriately. There is no mention of the low serum sodium and how this may have played a part in Claire's death.

17. Should there have been a meeting between the pathologists and the clinicians either before the Autopsy Report was finalised or after it had been and before any meeting with Claire's parents?

This is best practice. However many clinicians are happy to make their own interpretations of autopsy reports and discuss findings with parents. Practice varies greatly from place to place.

Evidence of Drs. Herron & Mirakhur

18. Please comment on the Witness Statements of Dr. Heron (Ref: WS-224-4) and Dr. Mirakhur (Ref: WS-247-2) and in particular the:

(a) Claimed differences between your opinion and that of Professor Harding

There are in fact very few differences between the opinions of Professor Harding and myself. The differences are in terminology and the extent and detail of our examinations of the brain tissue. In essence Professor Harding and I both note severe brain swelling and no evidence of a neuronal migration disorder. He finds nothing to support a diagnosis of meningo-encephalitis; I note occasional perivascular cells and am of the opinion that fulminant encephalitis may kill a child rapidly with little pathological evidence of it (Krous, Chadwick et al. 2007). While I agree with Professor Harding that there is not sufficient evidence to support a diagnosis of encephalitis in this case, I remain of the opinion that this diagnosis cannot be fully dismissed. I would note that Dr Harding is quoted as saying that "an acute and fulminating encephalitis causing cerebral oedema, coning and death in the space of three days cannot occur in the absence of neuropathological changes" (page 14 WS 224-4). In this case there are reasons to consider that the cerebral oedema resulted from hyponatraemia following Claire's admission. In this case the oedema may not have been due to encephalitis or in any way related

to the severity of any encephalitis, but was superimposed on it. If this is so, it is unwise to relate the oedema to the anticipated extent or severity of the neuropathology due to encephalitis. Further, interruption of the blood flow to the brain resulting from brain swelling would modify the inflammatory response, causing it to be muted due to inability of inflammatory cells in the blood stream to reach the brain tissue.

Neither Professor Harding nor I found evidence of tissue necrosis (or infarction) which was described in the pathology report; instead we found terminal hypoxic change in cells. I have made more detailed comments in my responses of September 24th.

(b) Comments made about your own opinion

Page 10:

i:I saw my own and the old material; I reviewed all the sections and my findings were submitted as an addendum on 22.08.12

ii: "Dr Squier described cellular reactions in perivascular spaces and brain parenchyma" This is incorrect. In my report of 16.06.12 page 8 (d) "The cells are close to the blood vessel walls and are not seen infiltrating the adjacent parenchyma as would be expected to be seen in encephalitis." At page 9 (k) "There is a small scattering of small dark cells around one parenchymal artery. They do not involve the vessel wall or extend into the parenchyma.",page 10 (t) "CD68 (a macrophage marker) which stains a small numbers of cells around parenchymal blood vessels. There is no substantial tissue infiltrate."

Page 11

"Dr Squier at times describes the swelling as severe and …she describes mild narrowing of the lateral ventricles and no tentorial notching" These comments reflect the inaccuracy of these descriptions in assessing brain swelling. Terms such as mild moderate and severe are necessarily subjective. This was Hausmann's view and he undertook a study in an attempt to identify the most reliable criteria by which to determine swelling. It is a shame that there is no similar study on cases of Claire's age. However I think that we are all in agreement that there is brain swelling and that the pathological observation is in accordance with the CT findings.

Page 12

i: "The pathologists who originally made the blocks are in a better position to assess [neuronal migration disorder] as they know the anatomical sites from where the tissue blocks were taken"

I agree that this is a disadvantage and the reason why most neuropathologists prepare a block list indicating the site of origin of each block and numbering the blocks for ease of reference. However, neuronal migration disorders may affect any part of the brain. Indeed in the original autopsy report the suggestion of a neuronal migration disorder was made in the areas described as "Periventricular grey matter, hypothalamus and mammillary bodies". These areas are readily identifiable anatomically.

ii:"The only relevant observation according to Dr Harding …. . It also contradicts her impression of severe oedema"

Dr Harding actually wrote that "the only relevant observation, albeit macroscopic (naked eye) is of brain swelling, as judged by the excessive brain weight".

This neither contradicts me nor Hausmann.

Page 14 " CSF …at the time of autopsy …supports an inflammatory condition"

(Morris, Harrison et al. 2012) Morris et al have recently addressed this issue.

19. Please also comment on the following in relation to those Witness Statements and the Autopsy Report:

(a) CT scan (Ref: 311-006-001)

This should be reviewed by a neuroradiologist.I have reviewed the CT scans with Dr Anslow. He describes severe brain swelling and has no further comment. He does not believe it would be possible to identify changes due to status epilepticus on a CT scan but that they may occasionally seen by MRI if the condition has been present for 24 hours or so.

(b) Photographs sent undercover of the DLS letter dated 19th January 2012 (Ref INQ-0657-12)

See below*

(c) Pie Chart and photographs sent undercover of the DLS letter dated 23rd October 2012 (Ref INQ-2078-12)

I have no idea what this pie chart means.

(d) The reference in the email from the DLS sent on 23rd October 2012 to the Inquiry to: "the attached files which demonstrate the presence of inflammatory cells in NPPM 114-960001.jpg and NPPM 114-96-2.jpg and neuroblasts in NPPM 114-960009.jpg", together with any specimen photographs of slides that illustrate what you regard as "inflammatory cells" and "neuroblasts"

(e) The slides that you prepared of the hippocampus and the hilum

* I have prepared two power point presentations which show the images forwarded and examples of pathology of encephalitis and neuronal migration disorders to compare. I have included images of the basic process of neuronal migration for information.

I commented on the photographs in my initial neuropathology report.

Waney Squier

November 14th 2012

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ACCOMPANYING DOCUMENTS

(i) Autopsy Request Form;

(ii) Autopsy Report;

(iii) CT scan;

(iv) DLS correspondence and pie chart and photographs

Reference List

Krous, H. F., A. E. Chadwick, et al. (2007). "Sudden death in toddlers with viral meningitis, massive cerebral edema, and neurogenic pulmonary edema and hemorrhage: report of two cases." Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society **10**(6): 463-469.

Morris, J. A., L. M. Harrison, et al. (2012). "Postmortem cerebrospinal fluid pleocytosis: a marker of inflammation or postmortem artifact?" International journal of pediatrics **2012**: 964074.

Pathologists, R. C. o. (1993). Guidelines for Post Mortem reports.

Royal College of Pathologists, R. C. o. P. o. L. a. R. C. o. S. o. E. (1991). The Autopsy and Audit.

Start, R. D. (1996). "Practice guidelines for necropsy: time for action." Journal of clinical pathology **49**(11): 867-868.

Start, R. D., Y. Delargy-Aziz, et al. (1993). "Clinicians and the coronial system: ability of clinicians to recognise reportable deaths." BMJ **306**(6884): 1038-1041.

Encephalitis

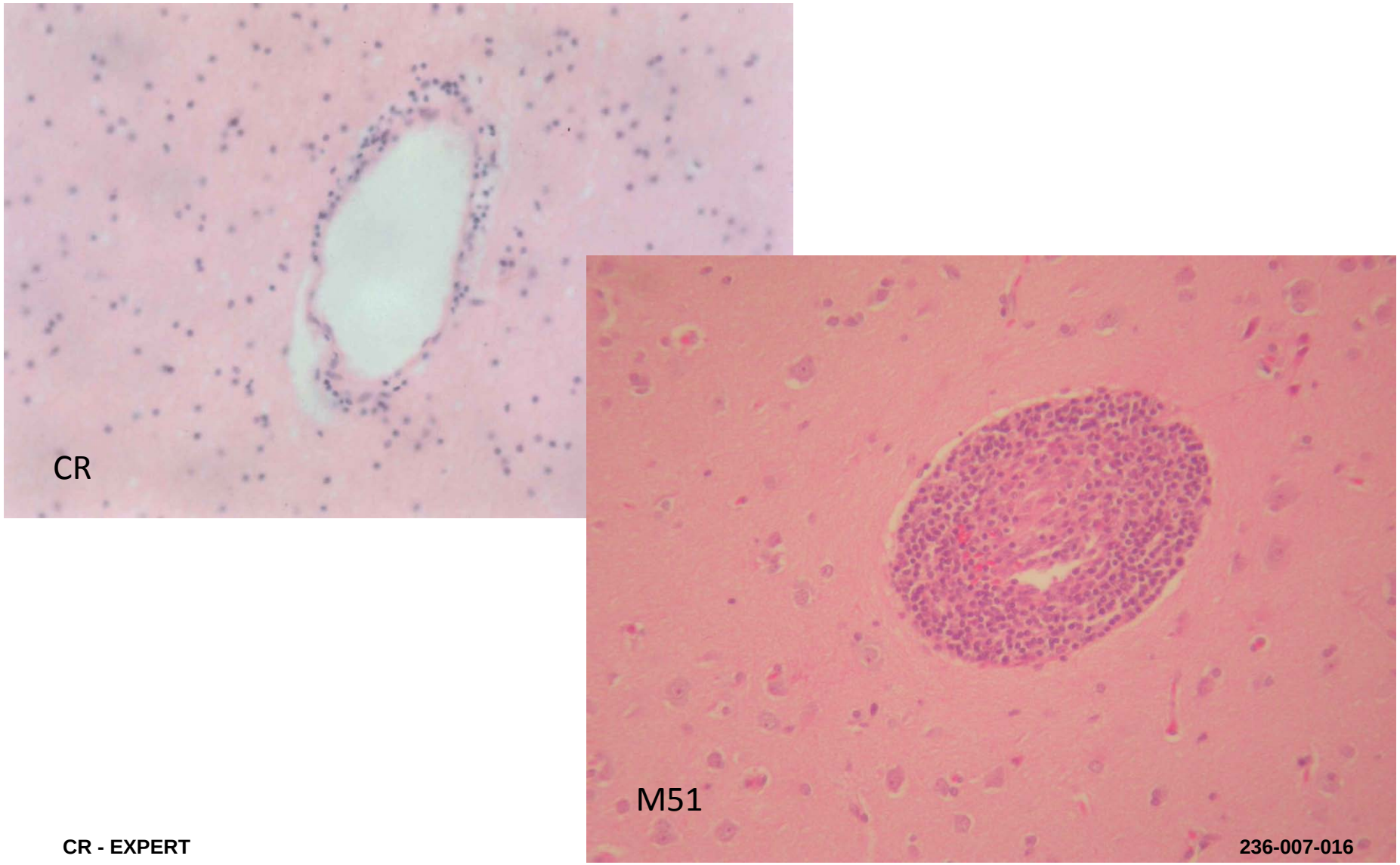
We have relatively few cases in our archive. I am not able to match for age but have chosen two examples of encephalitis to illustrate characteristic histological features as well as the range of appearances that may be seen.

M51 is a 51 year old man and B2 a two year old baby .

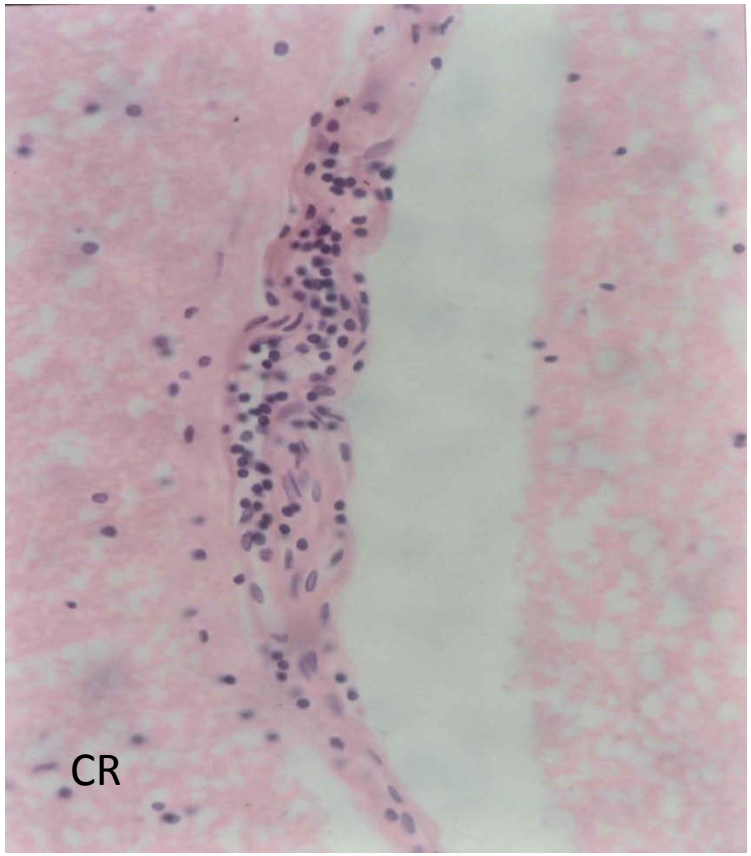
Waney Squier

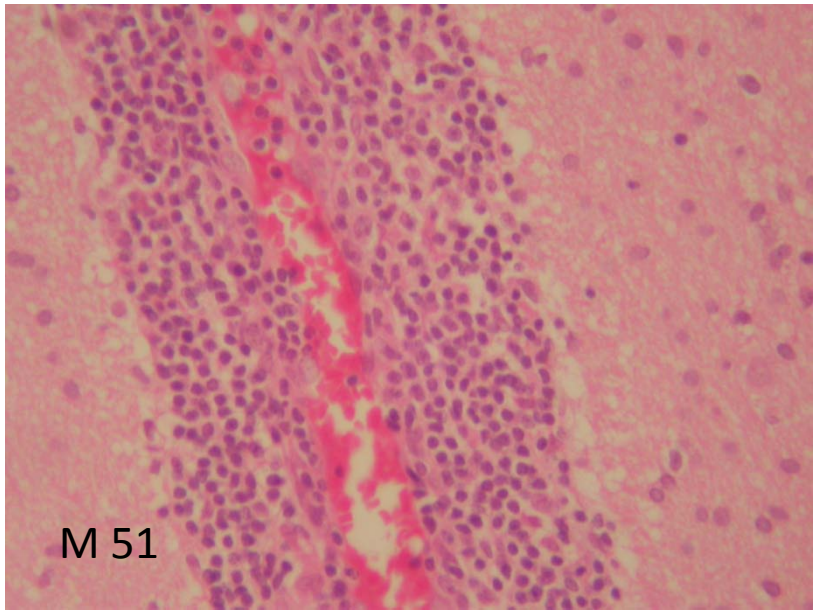
October 31st 2012

Left Claire (CR) and right a 51 year old male encephalitis at approximately similar magnification

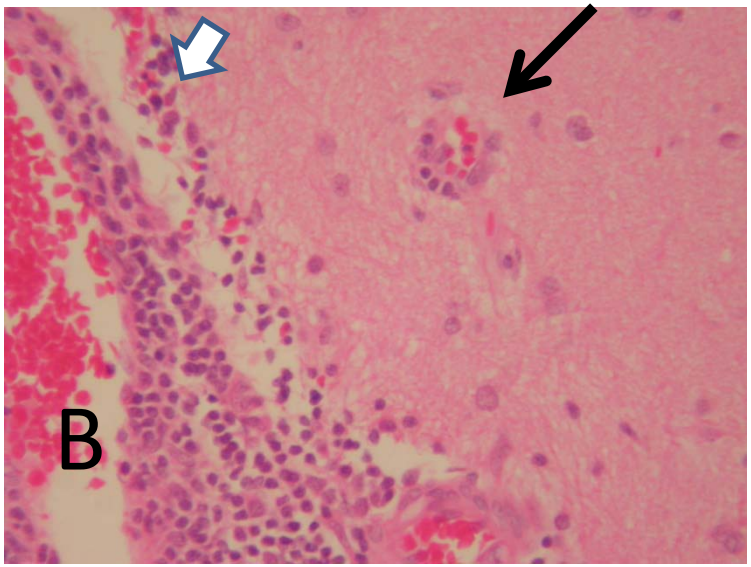


The same cases at higher magnification

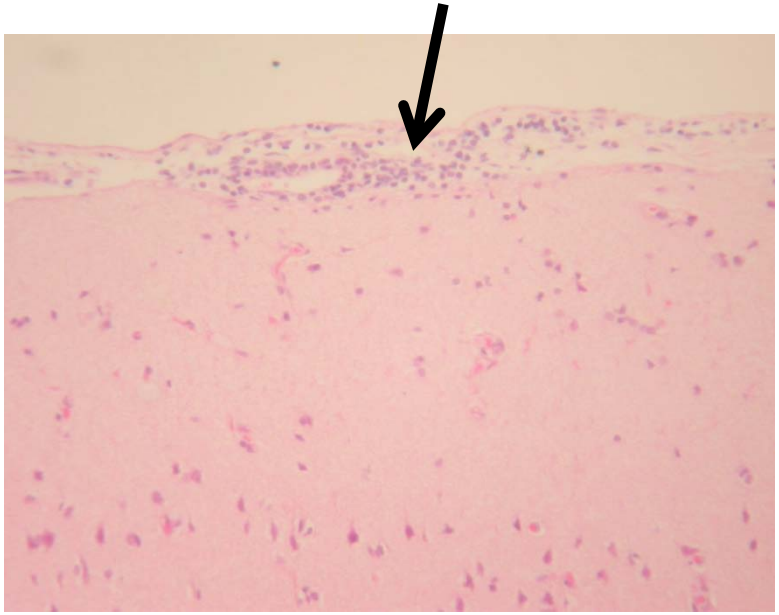




Male 51

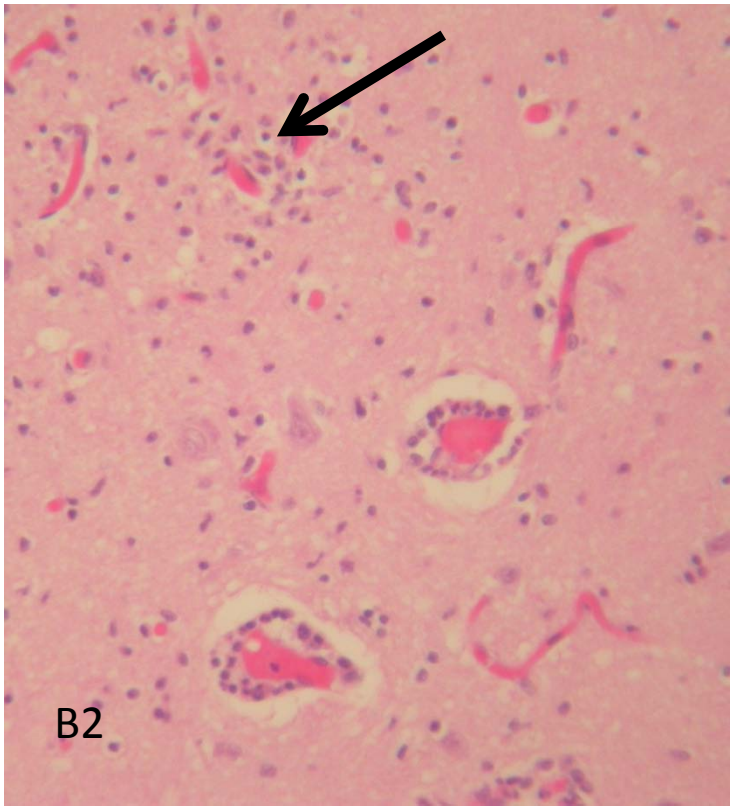


The image on the left shows some inflammatory cells extending from around the large blood vessel (B) and into brain tissue (solid white arrow). A few cells are seen around a smaller blood vessel (black arrow)

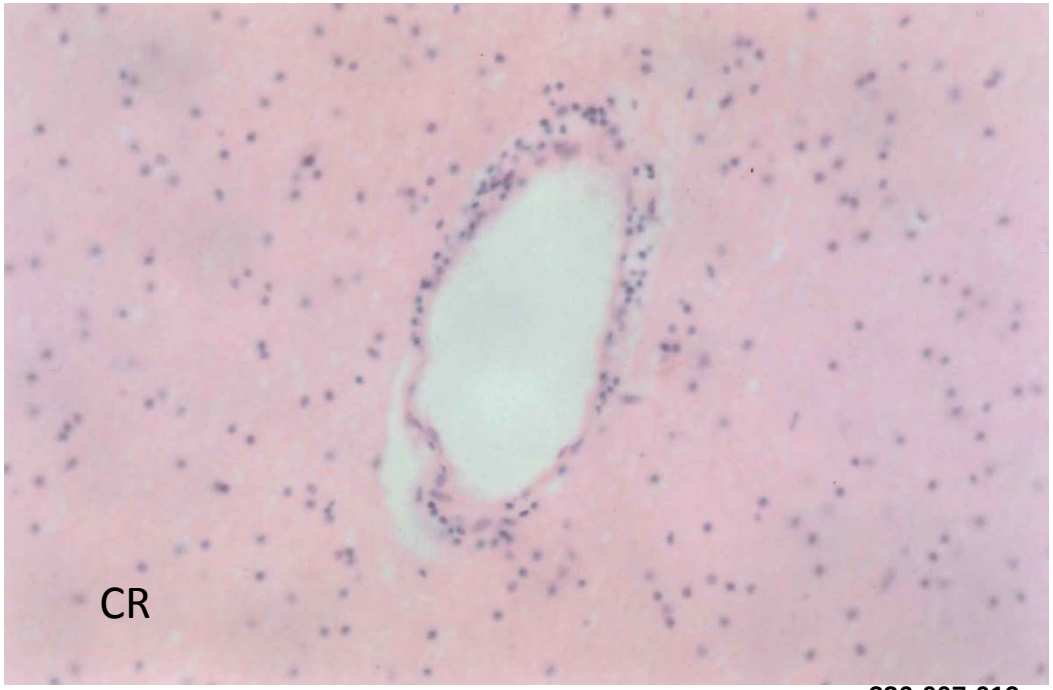


The image on the right shows the brain surface from the same patient where a very small and subtle collection of inflammatory cells is seen (black arrow). This indicates that the process can be patchy . Even subtle raise the suspicion that a serious inflammatory condition is present and a detailed search is necessary.

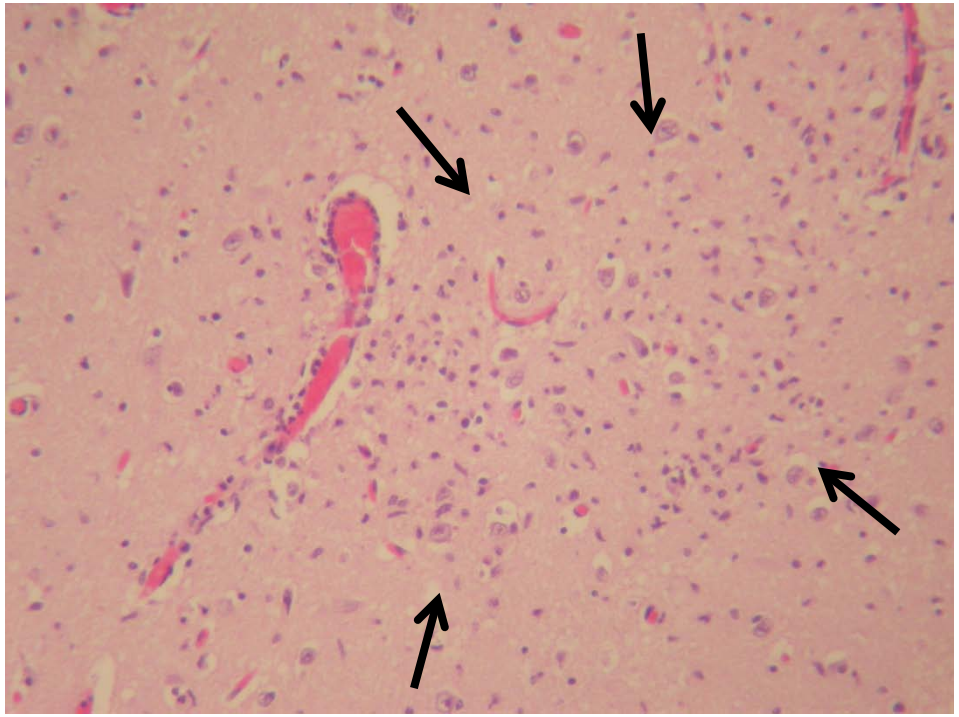
B2



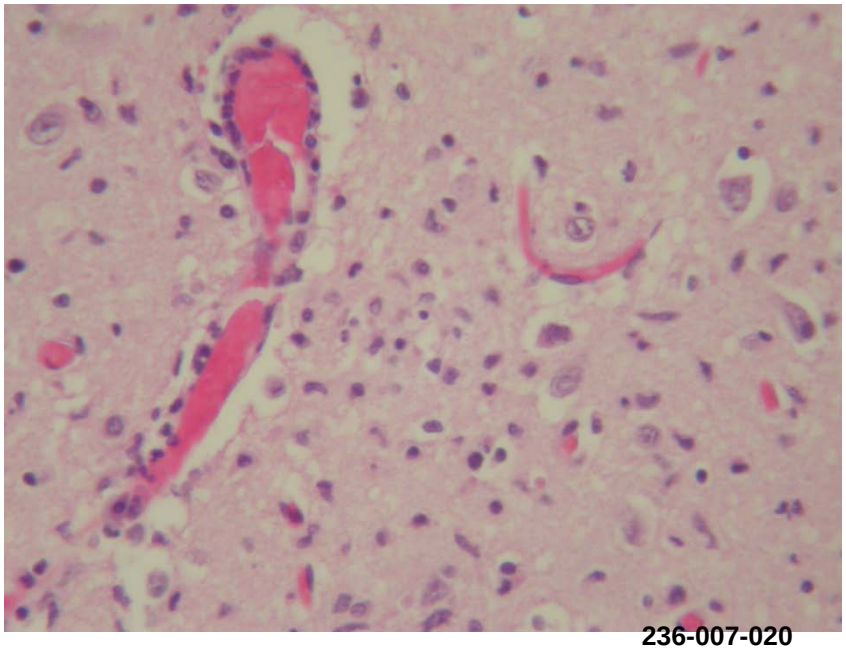
This baby (left) has fewer inflammatory cells around the blood vessels and is more like the vessel from Claire's brain (below). However, in B2 many vessels are involved and there are large numbers of cells infiltrating the brain tissue (arrow).

