ensure that medicines are used more safely and effectively in children.

TRANSPARENCY

As the number of paediatric clinical trials increases it is essential that the information from these trials is made readily available. The European Commission has already funded a European Paediatric Clinical Trials Register (www.dec-net.org).¹⁵ This is the only paediatric clinical trials register worldwide.¹⁶ There is no charge for investigators who wish to enter their trial onto the register. The European Paediatric Clinical Trials Register is freely accessible to both paediatric health professionals and the public. It is essential that information regarding paediatric clinical trials remains open and accessible to all. We have seen the problems associated with the lack of publication of important clinical information by the pharmaceutical industry,¹⁷ and paediatric health professionals have a duty to children to ensure that this information remains in the public domain.

SAFETY

It is important to remember that the rationale for the European legislation and the establishment of research networks to perform clinical trials in children is to improve the evidence basis on which medicines are used in children. This should hopefully result in the safer and more effective use of medicines. One needs to be aware that adverse drug reactions (ADRs) may occur during the course of a trial.¹⁸ If

such ADRs do occur, then it is essential that consideration is given to stopping the trial. Many clinical trials incorporate the establishment of a data monitoring committee/independent safety monitoring board.¹⁹ Such a committee has the responsibility to evaluate suspected ADRs and also to terminate the trial if this is felt appropriate. Every single clinical trial does not require such a committee but if there is any likelihood of significant toxicity then the creation of such a committee is essential. The responsibility for safe clinical trials in children rests primarily on paediatric health professionals rather than on the pharmaceutical industry or the regulatory authorities. These are exciting times in relation to the development of medicines for children but it is essential that the safety of children in clinical trials is paramount.

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Falling necropsy rates

Falling necropsy rates and risks to public health

W Squier, J Ironside

Perspective on the paper by Verity *et al* (see page 608)

Dr Verity and his colleagues publish the results of their continuing study of progressive intellectual and neurological deterioration (PIND) in childhood¹. The most surprising aspect of this study is the low rate of necropsies in this carefully followed group of children; only four of the 46

deaths were examined after death. This is an obstacle to detection of variant CJD (vCJD). Although most of this group of children had undergone investigations in life that allow a "probable" diagnosis to be made in the adult population, detailed neuropathological study remains the only way to confirm this

diagnosis. Although the annual incidence of new cases of variant CJD has declined overall since 1999, more onsets have been observed in 2004 than in 2003, suggesting that it is premature to assume that this disease will soon disappear.² Furthermore, the age specific incidence of variant CJD has remained essentially unchanged since the disorder was first described in 1996, reinforcing the need for continued paediatric surveillance.

While this low necropsy rate has serious implications for public health and for understanding of the epidemiology of vCJD, there are far wider implications. PIND is heterogeneous and 92 children (almost 10% of the study group) had no diagnosis; half of these died. They never will have a diagnosis. How will we begin to understand the nature of their disease? How can we prevent it?

WHY WERE NECROPSY RATES SO LOW?

Surely any parent who has watched their child succumb to such a slow and distressing syndrome must want a diagnosis in its own right, as well as to know any risks to siblings and their offspring. The authors did not have contact with the families so we do not know how often necropsy was requested or how the approach was made. There is no doubt, however, that these children and their families must have developed a close relation with their medical carers, where trust and confidence should favour consent for necropsy. In this context, it is interesting to note that in 2005, necropsy rates in adults with suspected sporadic and variant CJD in UK were 71% and 50%, respectively. The referral system for these patients to the National CJD Surveillance Unit allows early contact with local clinicians and the families, so a relationship can be formed which incorporates discussion of complex issues including necropsy and the benefits that it might bring for the families and for a better understanding of these devastating diseases. In these cases there is a very high suspicion of CJD at death, a major difference from the PIND study where the diagnosis was much less certain at death.

In general terms there are three potential reasons for low necropsy rates: reluctance of clinicians to request necropsies, reluctance of families to give consent, and inadequate paediatric pathology services to fulfil the demand. In England we have particular problems and this article specifically relates to them. We are still working in the shadow of the organ retention "scandal" of early 2001 and now must consider how three recent changes in the law prompted by it—the Human Tissue Act 2004 (to come into force from September 2006),³ the amendments to the coroners' rules of June 2005,⁴ and the National Organ Group litigation trial of January 2004⁵—may influence our ability to make complex diagnoses.

