Witness Statement Ref. No. 277/1

NAME OF CHILD: RAYCHEL FERGUSON (LUCY CRAWFORD)

Name: John Leckey

Title: Mr.

Present position and institution:

Senior Coroner for Northern Ireland

Previous position and institution: Her Majesty's Coroner for Greater Belfast
[As at the time of the child's death]

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 2000 – August 2012]

None

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

25/1/05

OFFICIAL USE:
List of previous statements, depositions and reports attached:

Ref:	Date:	
115-034-001	25/1/2005	Statement to PSNI

IMPORTANT INSTRUCTIONS FOR ANSWERING:

Please attach additional sheets if more space is required. Please identify clearly any document to which you refer or rely upon for your answer. If the document has an Inquiry reference number, e.g. Ref: 049-001-001 which is 'Chart No.1 Old Notes', then please provide that number.

If the document does not have an Inquiry reference number, then please provide a copy of the document attached

I. Questions Arising out of Your Statement to the Inquest [Ref: 013-004-006]

(1) ***"On 14th April 2000 Dr. Donncha Hanrahan, who is a Consultant in Paediatric Neurology at the Royal Belfast Hospital for Sick Children, telephoned my office to report the death of Lucy Crawford aged 17 months. Lucy had died that day in the hospital's Paediatric Intensive Care Unit following transfer from the Erne Hospital the previous day."*** **[Ref: 013-004-006]**

Arising out of the foregoing:

(a) Have you ever established the reason(s) why Dr. Hanrahan notified your office of the death of Lucy Crawford?

Dr Hanrahan deals with this in his statement.

(b) If so, please explain your understanding of his reason(s) for notifying your office of Lucy's death?

I assume it was because he was uncertain as to the cause of death or whether it was appropriate for him to issue a Death Certificate or whether the death should be the subject of a coronial investigation.

(2) ***"The clinical history given was of gastroenteritis, dehydration and brain swelling."*** **[Ref: 013-004-006]**

Arising out of the foregoing:

(a) It is the Inquiry's understanding that a note of this clinical history was made by Mrs. Dennison of your office. The note appears at [Ref: 013-053a-290]. Please confirm that this is also your understanding.

That is correct.

(b) Having been notified of Lucy Crawford's death, what procedures did you expect Mrs. Dennison to follow, and what steps did you expect her to take pursuant to those procedures?

Mrs Dennison [013-053a-290] acted in an appropriate manner and if I had been there I too would have suggested that Dr Hanrahan speak to the State Pathologist's Department.

(c) Insofar as you are aware, did Mrs. Dennison inform any other person(s) about the death of Lucy Crawford? If so, who did she inform?

I do not know.

(d) **If Mrs. Dennison informed you about the death of Lucy Crawford, please address the following:**

I cannot recall.

(i) **When did she inform you of the death?**

(ii) **What did she tell you about the death?**

(iii) **What steps did you take, having been told about the death?**

(3) *"Advice was then sought from a pathologist attached to the State Pathologist's Department as to whether the clinical history warranted a coroner's post-mortem examination being carried out. Following a consultation between the pathologist and Dr. Hanrahan my office was advised that it would be appropriate for a death certificate to be issued giving gastroenteritis as the cause of death."* **[Ref: 013-004-006]**

Arising out of the foregoing:

(a) **Describe the arrangements which were in place in April 2000 by which advice could be obtained from a pathologist in the State Pathologist's Department, and in particular state:**

At that time, and it remains the position, if a death is reported where the medical background is complex and it is not clear to either a Coroner or the staff whether it is appropriate for the death to be dealt with by the issue of a Death Certificate, the Pro Forma system or a Coroner's post-mortem, the advice of a pathologist in the State Pathologist's Department would be sought. For your information I am enclosing a copy of an article by the first Northern Ireland State Pathologist, Professor T K Marshall published in Medicine, Science and the Law, April 1968. This article explains the rationale for the establishment of the State Pathologist's Department, what it does and the fact that it provides a service to Coroners.

(i) **Why were those arrangements in place?**

(ii) **What was the function or purpose of those arrangements?**

(iii) **How did those arrangements operate in practice?**

(iv) **Were the arrangements the subject of any guidance, procedure or protocol, whether formal or informal?**

(v) **Were those arrangements supervised by your office in any way?**

(vi) **Do those arrangements remain in place?**

(b) Please identify the person who sought advice from the pathologist at the State Pathologist's Office?