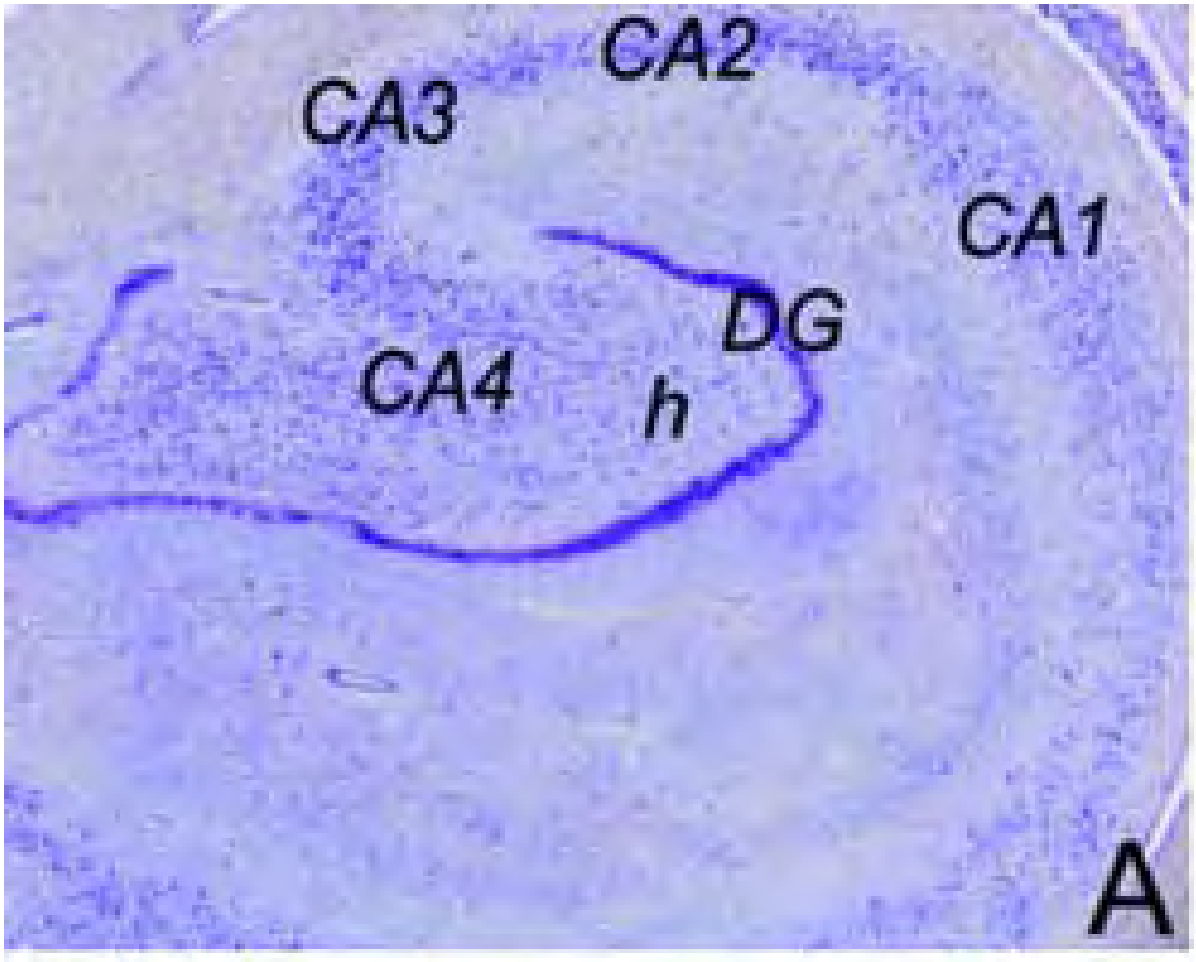


B2

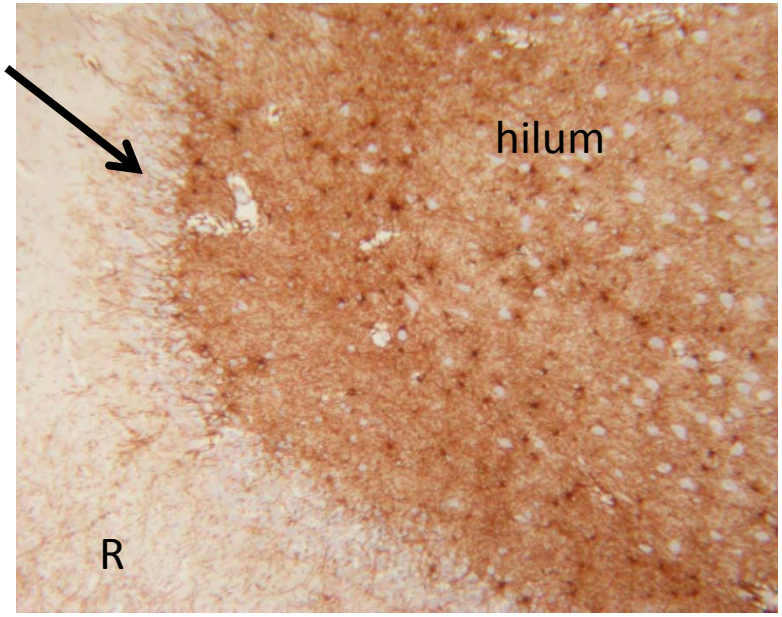


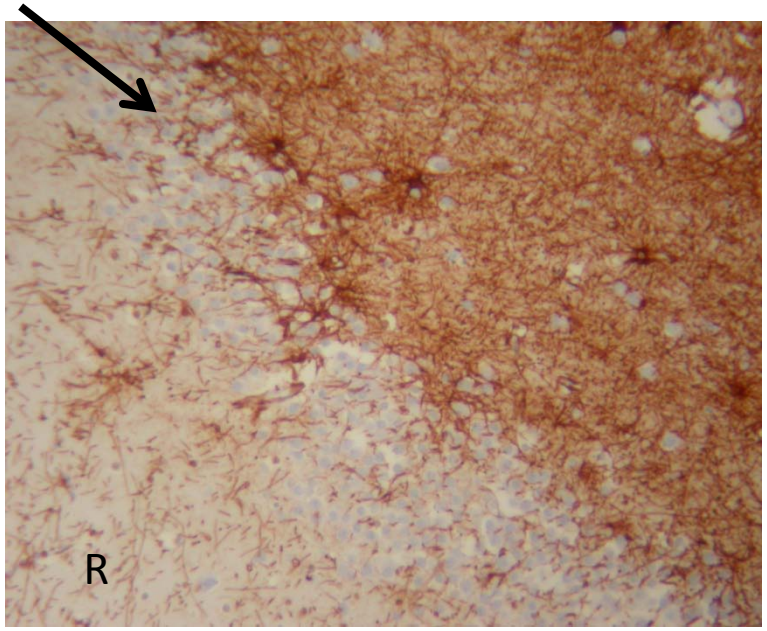
More images from B 2 show cells infiltrating the brain tissue and relatively few around blood vessels. The area between arrows has too many cells in it. It is hard to be more objective without special staining techniques.



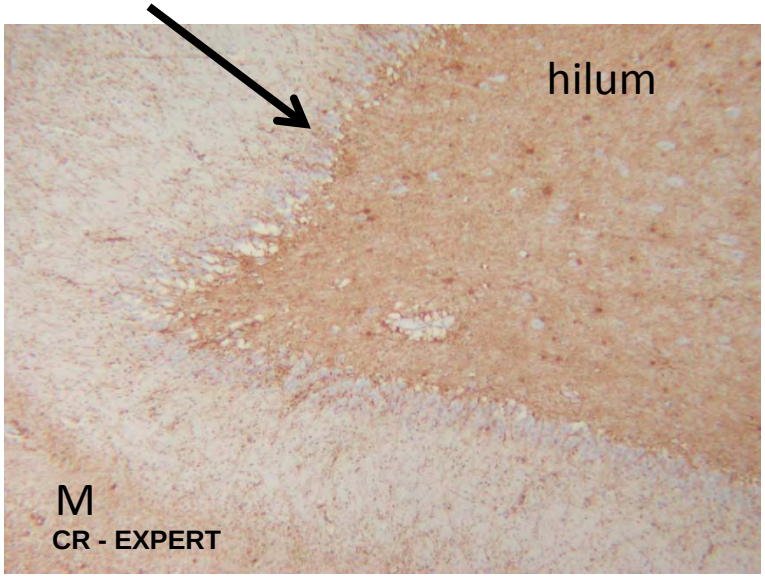


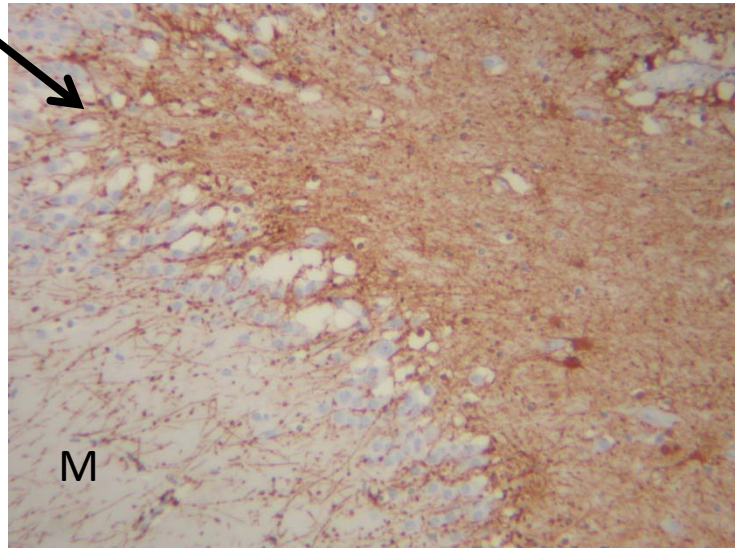
The hippocampus. H=hilum, DG = dentate fascia





Hippocampus stained with GFAP to demonstrate astrocytes (scarring).
Each reactive cell appears as a star shaped brown cell. Above is Claire Roberts (R). Below a 10 year old male who died suddenly with no history of epilepsy (M). On the left low magnification (x4) and on the right higher (x10). The arrow indicates the dentate fascia.





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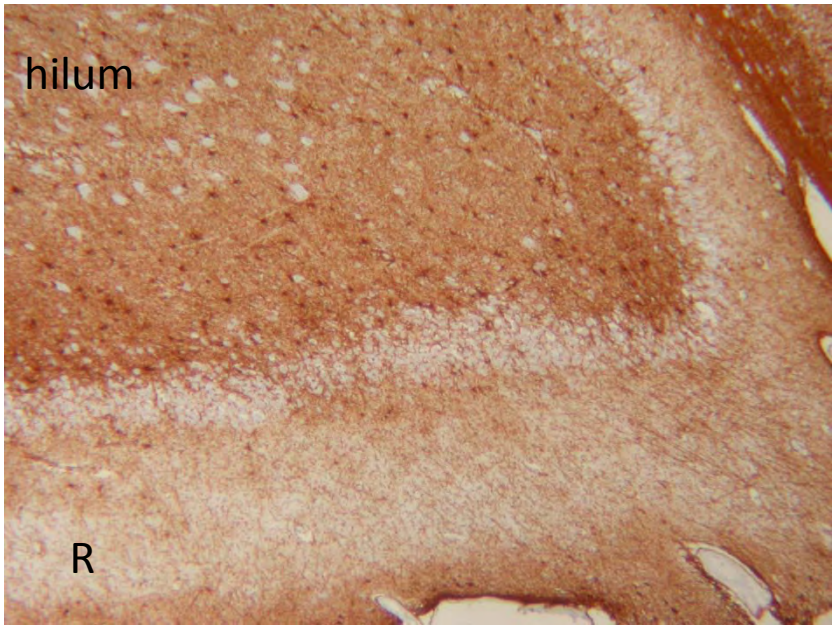
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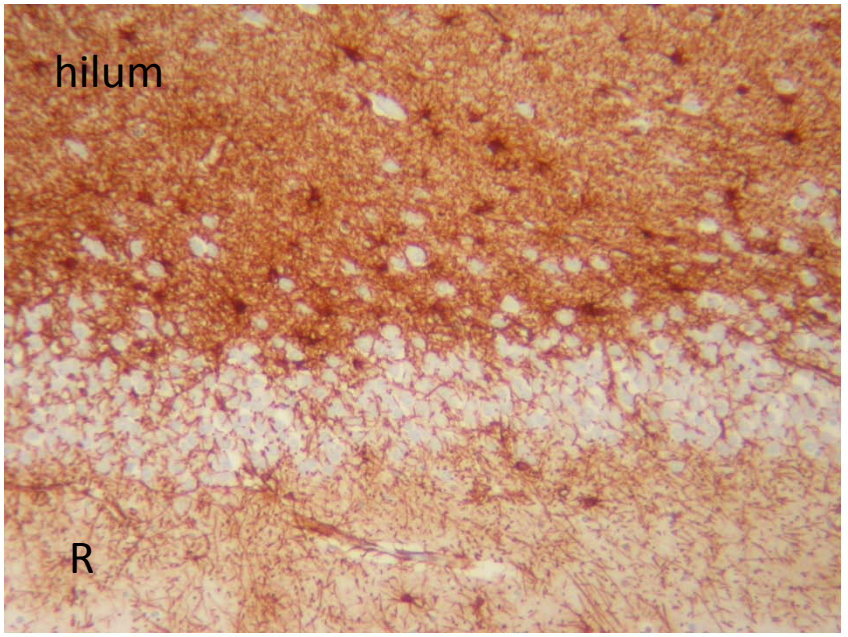
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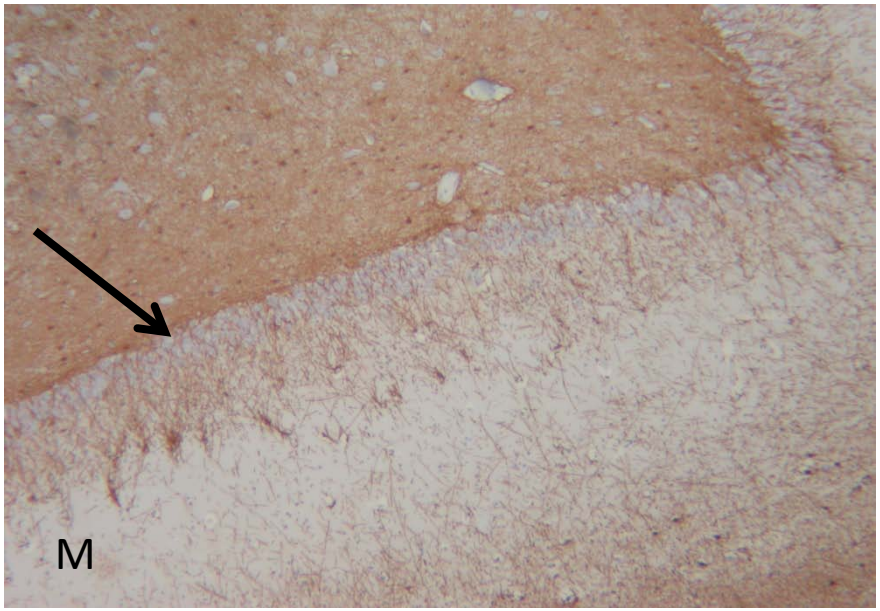
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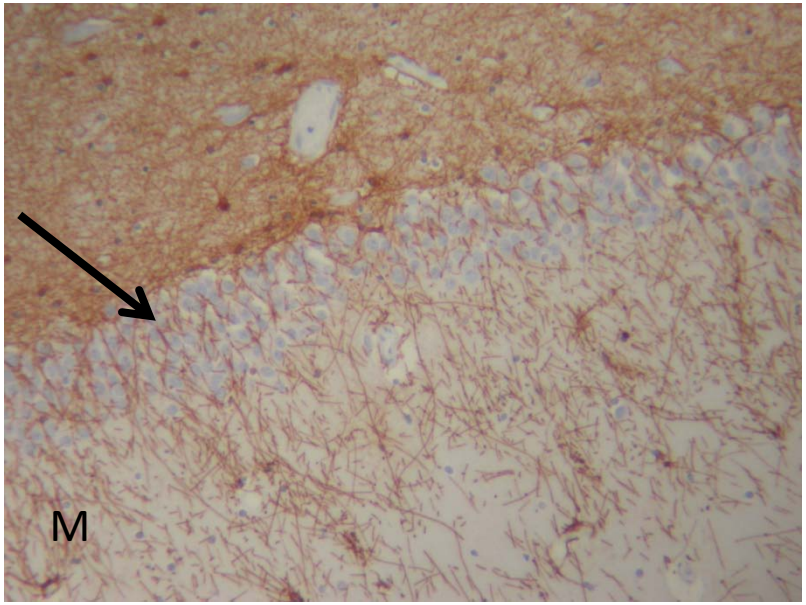
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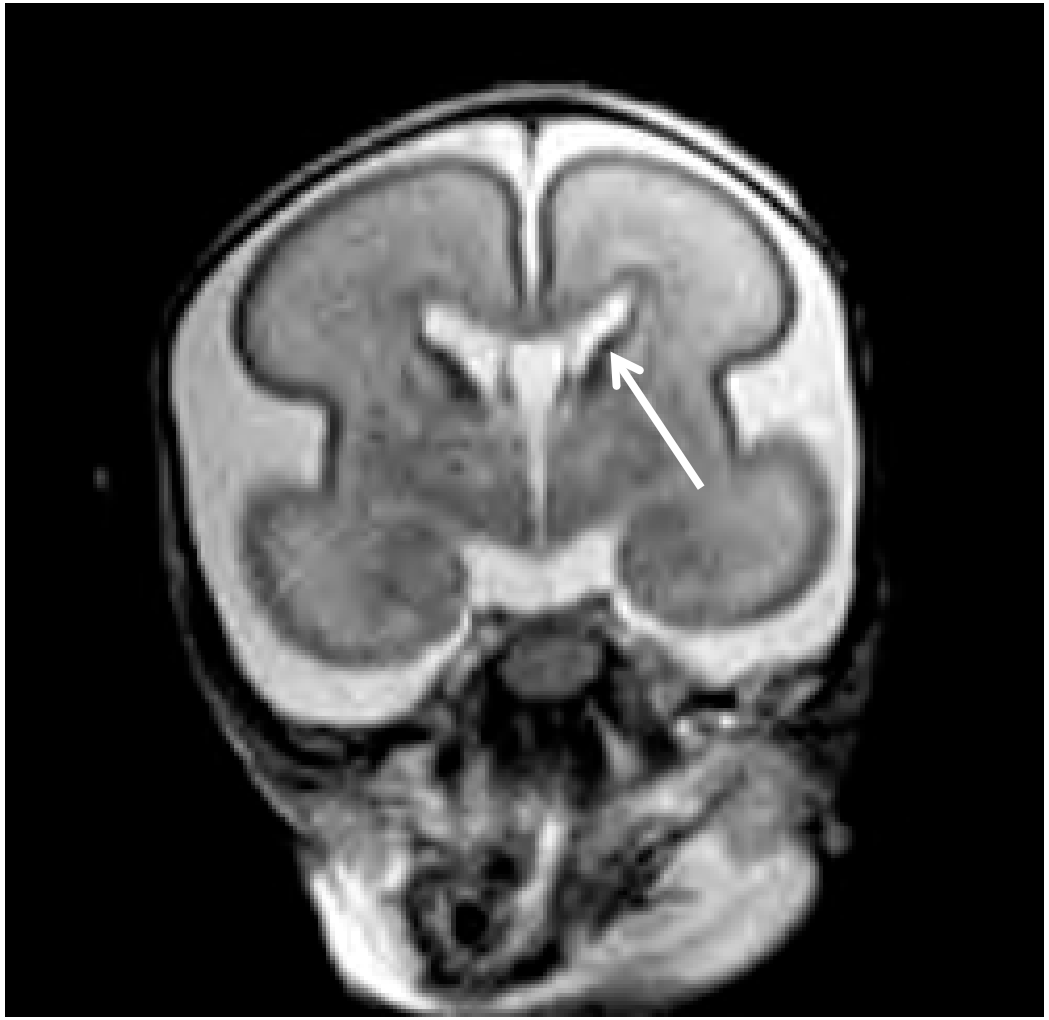
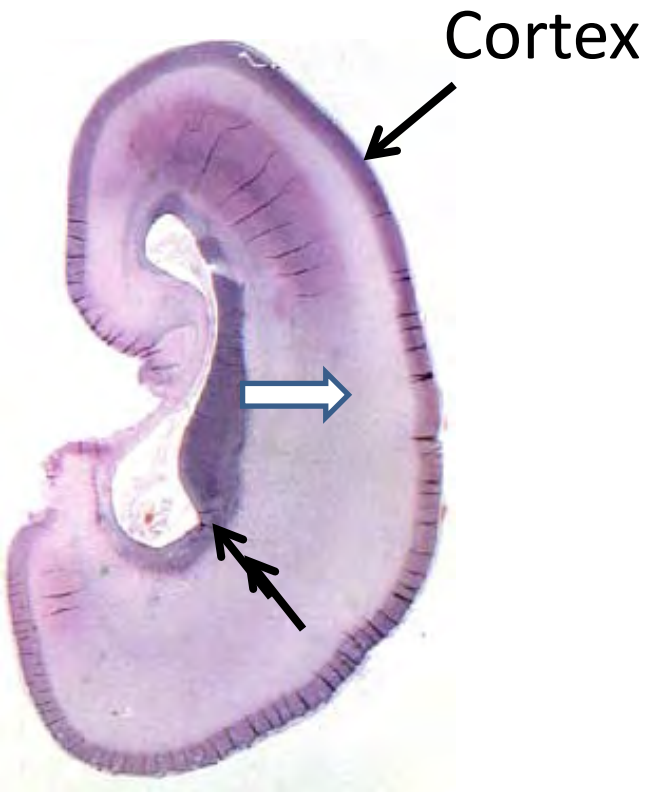
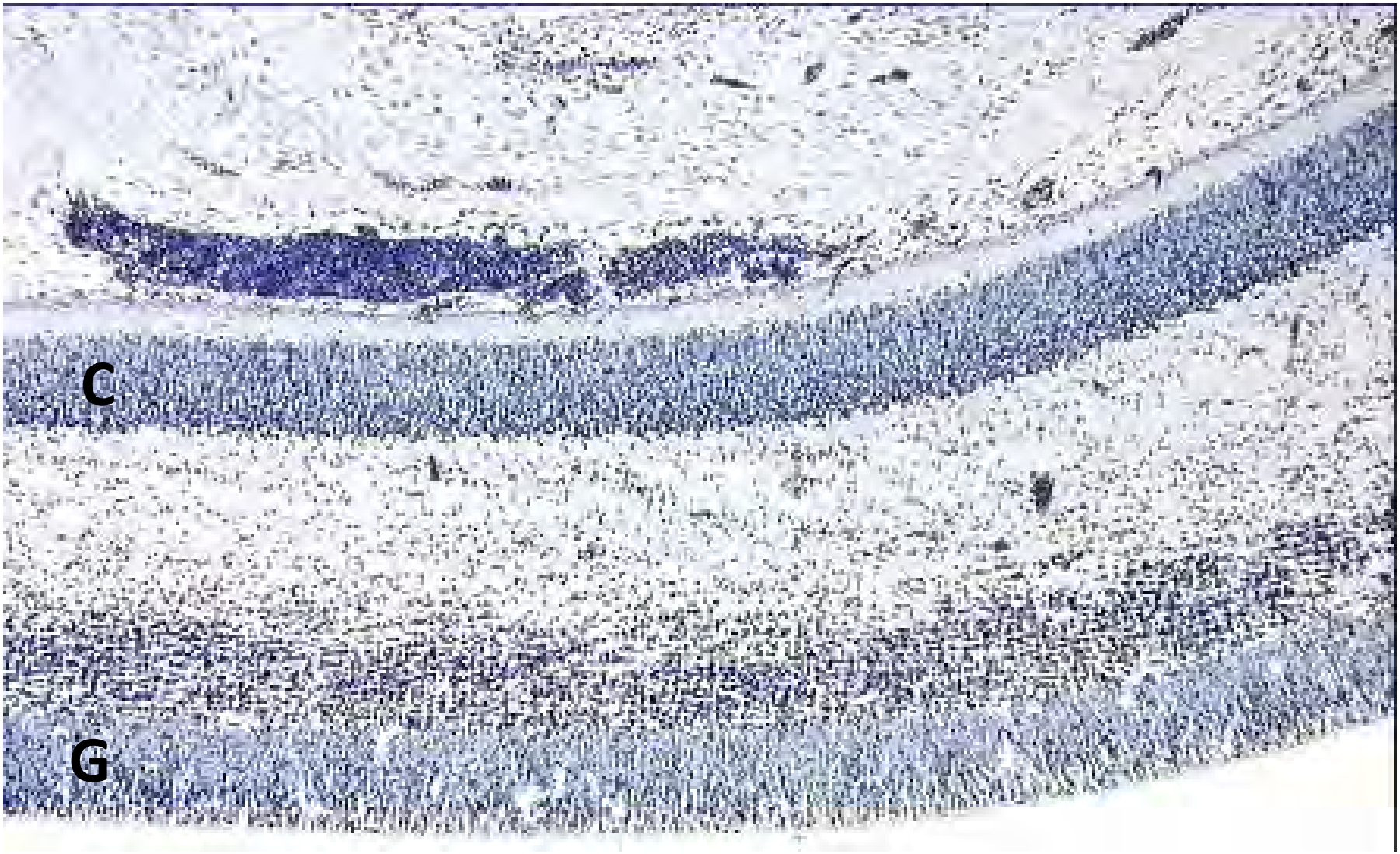
Neuronal Migration
6-20 weeks gestation

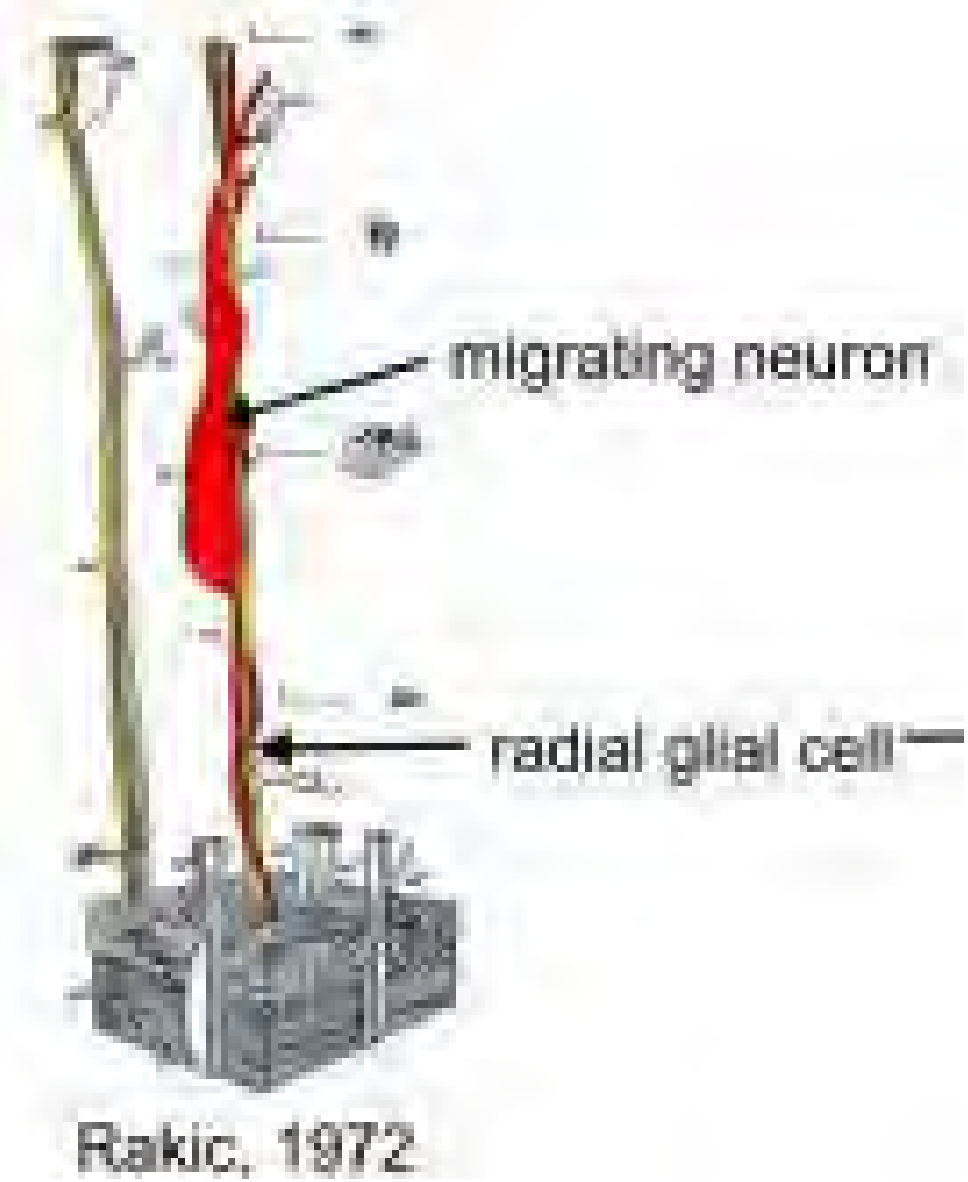




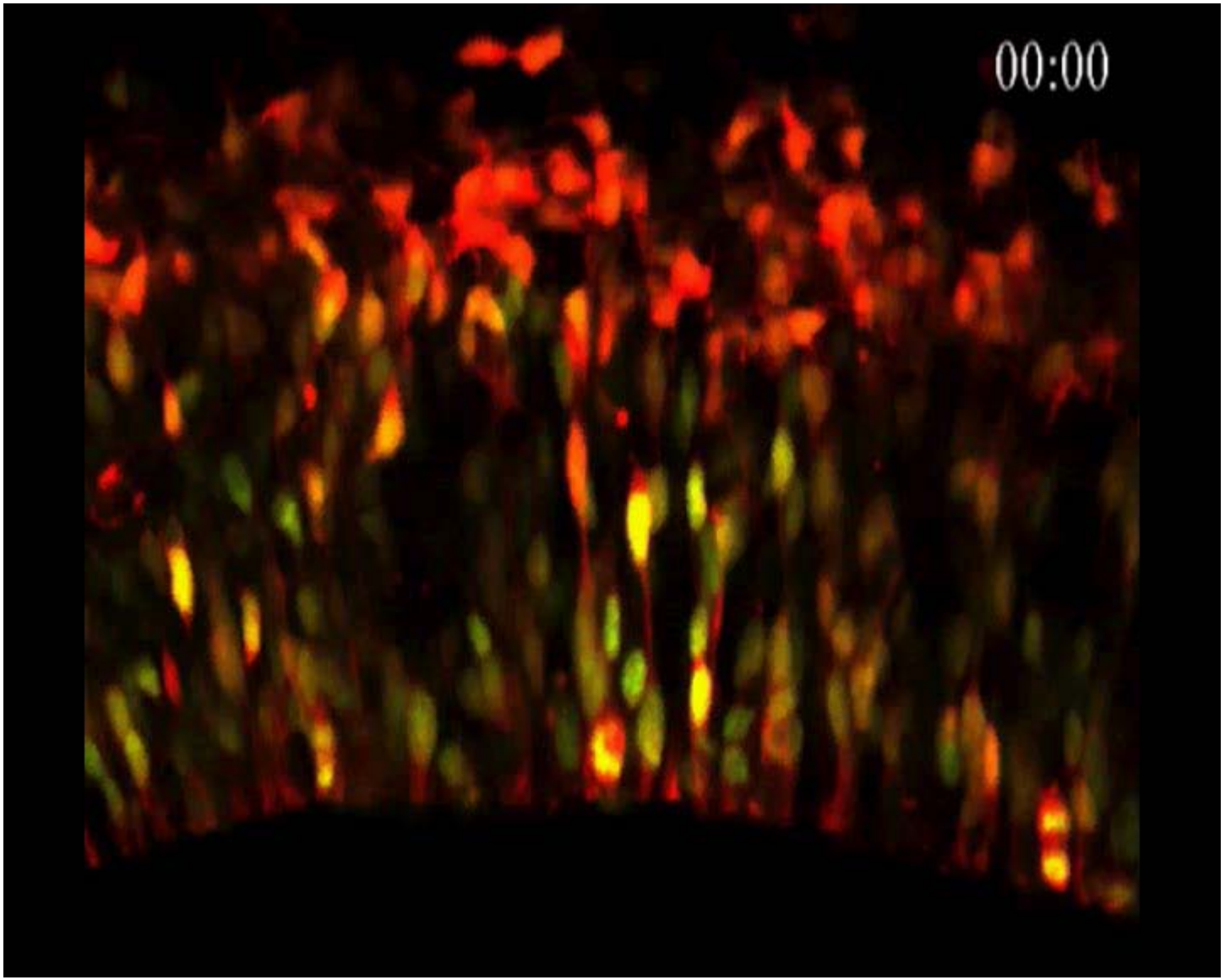
Brain scan and section of fetal brain to show germinal matrix (arrow) where nerve cells are formed and the thin primitive cortex to which the nerve cells migrate. The white arrow indicates migration direction



Brain wall in 8 week fetus. Cells migrate from the germinal zone (G) to form the cortex (C).