Comparison with other European countries is complex owing to the differing legal requirements in each country; although there seems to have been a widespread fall in necropsy rates, this is not always related to the organ retention problem. In Scotland a proactive approach to seeking consent has resulted in an increase in the rate of necropsies, at least in babies and children.

THE ROLE OF THE CLINICIAN IN REQUESTING CONSENT FOR NECROPSY

The Human Tissue Act, quite appropriately, makes consent central to carrying out necropsies and to the subsequent

use, handling, and disposal of retained material. Obtaining consent is "*part of the responsibility of the treating clinician*" and that person "*must have sufficient knowledge of the proposed treatment and intended use of the tissue, such as for research, and understand the risks involved, in order to be able to provide any information the patient or relative may require*". It would not be surprising if clinicians did not want to be involved in this process. It is time consuming and difficult; the family must be handled with utmost sensitivity, and, while it is incumbent upon the clinician to provide information, there must be a very fine judgement regarding just how much information is needed by any particular family. Many recently bereaved people simply do not want to know all the details that the Act requires us to be prepared to impart.

The new Act dictates that anyone taking consent "*should be sufficiently senior and well informed, with a thorough knowledge of the procedure*"... "*have been trained in the management of bereavement*" and "*should have witnessed a postmortem examination*". Many clinicians have never seen a necropsy and may not wish to; that is why they are clinicians, not pathologists.

Witnessing a necropsy will leave them unfamiliar with many processes: neuro-pathological examination requires a brain to be fixed, photographed, sliced, blocks taken, and multiple staining procedures carried out. The use of tissue for audit, teaching, or research and subsequent disposal options must be considered. This is a new departure in terms of consent, and satisfying GMC guidelines⁶ will require considerable training. How many clinicians will want to do this? A more sinister consideration is the legal precedent set in 2004 in the organ retention group litigation trial. Justice Gage found a breach of duty by *clinicians* in their failure to explain organ retention,⁵ implying that in future clinicians could be responsible for the actions of pathologists, possibly many years later.

WHO ELSE CAN CONTRIBUTE TO OBTAINING CONSENT?

The Act allows for delegation to, for example, a "*dedicated transplant coordinator or a member of a bereavement service team*". This approach has proven very successful in various centres with both clinicians and families, but it requires sufficient resources and appropriately trained staff in order to function effectively. Some pathologists may wish to become involved. Again, where pathologists have had the time and enthusiasm for the task⁷ this has worked well. Perhaps surprisingly, several parents

have expressed their reassurance at meeting the pathologist carrying out the necropsy. As one mother said, "The autopsy was the first time our baby was in the care of someone we did not know". The logistics of involving the pathologist become problematic when the necropsy is being carried out in another hospital distant from the place where the baby died. This is happening increasingly as paediatric pathology departments close and the national service is overstretched; and it is quite usual for brains to have to be referred to specialist neuropathology departments far afield.

WHY DO PARENTS REFUSE CONSENT?

The greatest negative influence must be the adverse publicity that surrounded the retained organs scandal in early 2001. This left the public misinformed and fearful and pathologists feeling demonised. Educating the public about the processes and benefits to be gained from postmortem studies is an uphill struggle. The media do not want to know about the important information and scientific advances that have arisen as a result of necropsies: pathology simply isn't "sexy".

An explanation of the reasons for necropsy has almost uniformly softened the anger of the families we have met since 2000 in the context of an organ retention inquiry. They have been comforted to know that we have learned from their babies and that our knowledge informs clinicians who help other children. "So his little life wasn't all in vain" one mother said. But it may take months or years after a death for parents to be able to understand this and by then it is, of course, far too late for necropsy. The clinician seeking consent has, we believe, a duty to inform families of the potential benefits to them in learning the diagnosis, in understanding the risks for surviving children, and for genetic counselling for further children. While this may smack of the old "paternalistic" approach to consent, we on the contrary consider it amounts to negligence to deny the family sufficient information regarding these potential benefits of necropsy.