I understand this was Dr Hanrahan.

(c) Who reached the view that a consultation between the pathologist and Dr. Hanrahan was necessary?

Mrs Dennison made the correct decision that it would be appropriate that Dr Hanrahan spoke to the State Pathologist's Department.

(d) What was the purpose of this consultation?

It would enable two medical professionals to consider the medical background to the death.

(e) Who made the arrangements for the consultation which took place between the pathologist and Dr. Hanrahan?

I presume Dr Hanrahan telephoned the pathologist direct.

(f) Please confirm that the pathologist who engaged in a consultation with Dr. Hanrahan was Dr. Mike Curtis?

Confirmed.

(g) On whose behalf was the pathologist acting when he engaged with Dr. Hanrahan in a consultation?

The pathologist would have been acting on my behalf as HM Coroner for Greater Belfast.

(h) Clarify whether the pathologist was providing advice to your office or to Dr. Hanrahan?

Both.

(i) Why was it necessary to obtain advice from a pathologist in this case?

The medical background to the death was complex.

(j) Were you or any member of your office a party to the discussions that took place between the pathologist and Dr. Hanrahan?

Not as far as I can recall.

(k) Arising out of the consultation which took place between the pathologist and Dr. Hanrahan, what advice or further information, if any, was provided to your office, and state:

I am unaware of any.

(i) Who provided this advice or further information to your office?

(ii) **Who received this advice or further information on behalf of your office?**

(iii) **When was it received?**

(iv) **What action, if any, was taken by any of your staff on foot of receiving this advice or further information?**

(l) **Who advised your office that it would be appropriate to issue a death certificate giving gastroenteritis as the cause of death?**

It appears from Mrs Dennison's statement that Dr Curtis advised her that in his view the issue of a Death Certificate would be appropriate.

(m) **Who in your office was given the advice that it would be appropriate to issue a death certificate giving gastroenteritis as the cause of death?**

I presume Mrs Dennison.

(n) **Was your office provided with any reasons or explanation to support the advice that it was appropriate to issue a death certificate giving gastroenteritis as the cause of death?**

Not that I am aware of.

If so,

(i) **What were those reasons or explanation?**

(ii) **Who provided the reasons or explanation to your office?**

(iii) **When were those reasons or explanation provided?**

(o) **Were you personally informed of the advice that it was appropriate to issue a death certificate giving gastroenteritis as the cause of death, or were you given any other information arising out of the consultation between the pathologist and Dr. Hanrahan?**

I cannot recall.

If so,

(i) **What information were you given?**

(ii) **Who gave you this information?**

(iii) **When were you given this information?**

(iv) **Did you make any decision or take any action on foot of receiving this information?**

II. Questions Arising out of Your Statement to the PSNI [Ref: 115-034-001]

(4) *"I personally did not take the telephone call from Dr. Hanrahan and I believe he spoke to a member of my staff called Maureen Dennison. From the note on the file it appears that he was asked to discuss the case with Dr. Mike Curtis, Assistant State Pathologist, to see whether it would be appropriate for a death certificate to be issued. The note on the file indicates that this conversation did take place and my office was subsequently advised that a death certificate would be issued giving gastroenteritis as the cause of death."* **[Ref: 115-034-001]**

Arising out of the foregoing:

(a) Why did you not take the telephone call from Dr. Hanrahan?

I presume this was because I was not in the office at the time Dr Hanrahan telephoned.

(b) Were you or a Deputy Coroner available to be contacted at the time when the death of Lucy Crawford was reported to your office? If not, please explain why you or a Deputy Coroner were not available to be contacted at that time?

It was impossible, and that remains the position, for me to be in the office available to take telephone calls at all times during office hours.

(c) Were you or a Deputy Coroner contacted by your office to be informed that the death of Lucy Crawford had been reported?

I cannot recall.

(d) On what date was your office advised that a death certificate would be issued giving gastroenteritis as the cause of death?

See the statement of Mrs Dennison.

(e) Who advised your office that a death certificate would be issued giving gastroenteritis as the cause of death?