A diagram indicating how precursors of the nerve cells migrate from the germinal zone (G) on guide wires provided by glial cells between 6 and about 20 weeks of gestation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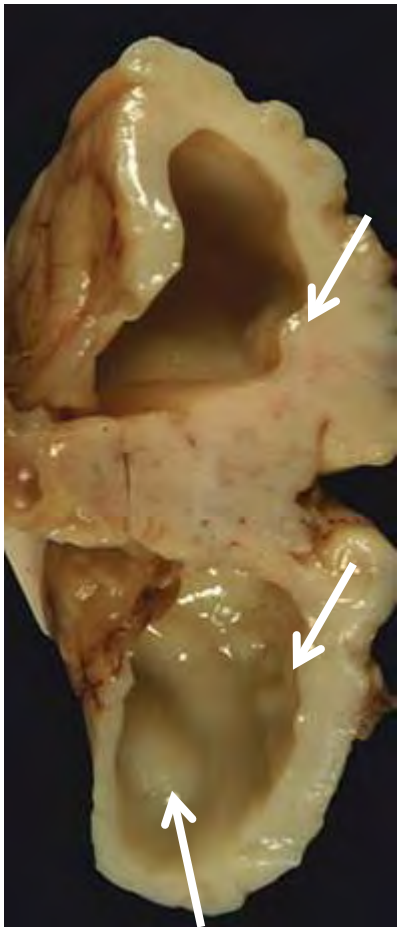
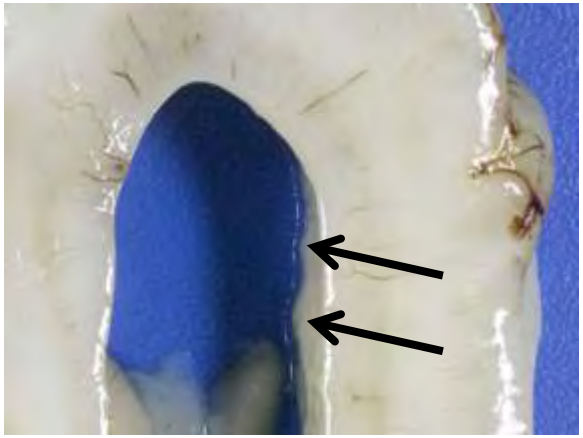
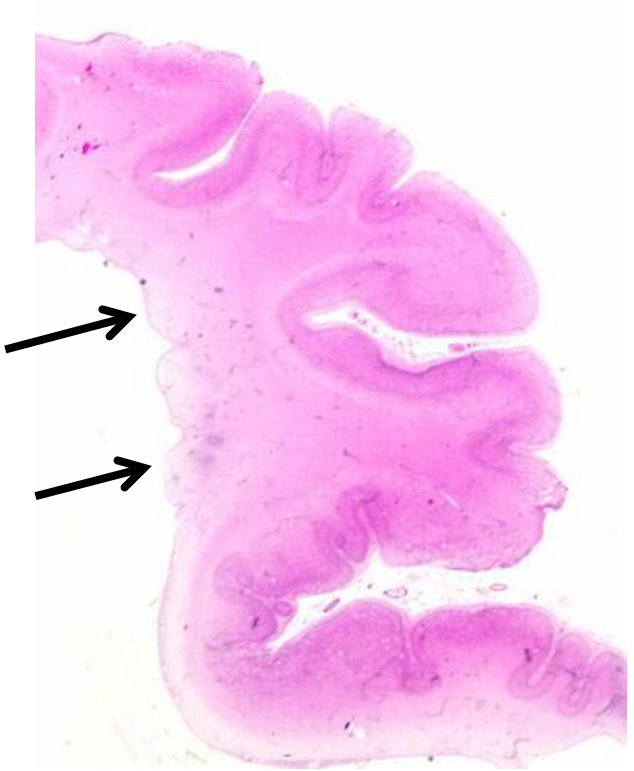
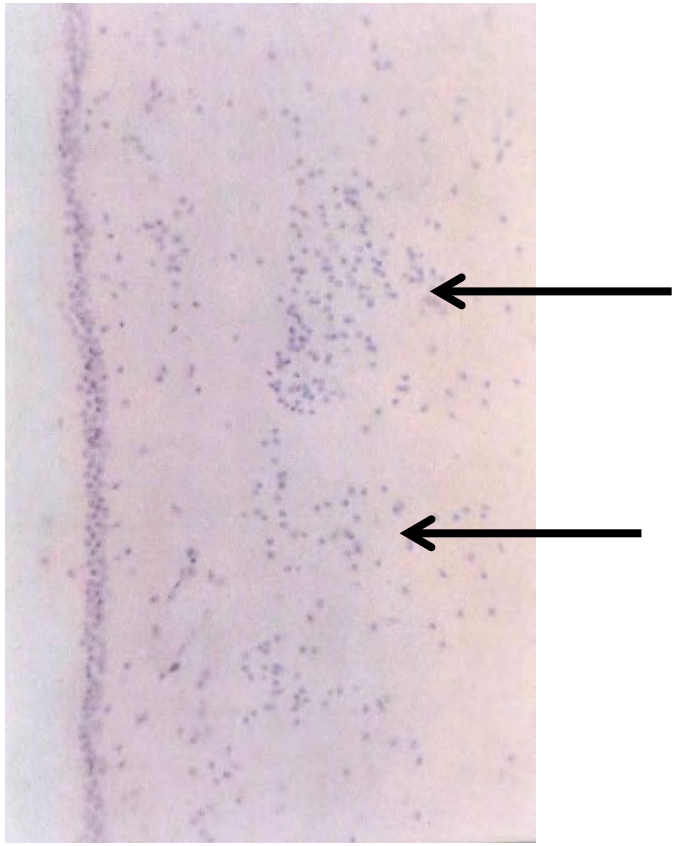
Examples of failed neuronal migration with nodules of neurones (arrows) in the lining of the ventricle

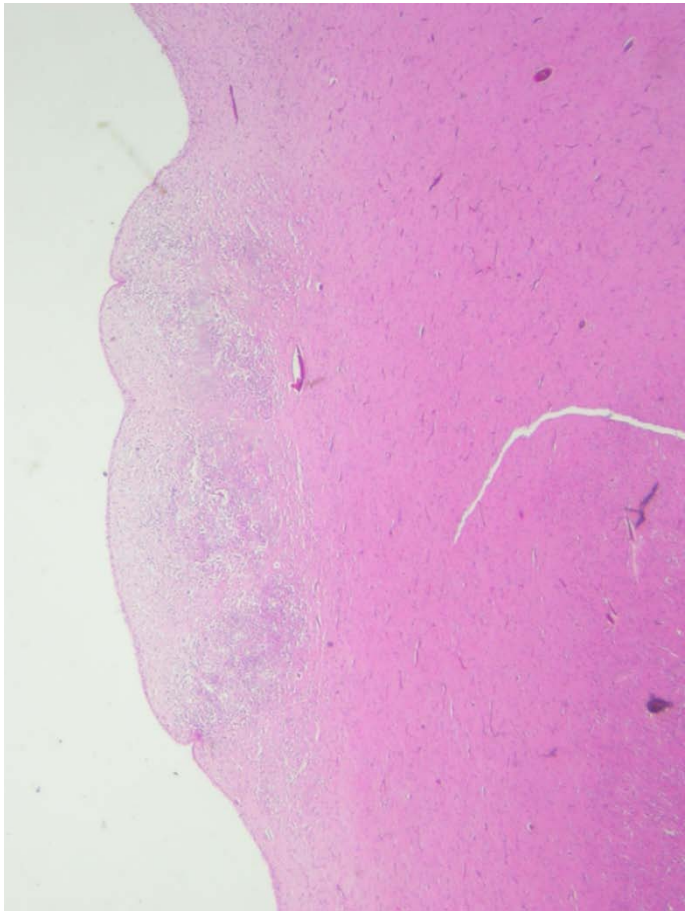






Claire’s ventricular lining (left) with groups of dark cells (neuroblasts) compared with migration disorder (right)





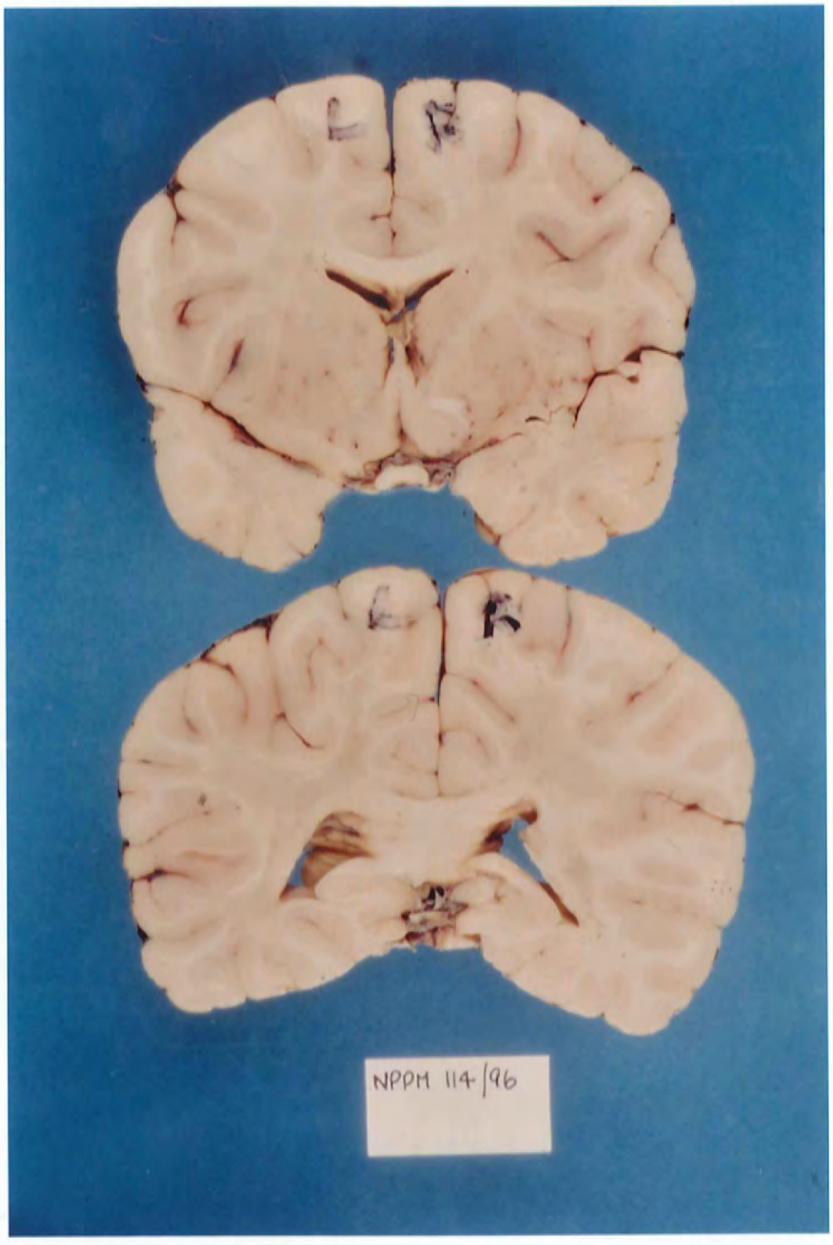


IMAGE 1

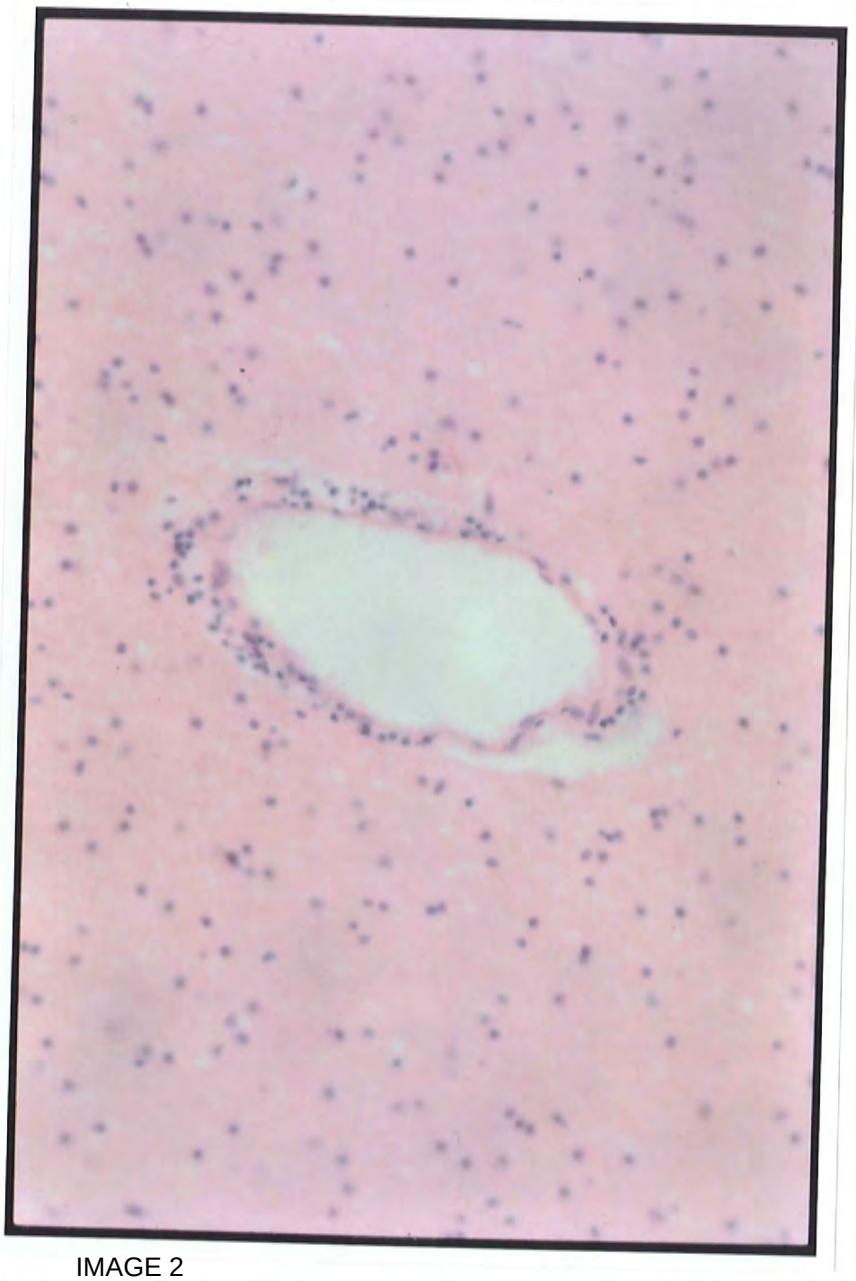


IMAGE 2

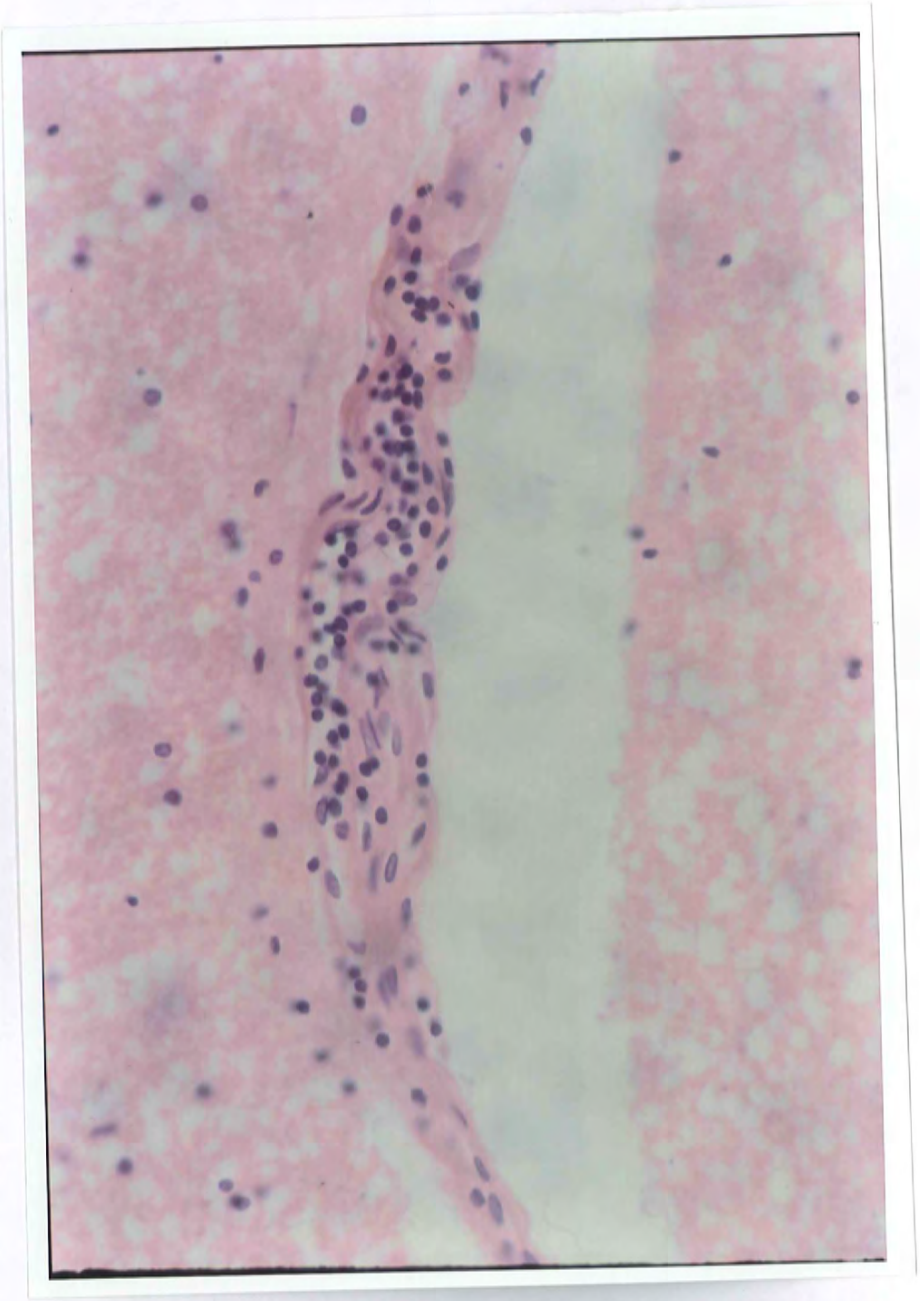


IMAGE 3

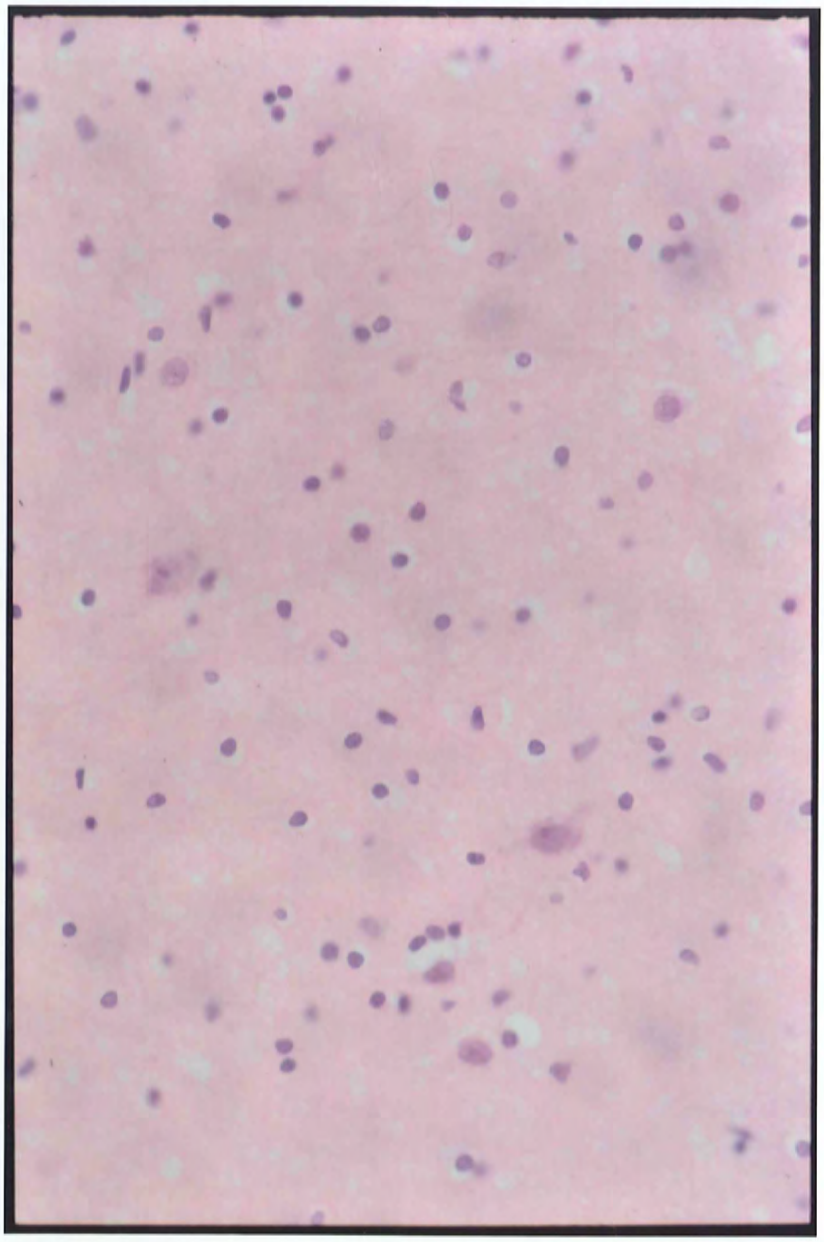


IMAGE 4

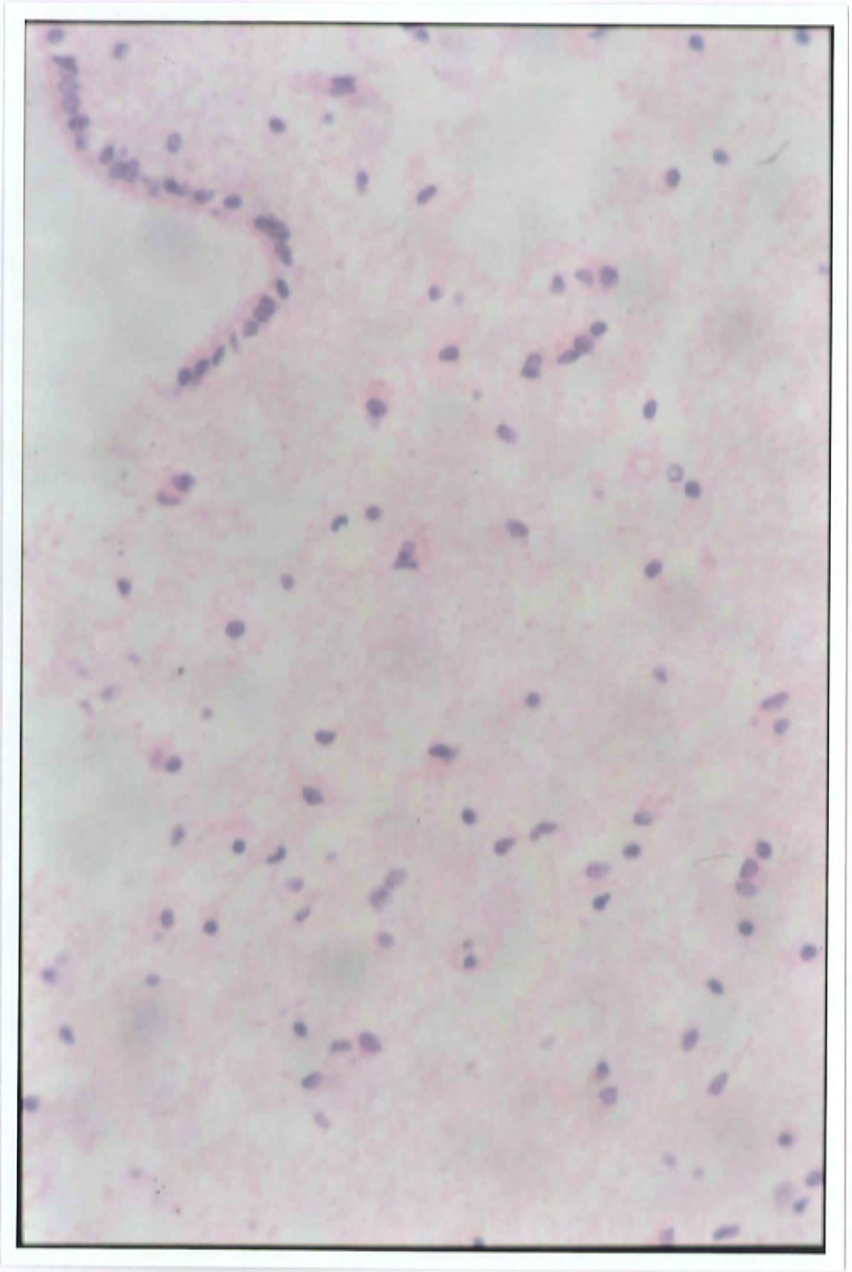
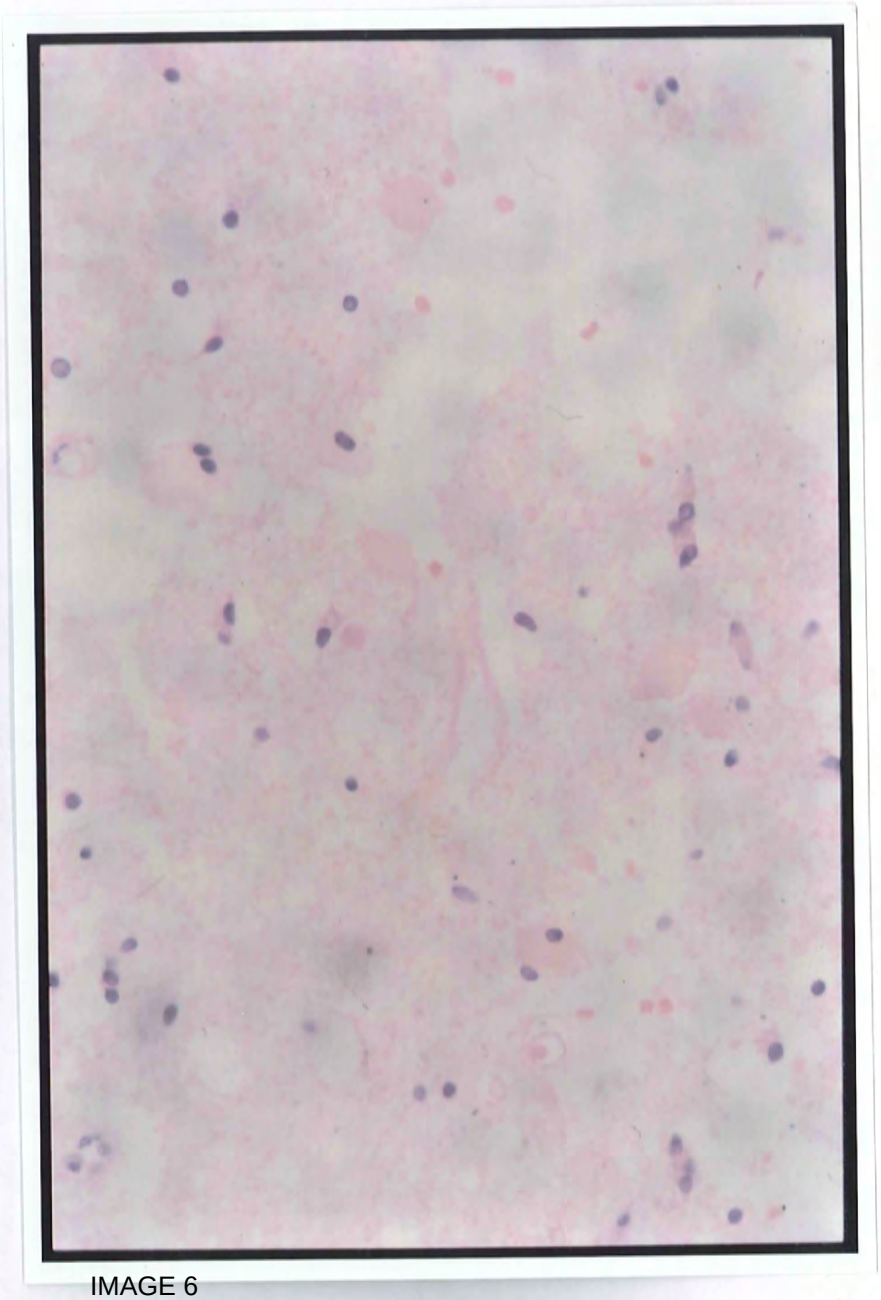