Amendments to the coroners' rules of June 2005 stipulate that consent must be obtained for retention of tissues beyond the coroner's purpose ("cause of death") and for teaching, research, or any other use. Families must be consulted, ideally before the necropsy, but again who will do this? The coroners' officers are often not trained, nor are they paid to perform this role, and it is generally in their interests to get the necropsy over and the paperwork completed as soon as

possible; protracted procedures and delayed reports are a hassle, and teaching and research are not relevant to them. One possible solution would be a bereavement officer who could act as an independent agent to discuss these issues with families, but the question of resources is again an issue here

INADEQUATE PATHOLOGY RESOURCES

Paediatric pathology continues to be understaffed. Today 30% of consultant posts remain unfilled and in the last few years whole departments have been lost. Following the closure of the paediatric pathology department in one of our major teaching hospitals, regional services are in chaos with cases being shipped many miles for necropsy with all the undesirable and potentially dangerous consequences. Recruitment to pathology in general is a problem in other European countries, although paediatric pathology is not recognised as an independent speciality throughout

Europe, so the specific problems for this discipline are not readily identifiable.

We hope the new legislation will make legal requirements clearer, prevent misunderstandings, and serve to reassure the public that necropsy practices are more closely regulated. It puts responsibility for consent firmly on the shoulders of clinicians who, in turn, need to be trained, and indeed will, it seems, be accountable for the actions of pathologists. This leads to the inevitable conclusion that studies such as this can only achieve higher necropsy rates if the clinicians involved actively seek consent for necropsies and brain retention. The days immediately after death are not a good time to discuss these matters and in studies such as this, the process can begin long before death so that the family have time to consider their feelings and wishes.

And then we need sufficient paediatric pathologists and neuropathologists to do the work.

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ARCHIVIST

Trying to diagnose meningococcal disease earlier

One Monday morning several years ago I had a telephone call from an acquaintance who told me that his 3 year old son had been seen by his GP over the weekend because of a feverish illness and had now come out in some red-blue spots. The child survived, but only after some very worrying days in the intensive care unit.

Mortality among children in hospital with meningococcal disease has been related to lack of paediatric care, inadequate supervision of junior staff, and inadequate use of inotropes (*BMJ* 2005;**330**:1475–8). Now the same study population has provided data about pre-hospital features (Matthew J Thompson, Nelly Ninis, and colleagues. *Lancet* 2006;**367**:397–403; see also Comment; *ibid*: 371–2).

Data were collected from primary care records and parent-completed questionnaires about 448 children with meningococcal disease in England, Wales, and Northern Ireland in a 15-month period beginning 1 December 1997. The early features (first 4–6 hours) were usually non-specific with fever and irritability prominent among preschool children and headache at later ages. The classical signs and symptoms came later; drowsiness at an average of 7 hours, haemorrhagic rash, meningism, photophobia, and confusion or delirium at 13–16 hours, and loss of consciousness at 22 hours. These researchers stress the importance of what they call early signs of sepsis (cold hands and feet, leg pains, and abnormal (pale or mottled) skin colour). At least one of these signs was present in 72% of the children at a median of 8 hours, on average 4 hours before being first seen by a GP.

Leg pains, cold hands and feet and abnormal skin colour may be relatively early signs of meningococcal disease but they do not solve the dilemma. Should all children with these features be sent to hospital right away or would that be alarming and unnecessary? We do not know the predictive values of such features. Thompson, Nellis, and colleagues suggest that they are likely to be of high diagnostic value because parents rarely report them to primary care doctors. They seem to imply that these symptoms and signs should indicate admission but stop short of giving that advice. It is suggested that a doctor in doubt should review the situation in 4–6 hours, but if the child does have meningococcal disease such a delay could be dangerous. The GP's, or casualty officer's, dilemma is real. Any child with a recent onset fever could be brewing meningococcal disease (just as any baby with the snuffles could be heading for SIDS). Admitting all such children to hospital immediately would be neither possible nor desirable but I would never criticise a GP for sending a child in. Sometimes it must almost seem as if the only other option is crossed fingers and a hope for the best.

General publicity given to the early signs of sepsis may get children to a doctor quicker but what the doctor should then do seems uncertain. Perhaps more research along these lines will give rise to clearer guidance. The real solution though would be a quick, easy, and reliable test for early meningococcal disease.