See the statement of Mrs Dennison.

(f) Was the advice that a death certificate would be issued giving gastroenteritis as the cause of death brought to your attention?

I cannot recall.

If so, please state,

(i) When was this information brought to your attention?

(ii) Who brought this information to your attention?

(g) In general, what role would your office play in determining whether a death certificate should be issued in relation to a death reported to your office?

Some 14,000 - 14,500 persons die each year in Northern Ireland and during my time as Coroner between 3,500 and 4,300 deaths are referred to my office.

In many instances this is not because the death needs to' be subject of a coronial investigation but because the medical practitioner wants reassurance that it is appropriate to issue a Death Certificate or wishes to check that the death does not necessitate a Coroner's post-mortem or is uncertain how to formulate the cause of death. Now that the Coroners Service has a full-time Medical Advisor in post it is much easier to give that advice. Before a Medical Advisor was in post it would be usual for the Coroner or a member of the staff to contact the State Pathologist's Department for advice if that was considered necessary.

(h) Was the advice that a death certificate would be issued giving gastroenteritis as the cause of death, the subject of any scrutiny by you or your office?

Please refer to the statement of Mrs Dennison.

(i) Did you direct that a death certificate could be issued in this case?

Dr Hanrahan took the decision that he could issue a Death Certificate. You should appreciate that although it is not unusual for Medical Practitioners to be asked to speak to the State Pathologist's Department that does not mean that the Medical Practitioner will always accept the views of the Pathologist. Following such a consultation the Medical Practitioner may refuse to deal with the death in any way and that then necessitates a Coroner's post-mortem examination.

(j) If you did not direct that a death certificate could be issued in this case, should a death certificate have been issued?

The decision about the issue of a Death Certificate was made by Dr Hanrahan.

(5) *"As far as I was concerned this was a natural death and no concerns about the appropriateness of a death certificate being issued giving gastroenteritis as the cause of death were raised by anyone, medical staff or the parents of Lucy."* **[Ref: 115-034-001]**

This has already been dealt with in the statements of myself and Mrs Dennison.

(a) What information did you personally receive that led you to the view that this was a natural death, and that it was appropriate to issue a death certificate giving gastroenteritis as the cause of death?

(b) When did you receive this information?

(c) Who provided you with this information?

(6) *"It was only when I read Mr. Miller's letter that I became aware that in fact a post-mortem examination had been carried out later by a consultant paediatric pathologist attached to the Royal Victoria Hospital. This was not a coroner's post-mortem but a "consent" post-mortem for which I assume the consent of Lucy's parents was sought and obtained. I then obtained a copy of the post-mortem report and considered the findings of the pathologist. These indicated to me that*

the deaths of Raychel and Lucy might have common features and that it would be necessary to obtain a further specialist report. With the benefit of hindsight, it would have been helpful if I had been advised of the post-mortem findings at an early stage." **[Ref: 013-004-006 & -007]**

Arising out of the foregoing:

(a) In April 2000, did you give any consideration to whether a post-mortem examination should be ordered?

Consent post-mortems routinely take place without that fact being brought to the attention of a Coroner. That is entirely appropriate and Coroners should be involved only if there is a statutory requirement for that. It is always open to a Pathologist carrying out a "consent" post-mortem to report the death to the Coroner if he believes there are reasons for doing so. The late Dr Dennis O 'Hara was a very experienced and highly regarded Paediatric Pathologist who during his career had performed many Coroners' post-mortem examinations. He concluded that the cause of Lucy's death was Cerebral Oedema and he did not give any underlying cause for that. However in the commentary section of his report he did mention that Lucy had been hyponatraemic. With the benefit of hindsight that fact might have been a reason for him to report the death to my office and ask that the "consent" postmortem be made a Coroner's post-mortem. If he had done so that would have been agreed to.

(b) If so, what information did you take into account when considering this issue?

(c) Why did you not order a post mortem examination in the case of Lucy Crawford?

(d) Should you have been informed in April 2000 that it was intended to seek the consent of the parents of Lucy Crawford to conduct a post-mortem?

(e) If so, please explain why or on what basis you believe that you should have been informed of this?

(f) Specify the findings of the pathologist which indicated to you that the deaths of Raychel and Lucy might have common features.