IMAGE 5



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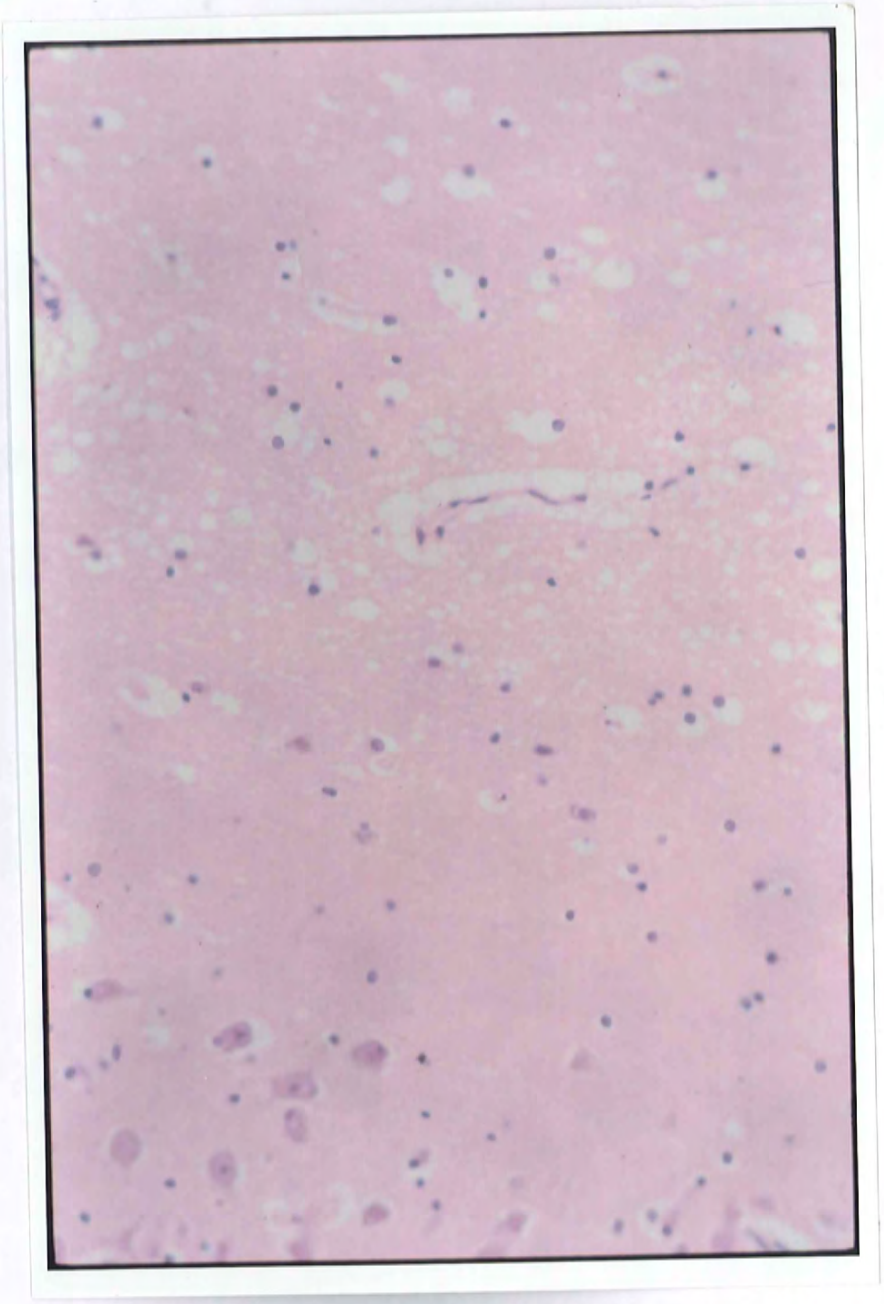

IMAGE 7

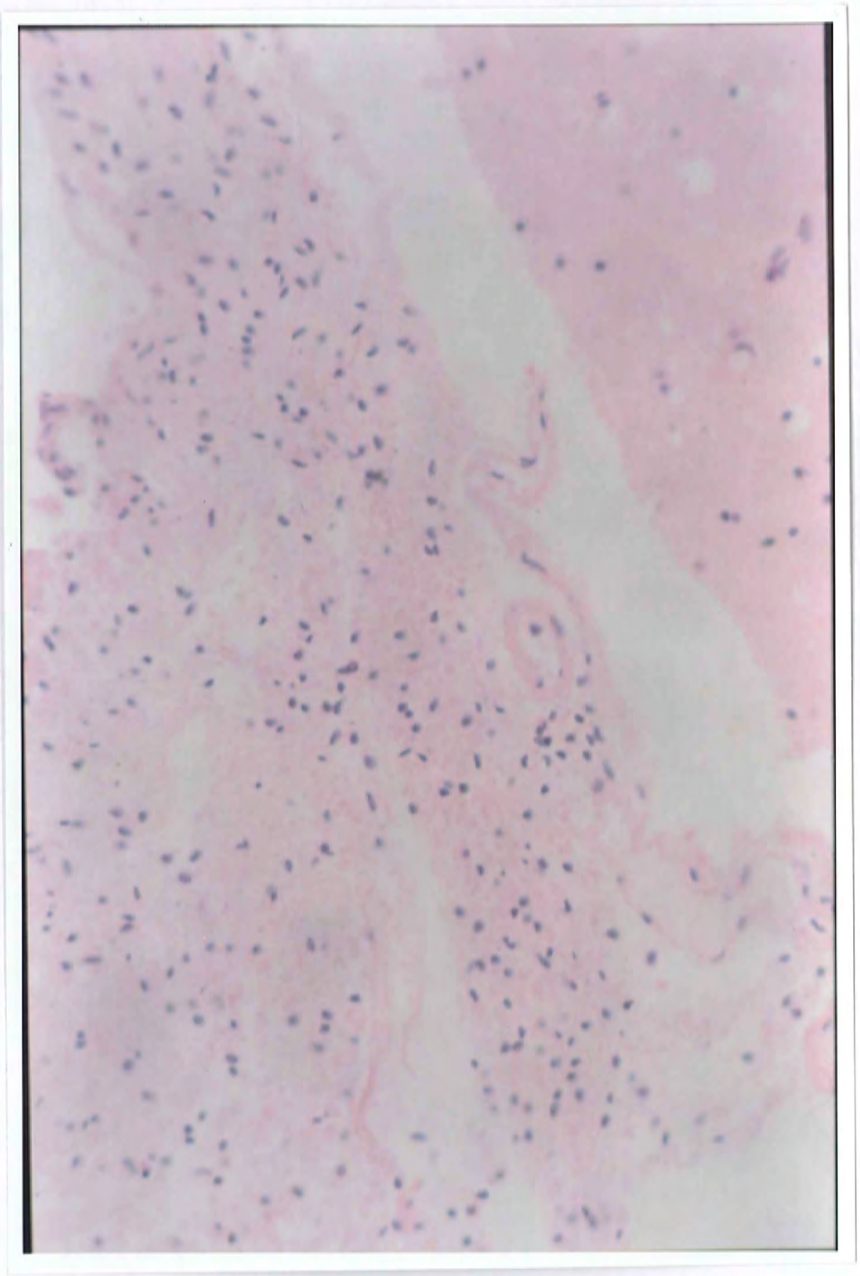

IMAGE 8

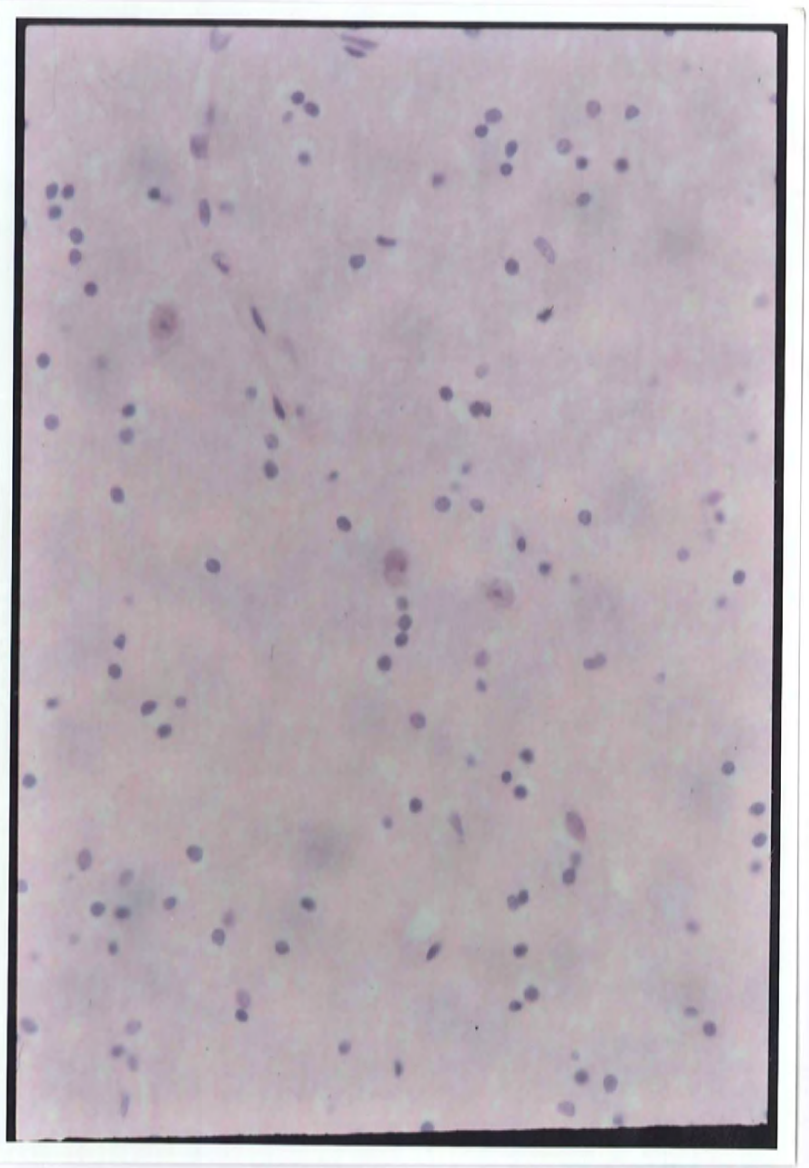

IMAGE 9

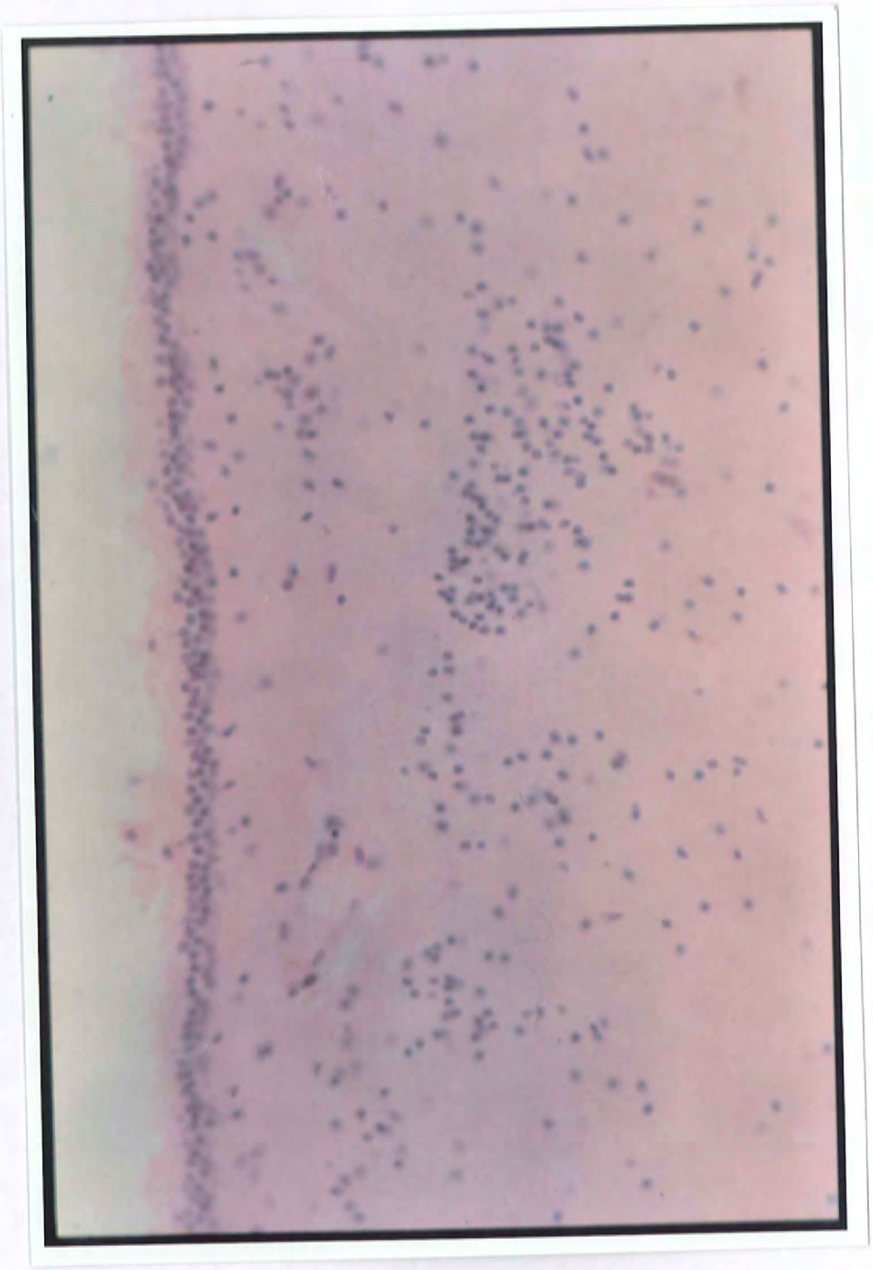

IMAGE 10

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CASE REPORTS

Sudden Death in Toddlers with Viral Meningitis, Massive Cerebral Edema, and Neurogenic Pulmonary Edema and Hemorrhage: Report of Two Cases

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ABSTRACT

Viral (lymphocytic) meningitis typically does not cause sudden death, especially in the absence of severe inflammation in the brain or other organs. We report 2 toddlers with clinical evidence of a viral infection who died unexpectedly and were found at autopsy to have lymphocytic meningitis associated with severe brain edema, transtentorial herniation, neurogenic pulmonary edema and hemorrhage, and cardiomegaly. Influenza A virus, demonstrated in tracheal epithelium by immunocytochemistry, is the presumed cause of the mild meningitis in 1 case; adenovirus was cultured from swabs of the brain and anus in the 2nd case. Current concepts of neurogenic pulmonary edema and acute cardiac dysfunction associated with intracranial disease are discussed in considering the mechanism of sudden death in these toddlers. These cases emphasize the possibility that mild intracranial viral infections may be a rare cause of sudden death via lethal cardiopulmonary complications. They also underscore the importance of a comprehensive autopsy, including detailed neuropathologic examination and viral testing, in determining of the cause of unexpected death in toddlers.

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Key words: adenovirus, influenza A virus, neurogenic pulmonary edema, SUDC, sudden unexpected death in childhood, viral meningitis

INTRODUCTION

Sudden and unexpected death in toddlers (1 to 5 years of age) is a rare entity about which little is known [1]. Of particular interest to the pediatric and forensic pathologist is the establishment of documented causes of death that he or she should consider in the autopsy evaluation of such cases. We are conducting a long-term study of the causes of sudden and unexpected death in children, called the San Diego Sudden Unexplained Death in Childhood (SUDC) Research Project [1]. A major goal of this study is to provide a comprehensive differential diagnosis as a guide to the forensic autopsy of such cases. In our analysis of the first 75 cases accessioned into the SUDC Research Project database, we identified 2 toddlers whose sudden deaths were associated with viral meningitis and

neurogenic pulmonary edema. We bring this entity to the attention of the pediatric and forensic pathologist for consideration in the differential diagnosis of the perplexing problem of sudden unexpected death in toddlers. Current concepts of fatal neurogenic pulmonary edema associated with intracranial disease are also discussed.

CASE REPORT 1

A previously healthy 30-month-old male was discovered unresponsive, cyanotic, and prone in his crib after an afternoon nap. Efforts at cardiopulmonary resuscitation were unsuccessful. During the 24 hours before his death, he appeared tired, irritable, and lethargic and had a decreased appetite. He experienced low-grade fever and sweating for which he was treated with Motrin with temporary improvement. His past medical history was significant for recurrent otitis media, frequent upper respiratory infections, and restrictive airway disease. There was no history of prior meningitis, head trauma, acute life-threatening events (ALTEs), seizures, or gastroesophageal reflux. His DtaP, Hib, IPV, Hep B, MMR, Varivax, and pneumococcal conjugate immunizations were current, and none were administered during the 2 weeks before his death. Two blood screens for lead were within the reference range. The family history was noteworthy for supraventricular tachycardia in the mother beginning at 6 years of age, which resolved without intervention by 25 years of age. The family history was negative for ALTEs, syncope, seizures, epilepsy, sudden infant death syndrome (SIDS), and SUDC.

Postmortem examination

The body measured 91.4 cm in length (25th–50th percentile for age) and weighed 14.5 kg (75th percentile for age). The nares and mouth revealed copious amounts of slightly blood-stained, watery fluid. Evidence of facial trauma was not identified. Petechiae were present on the thymus, pleura, and epicardium but not the conjunctiva.

The leptomeninges were transparent but not hemorrhagic. The 1540-g brain (expected brain weight for age [2] is 1149.2 g for a 2-year-old male and 1257.4 g for a 3-year-old male; $P \geq 0.95$, confidence limits 1083.1–1215.3 g and 1198–1316.7 g, respectively) revealed severe edema with flattened gyri and narrowed sulci associated with herniation of the cingulate and uncal gyri and cerebellar tonsils. The spinal fluid was slightly cloudy. Microscopically, lymphocytic infiltration was restricted to the meninges (Fig. 1) and was most severe over the medial temporal cortex but was not identified in the forebrain or brainstem parenchyma or perivascular spaces. Edema was confirmed, but viral inclusion bodies, microglial nodules, and ischemic changes were not present. The hippocampus and brainstem were unremarkable. Neurodevelopmental abnormalities were not identified.

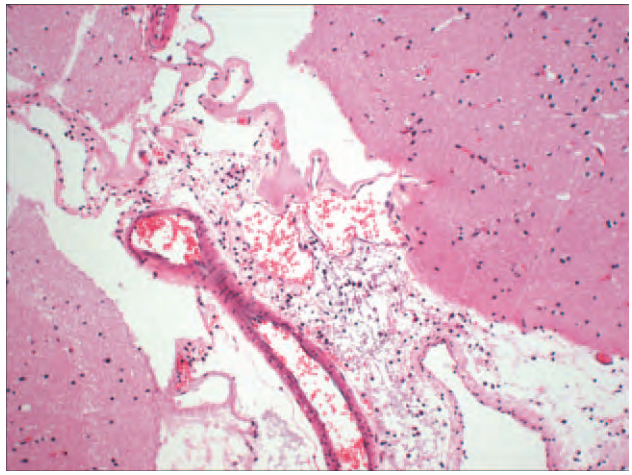

Figure 1. The meninges over the temporal lobe of case 1, a 30-month-old male, display mild infiltration by lymphocytes. H&E ×100.

The lungs were severely congested and hemorrhagic but not consolidated; the right lung weighed 220 g (expected weight for body length [3] 89 g) and the left lung weighed 200 g (expected weight for body length [3] 80 g). Microscopic examination confirmed severe pulmonary congestion and hemorrhage (Fig. 2). Acute bronchopneumonia, interstitial pneumonitis, fibrosis, thromboembolization, infarcts, and hypertensive arteriopathy were not present. The tracheal mucosa was moderately eroded and congested but not inflamed. The enlarged heart weighed 90 g (expected heart weight for body weight [4] 65 g), and the left ventricle was mildly hypertrophied. Microscopic examination was unremarkable; specifically, inflammation, interstitial edema, myocardial necrosis, and infarcts were not present. The liver and spleen were enlarged and severely congested; the liver also revealed bridging centrilobular necrosis.

Rapid antigen testing of nasal swabs taken

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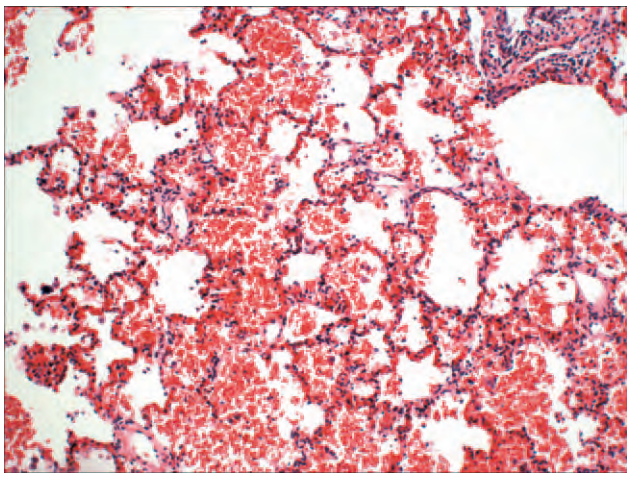

Figure 2. The lung of case 1 shows severe pulmonary congestion and intra-alveolar hemorrhage. H&E ×100.

during the terminal emergency department visit were positive for influenza viruses A and B. Immunocytochemical tests performed by the National Center for Infectious Disease at the Centers for Disease Control and Prevention (CDC) revealed influenza A virus in scattered epithelial cells of the trachea but not the larynx. Influenza B virus was not detected in the trachea or larynx. Postmortem blood and urine toxicology screens were negative, and metabolic screening of the blood (including for disorders of fatty acid metabolism) was within normal limits.

CASE REPORT 2

A previously well 21-month-old male was discovered unresponsive, apneic, and prone (face down) in his crib after an afternoon nap. On the morning of his death, he awoke at 0500 hours irritable, restless, and "warm to the touch." His mother gave him Motrin, and then mother and child fell asleep on the couch. Upon awaking at 0700 hours, the child's fever had resolved, and he was playful, although without appetite. At 1100 hours, his temperature was 102.7°C, and he was given Motrin again. After lunch, he was placed in his crib for a nap at 1430 hours; at approximately 1600 hours the mother checked him from the bedroom door and assumed that he was sleeping. At 1745 hours, the mother went to wake the child for dinner and found him apneic, with nasal frothy blood-tinged fluid. Efforts at cardiopulmonary resuscitation were unsuccessful.

The child's past medical history was noteworthy for a head circumference greater than the 95th percentile for age, which was first noted at the 4-month-old well baby visit. His head circumference at birth was 37 cm (75th percentile for age), with a birth weight of 3743 g (50th–75th percentile for age) and birth length measuring 54.6 cm (95th percentile for age). At the 4-month-old visit and all routine visits thereafter, his head circumference was noted to be substantially greater than the 95th percentile for age; his height and weight also exceeded the 95th percentile for age. The child's growth and neurodevelopment were normal, and the increased head circumference was attributed to a "familial trend." There was no history of prior meningitis, head trauma, ALTEs, seizures, or gastroesophageal reflux. His DtaP, Hib, IPV, Hep B, and MMR were current, and none were administered during the 2 weeks before his death. One blood screen for lead was within the reference range. The family history was negative for ALTEs, syncope, neurological disease, seizures, epilepsy, SIDS, and SUDC.

Postmortem examination

The body measured 87.6 cm in length (>95th percentile for age) and weighed 17 kg (>95th percentile for age). The head circumference was 52 cm (>95th percentile for age). The nares and mouth contained slightly blood-stained, watery fluid. Evidence of facial trauma was not identified. A few petechiae were present on the thymus and epicardium but not the conjunctiva.

The leptomeninges were transparent but not hemorrhagic; purulent exudates were not present. The edematous 1398-g brain (expected brain weight for age [2] is 851.4 g for a 1-year-old male and 1149.2 g for a 2-year-old male; $P \geq 0.95$, confidence limits 738.2–964.6 g and 1083.1–1215.3 g, respectively) revealed flattened gyri and narrowed sulci associated with herniation of cerebellar tonsils bilaterally. Uncal and cingulate gyrus herniation were not present.

Microscopically, lymphocytic infiltration was restricted to the meninges (Figs. 3,4) and was most severe over the ventral pons but was not identified in the forebrain or brainstem parenchyma or perivascular spaces. Edema was confirmed, but viral inclusion bodies, microglial nodules, and ischemic changes were not present. The hippocampus and brainstem were unremarkable. There

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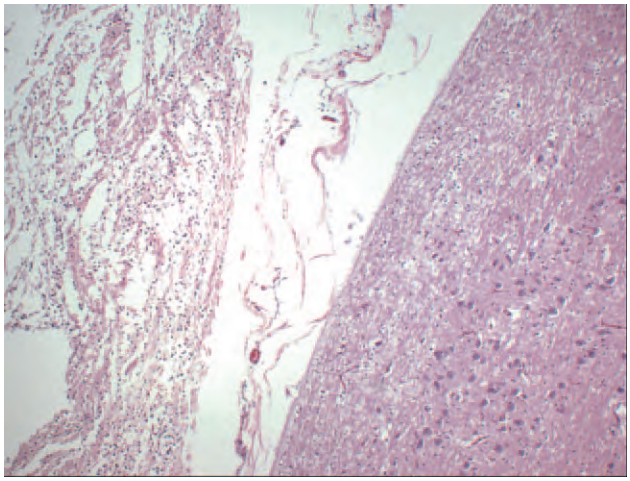

Figure 3. The leptomeninges overlying the ventral pons of case 2, a 21-month-old male, show mild inflammatory cell infiltration. H&E ×40.

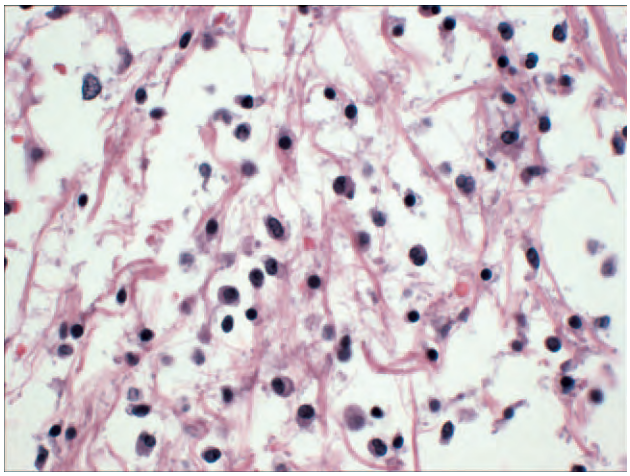

Figure 4. The pia-arachnoid of case 2, shown at higher magnification, reveals an infiltrate predominately of lymphocytes and to a lesser extent plasma cells. H&E ×400.

were no developmental abnormalities of the cerebral cortex or other structures.

The lungs were severely congested, edematous, and hemorrhagic but not consolidated; the right lung weighed 198 g (expected weight for body length [3] 89 g), and the left lung weighed 138 g (expected weight for body length [3] 77 g). Microscopic examination confirmed hemorrhagic pulmonary edema (Fig. 5). There was minimal lymphocytic infiltration in the tracheal mucosa, bronchi, and bronchioles, and the epithelium was unremarkable and without cytopathic effect. Fibrosis, thromboembolization, infarcts, and hypertensive arteriopathy were not present.

The enlarged heart weighed 78 g (expected heart weight for body weight 61 g [4]), and the left

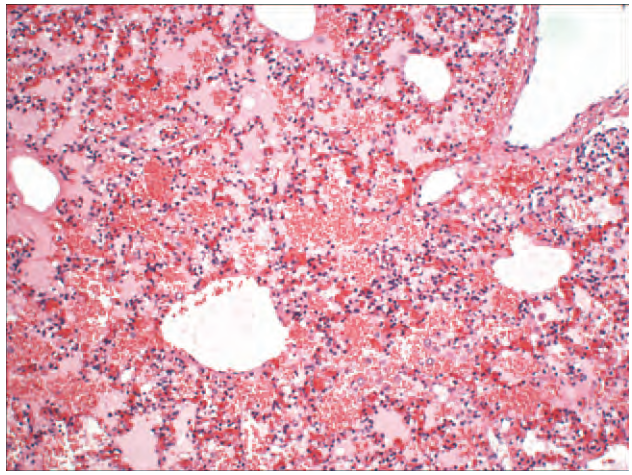

Figure 5. The lung of case 2 reveals severe hemorrhagic edema. H&E ×100.

ventricle was moderately hypertrophied, but the chambers were not dilated. Microscopic examination was unremarkable; specifically, inflammation, interstitial edema, myocardial necrosis, and infarcts were not present. The liver and spleen were enlarged and severely congested. Swabs of the brain and anus grew adenovirus. Postmortem blood and urine toxicology screens were negative, and metabolic screening of the blood (including for disorders of fatty acid metabolism) was within normal limits.

DISCUSSION

We report here 2 toddlers, 21- and 30-month-old boys, who died suddenly and unexpectedly during a sleep period after a brief viral-like prodrome of fever, irritability, lethargy, and anorexia. Neither case had clinical evidence of past infection of the central nervous system. Postmortem examination revealed histologically mild lymphocytic meningitis; massive cerebral edema with uncal, cingulate, and/or cerebellar tonsilar herniation; severe pulmonary hemorrhagic edema; cardiomegaly with left ventricular hypertrophy; and congestive hepatosplenomegaly. In both cases, a specific virus was identified: in case 1, influenza A virus was identified in the nuclei and cytoplasm of tracheal epithelial cells by immunocytochemistry performed at the CDC, and in case 2, adenovirus (serotype undetermined) was cultured from brain and anal swabs. We suggest that influenza A virus and adenoviral infection caused these toddlers' clinical viral illness and that mild lymphocytic meningitis initiated a chain of events characterized

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by severe cerebral edema that triggered transtentorial and/or tonsillar herniation, neurogenic pulmonary edema, and acute left heart failure leading to death.

Influenza A virus is a rare but well-established cause of meningitis [5,6]. Influenza A virus was the only offending organism documented in case 1 at autopsy, in keeping with the finding in the literature that bacterial coinfection is rare in toddlers infected with this virus [5]. The absence of neutrophilic infiltrates in the meninges and lungs in case 1, as well as negative bacterial cultures, also argues against a coexistent bacterial infection. Adenovirus is a common pediatric pathogen responsible for respiratory, gastrointestinal, and renal infections [7,8]. Neurological complications include aseptic meningitis, encephalopathy, encephalitis, and Reye-like syndrome [7,8].

The severity of the lymphocytic meningitis in both toddlers was mild; yet both brains were severely edematous with transtentorial and/or tonsillar herniation. The medical literature is fundamentally lacking with respect to severe cerebral edema complicating viral meningitis without coexistent encephalitis. The mechanism by which mild meningitis instigates severe cerebral edema remains unexplained, especially because we did not identify concomitant encephalitis or cerebral vascular thrombosis in our 2 cases. The possibility that the meningitis triggered an unwitnessed seizure during the sleep period, with secondary anoxic brain injury complicated by massive cerebral edema and herniation, must be considered. We propose that neurogenic pulmonary edema developed in our 2 cases as a function of the brain edema and herniation. Neurogenic pulmonary edema is defined as the development of lung edema and intra-alveolar hemorrhage within minutes to hours after acute central nervous system disease or injury [9,10]. First described by Shanahan in 1908 (cited by Weir [11]), it has been identified in association with meningitis [12–15], encephalitis, seizures, acute hydrocephalus, encephalopathy, head trauma, myelitis, Guillain-Barré syndrome, Reye syndrome, brain tumors, neurosurgical procedures, and subarachnoid hemorrhage after rupture of intracranial aneurysms or arteriovenous malformations [16–23]. A recent study of 2 cases, supplemented by a review of an additional 21 cases with neurogenic pulmonary edema reported since 1990, reports that the mean age of affected cases is approximately 21 years, with a range of 7 months to 57 years [16]. In this review, subarachnoid hemorrhage was the most common underlying disease; the interval between the neurologic event and pulmonary edema was less than 4 hours in 71% of the cases. The mortality rate was high, with nearly 20% fatalities, 9.5% directly from neurogenic pulmonary edema. Cases have been identified in children as well [16–18,21]. The youngest in the series reported by Fontes and others [16] was a 7-month-old male who sustained head trauma and developed bilateral subdural hematomas and seizures. Neurogenic pulmonary edema is uncommon in meningitis but has been reported in both viral or bacterial (pneumococcal) types [12–15]; it has not, however, been previously reported in association with influenza A or adenoviral meningitis. Death is typically caused by severe cerebral edema and/or coexistent encephalitis. In Taiwan, several hundred children, most of whom were younger than 3 years of age, developed an enteroviral infection with a variety of clinical manifestations, including 10 with meningitis or meningoencephalitis; among the 78 children who died, 9 did so as a result of neurogenic pulmonary edema [17].

The pathogenesis of neurogenic pulmonary edema involves an interplay between increased pulmonary microvascular permeability and venous pressure mediated through massive sympathetic discharge [24–29]. Microvascular permeability is suggested by the finding in patients that concentrations of protein in lung edema fluid are similar to that in plasma [10,19,23,26], an observation supported by research in animal models [23,26]. In the setting of elevated intracranial pressure, pulmonary venous hypertension results in pulmonary venoconstriction that increases the intravascular pulmonary capillary pressure and volume [27–29]. Pulmonary capillary pressure is increased by catecholamines discharged from the sympathetic nervous system that constrict the pulmonary veins [28,30]. The nucleus of the solitary tract in the dorsal medulla has been implicated in the pathogenesis of neurogenic pulmonary edema because it plays a critical role in control of the pulmonary musculature and respiration [30–34]. It is also interconnected with the hypothalamus and ventrolateral medulla, which have likewise been implicated in causing neurogenic pulmonary edema [30–34]. Compression of the nucleus of the

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solitary tract and/or ventrolateral medulla in the medulla secondary to massive cerebral edema and transtentorial herniation likely impairs their function and triggers neurogenic pulmonary edema via efferent and afferent pulmonary pathways. Deformation of the ventrolateral medulla (which contains catecholaminergic neurons involved in vascular control) by subarachnoid hemorrhage from ruptured vertebral artery aneurysms has been reported as a mechanism initiating neurogenic pulmonary edema [32].

At autopsy, our cases revealed enlargement of the heart and mild to moderate left ventricular hypertrophy but no evidence of myocarditis, interstitial edema, myocardial necrosis, or endomyocardial fibrosis. There is evidence that acute left ventricular failure contributes to neurogenic pulmonary edema. Cardiac enlargement has been reported in a case with a ruptured arteriovenous malformation causing subarachnoid hemorrhage complicated by neurogenic pulmonary edema [34]. In another study, echocardiographic evidence of diminished left ventricular systolic function has been reported in adult women with subarachnoid hemorrhage and neurogenic pulmonary edema but without a history of prior heart disease [9]. In an experimental animal model employing increased intracranial pressure, aortic flow was shown to decrease before pulmonary flow, thereby increasing pulmonary venous pressure [29]. Myocardial injury has been documented by elevated levels of cardiac troponin I in cases of subarachnoid injury [33]. In a study of patients with brainstem encephalitis, findings of myocardial apoptosis, myocytolysis, and myofibrillar degeneration, but not myocarditis, suggest neurogenic-mediated cardiac damage [35]. Finally, creatine kinase MB isoenzyme elevation in the absence of demonstrable heart disease in a middle-aged woman with no history of heart disease who sustained a subarachnoid hemorrhage provides additional evidence that direct myocardial injury can occur in association with neurogenic pulmonary edema [36].

Importantly, the 2 cases reported here add to the differential diagnosis in cases of sudden and unexpected death in toddlers. They also challenge current concepts that minor viral infection does not cause sudden death. In our previous report of 50 cases, a diagnosis of SUDC was made in 36 after extensive review of the medical history, circumstances of death, and postmortem records and microscopic slides [1]. These 2 cases are significant because a seemingly mild viral illness was associated with sudden death. The key finding was massive cerebral edema with transtentorial herniation that triggered neurogenic pulmonary edema, left heart failure, and death. Thus, these 2 cases emphasize the possibility that mild intracranial viral infections may, in rare instances, cause sudden death via lethal cardiopulmonary complications. They also underscore the importance of a comprehensive autopsy, including detailed neuropathologic examination and viral testing, in the determination of the cause of unexpected death in children, as well as adults. Standardized protocols are available to assist in this process [37].

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Review Article

Postmortem Cerebrospinal Fluid Pleocytosis: A Marker of Inflammation or Postmortem Artifact?

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The aim of this paper is to reassess the significance of postmortem cerebrospinal fluid pleocytosis. Published articles of CSF changes after death were reviewed, and reanalysis, in the light of modern views on the significance of bacterial postmortem isolates, was undertaken. There is theoretical and experimental evidence that the blood brain barrier to the movement of protein and cells is preserved in the first few hours after death. The number of mononuclear cells in the cerebrospinal fluid does rise in the first 24 hours after death, and this is most probably due to detachment of leptomeningeal lining cells. But the marked increase in lymphocyte counts seen in some cases of sudden infant death syndrome (SIDS) and in other deaths in the paediatric age range could well be a marker of inflammation.

1. Introduction

In a healthy individual, the cerebrospinal fluid (CSF) is clear and colourless. It has a low concentration of protein and contains very few cells. The composition is different than that of the blood due to a highly selective blood brain barrier. Any increase in cellular content or protein composition of the cerebrospinal fluid (CSF) above the normal range for the specific age group is an absolute indicator of meningeal disease (inflammation) [1]. But after death the number of cells in the CSF rises, even in the absence of evidence of meningitis, and this is viewed as a postmortem artifact [2, 3]. Thus counting cells in CSF obtained postmortem is not considered to be useful in diagnosis. In this paper we examine the evidence for this assumption.

2. Studies of Postmortem CSF Pleocytosis

Platt and colleagues obtained postmortem specimens of CSF from 26 cases of sudden infant death syndrome (SIDS), 24 paediatric deaths from a hospital setting, and 14 adult deaths [2]. The age range, the postmortem interval, and the CSF cell count per cubic mm are shown in Table 1.

The CSF cell count in the SIDS cases varied from 37 to 3250 cells per cubic mm (mean 647). These counts were significantly higher ($P < 0.005$) than in the hospital paediatric group and the adult group. The cells were mononuclear; the authors do not record the presence of neutrophil polymorphs in any of the cases. The typeable cells were 60–70% macrophages and 20–40% lymphocytes, but beyond 12 hours postmortem, the cells became vacuolated and were difficult to type. It is stated that "none of the postmortem cultures grew bacteria, and sections of the brain revealed no inflammation."

Wyler and colleagues obtained CSF by lumbar puncture from 69 adult deaths aged 16 to 90 years [3]. Thirty five of the corpses were stored at room temperature (20°C) and 34 were placed in cold storage (4°C) shortly after death. The specimens of CSF were obtained between 3 and 39 hours for the 35 cases stored at room temperature and 3 and 53 hours for those in cold storage. The CSF cell count increased with postmortem interval and the rate of increase was more

Table 1: Data from Platt et al [2].

CASES	Number of cases	Age range	Postmortem interval (mean)	CSF cell count per cubic mm, range (mean)
SIDS	26	5 weeks–5 months	2–28 hours (16.1)	37–3250 (647)
Hospital paediatric gp.	24	1 day–16 years	1.5–22 hours (10.58)	0–593 (141)
Adults	14	30–74 years	5–48 hours (15.14)	1–108 (28)

Table 2: Data from Wyler et al [3].

Postmortem interval	Number of cases	CSF cell count per cubic mm	CSF cell count-mean
0–6 hours	12	3–19	7.8
0–5 hours	11	3–45	17.9
12–24 hours	29	5–81	31.6

marked for the bodies stored at room temperature. Part of the data is presented in Table 2.

In this study, the CSF cell count in the first few hours after death was only slightly raised above the levels regarded as normal in life, and even after 24 hours was below 100 cells per cubic mm. These results are similar to those obtained by Platt et al. [2] in adults, but the CSF cell counts are significantly less than those seen in SIDS and in the paediatric non-SIDS deaths.

3. The Blood Brain Barrier

The anatomy and physiology of the blood brain barrier is reviewed in detail by Fishman [1] in his comprehensive treatise and more recently by Ballabh et al. [4] and Abbott et al. [5]. The leptomeninges have an outer layer of arachnoid mater and an inner layer of pia mater. These membranes are formed of connective tissue, and the subarachnoid space that lies between these layers is traversed by connective tissue trabecula. There are cells lining the pia and arachnoid membranes and desquamation of these cells postmortem could have contributed to the CSF mononuclear cells observed in the above studies by Platt et al. [2] and Wyler et al., [3].

The main barrier to the transfer of protein and cells between the blood and CSF is the endothelium of the cerebral capillaries [4, 5]. The brain capillaries are different than most systemic capillary vessels in that the endothelial cells have tight junctions and transfer of material is through the cells rather than between the cells. Furthermore, the brain endothelial cells have more mitochondria than systemic vessels, and this reflects the additional energy required to pump protein and other chemicals from the lumen through the cell cytoplasm rather than relying on passive diffusion between leaky cell junctions or through endothelial fenestrations. The endothelial cells, however, have lower energy requirements than brain neurons and the brain cells die first if the oxygen supply is disrupted.

Lymphocytes pass through the endothelial cells by emperipolesis; this is a complex process in which the inflammatory cell invaginates into the endothelial cell and literally passes through to emerge intact at the opposite side [1, 5–7]. The process depends on the active cooperation of both cells, and it is difficult to imagine how it could occur after death. Inflammation in the systemic circulation leads to increased permeability of the vasculature and protein molecules and cells pass between the endothelial cells. If inflammation involves the meninges the tight junctions might open to allow the egress of neutrophils, mononuclear cells, and proteins, but this does not occur in the absence of inflammation [4, 5]. The pro-inflammatory cytokines TNF-alpha and IL1-beta increase permeability of the blood brain barrier and disrupt tight junctions [4]. These cytokines are released in infection and as a consequence of hypoxic ischaemic change.

There are capillary vessels within the dura mater, which are similar to systemic capillaries in having leaky junctions and fenestrations. Protein and cells could cross these vessels passively but the arachnoid lining cells have tight junctions and maintain a barrier to diffusion into the CSF [4, 5].

In the ventricles, the choroids plexus is the site of transfer of protein and other chemicals into the CSF. The capillaries in the choroids plexus resemble endothelial cells elsewhere in the body but there are tight junctions between the lining ependymal cells of the choroids plexus, which maintain the blood brain barrier at this level. [1, 4, 5].

An interruption to the oxygen supply to the brain will cause cessation of neuronal function and death will ensue. The activity of the cerebral endothelial cells will decrease and the transfer of protein and other substances will be brought to a halt. However, the endothelial cells will survive intact for some time and at least initially we would not expect to see any leakage of protein or cells into the CSF from the cerebral circulation.

4. Changes in CSF Protein after Death

The normal range of CSF protein is shown in Table 3. However, the protein concentration varies not only with age but also to a small extent by site. It is lowest in the ventricular CSF, intermediate in the cisterna magna, and highest in the lumbar region. The difference between the cisterna magna and lumber region is of order 0.1 g/L.

The blood brain barrier to the free movement of protein was first defined by Ehrlich [8] and his students. They injected aniline dyes intravenously in experimental animals and noted that at postmortem the tissues were stained blue but the CSF and the brain were unstained [1]. The aniline dyes attached to albumin and, therefore, the stain reflected the distribution of albumin in the body. The fact that the differential staining was noted at autopsy indicates that the

Table 3: Data adapted from Fishman [1].

Age	CSF protein g/L
Neonate	0.2–1.7
1–30 days	0.2–1.5
30–90 days	0.2–1.0
3–6 months	0.15–0.5
6 months–10 years	0.15–0.3
Adult	0.2–0.45

blood brain barrier was maintained after death for at least a short interval.

Mangin and colleagues investigated CSF protein levels in 44 cadavers aged 5 to 74 years. CSF was obtained by cisternal puncture between 3 and 24 hours after death [9]. They divided their cases into three groups.

Group 1. 15 subjects who died suddenly (less than 10 minutes) due to homicidal firearm wounds, stabwounds, or hanging. The mean CSF protein level in these cases was 0.373 g/L with a standard deviation of 0.181 g/L.

Group 2. 13 subjects whose "death agony duration lasted between 10 minutes and 6 hours." No more clinical information is given but these are cases who became acutely unwell and died within 6 hours of the onset of the illness. The CSF protein in this group was 1.546 ± 0.46 g/L (mean ± SD).

Group 3. 16 subjects whose "death agony duration was more than 6 hours" and who died in spite of intensive care. The CSF protein was 8.267 ± 6.249 g/L.

These results indicate that if death is rapid and the CSF protein is normal at the time of death, then it will remain within the normal range for a few hours after death. In those first few hours there is no significant passive leakage because the endothelial cells and their tight junctions are still intact. However, over a period of 24 hours the endothelial cells will start to lyse, the junctions will start to leak, and passive transfer will gradually ensue. The passive leakage involves proteins to a small extent but not red cells and by inference not white cells. In groups 2 and 3, the subjects were unwell prior to death and the most likely explanation is production of cytokines as part of the illness causing a generalized inflammatory process throughout the body including the blood brain barrier [4]. The movement of proteins, and cells, would be an active process in the brain requiring intact and functioning brain capillary endothelial cells but with some loss of permeability due to cytokine secretion. Following death, however, the endothelial cells might well lyse more quickly and passive leakage of protein would ensue within 24 hours. Thus the raised levels of CSF protein noted in groups 2 and 3 are probably a combination of increased levels prior to death and further increases after death. The authors did not count cells in the CSF samples, but the inference we can draw is that there would be few or no lymphocytes in group 1 but there could well have been lymphocytes and even neutrophils present in groups 2 and 3 as the proinflammatory cytokines TNF-alpha and IL1-beta increase leukocyte transmigration as well as increase blood brain barrier permeability and disrupt tight junctions [4].

Osuna and colleagues also studied CSF protein levels in autopsy cases [10]. They examined 11 cases of head trauma, 7 cases of hypoxia (4 carbon monoxide or drug poisonings and 3 hangings), 7 sudden cardiac deaths, and 9 others (natural and unnatural). The CSF samples were obtained by cisternal puncture. A number of biochemical investigations were done including CSF protein. The results are shown in Table 4. The CSF levels are markedly raised in all cases and are of no value in diagnosis. But the key difference between this paper and that of Mangin et al. [9] is the postmortem interval. It would appear that the CSF protein leak starts in the first 24 hours but gathers speed thereafter.

5. Correlation of CSF Cell Counts with Histological Assessment of the Meninges

In the study by Platt et al. [2], there was no histological evidence of meningitis even in cases with over 3000 mononuclear cells per cubic mm of CSF. Since the CSF bathes the leptomeninges, we would expect to see a similar concentration of cells in the meninges at autopsy as were found in the CSF [11]. But what exactly is the correspondence between the CSF cell count determined objectively and our subjective impressions of the mononuclear content of the meninges assessed by histology? The mean diameter of a high power field is 0.5 mm and the thickness of a histological section is 0.005 mm. Thus if 800 cells of the size of a lymphocyte or a neutrophil polymorph were distributed in one cubic mm of tissue and the tissue were serially sectioned, we would have 200 histological sections each with 4 high power fields. There would be one inflammatory cell per high power field (This assumes we count all the cells and never count a cell twice. In fact, we would miss some cells and count some twice but the former error is likely to exceed the latter and therefore the one per high power field estimate will be, if anything, too high). Thus even 3000 mononuclear cells per cubic mm of CSF will mean fewer than 4 cells per high power field; not a number that would lead to a diagnosis of meningitis [11]. But 10 lymphocytes per cubic mm of CSF in life would be enough for a diagnosis of lymphocytic meningitis in its earliest stages. Thus an objective count of mononuclear cells in the CSF will be a far more sensitive way of diagnosing meningitis than histological examination of the meninges.

6. Infection and SIDS

In the publication by Platt et al. [2], the following statement occurs in the discussion "It is clear from this study that children and adults develop a postmortem CSF pleocytosis. However, the degree of pleocytosis is significantly greater in children, particularly in cases of SIDS." The assumption that the CSF pleocytosis is a postmortem artifact is based on two factors. The first is that there was no evidence of meningitis as assessed histologically. The second is that there was no evidence of any other infection at autopsy to explain

Table 4: Data from Osuna et al [10].

Diagnostic group	Number of cases	Survival time in hours, mean (SD)	Postmortem interval in hours, mean (SD)	CSF protein in g/L, range (median)
Head trauma	11	0.9 (0.8)	51.5 (18.8)	2.8–42.4 (14)
Hypoxia	7	1.0 (1.0)	49.7 (23.3)	2.4–28.5 (7)
Sudden cardiac death	7	0.0 (0.0)	41.1 (26.9)	0.5–6.1 (2)
Other	9	2.0 (1.7)	51.2 (30.5)	1.2–9.2 (6)

the sudden infant death. Neither of these assumptions is any longer valid. Counting cells in the CSF is a more sensitive way of diagnosing meningitis than is examination of histological sections of meninges. And there is now a considerable body of evidence that some cases of SIDS are caused by bacterial infection even if the autopsy is completely negative.

The latest in a long line of publications linking bacterial infection and SIDS appeared in the Lancet in 2008 [12]. A group from Great Ormond Street undertook a retrospective review of 546 cases of sudden unexpected death in infancy (SUDI) examined at their institution over 10 years. They found that isolation of *Staphylococcus aureus* and *Escherichia coli* from lung, blood, spleen, or CSF was more common in unexplained SUDI (synonymous with the term SIDS as used in the Platt et al. study, [2]) than in cases of SUDI explained by a noninfective cause. *S. aureus* was found in 16% of cultures from unexplained SUDI compared with 9% of cultures from explained, noninfective, SUDI ($P = 0.005$). *E. coli* was found in 6% of cultures from unexplained SUDI compared with 1% of cultures from explained noninfective SUDI ($P = 0.003$). The authors are cautious in their analysis and emphasise that they have shown an association and not proven a causal link. But other evidence from a number of studies, reviewed in a lead article in the same issue of the Lancet, supports this link [13]. The organisms *S. aureus* and *E. coli* have been linked to unexplained SUDI in a number of studies extending back to 1987 [14]. There is now sufficient evidence to regard these organisms as a possible cause of some cases of unexplained SUDI [15–17].

The mode of death in unexplained SUDI is not known but we do know that it is rapid in many cases. In the CESDI SUDI study carried out in England between 1993 and 1996, a total of 318 cases of unexplained SUDI were investigated [18]. The majority (76.8%) appeared to be well when last seen, that is, they had a Cambridge Baby Check score of between 0 and 7 in the 24 hours prior to death. Amongst the daytime deaths in this group, 38% were observed alive 30 minutes prior to discovery and 9% within 10 minutes of discovery [19]. In the small number of infants who have died whilst on a monitor, the physiological changes of progressive hypoxia, bradycardia, and finally cardiorespiratory arrest take less than 20 minutes [20]. If bacteria such as *S. aureus* and *E. coli* present in the blood, but in the absence of overt inflammation, can cause death in a short interval, the possible mechanisms include the following.

(i) The release of toxins, which directly combine with neural and or cardiac membranes and interfere with homeostatic control of cardiorespiratory function.

(ii) A heightened or abnormal host response to the bacteria with lymphocyte proliferation, cytokine release, and generalized but subtle signs of inflammation. But since lymphocyte proliferation takes time, there would have to be a subclinical prodromal period prior to the dramatic final episode.

A specific mechanism that includes both the above possibilities is the release of pyrogenic toxins (such as toxic shock syndrome toxin [TSST] and staphylococcal enterotoxin C [SEC]) by *S. aureus* leading to the explosive release of cytokines from lymphocytes primed by previous episodes of staphylococcal bacteraemia. The cytokine cascade causes toxic shock and a transfer of protein and cells across capillary cell walls in both the systemic and cerebral circulations.

7. Discussion

The morphology, physiology, and pathology of the blood-brain barrier has been studied in detail in animal models and in human subjects. Fishman published a comprehensive review in 1992 and since then there have been further reviews by Ballabh et al. [4] and Abbott et al. [5]. However, there is a paucity of information on changes in the blood-brain barrier after death in human subjects, and pathologists have been too ready to dismiss the changes noted in the CSF as a postmortem artefact.

In life, a normal specimen of CSF contains no more than 2 to 4 mononuclear cells per cubic mm and no neutrophil polymorphs. If more cells are found, the sample is not normal and CSF pleocytosis is diagnostic of meningeal inflammation as long as an acute CSF bleed can be excluded [1]. However, the studies of Platt et al. [2] and Wyler et al. [3] show that a CSF pleocytosis does occur as a postmortem artifact. In adults, the number of mononuclear cells in the CSF gradually increases over the first 24 hours. This plainly is a consequence of postmortem events and does not indicate or reflect the number of cells in the CSF prior to death. The most likely explanation is that cells lining the leptomeninges progressively detach with time after death and float into the CSF. But it is much more difficult to postulate a mechanism by which lymphocytes can enter the CSF from the blood after death.

If death is sudden, the endothelial lining cells of the cerebral blood vessels will remain intact for a few hours at least. This is what we would expect from our knowledge of their anatomy and physiology. It is also what was observed by Mangin et al. [9] in their study of CSF protein in cases of sudden death due to shooting, stabbing, and hanging. In

those cases, there was not a significant rise in CSF protein in the first 24 hours after death. Lymphocytes pass from the cerebral blood to the CSF by a process of emperipolesis [1, 5–7]. This is a complex movement through the cell in which the endothelial cytoplasm wraps around the lymphocyte. There is no evidence of which we are aware that this process can occur after death. It is theoretically possible that lymphocytes could exit from blood vessels in the dura mater and track through the arachnoid mater into the CSF by a passive process. Or indeed pass from capillaries in the choroids plexus through into the ventricles. But we would expect them to be prevented by tight junctions in arachnoid lining cells and in choroid plexus ependymal cells in the first few hours after death [5, 11]. Indeed the observation that the CSF protein does not rise in the first few hours after death argues against this route. The CSF protein does rise eventually in all cases as shown by the study of Osuna et al. [10], but it is a protein that leaks not red cells. If red cells do not move passively into the CSF even after 48 hours, then one would not expect the larger white cells to move in this way. Furthermore, Platt et al. [2] did not record the presence of neutrophil polymorphs in the CSF, which would be unusual if the lymphocyte entry was purely passive.

In summary, if the lymphocyte entry is passive one would expect to see red cells and neutrophil polymorphs as well as mononuclear cells and a much more marked increase in CSF protein than was observed in the Mangin et al. [9] study. It is difficult to see how the process could be active after death as endothelial cells depend on energy from mitochondria to move cells and protein into the CSF. That should cease at the time of death. The final possibility is that the lymphocytes seen in SIDS cases and in the paediatric hospital death group in the Platt et al. [2] study were in fact present at the time of death and indicate inflammation.

There were two reasons for regarding the lymphocytes seen in the SIDS cases as a postmortem artifact. The first was that there was no evidence of meningitis as assessed by histology. The second was that there was no evidence of infection as the cause of death. The first objection is no longer valid because simple calculations indicate that counting cells in the CSF is a much more sensitive indicator of meningitis than is histological assessment of the meninges. The second objection is also not valid because there is now a considerable body of evidence pointing to an infectious aetiology of SIDS [12–17].

It is time to reassess the pathogenic significance of lymphocytes seen in postmortem CSF samples. We need to collect CSF samples in the first few hours after death and examine them urgently as we would in life. A cell count is essential but we should also use the full armory of modern immunohistological techniques with a wide range of cluster differentiation (CD) markers to differentiate lymphocytes from other mononuclear cells. We need to compare unexplained SUDI with cases in which an explained noninfective cause appears likely. We should also investigate deaths at other ages, not just the paediatric age range but also adults. Bacteria are commonly found at autopsy and too readily dismissed as contaminants or as the consequence of agonal events [21]. It could well be that episodes of bacteraemia are a common last event on the road to death in a range of conditions.

Studies are planned, and in some cases underway, to investigate unexplained SUDI using the full array of modern molecular techniques. These include microarray analysis to identify genetic signatures of the host response to infection as well as genetic signatures to mark the presence of pathogens. Proteomic analysis of fluids for bacterial toxins is another area of considerable promise. But we should not forget something which is much simpler-counting lymphocytes in the CSF.

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GUIDELINES FOR POST MORTEM REPORTS

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CONTENTS

INTRODUCTION

The post mortem report clearly should inform the clinician, coroner, general practitioner and pathologist. The format must be flexible and widely comprehensible. The extensive use of information technology must be anticipated.

The Royal College of Pathologists emphasises that a single standard should be applicable to all post mortem examinations, whether funded by the National Health Service, Coroner, or Procurator's Fiscal. The major difference between these types is in the frequency of histological examination. Recent publications indicate the desirability of retention of tissues for histological examination in most cases. The extent to which Coroners will support and finance this is limited, but the principle is clear.