(g) Should you have been informed in 2000 of the findings which the pathologist (Dr. M.D. O'Hara) made?

(h) If so, please explain why or on what basis you should have been informed of those findings?

(7) *"Dr. Hanrahan did report the death promptly to my office and did consult with the assistant state pathologist. I assume that neither was able to identify inappropriate fluid management as the underlying cause of Lucy's death."* **[Ref: 115-034-003]**

Arising out of the foregoing:

(a) Please clarify the basis for your assumption that neither Dr. Hanrahan nor Dr. Curtis were able to identify inappropriate fluid management as the underlying cause of Lucy's death.

I assumed that if either Dr Hanrahan or Dr Curtis had identified inappropriate fluid management then Dr Hanrahan would have declined to issue a Death Certificate and Dr Curtis would have advised that the death should be the subject of a Coroner's post-mortem. That is a matter for Dr Hanrahan and Dr Curtis to comment on.

(8) *"However, I would wish to draw attention to the fact that shortly after I received the letter from Mr. Millar, I wrote to Lucy's parents explaining my involvement, I wrote to Professor Crane, the state pathologist about the conversation between Dr. Hanrahan and Dr. Curtis and the subsequent issuing of a death certificate and I wrote to the Chief Medical Officer, Dr. Henrietta Campbell, informing her of the concerns raised by Mr. Millar."* **[Ref: 115-034-002]**

Arising out of the foregoing:

(a) It would appear that you wrote to Professor Crane on the 11 March 2003 [Ref: 013-060] and 24 April 2003 [Ref: 013-060a]. Did you receive a response to this correspondence? If so, please provide the Inquiry with a copy of Professor Crane's response.

(b) In your correspondence to Professor Crane you proposed meeting with him to discuss your concerns that when deaths of children are reported to your office the proper questions may not be asked. Did such a meeting take place? If not, please explain why it did not take place.

(c) If such a meeting did take place, please address the following:

(i) When did the meeting take place?

(ii) Who attended the meeting?

(iii) What issues were discussed at the meeting?

(iv) Did the meeting lead to any changes in the practice of your office in terms of how reports of deaths involving children are handled? If so, what changes were initiated?

(d) Please explain what you meant when you said in your letter to Professor Crane that,

"My concern is that when deaths of children in particular are reported to my office <u>the proper questions may not be asked.</u> There is now a concern that other Hyponatraemia related deaths may not have been picked up." **[Ref: 013-060-374] Emphasis added**

(e) When the death of Lucy Crawford was reported to your office do you consider that the proper questions were directed to Dr. Hanrahan? Please fully explain your view.

(f) You have indicated that you wrote to Dr. Henrietta Campbell (Chief Medical Officer) after receiving Mr. Millar's letter. Please provide the Inquiry with your correspondence to Dr. Campbell and any response which you received from her.

I have provided you with a copy of my file and all correspondence is available for you to inspect and consider. Having said that I cannot recall any meeting having taken place. My reference to "the proper questions may not be asked" refers to the fact that the cause and effects of hyponatraemia appeared to me to be not known within the broad medical

profession beyond the speciality of paediatric anaesthesia. I would refer you to the penultimate paragraph of my letter to Professor Crane of 11th March 2003 [Ref: 013-060] when I refer to what Dr Sumner said on this issue. I do not know the content of the conversation between Dr Hanrahan and Dr Curtis. In relation to Dr Henrietta Camp bell I assume you have this correspondence as I made available to you all my files. The copy file you have provided me with contains copies of my correspondence with Dr Henrietta Campbell and in particular I would refer you to my letter to her of 22nd March 2004. Also, I am enclosing a copy of her letter to me of 28th June 2004.

Finally, I would wish to emphasise my ongoing concern that the "message" relating to how hyponatraemia might arise and how it may be avoided should be appropriately disseminated and targeted. Dr Sumner felt the best conduit for that was the journal of Paediatric Anaesthesia of which he was editor and my recollection is that he wrote an editorial and Professor Arieff an article.
Also, I am enclosing correspondence I received from Dr John Jenkins, Dr Ian Carson and Mr Peter Walby together with the copy articles they refer to. There was no obvious method of ensuring effective delivery of the "message".