A post mortem report will normally include:

1. Demographic details
2. History
3. External examination
4. Internal examination
5. Histology report
6. Summary of findings
7. Commentary/conclusions
8. Cause of Death (OPCS format)

GENERAL COMMENTS

It is envisaged that these guidelines should serve for all hospital, Coroner's and Fiscal post mortems other than Home Office cases. The report should be typewritten on a form of adequate size. Pre-printed single page forms impose excessive brevity. A summary of findings, or parts 1-4 should be sent out within 48 hours. Any conclusions and cause of death at this stage are tentative and may be modified. The histological findings, commentary/conclusions and cause of death should be sent out as soon as possible, *ie* within two to three weeks. *(Neuropathology will require 4-6 weeks for completion)*. The final document should contain all the material issued initially since experience shows that isolated supplementary reports are easily lost.

POST MORTEM REPORT

1. Demographic Details

Hospital number/Mortuary sequential number

Name, forenames, title
Family or maiden name
Home address
Name of GP and/or hospital consultant
Sex, age/date of birth
Next of kin, person giving permission for post mortem
Source of the patient, or hospital and ward details

Details of those individuals to whom the report should be sent:

Normally

Coroner/Fiscal
General Practitioner
Hospital Consultant

(In Coroner's and Fiscal cases it is highly desirable that the report should be sent to the general practitioner and hospital consultant, though the decision on issue and timing of reports will depend on hearings, inquests, and on the Coroner's or Fiscal's policy).

Optional

Anaesthetists
Radiotherapists and other professional groups
Audit and other Confidential Enquiries *(see Appendices 3 and 4)*

Persons present at post mortem, as appropriate:

Pathologist(s)
Post mortem attendants
Medical staff
Police and other observers

Dates, times and place:

Date and time and place of death
Date and time and place of post mortem
Date of preliminary report
Date of final report

Authority for post mortem (hospital, Coroner, Fiscal)

Identification of body (hospital tag, or name of person making identification)

Type of post mortem:

Complete
Partial, with exclusions
Fetal/neonatal/sudden infant death *(see Appendix 1)*
Neuropathological *(see Appendix 2)*
Maternal deaths *(see Appendix 3)*

Pathologists must be alerted to any potential hazards *eg* Hepatitis B, HIV or the possibility of Creutzfeldt-Jakob disease. *[Reference: Safety in Health Service Laboratories: (a) Safe Working and the Prevention of Infection in Clinical Laboratories (ISBN 0-11-885446-1), (b) Safe Working and the Prevention of Infection in the Mortuary and Post Mortem Room (ISBN 0-11-885448-8), (c) Safe Working and the Prevention of Infection in Clinical Laboratories; Model Rules for Staff and Visitors (ISBN 0-11-885442-9). These publications are available from Her Majesty's Stationery Office]*

2. History

(a) History of present illness in chronological order, and circumstances of death. It is the pathologist's responsibility to be satisfied that a full account has been obtained. The history should be an integral part of the report, reference to notes or letters is not an adequate substitute

(b) The past history often explains the findings. Absence or difficulty in obtaining this information should be recorded

(c) Clinical and laboratory investigations should be quoted where relevant

Radiology and photography before post mortem should be considered.

3. External description

Weight in kilograms (Imperial weights are now largely obsolete)
Height in centimetres
External appearances, sex, age, build, nutrition, colour, racial pigmentation, lividity and rigour

Measurements of significant surface features, scars, operation sites, bruises *etc* with a clear description of the site including diagrams/ photography

Infant/neonatal/fetal deaths require additional measurements, studies of dysmorphism, placental studies, and x-ray *(see Appendix 1)*

4. Internal examination

The examination must be described in a uniform and clear manner. Each organ system should be described in turn. The order of recording the examination is not mandatory but will usually be:

Cardio-vascular system
Pulmonary system and pleural cavity
Gastro-intestinal system (including liver and peritoneum)

Genito-urinary system
Endocrine system
Locomotor system *(see Appendix 2 for cases of muscular and nerve disorders)*

Bone marrow, spleen and lymph nodes
Brain *(see Appendix 2 for preliminary inspection of brain and spinal cord in neuropathological cases)*

(a) The central nervous system should be examined in all cases

(b) The weight of the heart, lungs, brain, liver and kidneys should be taken in all cases

(c) The weights of spleen, adrenal, thyroid, parathyroids, ovaries and testes are desirable in appropriate cases

(d) Describe positive findings, and list all normal organs to avoid later uncertainty

(e) Special examinations such as marrow, vertebral slice, examination of inner ear, vertebral arteries, *etc* depending on the clinical context

(f) Examination of sites of fractures and recent operation, preferably with clinician present

5. Histology report and other investigations

(a) Indicate whether material has been taken for histology

(b) Indicate what other material has been saved, *ie* toxicology, microbiology, *etc*

(c) Record tissues sent to any third party for further investigation, such as genetic analysis, tissue culture, *etc*

(Infant/neonatal/fetal histology and special investigations in Appendix 1)

6. Summary of findings

A list of the major pathological lesions present. It is desirable to code these for future retrieval, *eg* SNOP, SNOMED, Read Codes.

7. Commentary/Conclusions

(a) A commentary should be written in the light of all the information available; the length will be determined by the complexity of the case

(b) Reconcile as far as possible the major clinical problems with the pathological findings

(c) Indicate new pathological lesions and explain how these illuminate the clinical observations

(d) Present any inconsistencies in the findings and suggest any steps to be taken, such as further opinions, audit meetings, *etc*

8. Cause of death

The cause of death must be given in the standard form required by the OPCS (Office of Population, Censuses and Surveys). Discussion with the responsible clinicians should avoid discrepancies or indicate points of disagreement.

COMMUNICATION

Failure of information to reach its intended recipient is the greatest cause of misunderstanding between pathologists and those they serve.

(a) Ensure that the report is typewritten to a high standard

(b) Check that all sections (*ie* 1 – 8 above) are present

(c) Audit the time taken for reports to be issued and delivered.

APPENDICES

Appendix 1 MINIMUM GUIDELINES FOR POST MORTEM INVESTIGATION OF LATE FETAL, PERINATAL AND NEONATAL DEATHS (FROM 20 WEEK 0 DAYS GESTATION TO 1 MONTH OF AGE)

Note: *It is recognised that pathologists will need to use their clinical judgement and conduct investigations appropriate to individual case histories. This list contains investigations probably indicated in ALL cases. Other investigations that may be indicated are listed at the end.*

Audit
Date of death and date of post mortem; date of report; local code number and identifiers

Bacteriology
Blood sample (particularly if consent not obtained for full post mortem)

External Examination

Measurements
Body weight (electronic scale)
Head circumference
CH and CR length
Foot length

Dysmorphism
Photographs and additional x-rays if abnormality present

Placenta
To be examined in all cases (implies making arrangements for placentae from babies admitted to Special Care Baby Units to be stored for 1 month after birth). A convenient method may be to send placentae from Special Care Baby Unit/Neonatal Intensive Care Unit admissions to the pathology department. Whilst these need not be

examined unless the baby dies, many departments would, in any case, consider it good practice to examine them.

Whole body x-ray: If available

Internal Examination
Inspection of cranial, thoracic and abdominal cavities

Weight of all major organs (digital balance)

Systematic description of skull, ribs and major organs including brain, heart, upper airways, lungs, thymus, liver, intestines, kidneys, bladder, adrenals, pancreas and gonads, noting whether other organs normal or abnormal

Histology
Paraffin section: at least one block of major organs, especially lung, kidney, liver, placenta and membranes. (Needle biopsies of lung and liver if consent to full post mortem not obtained)

Other Investigations
As indicated from history or type of delivery; *eg* for twins, blood group analysis. Detailed placental examination would be advisable.

MINIMUM GUIDELINES FOR POST MORTEM INVESTIGATION IN POST NEONATAL INFANT DEATHS OR SUDDEN UNEXPECTED DEATHS IN INFANCY

Audit
Date of death and date of post mortem; date of report; local code number and identifiers

Bacteriology
Blood and CSF

External Examination

Measurements
Weight, CR, CH, OFC, foot length

Dysmorphism
Photographs and x-ray screening if abnormality present

Hypostatic staining

Evidence of injury
(X-ray if present)

Internal Examination
Inspection of cranial, thoracic and abdominal cavities

Weight of all major organs on digital balance

Systemic description of skull, ribs and major organs including brain, heart, upper airways, lungs, thymus, liver, intestines, kidneys, bladder, adrenals, pancreas and gonads, noting whether other organs normal or abnormal

Histology

Paraffin section: at least one block of:

epiglottis and larynx;
trachea (including thyroid);
4 lobes of lung;
heart (posterior LV and RV wall, IV septum);
thymus;
duodenum (including head of pancreas);
ileum;
liver (left triangle, right square);
spleen;
mesenteric lymph node;
adrenal gland;
kidney;
costochondral junction of right 6th rib; muscle (diaphragm and pectoralis major)

Neuropathology
4-6 blocks, including cerebral hemisphere, brain stem, cerebellum and meninges. *(Consider submitting brain for formal neuropathology)*

Additional investigations that may be indicated:

(a) Virology (postnasal swabs or aspirate, lung, CSF, ileal content)

(b) Samples of skin or pericardium for fibroblast culture (tissue and method as advised by local laboratory)

(c) Biochemistry (vitreous fluid, urine)

(d) Immunology, toxicology and genetic investigations: (*eg* storage of pericardium for tissue culture and spleen for future DNA studies)

(e) Frozen section of liver and kidney for fat stain.

Appendix 2 NEUROPATHOLOGY

The following is a summary of the main points which should be noted in post mortems involving neurological, neuro-surgical and psychiatric deaths. Further details are given in the full guidelines prepared by the Neuropathology Sub-committee of the Royal College of Pathologists, and available from the College.

Pathologists should consider whether cases need referral to Regional Centres of Neuropathology. Disorders of skeletal muscle and peripheral nerve disorders may require complex histochemistry of snap frozen tissues and electron microscopy.

(a) Surgeons or interventional radiologists should be invited to observe or participate in dissection

(b) Pathologists should be particularly alert for potential hazards such as Hepatitis B, HIV or Creutzfeldt-Jakob disease

External Examination
CSF should be taken before starting

Histology
Additional organs may include the pituitary, sensory and autonomic ganglia, middle ear, and orbital contents

Dissection of the Neck
Major extracranial carotid vertebral arteries should be removed *en bloc* from the mastoid process to the level of the upper sternum. Vertebral arteries should be examined *in situ*, or as part of *en bloc* removal of the cervical spine.

Examination of Skull and Brain

(a) Careful examination of scalp for haemorrhage or bruising

(b) Care should be taken not to induce fractures during removal of the calvaria. A rough estimate of thickness should be made.

(c) Special techniques may be needed for examination of the posterior fossa or upper spinal cord, cutting a wedge from the occiput combined with laminectomy

(d) Hydrocephalus may require *in situ* examination with removal of the upper vertebral column and sectioning through the facial bones. Careful reconstruction is essential if a satisfactory cosmetic result is to be obtained.

The neonatal brain is extremely soft requiring great care and, sometimes, immersion in saline for atraumatic removal.

Preliminary Inspection of the Brain

(a) The brain should not be sliced before fixation. Careful macroscopic examination will often provide information for a preliminary cause of death.

(b) Fresh samples should be taken for microbiology, virology, or neurochemistry as needed. Direct smears or aspiration cytology may assist tumour diagnosis.

(c) Dissection of arteries prior to fixation is recommended in the identification of aneurysms.

(d) Suspension of the brain in 10% formol saline for 3-4 weeks is recommended with weekly changes of fixative. The spinal cord should be suspended vertically.

Dissection

(a) While coronal sectioning of the cerebral hemispheres is traditional, midline sagittal or horizontal planes may help correlation with CT scan or magnetic resonance images

(b) Routine blocks should normally include dura, frontal, temporal, parietal, occipital, basal ganglia, thalamic nuclei, hippocampi, mamillary bodies, corpus callosum, cerebral white matter, and cerebellum (including dentate nucleus, pons, medulla mid-brain and brain-stem). In cases in which the pathology is limited to a particular part of the brain histological sampling may be more restricted.

Appendix 3 MATERNAL DEATHS

Definitions

Deaths occurring during pregnancy or within 42 days of childbirth are classified as maternal deaths and should be notified to the UK Confidential Enquiry into Maternal Deaths. Those resulting from obstetric complications of pregnancy, labour and the puerperium are termed 'direct' maternal deaths, whereas those due to disease which pre-dated, or occurred during pregnancy, but which was aggravated by the pregnancy, are termed 'indirect'. 'Fortuitous' deaths are due to causes not related to, or influenced by pregnancy. The Enquiry is also interested in 'late' deaths, occurring up to one year following delivery, although these are not at present formally included in the statistics of maternal mortality.

Notification

Notification will normally be initiated by the clinicians concerned, but pathologists will sometimes encounter cases which were not under the formal care of an obstetrician, or in which death has occurred after the patient has left direct clinical supervision. In such cases, the pathologist should ensure that the formalities of notification to the Enquiry are completed. Each Region has a Pathology Assessor for Maternal Deaths who can be consulted whenever necessary. The Royal College of Pathologists maintains a list of Assessors. Regional Directors of Public Health will advise on the procedures for notification.

Conduct of post mortem

In relative terms, maternal deaths are now so few that individual pathologists may have little personal experience of the problems involved. For example, in the three years from 1985 to 1987, only 265 maternal deaths were reported to the Enquiry. The proper conduct of a maternal post mortem calls as much for routine good pathological practice as for special expertise, but an awareness of certain common obstetric problems is essential. Pathologists involved in such a case should refer to the review article on the maternal post mortem by Rushton and Dawson in the Journal of Clinical Pathology, volume 35,

909-921 (1982) which summarises the areas requiring special attention. The assistance of an obstetric pathologist, neuropathologist or other specialist should be requested whenever appropriate.

Surgical specimens

The pathologist undertaking a maternal post mortem should also examine or review any recent surgical resection specimen, such as a caesarian or post-partum hysterectomy. The post mortem report should cross refer to the surgical specimen, with particular reference to the context of the post mortem findings.

Reports of the Confidential Enquiries

Pathologists are recommended to consult the reports of the Confidential Enquiries into Maternal Deaths for the last 4 triennia which contain chapters devoted specifically to the maternal post mortem. These reports have found it necessary to draw attention to certain shortcomings in maternal post mortem practice which are regarded as constituting substandard care; in particular, the omission of a histological report, or of other necessary laboratory investigations. The Confidential Enquiry is concerned not simply to establish a basic cause of death, but to reach as full an understanding as possible of all the circumstances surrounding the death. A detailed post mortem is invaluable in these assessments.

Clinicians and Coroners

The pathologist should consult fully with all clinicians who were involved in the obstetric and anaesthetic care of the deceased so that all relevant issues are properly addressed at the post mortem. The pathologist should personally ensure that the clinicians are given notice of the time and place of the post mortem, that a copy of the full report reaches them personally on its completion and that this is also supplied to the Confidential Enquiry. Since many maternal post mortems are carried out on the instructions of the Coroner, the pathologist may on occasion have to press the Coroner's office to facilitate such communication. In framing the report to the Coroner the pathologist should not be deterred from writing a full report on a maternal death on account of the limitations of a Coroner's post

mortem pro-forma. If the Coroner declines to order a post mortem in a case of maternal death, all possible steps should be taken to obtain a hospital post mortem to assist the Confidential Enquiry in its assessment of the case.

Appendix 4 NCEPOD – National Confidential Enquiry into Perioperative Deaths

NCEPOD is an independent body supported by Colleges and Associations including the Royal College of Surgeons of England, the Royal College of Anaesthetists, the Royal College of Pathologists, and the Associations of the Surgeons and Anaesthetists. The management of NCEPOD is undertaken by three clinical coordinators; there is a Steering Committee on which the Royal College of Pathologists is represented.

NCEPOD was founded in 1988 following a Regional Pilot Study. The Study undertaken in 1989 concentrated on paediatric surgery. All available post mortem reports were examined by Dr J Keeling (1). In 1990 a random sample of perioperative deaths other than those in children were examined. The post mortem reports were examined by a panel of nine pathologists (2,3). The 1991-92 report (to be published September 1993) examines selected operations.

Post mortem examination is an important form of audit in perioperative deaths. The majority are performed under the Coroner's authority. Surgeons are aware of the value of the post mortem but need to be informed of the findings as soon as possible in a clear format which addresses their clinical problems. While improvements in presentation, completeness of description, histological examination, and commentary are all desirable, the most immediate impact could be achieved by ensuring that the results of hospital and forensic post mortems are made available to clinicians.

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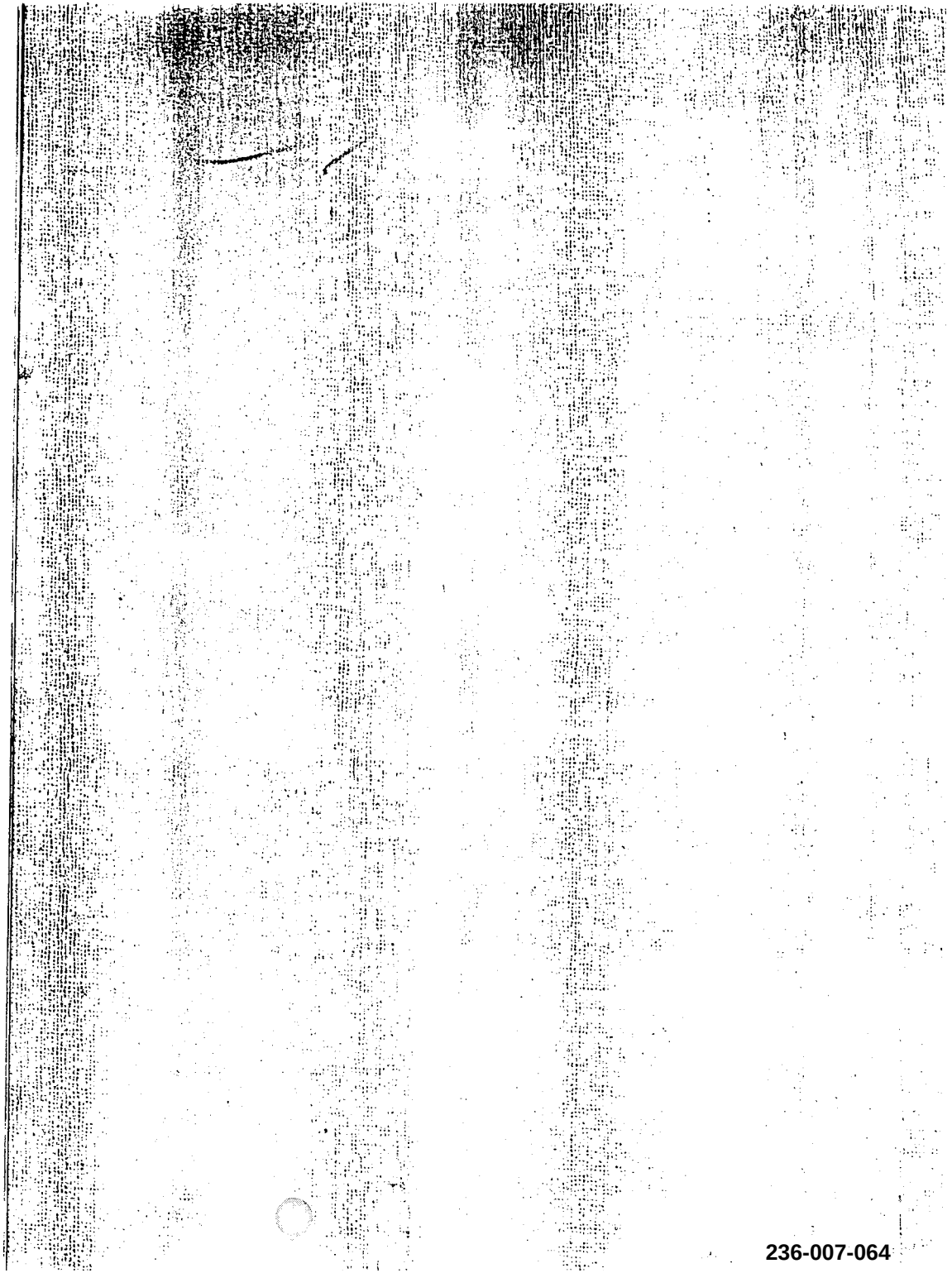
THE AUTOPSY AND AUDIT

Report of the Joint Working Party of the Royal College of Pathologists, the Royal College of Physicians of London and the Royal College of Surgeons of England

August 1991



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THE AUTOPSY AND AUDIT

Report of the Joint Working Party
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August 1991

Membership of the Joint Working Party

Royal College of Pathologists

Professor G Slavin (Convenor)
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TERMS OF REFERENCE

i) to consider the present use of the autopsy in clinical audit;

ii) to consider ways in which clinically useful information gained at autopsy may be enhanced in a timely fashion;

iii) to consider how this information may be widely propagated and presented within each hospital in order to contribute to satisfactory audit of the care of patients;

iv) to consider minimum standards of audit based on clinical autopsies and to indicate ways of encouraging those hospitals not achieving them to achieve those standards.

INTRODUCTION

In this report the term clinical audit is used to describe a process of systematic critical analysis of the quality of patient care, to include the procedures involved in diagnosis and treatment, the use of resources, and the outcome, with the aim of assessing current practice and instituting change where deficiencies are identified *[1,2,3,4,5]*.

This process of auditing patient care has been divided into three main, interrelated categories: structure, which includes more readily quantifiable factors such as the quantity and type of resources available; process, which is what is done to the patient in the structure; and outcome, which is the result of the clinical intervention. The autopsy provides a means of examining aspects of all three but in particular it offers the opportunity to study mortality in detail, on the basis that much can be learned about the living from the study of the dead *[6]*.

CHAPTER 1 THE PRESENT USE OF THE AUTOPSY IN CLINICAL AUDIT

1.1 Despite the advent of progressively more sophisticated investigative and imaging techniques, discrepancies between clinical and autopsy diagnosis have remained around the 10% level *[7,8,9,10,11]*. For instance, in a study of 100 intensive care unit deaths, 10% of autopsies revealed findings which, if detected before death, would probably have led to a change of management which might have resulted in cure or prolonged survival *[12]*. Similarly in a study where the autopsy rate was 52% for in-patient hospital deaths, 90% confirmed the clinical diagnosis, 75% disclosed previously unknown and clinically important findings, and major discrepancies were found in 10% *[13]*. Furthermore, 10% of the autopsy findings were of potential therapeutic relevance had they been known before death.

In autopsies performed on patients thought to have died of malignant disease there was only 75% agreement that malignancy was the cause of death and in only 56% was the primary site identified correctly. Tumours of the pancreas, liver and biliary tract produced the most difficulty *[14]*. In the same way the tendency of doctors to attribute most sudden unexpected deaths to heart disease probably leads to an overestimate of cardiac causes of sudden unexpected death *[15]*. An audit in a paediatric cardiology unit showed unsuspected abnormalities in 80%, with undiagnosed abnormalities or surgical problems contributing to death in 38% *[16]*.

1.2 Such high levels of discordance mean that mortality statistics which are not supported by autopsy examinations must be viewed with caution *[17]*. It is not possible to predict with any degree of accuracy which autopsies will yield discrepant diagnoses *[18,19,20]*. Several studies have shown that autopsies are necessary to ensure the accuracy of death certificates *[21,22]*.

1.3 It is generally assumed that autopsies provide a good index of the quality of patient care, and for this an autopsy rate high enough for analysis is needed. An overall rate of about 35% of hospital deaths has been suggested as adequate *[23]*.

The number of discrepancies between clinical and autopsy diagnoses is an important index of care. However, it has never been shown that there is a correlation between an increase in the autopsy rate and a subsequent decrease in clinicopathologic discrepancies *[24]*. If this were to be demonstrated then the indispensability of the autopsy in clinical audit would be beyond question *[25]*.

The Decline in Autopsies

1.4 There has been a progressive decline in autopsy rates throughout the world *[26]*. This has been not just an absolute decline, but is seen especially in the elderly, where there is a potentially higher discrepancy rate, and a correspondingly higher rate of undiagnosed but potentially treatable conditions *[27,28,29,30]*.

1.5 The reasons for the decline are many and complex. Religious objection is often cited as a cause, but few religions take a stand against autopsies *[31]*. For instance, the Koran places no restriction on them, but because of Islamic respect for the dead they were not performed in Turkey until 1838, when a medical school was established in Istanbul and an Imperial edict was issued directing that autopsies should be performed as part of the activity of the school *[32]*. More recently, new legislation in Israel, enacted as a result of religious pressure led to a rapid decline *[33]*.

1.6 It is often thought that families may suffer extra distress when an autopsy is requested and reasons for refusal of permission include fear of disfigurement, lack of information about the autopsy, other family member objections and the stress of giving permission for the examination. These considerations may inhibit doctors from requesting permission. However, in a study of the families of patients undergoing an autopsy, 88% considered they had benefited. Their benefits included reassurance that all appropriate medical care had been given, comfort in knowing the cause of death and comfort in advancing medical knowledge *[34]*. In perinatal pathology, autopsy findings may provide significant evidence for counselling parents about future children.

If these benefits are to be achieved there must be early communication with the family. Distressingly, many families receive no information about the results of the autopsy and others frequently complain of long delays in receiving information. There are clearly grounds for

improving the way in which informed consent is obtained and particularly in conveying the results to the family and in counselling them in their bereavement.

1.7 Medical reasons for the decline include advances in diagnostic techniques and increasing faith in their results, failure to obtain consent, fear of litigation and cost *[35,36]*. For instance, in the United States, the decline in the autopsy rate in the Mayo Clinic has been associated with the failure of the autopsy service to provide income to the institution, even though it has been shown to play an advantageous role in quality control, cost containment and efficient allocation of resources *[37]*. It has been suggested that ways should be found to ensure the reimbursement of costs, perhaps by categorising the autopsy as a clinical activity, and by voluntary and government regulation, to assure the role of autopsy in quality assurance programs *[38]*.

1.8 Pathologists must take the lead in establishing the medical and scientific value of the autopsy in order to justify the cost within the hospital. Without the enthusiastic participation of pathologists justification is unlikely to succeed *[38,39,40]*. Indeed, the converse may sometimes be the case and pathologists may actually play a part in resisting the improvement of an autopsy service in order to develop other services *[41]*.

CHAPTER 2 OBTAINING CLINICALLY USEFUL INFORMATION AT AUTOPSY

Clinical Awareness of the Value of Autopsies

2.1 Clinical post-mortems may not be performed without the permission of the deceased's relatives and this is the most important enabling step in the procedure. Permission for post-mortem examination must be obtained positively but sympathetically by the clinicians who appreciate the value of the autopsy in problem solving and in clinical audit. This appreciation must begin in medical schools where the role of the autopsy is often undervalued in the curriculum. Many schools hold demonstrations of autopsy material but few offer the opportunity to take part in the autopsy, analyse the findings and prepare the report *[42]*. There should be an increased emphasis on the autopsy in the medical school curriculum where it has a place in developing problem-solving skills *[43]*.

Asking for Permission for Autopsy

2.2 Great care should be taken in obtaining permission for an autopsy. The responsibility lies with the consultant in charge of the case, but there is frequently uncertainty about who is to undertake this task. Whilst it may be delegated, this should be a positive step and not merely left to the most junior doctor, nurse or manager. Those responsible for approaching the relatives should be trained in a sympathetic and informative approach. Such training should be regarded as a proper duty of consultants for junior staff. Pathologists should also have the right to initiate a request for autopsies on patients when they think that this might be useful.

The nature of the consent forms may act as a barrier *[44]*. The person obtaining permission should explain to the next of kin the benefits of the autopsy examination in providing information for them, for the medical staff and in the provision of tissue for homografts, for teaching

nd for research *[45]*. The consent form must allow relatives to permit a full autopsy examination or to restrict the examination or the use of tissue, in keeping with the Human Tissue Act (1961).

Bereavement officers within hospitals can aid in explaining the process to families and in obtaining permission particularly in surgical cases where theatre duties may preclude a convenient meeting between the doctor and with the relatives. The training of bereavement officers should include a proper understanding of why autopsies are important. Those requesting permission for post-mortems should also be aware and take into account the religious or cultural sensitivities of the relatives. Pathologists should, where possible, perform post-mortems at times which accord with these sensitivities.

Posing the Problems for the Pathologist

2.3 Each request form for autopsy should give a summary of the clinical illness and should indicate particular problems which the pathologist should address. Any potential hazards such as HIV infection should be indicated. The completed form should indicate those staff who wish to be contacted at the time of the autopsy. The notes and results of investigations should be available for study at the time of the autopsy. Radiographs and viewing facilities should be present in the post-mortem room. Where cases are difficult or complex it is wise for the requesting consultant to discuss the problem with the pathologist prior to the autopsy and not merely rely on a written request. An example of a request form is given in Appendix I.

Autopsy Techniques

2.4 In hospitals with junior pathology staff, all autopsies should be performed under consultant supervision and not by complete delegation of the examination to a junior doctor. Conventional autopsies properly performed will answer the questions posed in the majority of cases *[39]* but occasionally other techniques such as post-mortem radiography and injection studies may be of help. The use of biopsy techniques to perform a 'needle autopsy' is a useful means of obtaining small amounts of tissue when time is of the essence. For instance, during the first hour after death it is possible to obtain tissues for correlative biochemical and morphological studies, which reflect the conditions present in life *[46]*. This is hardly ever

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exploited when investigating complex biochemical deaths. The same technique is of value when permission is granted only for a limited examination or there is a significant risk of infection.

Disciplines other than Histopathology, such as Medical Microbiology, have an important part to play in the autopsy and should be used wherever appropriate.

Where medico-legal autopsies are performed for the Coroner or Procurator Fiscal, the same standards of information provision, and autopsy performance should be those of conventional clinical post-mortems. Medico-legal autopsies on cases of head injury should be performed, where possible, by pathologists with experience of neuropathology; similarly in cases of sudden death in infants it is best if the pathologist has experience in paediatric pathology.

2.5 The standard of autopsy performance overall will be best maintained if the Royal College of Pathologists continues to emphasise autopsy techniques in training programmes for pathologists and to insist on the highest standards in its examinations.

CHAPTER 3 COMMUNICATIONS

Attendance at the Autopsy

3.1 It is a common criticism that whilst the operating theatre and the delivery suite have changed considerably, there has been little change in the autopsy room in the last century. Some hospitals have new facilities which provide easy access for viewing, but in many others the autopsy rooms are unattractive places in which there is little room to stand and in which it is difficult to see all but the most gross changes. If attendance at autopsies is to be encouraged then more effort should be made to present the autopsy room as a clinical area that is not aesthetically offensive *[47]*.

3.2 Close liaison between physicians, surgeons and pathologists must be encouraged. A member of the team requesting the autopsy should attend the autopsy or a demonstration of the findings. Autopsies may be performed at times when it is difficult for them to attend because of other commitments; regular daily demonstrations of autopsy findings at a convenient time helpful.

Attendance of others such as radiologists involved in the investigation of a patient should be encouraged and there should be opportunity to compare radiological and imaging investigations with the anatomical findings in the post-mortem room.

Reports and Records of the Autopsy

3.3 A high priority should be given to the production and presentation of reports. An interim report based on the macroscopic examination, possibly supplemented by frozen section histology, should be issued within 2 days.

The increasing use of word processors and computers in laboratories should allow the clerical work to be reduced and the reports produced in a standard format. All reports should include not only a description and listing of the findings but a summary and commentary which puts the findings into clinical perspective. In normal circumstances autopsy

reports should be completed in 3 weeks but the need for special techniques or prolonged fixation in neurological cases may lengthen this period.

Histological examination of paraffin sections should be performed in every case. Such examination not only reveals changes not apparent macroscopically but, in addition, the place of autopsy histology in training junior pathologists and in producing archives of tissue for study is emphasised. Nevertheless, by limiting the amount of histopathology done on each case, in a critical fashion, the final report can be produced rapidly without losing significant information *[48]*.

It is emphasised that retention of tissue for purposes other than to establish the cause of death is subject to the Human Tissue Act, 1961. The constraints apply equally to clinical autopsies and those performed for the Coroner. Any restrictions imposed by the autopsy consent form must be observed. Pathologists must also comply with the Coroner's Act (1988).

Permanent records of autopsies can be made using a combination of still and video photography *[49]*. Video recording is of increasing importance in the use of autopsy material for undergraduate and postgraduate teaching as well as part of audit procedures. Autopsy records and findings including illustrations should be coded using systems such as SNOMED, or its predecessor SNOP, to allow easy manual or computer retrieval for analysis of data. In Coroner's cases the WHO ICD 'E' codes are essential for coding the manner of death. Such records form an important resource for postgraduate teaching within the hospital and as illustration for audit meetings. The encoded records of autopsy findings should form part of the clinical record used in any analysis of hospital clinical activity.

Communicating with the Relatives through a Consultant or General Practitioner

3.4 It is important that after the post-mortem the results are communicated and explained to the patient's relatives as soon as possible. This may be done by the hospital consultant (or a delegate) in charge of the case or it may be done by the general practitioner. In either case a copy of the final post-mortem report should be sent to the general practitioner for information. It is not appropriate for pathologists to speak directly to relatives without the prior knowledge of the consultant in charge of the case.

Autopsies for General Practitioners

3.5 From time to time pathologists are requested to undertake clinical post-mortem examinations by general practitioners on patients dying at home. These requests may be because of particular interest of the practitioner or because a patient has been treated for a long period in hospital. Such referrals from general practitioners are to be encouraged. In the future more formal audit of deaths in general practice may have an important role.

Medico-Legal Autopsies

3.6 The practice of removing bodies from the hospital to a public mortuary for medico-legal purposes, in patients dying in hospital, has little to commend it. Consultants may find it difficult to attend. The results and final report often fail to reach the appropriate clinician. Wherever possible, permission should be obtained from the Coroner so that such autopsies can be performed in the hospital. They should be performed and recorded in the same appropriate detail as autopsies requested for clinical reasons.

Medico-legal autopsies are part of the clinical process and would have little value in clinical practice unless the reports reach the appropriate clinician. When the death has been referred to the Coroner or Procurator Fiscal, providing that their consent has been given, it is still appropriate to send a report to the deceased's general practitioner.

Many pathologists undertake a heavy workload of Coroners' autopsies which is outwith their clinical practice. They must ensure that such a workload does not conflict with their duty to provide a clinical autopsy service which meets the demands of clinical audit.

CHAPTER 4 MINIMUM STANDARDS OF AUDIT BASED ON CLINICAL AUTOPSIES

Sampling of Hospital Deaths

4.1 It is not possible to set a standard autopsy rate which is appropriate for all hospitals, because of the varying ages of patients and case mixes between hospitals. In all cases when a Death Certificate cannot be completed, the death must be referred to the Coroner. As a minimum, clinical autopsies should be requested:

i) to verify a cause of death based on a clinical diagnosis and/or to determine the extent of known or assumed lesions in problematic cases;

ii) to investigate cases which are important for training, education and research;

iii) to monitor the effects of therapy, especially newly introduced drugs, and the reliability of new diagnostic procedures;

iv) to provide a degree of sampling within the patient population. From time to time the sampling may be random or targeted on a particular service. The target figure for sampling general hospital deaths in which there is no perceived prior necessity to perform an autopsy should be at least 10%. Each hospital will need to develop its own system of random sampling, in order to select such cases for autopsy;

v) in the case of perinatal pathology an attempt should be made to obtain permission for autopsy in all cases.

Assessing the Results of Autopsy

4.2 Regular mortality meetings should be held to discuss and analyse the autopsy findings in individual patients or groups of cases. The major and primary purpose of these meetings should be educational. There should be frank discussion concerning diagnostic procedures, clinical management and outcome as part of normal hospital

procedures. They should be used to evaluate both individual cases and the organisation of the hospital as a whole to ensure that in all its aspects it is functioning for the benefit of individual patients.

Besides critical evaluation of individual cases the rates of discrepancy between ante-mortem diagnosis and post-mortem diagnosis should be noted for the hospital as a whole and for individual services. The emphasis should be on major discrepancies where therapeutic decisions might be affected. It is not possible to set norms for such discrepancy rates but within a hospital the scrutiny of figures will identify topics for further investigation and action. Approaches to the quantification of the level of agreement or disagreement between clinical and autopsy findings have been described *[50,51]*.

Auditing the Autopsy itself

4.3 In any evaluation, the autopsy procedures should themselves be scrutinised and evaluated. This might include:

i) the performance in obtaining permission from relatives and the reasons for refusals;

ii) the adequacy of post-mortem request information provided to the pathologist;

iii) the level of information provided in the autopsy report by the pathologist and its promptness;

iv) the value of the autopsy and its use in clinical audit as a means of reducing significant discrepancies between ante-mortem and post-mortem diagnoses;

v) the value of communicating to relatives autopsy findings as an aid to the bereavement and grieving process.

Monitoring the Autopsy in Audit

4.4 If the autopsy is to play a significant role in clinical audit, there must be enthusiasm and active collaboration for the procedures from pathologists, from physicians and from surgeons. The responsibility for co-ordinating the scheme should lie with the District Medical Audit Advisory Committee, but the successful and continuing performance of such a scheme should be monitored and assessed by visitors from the various Royal Colleges when they visit hospitals for training and accreditation purposes. A successfully functioning autopsy-audit procedure should be an important criterion in such assessments.

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CHAPTER 5 COSTS OF THE AUTOPSY-AUDIT PROCEDURES

5.1 Autopsy-audit procedures should be properly funded and not merely added as an extra commitment to a clinical service that is already extended. As well as pathologists' time for collection, analysis and presentation of data it is likely that extra technical and clerical help will be required within the laboratory *[52]*. It is a concern that in a cost conscious health service, with an emphasis placed on income generation, the overall resources for the autopsy service may decline. If hospitals were paid for the costs of clinical autopsies as part of the audit process then this concern would be alleviated.

Audit is an activity in addition to current clinical activity and it is appropriate to recognise this new development. The need for extra funding has been recognised in the Working Paper on Audit of the Government's White Paper 'Working for Patients' *[1]*. Implicit, however, in any requests for extra funding is the premise that autopsy findings would be recorded in sufficient detail to provide a satisfactory data base for audit studies in a timely fashion.

5.2 The Royal College of Pathologists has previously recommended that each consultant should not be required to perform more than 300 autopsies a year. A consultant in an undergraduate teaching department may only be able to deal with less than half this load *[53]*.

5.3 In any hospital scheme, the actual costs incurred should be monitored at regular intervals so that inadequate funding does not impede its success.

CHAPTER 6 SUMMARY OF RECOMMENDATIONS

Concerning the performance of autopsies

6.1 The Joint Working Party makes the following recommendations:

i) responsibility for obtaining permission for an autopsy should lie with the consultant in charge of the case. The task may be delegated to junior medical staff in individual cases. Specially trained bereavement officers could approach relatives for consent at the request of the consultant in charge;

ii) medical staff and bereavement officers should be trained to seek permission in a sensitive and sympathetic manner with proper and adequate explanation to the relatives;

iii) autopsy request forms must provide an adequate clinical summary and identify any particular problems or hazards;

iv) request forms should be accompanied by the case notes and radiographs;

v) all autopsies should be performed under consultant supervision;

vi) the autopsy or at least a demonstration of the major findings should be attended by a member of the clinical team;

vii) an interim report on each autopsy should be sent to the consultant in charge of the case within 2 days;

viii) the final complete report should normally be issued within 3 weeks of the autopsy, except in cases where the report may be further delayed by special investigations, and should include coding data for the hospital coding department;

ix) diagnostic or confirmatory paraffin section histopathology should be done in every case. Retention of tissue for purposes other than to establish the cause of death is subject to the requirements of the Human Tissue Act, 1961;

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x) Coroner's autopsies should be performed with the same thoroughness demanded by autopsies prompted by clinical requests;

xi) the Royal College of Pathologists should maintain the importance of autopsy skills by an emphasis on them in its examinations in histopathology;

xii) in their approval and accreditation procedures, the Royal Colleges should include an assessment of the autopsy rate and the use made of autopsy findings.

Concerning the use of autopsies in clinical audit

6.2 The Joint Working Party make the following recommendations:

i) the minimum requirement for clinical autopsies should be to perform autopsies to verify a cause of death based on a clinical diagnosis and/or to determine the extent of known or assumed lesions in problematic cases;

ii) in addition to this, sampling of general hospital deaths in which there is no perceived prior necessity to perform an autopsy should be at the rate of at least 10%;

iii) regular mortality meetings should be held, with the active participation of pathologists;

iv) discrepancy rates between ante-mortem and post-mortem diagnoses should be monitored and made available to consultants on an individual basis and more widely within the hospital with their consent;

v) responsibility for organising and promoting clinical audit schemes utilising autopsy data should lie with the District Medical Audit Advisory Committee;

vi) the value of the autopsy in medical audit should be emphasised in the undergraduate medical curriculum;

vii) the autopsy service in hospitals must be adequately funded with a requirement to maintain funding at a level to sustain effective clinical audit.

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Appendix I

A combined clinical request and consent form granting permission for autopsy is appended. The clinical request has a simple layout and asks simple positive questions. One form is unlikely to satisfy the varying requirements and each hospital is encouraged to design its own request to suit local needs.

On the reverse side, formal permission for autopsy is given. The format should be adhered to. In particular there should be no lessening of the relatives' rights to restrict the use of tissue or extent of the examination. Nevertheless the starkness of the format may be distressing to some relatives and a simpler explanation which may be helpful for them to read **in addition** to the request form is:

> "Many relatives are understandably reluctant to give permission for an examination of the body after death and you should not feel under any pressure to give consent if you feel unable to do so. However, to help us learn how to give the best treatment to future patients, doctors find it helpful to carry out such examinations. If you give permission it will allow us to carry out a careful internal examination which may reveal new information and, therefore, benefit future patients suffering from the same disease. It also allows us to remove tissue for laboratory investigations which are not possible during life but which let us learn more about diseases and their treatment. Moreover, we have found that a full understanding of a patient's illness and its cause is helpful to the relatives in adjusting to their loss".

Autopsy Request and Clinical Summary

Consultant: Ward: Date of admission:	Label
Date and hour of death:	Coroner informed: Yes / No

Clinical diagnosis:

Main complaint(s) necessitating admission, and duration:

Relevant previous medical history:

Relevant clinical findings and investigations (summarise):

IMPORTANT – indicate any hazard for dissection e.g. tuberculosis, hepatitis or possible AIDS

Previous biopsies (quote number):

Specific questions for the Pathologist:

Requesting Doctor: *(CAPITALS)* .....

Signed: .....

Date: .....

RO39-70-1

Post Mortem Declaration Form

I do not object to a post mortem examination being carried out on the body of .....

..... and I am not aware that he/she had expressed objection or that another relative objects.

I understand that this examination is carried out:

(a) to verify the cause of death and to study the effects of treatment, which may involve the retention of tissue for laboratory study.

(b) to remove amounts of tissue for the treatment of other patients and for medical education and research.

Signed: .....

Relationship to deceased: .....

Witnessed by: .....

NOTES ON COMPLETION OF THIS FORM

1. The signature of a relative of the deceased should be witnessed by the member of staff administering the form.
2. A relative of the deceased should not be invited to sign this form if the hosptial is itself aware of objections on the part of other relatives.
3. Should a relative agree to paragraph (a) but not paragraph (b) appropriate deletions may be made to the form.

Editorials

Practice guidelines for necropsy: time for action

The necropsy is a professional activity which requires extensive knowledge and technical ability in order to identify and interpret important findings within a wide range of clinical contexts. The central role of the medicolegal necropsy in the investigation of death necessitates the highest possible standards of practice. Similarly, the clinical necropsy represents one of the few situations when clinicians elect to submit their management of cases to assessment by other doctors. This issue of the Journal contains yet another study describing a high rate of discrepancies between clinical diagnoses and necropsy findings.[1] Such studies are useful in that they demonstrate the amount of data that can be obtained from high quality necropsies. Pathology has been at the forefront of the introduction of quality control into medicine and it must surely be time for formal quality control in necropsy practice.

Practice guidelines represent recommendations that identify a range of voluntary strategies for the management of a specific problem and that also allow for practice variation due to individual circumstances.[2] Standards differ from guidelines in that practice variation is not expected. Variation in necropsy practice is to be expected as each necropsy involves the incorporation of substantial patient specific information and consequently practice guidelines rather than standards are desirable and could be achievable if formulated through the framework of the appropriate professional pathology organisations.[2-4]

The necropsy examination

Patient notes and consent forms should be studied carefully, particularly in relation to clinical problems and possible limitations placed on the examination by relatives. After identification and a careful external examination, the body is opened by a pathologist who should also remove the internal organs whenever practicable. The standard 'Y' incision is recommended for the basic examination of both sexes.[5] This incision minimises visible evidence of necropsy and permits easy access to the neck structures. The internal organs may be removed individually (Rokitanski's method), together in a single block (Letulle's method) or in three main blocks (thoracic, abdominal and pelvic blocks). Organs often overlooked at necropsy include testes, breasts and intestines. Unless the examination requires alternative approaches to demonstrate specific pathological processes, the pelvic floor should be left intact. The internal female genitalia should be removed with a short length of vagina, leaving generous cuffs of vagina and rectum. Sites of recent surgery are best examined with the appropriate clinician present.

The precise order in which individual organs and systems are dissected is not important but effort should be made to demonstrate important pathological processes. This may require modification of normal dissection routines and delay of final dissection until the demonstration of necropsy findings. The frequency with which individual organs should be dissected and weighed is contentious. All major organs (heart, lungs, brain, liver, and kidneys) should be dissected in order to facilitate examination of the blood and lymphatic supply in addition to relations with adjacent structures. These organs should be separated and weighed, although other organ weights may often be necessary. Fixation of the intact brain followed by detailed neuropathological examination produces a higher detection rate of abnormalities but may be impracticable in many centres.

Awareness of how to obtain appropriate samples for biochemical, microbiological or toxicological analyses is important and pathologists should have a full repertoire of special dissection techniques to enable examination of unusual sites.[5] Examples would include the cardiac conducting system, vertebral arteries, temporal bone, sinonasal block, orbital contents, cervical spine, and other musculo-skeletal sites. Specific consent should be obtained for any potentially disfiguring procedure.

Necropsy histology

The retention of material from medicolegal necropsies is problematic and practices must be agreed with local coroners. Limited resources prevent histology on all cases and the aim should be to extract the maximum amount of information in the most cost-effective manner. Necropsy costings should include a basic histology component which is reduced by producing composite blocks containing several tissues. Some centres sample a standardised selection of tissues from every necropsy.[2] This facilitates retrospective studies, particularly when these data are linked in an appropriate database.

The necropsy report

Organ weights and internal and external macroscopic findings should be recorded contemporaneously on a simple proforma. This can also serve as a histology request form for laboratory use and can be retained permanently unlike cassette tapes which are used repeatedly. The final necropsy report should include basic demographic details, a brief clinical summary, descriptions of the external and internal examinations with reports of histology or other investigations, a summary of findings with appropriate pathology coding, and a concluding commentary.[3 6 7] This commentary should reconcile the clinical problems with the pathological findings, both expected and unexpected. All reports should include a cause of death in the standard international form of the medical certificate of cause of death as required by the Office for National Statistics. A summary of findings should be issued to clinicians within 48 hours. Any conclusions may be modified by further investigations and outlined in the final report, which should be issued within two to three weeks (neuropathology reports will require four to six weeks for completion). Performance should be monitored by regular audits of necropsy report quality and production times.[8]

Clinicopathological considerations

Necropsy reports are just one component of necropsy based clinicopathological communication, which is an integral part of necropsy practice.[6] This process begins with completion of the necropsy consent form which should outline the relevant clinical problems. Necropsy demonstrations and clinicopathological meetings provide opportunities to enhance interest and knowledge by

linking basic pathological science with applied clinical situations. Such interactions are enhanced by the use of photography or still video imaging.

Conclusions

Historically, the medical profession has ensured the quality of medical care by controlling the credentials of medical practitioners. In recent years attention has turned towards the assessment of outcomes or performance measures. Although necropsy represents an opportunity to study outcomes, the non-random nature of necropsy populations, the failure to collect relevant data and the lack of quality assurance for necropsy examinations currently precludes any meaningful benefits. If this situation is to change then pathologists must first put their own house in order and introduce guidelines for necropsy practice.

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J Clin Pathol 1996;**49**:868–869

Proliferative activity in invasive breast carcinoma

Determination of proliferative activity provides important diagnostic and prognostic information in many tumours, including invasive breast cancer. Histological grading of breast carcinoma (which includes mitotic count), is now not only widely accepted as providing robust prognostic information but also as showing acceptable reproducibility. However, if grading is not carried out diligently by histopathologists on well fixed samples, the prognostic information provided is likely to be of relatively poor quality and in such a setting a more objective system, and also a simple technique for the determination of the growth fraction of a tumour, has long been sought.

Thymidine and 5-bromodeoxyuridine labelling, S-phase fraction assessed by flow cytometry and determination of the proportion of the tumour showing immunostaining with the Ki-67 antibody on frozen sections all have disadvantages. Disaggregation of tumour cells or access to fresh or frozen tissue may be needed. Large studies of patients with long term follow up have therefore been difficult to validate using these techniques. More recently, antibodies which can be used to determine the proliferation index of a tumour on paraffin wax sections have been described including MIB-1, Ki-S1 and anti-proliferating cell nuclear antigen (PCNA). The former recognises the Ki-67 antigen, which is present in all cells active in the growth cycle—that is, not in G_0 phase, in routinely processed paraffin wax sections with the use of antigen retrieval[1] and seems to be the most suitable of these antibodies. The technique is simple (although it may be affected by the pH of the buffering solution used) and correlates well with Ki-67 immunoreactivity on frozen specimens, as described by Querzoli *et al* in this issue.[2] A strong correlation between MIB-1 expression and histological grade has been described previously.[3 4] There is also some evidence that MIB-1 expression may be relatively resistant to a delay in fixation of up to eight hours,[5] whereas mitoses are significantly less robust and notoriously difficult to identify in poorly fixed tumours. Thus, MIB-1 evaluation may be valuable in the determination of the proliferation index in tumours which have not been fixed immediately and in which grading is therefore sub-optimal.

The MIB-1 labelling index shows strong correlations with other biological and histopathological features of invasive breast carcinomas, and also with clinical outcome.[2 4] The results of Querzoli *et al* in this issue, assessing the proportion MIB-1 immunoreactivity by image analysis confirm that correlations with tumour size and survival are seen, but also a correlation with p53 and c-erbB-2 expression and inverse correlations with both oestrogen and progesterone receptor status.[2] A correlation with lymph node stage (although using the TNM staging system) is more unexpected and has not been seen by other authors.[3 4]

The major benefit of determining the percentage area showing immunoreactivity by image analysis is the objectivity of the technique, but it should not be taken for granted that this ensures good intra- and inter-observer reproducibility. Poor reproducibility of the cell proliferation index using image analysis has been reported—for example, only 56% agreement in Ki-67 immunostaining by three observers was seen by Makkink-Nombrado *et al*.[6] These authors found that the poor reproducibility seemed to be related to a bias in the "random" field selection. In addition, although direct light microscopic visualisation ensures that only malignant cells are included in the proliferation index by image analysis, this necessitates accurate interpretation of tissue sections by fully trained staff to ensure only tumour tissue is included in the analysis. Despite these difficulties, previous small series have shown a good correlation ($r = 0.77$) between the image analysis determination and light microscopic estimate of the percentage nuclear immunostaining with MIB-1.[7] Semi-quantitative light microscopic assessment of MIB-1 immunoreactivity may be of use in examining proliferation in imperfectly fixed tumours

Whichever technique is selected for determination of the proliferation index of a tumour, it is imperative that strict criteria must be agreed and adhered to, whether in defining the characteristics of a mitotic figure or in ensuring the

services. Horst Seehofer, the minister of health, has already announced that statutory health insurance is in his sights. Redefining its scope is promised within the decade.

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Reporting deaths to coroners

All the legal aspects of dying need re-examining

Start and colleagues confirm the long held suspicion that knowledge of which deaths should be reported to the coroner is no better among senior doctors than it is among their juniors (p 1038).[1] Embarrassingly, doctors in this analysis of fictitious case histories performed "only about half" as well as "experienced local coroners' staff." The fact that these lay officers rely on information supplied by doctors—whose awareness of what may be of medicolegal importance seems questionable—is entirely congruent with other anomalies inherent in the law concerning the disposal of the dead.[2]

Even with a knowledge of the law greater than that offered to the average medical student,[3] the precise legal duty placed on any doctor to report any death remains obscure. There is no statutory duty, and the common law duty referred to by Start and colleagues is that "of every person to give information which may lead to the coroner having notice of circumstances requiring the holding of an inquest."[4] The foundations of this common law duty are difficult to define: the case cited most often dates from 1702 and seems more concerned with the nature of the evidence required for a verdict of suicide.[5] As noted by Polson and Marshall, the duty cannot be enforced unless the failure to report obstructs the coroner,[6] and for such a charge to be proved it is necessary to prove intent to obstruct.[7] It can hardly be argued that lack of knowledge constitutes intent; it might be argued that the common law duty is so nebulous as to be meaningless.

The "local rules" cited by Start and colleagues,[1] having no statutory force, may represent a coroner acting in excess of his jurisdiction. We would not consider that the death in their case 1 would need to be reported, despite the short period of admission, so long as the attending doctor felt able to state the cause of death "to the best of his knowledge and belief."[8] We realise that this may run counter to the conclusion of Brodrick that a primary function of the coroner "is to help to establish the cause of death"[9] but, where the death is not both sudden and of unknown cause, we believe that the proper means of confirming a clinical diagnosis is a hospital postmortem examination.

What is less defensible—whether the clinical opinion of the cause of death is confirmed by a hospital postmortem examination or not—is the apparent inability of doctors to complete a death certificate accurately. In his recent analysis of 500 causes of death Slater found one or more inaccuracies in 29% of certificates,[10] in line with previous findings.[11] Comparison of these two papers is difficult: Slater views "a mode of dying" as unacceptable for inclusion in the cause of death, incorrectly citing recent guidance on completing death certificates published by the Office of Population Censuses and Surveys which, in fact, suggests only that a statement of mode of dying may be unacceptable if it is used alone on a medical certificate.[12] Removing "mode of dying (qualified)" from Slater's analysis almost halves the proportion of inaccuracies to 14·4%—appreciably less than Leadbeatter's estimate that 27·5% of 2085 causes of death were inaccurate.[11] That study also showed that it might be unwise to rely on such inaccuracies being corrected by what Slater refers to as "expert intervention by the Registrar of Births and Deaths."

What can be done? A short term solution that we have adopted, arising from regular audits of deaths in hospital, is for one of us to scrutinise the case notes of all patients who die after admission to medical wards. This is then followed by discussion with junior doctors of the certification or reporting of those deaths. Although time consuming, this appears to help and is similar to practice in Finland, where all death certificates are scrutinised by the provincial forensic pathologist, who requests revision of unsatisfactory entries before the documents are forwarded to the registrar general. Cooperation between committed pathology and clinical staff may also influence the hospital necropsy rate.[13]

A national long term solution, however, requires both debate and reworking of all legislation concerning the dead. A coherent legislative framework is needed to address all activities relating to death. These include the definition, diagnosis, and certification of death; transplantation; the need for hospital postmortem examinations as a part of audit; the role of the present coroner system versus a "medical examiner" system; and the retention of postmortem material for research. Even were parliamentary time and will sufficient to allow such legislative change it would remain necessary to ensure that doctors received education—if not examination—in their medicolegal responsibilities.

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Analysis of necropsy request behaviour of clinicians

R D Start, S G Brain, T A McCulloch, C A Angel

Abstract

***Aim*—To develop a necropsy related audit system to record accurate information in relation to necropsy requests, necropsy rates and coronial referrals.**

***Methods*—A simple audit form was used to record detailed necropsy related data via an integrated questionnaire design and data entry system based on available optical image scanning technology. The system recorded the numbers and locations of deaths, referrals to the coroner, clinical necropsy requests, hospital and medicolegal necropsies, the grade of clinician involved in these processes, and the identity of the consultant in charge of the case. The overall, hospital and medicolegal necropsy rates were calculated by individual consultant, specialty and for the whole hospital. Necropsy request rates and coronial referral rates were also calculated and these data were related to the grade of clinician. All data were available on a monthly or an accumulative basis.**

***Results*—Of 1398 deaths, 534 (38%) were discussed with the local coroner's office and 167 of these were accepted for further investigation. House officers and senior house officers referred over 80% of all cases, whereas consultants referred only 2%. There were no significant differences in case acceptance rates by grade of clinician. Clinicians made 307 hospital necropsy requests (overall hospital necropsy request rate 22%). House officers made 65% of all necropsy requests. Consultant necropsy requests represented 13% of all requests. There were no significant differences in necropsy request success rates by grade of clinician.**

***Conclusions*—The referral of cases to coroners and clinical necropsy requests are still being inappropriately delegated to the most junior clinicians. This study illustrates the type of useful information which can be produced for individual clinicians, specialty audit groups and pathology departments using a simple necropsy related audit system.**

(*J Clin Pathol* 1996;**49**:29–33)

Keywords: audit, necropsy requests, optical image scanning.

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The concept that necropsies provide a good index of the quality of patient care is controversial. A significant factor in this debate has been the lack of nationally agreed standards of practice, such as standard necropsy rates, which can only be set with difficulty because of varying patient age and case mixes between individual departments and hospitals. Nevertheless, the continuing high levels of discordance between clinical diagnoses and necropsy findings have ensured a central role for necropsies in medical audit and an operational system of necropsy audit is considered to be an important criterion in the assessment of clinical departments for training and accreditation purposes.[1]

One consequence of this recognition of the role of necropsy in audit has been increased demand for more accessible information in relation to hospital deaths, clinical necropsy requests and subsequent necropsy examinations. Some of this information is already available from different sources such as patient administration system, bereavement office and mortuary records. Other details, such as referrals to the coroner, are not routinely recorded centrally and relevant information can only be assembled with considerable effort, if at all. This experience stimulated the development of a simple system of necropsy related audit which uses optical scanning technology to provide a valuable and regularly updated information service for clinicians. The system records detailed information about hospital deaths, necropsy requests, hospital and medicolegal necropsy rates, and referrals to the coroner.

Data collection by optical scanning technology has been available for some time to mark multiple choice examination papers and to input data from questionnaires. This technology is becoming increasingly sophisticated and the use of optical page scanning in association with more flexible software programs has permitted data input from more complex source forms. The necropsy related audit system represents just one of many potential applications for such an integrated questionnaire design and automated data entry system within medical audit.[2] Optical scanning systems can already be found in many medical audit departments.

This paper will discuss the technical merits of this type of system in the context of necropsy request and coronial referral data compiled using a necropsy related audit application during the first year of its operation at a large teaching centre.

Methods

A simple audit form was designed and introduced to provide quantitative data which can be captured via the Formic Optical Mark Reading system (Formic Limited, Unit 4 Ransome's Dock, 35-37 Parkgate Road, London SWIG 4NP). Formic is a versatile PC based software product which is designed to capture data automatically using optical image scanning technology. The integrated system has four main functions which are questionnaire/form design, optical scanning, logic based error, and

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inconsistency detection and a data export option to most database and spreadsheet packages. The sheet-fed scanner (Fujitsu M3093E Document Image Scanner) is capable of scanning 1380 single-sided pages per hour with far greater accuracy than manual data entry through the inclusion of an integral logic based error and inconsistency detection function.[3] In our hospital the monthly data entry of approximately 150 forms, each with eight data elements, now takes less than 15 minutes compared with 120 minutes using the previous manual data entry system and an experienced keyboard operator. The design of an appropriate audit form with a companion database is relatively simple and requires no additional time input when compared with the development of a conventional manual database entry system. There is no requirement for specialist printing as the system uses photocopied images of appropriate forms.

The cost implications for individual users is low because a single system can serve a large number of applications for any number of individual departments within one or more health care centres. Although the cost benefit for individual applications may be modest (we have calculated an approximate saving of £150 per

ROYAL HALLAMSHIRE HOSPITAL POST-MORTEM AUDIT - FORM RHH/PM1

TO BE COMPLETEDBY THE DOCTOR FILLING IN THE DEATH CERTIFICATE AND/OR REFERRING TO THE CORONER'S OFFICE.

The information requested below is necessary in order that a complete database of deaths, post-mortems and requesting information can be compiled. It is important that a form is completed for every death, including those in which a post-mortem is not requested and where there is no necessity to refer to the Coroner's office. If you intend to request a post-mortem, please complete the form **after** speaking to the relatives.

If you require any further information or assistance, please contact Dr Tom McCulloch or Dr Roger Start on 3116, or Dr Carole Angel on Bleep 289.

Reg No.
Name
Date of Birth
Ward/Dept.
Consultant
(or affix addressograph lable)

For office use only

Consultant Number 0 1 2 3 4 5 6 7 8 9 (10, 1)

Ward 0 1 2 3 4 5 6 7 8 9 (10, 1)

Please cross the boxes as shown thus: ☒

Has the case been discussed with the coroner's office ? ☐ Yes → By whom ? CONS ☐ SR ☐ REG ☐ SHO ☐ HO ☐

☐ No

Has the case been accepted by the coroner's office ? No ☐ Yes ☐

Was a hospital post-mortem requested ?

No ☐

Yes ☐

By whom ? CONS ☐ SR ☐ REG ☐ SHO ☐ HO ☐

Was the request granted ? No ☐ Yes ☐

Name ..... Signature ..... Bleep No ..... Date .....

Survey : 7000

Royal Hallamshire Hospital (0742 766222)

Figure 1 Royal Hallamshire Hospital necropsy related audit form. CONS = consultant; SR = senior registrar; REG = registrar; SHO = senior house officer; HO = house officer.

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POST-MORTEM AUDIT

From 01/02/94 to 31/01/95

Consultant	Total Deaths	Case Referred	Case Accepted	HPM Requested	HPM Granted
16	60	29	6	39	22

Overall Autopsy Rate	46.7%	(HPM Granted+Case Acc)/Total Deaths
Coroner Autopsy Rate	10.0%	Case Accepted / Total Deaths
Hospital Autopsy Rate	36.7%	HPM Granted / Total Deaths
Corrected Hospital Autopsy Rate	40.7%	HPM Granted / (Total Deaths - Case Acc)
Hospital Autopsy Request Rate	65.0%	HPM Requested / Total Deaths
Corrected Hospital Autopsy Request Rate	72.2%	HPM Requested / (Total Deaths - Case Acc)
Hospital Autopsy Request Success Rate	56.4%	HPM Granted / HPM Requested
Coroner Referral Rate	48.3%	Case Referred / Total Deaths
Coroner Acceptance Rate	20.7%	Case Accepted / Case Referred

Case Referred By		HPM Requested By	
REG	5	REG	5
SHO	2	SHO	1
HO	20	HO	30
BLANK	2	BLANK	3
	29		39

Case Accepted		HPM Granted	
SHO	1	REG	3
HO	4	HO	17
BLANK	1	BLANK	2
	6		22

Figure 2 Royal Hallamshire Hospital individual consultant accumulative necropsy related audit data sheet (the location of deaths data have been omitted for simplicity). HPM = hospital postmortem; REG = registrar; SHO = senior house officer; HO = house officer; Acc = accepted.

year for the necropsy related audit, based on the replacement of the previous manual data entry system by the described optical scanning application), the overall cost saving derived from a large number of applications for multiple users can be considerable when these applications are based on a single optical scanning system.[3] The cost benefit is generally achieved through reductions in costs related to keyboard operator personnel.

The audit form was designed in conjunction with local clinicians in order to ensure that all of the necessary information was recorded with a minimal requirement for additional documentation (a specimen form is shown in fig 1). Clinicians complete an audit form for every hospital death at the time of death certification or discussion with the coroner, and the results are exported to a database after optical image scanning at the end of each calendar month. The simplicity and speed with which the audit form can be completed has resulted in acceptance by clinicians and administrative staff. Forms are completed immediately for over 85% of deaths and the remainder are obtained through personal contact with the certifying doctor.

The audit form records information relating to the location of deaths, the referral of cases to the coroner, hospital necropsy requests, the numbers of clinical and medicolegal necropsies, the grade of doctor involved in each process, and the identity of the consultant in charge of the case. The completed forms are stored and represent a useful risk management resource through the formal recording of individual hospital necropsy requests and referrals to the coroner.[4] Each consultant has an individual identification number known only to that consultant and the medical audit department, which codes each form with the appropriate consultant identification number and location code using the boxes in the upper right corner of the audit form (fig 1). All material produced by the system bears one or more consultant identification numbers without actual names in order to maintain complete confidentiality.

The database automatically calculates the overall, hospital, corrected hospital, and medicolegal necropsy rates by individual consultant and for the whole hospital. The methods for calculating these necropsy rates have been defined elsewhere.[5] Hospital necropsy request

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Table 1 Cases discussed with local coroner's office by grade of clinician

Grade of clinician	Number of cases discussed	Proportion of all cases discussed	Number of cases accepted	Acceptance rate*
Consultant	13	2%	7	54%
Senior registrar	37	7%	12	32%
Registrar	24	5%	9	38%
Senior house officer	118	22%	28	24%
House officer	321	60%	104	32%
Blank	21	4%	7	
Total	534	100%	167	31%

* See fig 2 for definition.

Table 2 Hospital necropsy requests by grade of clinician

Grtade of clinician	Number of necropsy requests	Proportion of all requests	Number of necropsies granted	Hospital necropsy request success rate*
Consultant	38	13%	15	39%
Senior registrar	15	5%	7	47%
Registrar	13	4%	7	54%
Senior house officer	28	9%	13	46%
House officer	200	65%	86	43%
Blank	13	4%	8	
Total	307	100%	136	44%

* See fig 2 for definition.

rates and coronial referral rates are also calculated with data related to the grade of clinician (a specimen result sheet for one consultant is shown in fig 2). Individual consultants are currently supplied with necropsy related data on a monthly basis by personal request. This information consists of the figures for the previous month together with an accumulative record of necropsy related practice. The system can provide information over any time period based on complete calendar months and this enables comparisons and analysis for trends as required. Data relating to any combination of individual consultants can also be provided and this type of information is readily available in confidential form to specialty audit groups within the hospital.

The distribution of deaths within the hospital is monitored in several ways. Individual consultants are supplied with details of the location of all patient deaths under their care (fig 2). The monthly and updated accumulative figures for the whole hospital also include details of the locations of all deaths and those departments in which patients are cared for by more than one consultant—for example, coronary and intensive care units, are supplied with location specific necropsy related data on request. Any unusual clusters of deaths in a particular location within the hospital would be easily identified by the system.

The system has also facilitated the monitoring of necropsy practice by the pathology department and the results of a detailed analysis of clinician necropsy requests and coronial referrals are presented for the first year of operation of the necropsy audit system. The analysis excludes deaths occurring in the accident and emergency department which are subject to a separate system of audit.

Results

A total of 1398 deaths occurred in the hospital during the year. The local coroner's office was contacted about 534 (38%) cases and 167 of these were accepted for further investigation (table 1). A necropsy was performed in all accepted cases. House officers and senior house officers together referred over 80% of all cases. Consultants referred only 2% of all cases. There were no significant differences in case acceptance rates by grade of clinician.

Table 2 shows that a total of 307 hospital necropsy requests were made by clinicians (overall hospital necropsy request rate 22%). House officers made 65% of all necropsy requests. Consultant necropsy requests represented 13% of all requests. There were no significant differences in necropsy request success rates by grade of clinician.

Discussion

Standards of practice have not been established in many death related procedures but some standards have been agreed by a Joint Working Party of three Royal colleges.[1] These standards clearly state that the responsibility for necropsy requests lies with the consultant in charge of the case. Whilst this responsibility may be delegated, this should be a positive process and not merely left to the most junior doctors. The level of supervision cannot be determined by the audit system in its present form, but the high proportion of necropsy requests made by house officers in this study suggests that these standards are not being maintained by many senior clinicians. Frequent rotation of junior staff may be a contributory factor and those consultants or specialty audit groups which operate specific necropsy request protocols within their clinical practice have found the audit system to be useful for monitoring the application of these request policies.

Formal training of junior doctors in how to request necropsies in an informative and sympathetic manner should be an integral part of undergraduate medical education but further practical training must be the responsibility of consultant clinicians.[1] There is considerable evidence to suggest that the way in which nec-

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ropsy requests are made can influence the decision of the relatives.[6] Some clinicians have found that the regular provision of information in relation to necropsy request success rates is useful for identifying those individuals who may benefit from further training in necropsy requests. The success of necropsy requests is also thought to be influenced by the grade of clinician making the request.[7] Previous studies have found consultants to be more successful in this respect but the relatively low number of consultant necropsy requests in our current audit prevents detailed assessment of this correlation. This information will become available in time, with the ability to study necropsy request behaviour on a long term basis.

The responsibility for communication with coroners or an equivalent authority must also lie with senior clinicians even though some may have less understanding of the indications which require referral than the junior clinicians under their supervision.[8] In this study consultants were directly involved in just 2% of all cases discussed with the local coroner's office. The high proportion of cases involving junior clinicians is unacceptable, particularly in view of recent local initiatives to improve performance in this area of clinical practice. These initiatives may partly explain the large number of cases, over one third of all deaths, which were discussed with the coroner's office. Other influential factors would be a local requirement to inform the coroner of all deaths which occur within 24 hours of admission to hospital and the accessible nature of the daily advice service offered by the local coroner's office. Many case discussions will have involved the clarification of minor details only and these would not previously have been formally recorded. The retention of the completed audit forms provides a permanent risk management resource if problems arise later.

Any failure to recognise those deaths which should be reported to the coroner can lead to administrative difficulties, delays in funeral arrangements and unnecessary distress to bereaved relatives. Other cases may evade medicolegal investigation altogether because they are not recognised as deaths due to unnatural causes.[8] Such situations represent poor quality service and inevitably lead to loss of respect for both the clinicians and the hospital. Although advice may be sought from senior clinicians, pathologists and the local coroner's office, this advice may be misleading or incorrect if the clinician fails to recognise and disclose all of the relevant information. All pathologists must be aware of the persisting problems with inaccurate death certification and failure to recognise deaths which require referral to coroners or equivalent authorities. In some centres pathologists have adopted the practice of scrutinising case notes of all patient deaths before direct discussions with the certifying or reporting clinician. This system provides an excellent opportunity for education, training and encouragement to make necropsy requests but must be time consuming for the participating pathologists.[9] Clearly, there are no simple solutions to these problems but the provision of detailed local information in relation to these areas of clinical practice must be an important step in the right direction. The provision of accurate information in relation to hospital deaths and necropsies is rapidly becoming an essential component of medical audit for individual clinicians, departments and hospitals. Our system provides a single and central source for all relevant information in relation to necropsies. Computer based protocols have been described for recording the accuracy of clinical diagnoses in relation to necropsy findings and this represents an important role for necropsies within medical audit.[10] Many of these systems do not seem to include details relating to clinical necropsy requests, referrals to coroners and the grade of doctors involved in these processes. This elementary information is essential to the appraisal of the procedures which occur after a death in hospital but the data can often only be collected with difficulty from a variety of different and potentially unreliable sources. Our hospital is currently developing a formal system of monitoring the accuracy of clinical diagnoses in cases where necropsy examinations are performed and the necropsy related audit will incorporate this additional information.

Our necropsy related audit system is based on the necropsy practice of a large teaching centre but would be equally applicable to a district general hospital. The development of the necropsy related audit system in association with local clinicians and administrative staff has ensured that all of the required information is recorded in the simplest and most cost effective manner. The accessibility and flexibility of the system has already proved beneficial to individual clinicians, specialty audit groups and the department of pathology. The increasing availability of accurate information in relation to hospital deaths and necropsies in this and other centres should facilitate the definition of further national standards for an area of medical practice in which this has so far proved extremely difficult.

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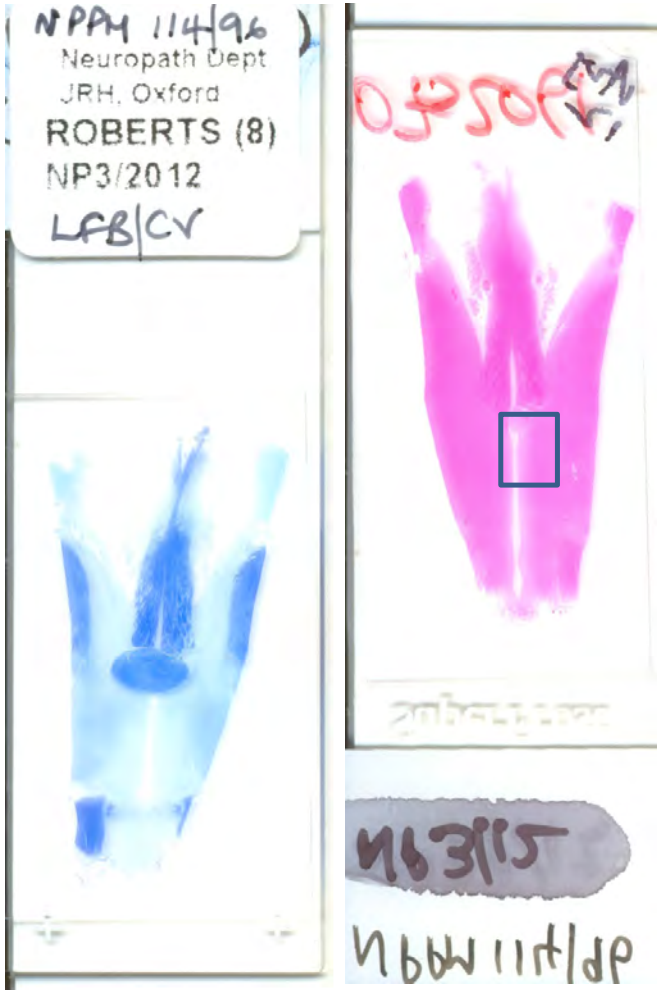
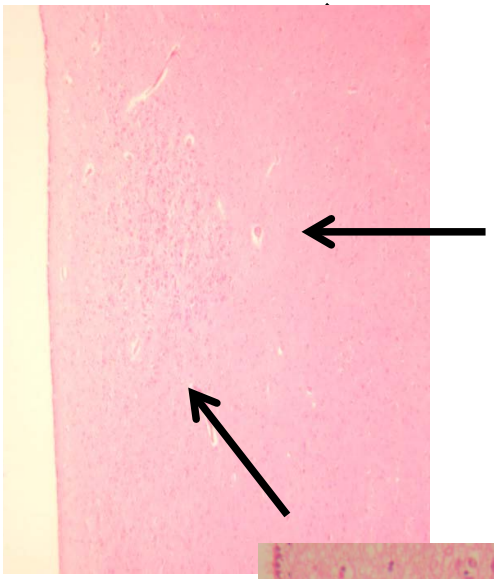
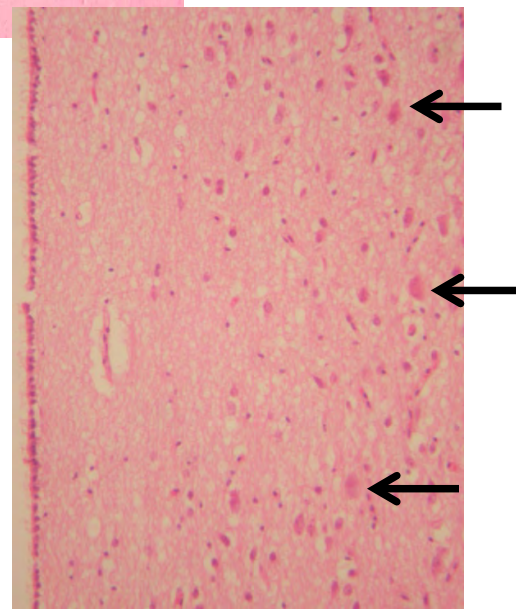
Claire Roberts: Subependymal dark cells and control female aged 10 years.

W Squier November 16th 2012

Sections of Periventricular grey and hyothalamus

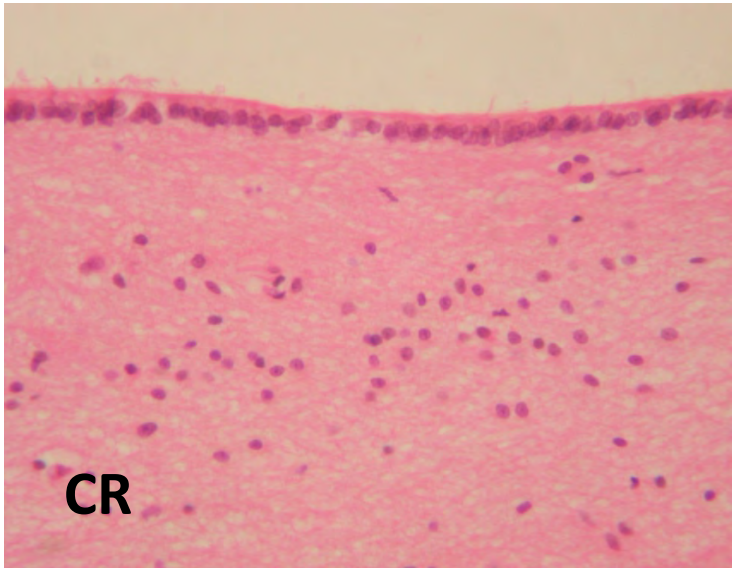


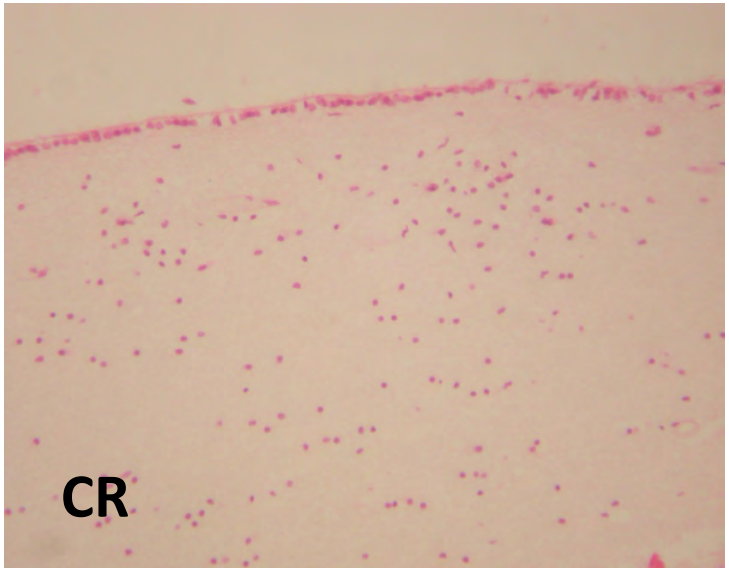


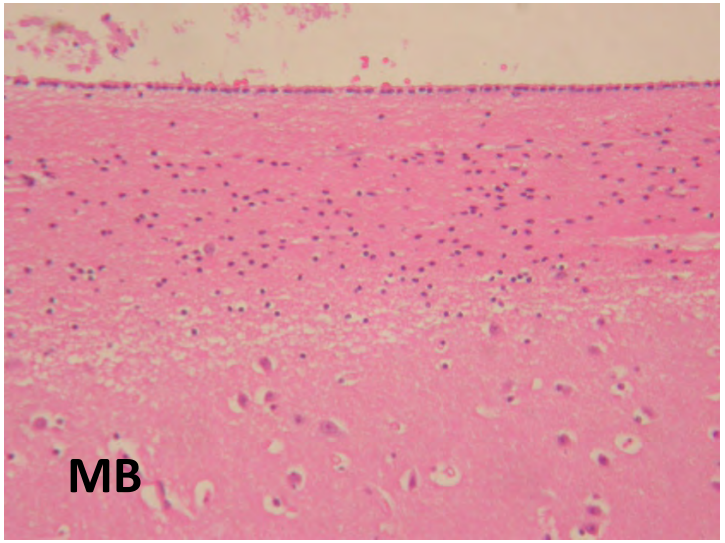


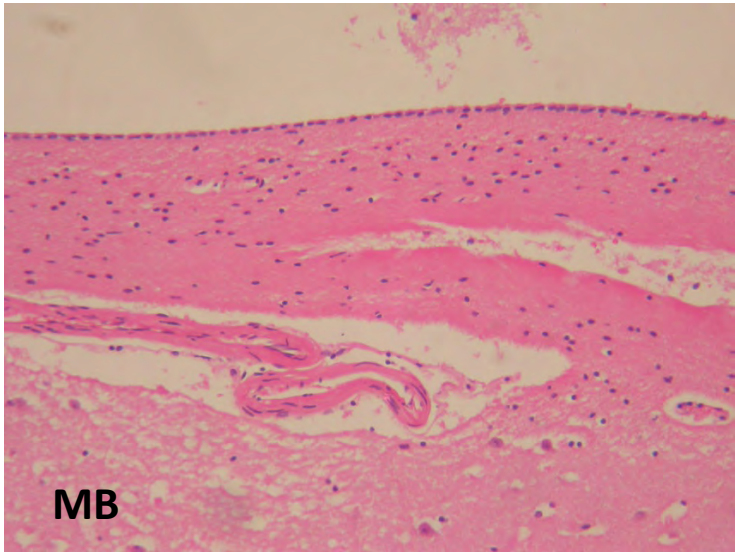
Sections of the tissue in black box. At low power(above) an irregular collection of cells is seen beneath the ependymal lining. These are the paraventricular nuclei. Higher power (below) indicates mature neurones.

Subependymal cells: CR above, control female aged 10 (MB) below.
Small dark cells are seen in both cases.







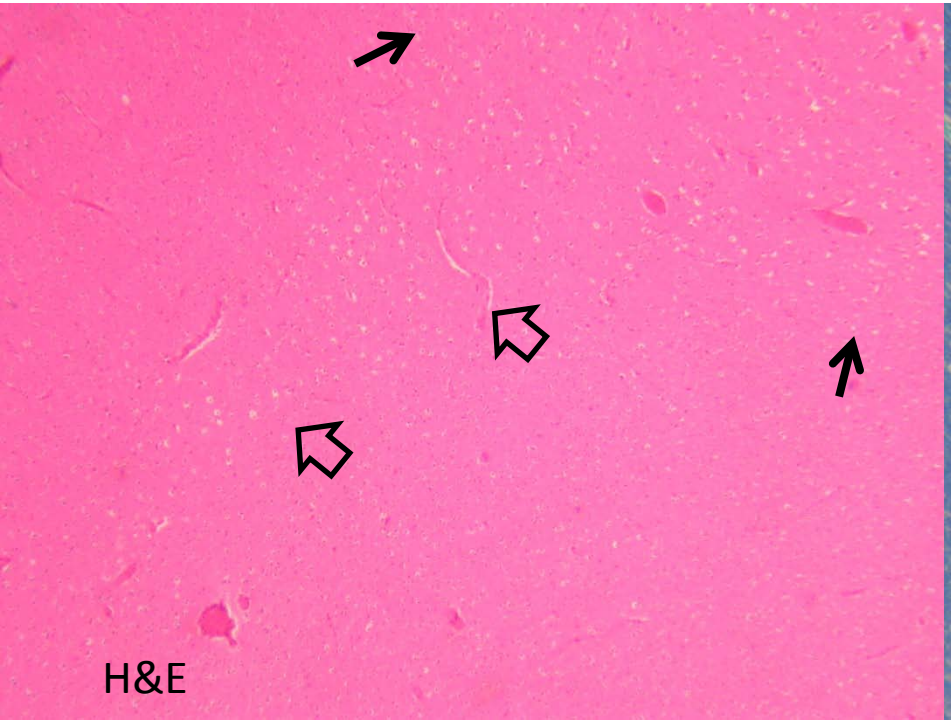


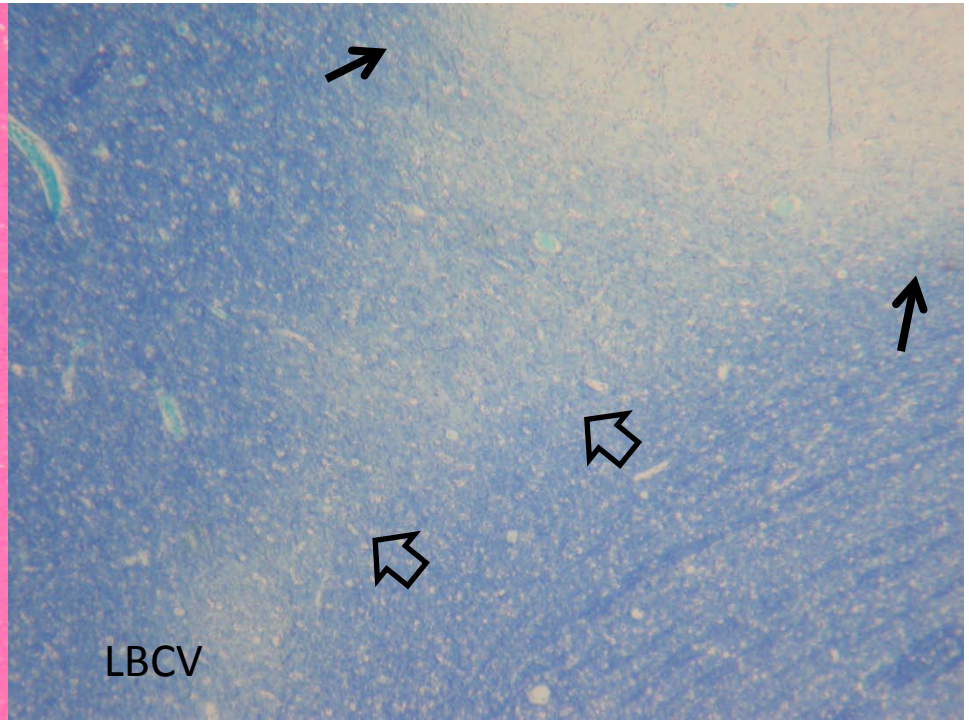
Claire Roberts

- Sections stained with LBCV are compared with sections from the brain of a child of 5 years of age with a neuronal migration disorder. By using this stain it is much easier to see the anatomy of the cortex and to detect subtle irregularities of the deep cortical border which may be seen in a neuronal migration disorder. These subtle changes are not easy to identify with the routine H&E stain.

Sections were stained with LBCV to demonstrate more clearly the cortex and its distinction from the underlying white matter.
Two of these sections are seen naked eye on the left. In the following images they are shown by microscopy. Comparison is made with routine H&E stains to show the value of this staining method for detecting subtle malformations.
Sections of Claire's cortex is compared with comparable areas from a 5 year old child with a known neuronal migration disorder.

Female 5 years with neuronal migration disorder





Two pictures from adjacent sections of the same area of the brain. The deep cortical border is indicated with short arrows. It is irregular; incompletely migrated cells extend in a rather poorly defined column (indicated with open arrows) into the underlying white matter. These features are far more readily appreciated with the LBCV stain in the right picture.

Representative images of the deep cortical border stained with LBCV. The cortex stains pale with purple nerve cells, the white matter is deep blue. Images from Claire Roberts are on the left and from a female child of 5 years with neuronal migration disorder on the right. Note that the child F5 has a less distinct margin between the deep cortex and the white matter. Further F5 has several nodules of incompletely migrated neurones (*) in the white matter just beneath the cortical border.