Finally, I would draw two matters to your attention:-

(1) The chart relating to hyponatraemia that is currently displayed in hospitals throughout Northern Ireland was approved by Dr Edward Sumner. He had been approached by the then Chief Medical Officer, Dr Henrietta Campbell.

(2) Dr Sumner quite candidly told me that his views in relation to hyponatraemia would not necessarily be the views of other paediatric anaesthestists - even those who were colleagues in Great Ormond Street Hospital for Children along with him. Also, I have recollection of him telling me that any deficiencies in knowledge of hyponatraemia (whether cause, prevention or management) were not unique to N Ireland and would be UK wide.

(9) *"At the time Mr. Millar wrote to me I was aware that Dr. O'Hara was terminally ill and because of that I saw little point in making it an issue with him. However, my view is that he should have referred Lucy's death to my office with a request that I direct that the post-mortem examination he conducted should become a coroner's post-mortem examination rather than consent post-mortem examination. Also in my view a duty to report was imposed no (sic) doctors at the Erne Hospital who would have been aware that when Lucy left the Erne Hospital for transfer to the Royal Belfast Hospital for Sick Children she was in a moribund state."* **[Ref: 115-034-003]**

Arising out of the foregoing:

(a) What factors did you take into account when reaching the conclusion that Dr. O'Hara should have referred Lucy's death to you with a request that the post-mortem examination should become a coroner's post-mortem?

I have already dealt with this.

(b) What factors did you take into account when reaching the view that doctors at the Erne Hospital should have reported Lucy's death to your office.

In my view following the results of the consent post-mortem examination it would have been open to either Dr O'Hara or the medical staff at the Erne Hospital to report Lucy's death for the purpose of a coronial investigation.

III. Other

(10) **In his letter to you of the 27 February 2003 Mr. Millar explained:**
"In my supporting role I arranged for the parents to meet the Consultant Pathologist who conducted the P.M. I also contacted the Coroner's Service to ask about the arrangement of an Inquest but I was told it was not necessary." **[013-056-320]**

Arising out of the foregoing:

I have no recollection about this.

(a) **Did you take any steps to investigate the circumstances in which Mr. Millar was told by the Coroner's Service that an Inquest was not necessary?**

(b) **If so, please explain what steps you took to investigate this issue and outline any findings that you reached.**

(11) **Was there, insofar as you are aware, a pathologist with expertise in paediatric pathology on the list of pathologists furnished to coroners under section 26 of the Coroners Act (Northern Ireland) 1959 at the time of Lucy's death?**

Dr O'Hara was the senior Paediatric Pathologist at that time and was on the list of pathologists authorised to conduct post-mortems for Coroners.

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: John L. Loughrey **Dated:** 26/10/12

A NATIONAL FORENSIC PATHOLOGY SERVICE—THE NORTHERN IRELAND SOLUTION

By
T. K. MARSHALL

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A NATIONAL FORENSIC PATHOLOGY SERVICE
THE NORTHERN IRELAND SOLUTION

T. K. MARSHALL *

THE Editorial entitled "Decline and Fall" in a recent issue of the *Journal of the Forensic Science Society* (1967, **7**, 121) draws attention to the considerable disquiet felt by many over the position of forensic pathology in England. The present situation was foreseen as early as 1951 when Professor John Glaister in his address to the British Association in Forensic Medicine (*British Medical Journal*, 1952, ii, 473) talked of the difficulties which would arise out of the exclusion of forensic medicine from the newly formed state medical service and the absence of any provisions for the specialists practising the subject. He drew attention to the effect this would have on the recruitment of suitable doctors to the specialty but his remarks caused little reaction; as Professor Glaister himself suggested, "Perhaps there is small desire to change the existing position. Some of us who have worked long under the old régime are unlikely to savour the fruits of any changes."

Since then, as the Editorial pointed out, forensic medicine has declined as an undergraduate university subject; some university departments have been demoted and others abolished. No blame can be attached to the universities. Their only need is to teach undergraduates the essentials of forensic medicine and an adequate course of lectures can be provided for much less cost than it takes to maintain an independent department. The universities can claim with considerable justification that the provision of forensic medicine for the community is not their concern and when money is short and new medical specialties are clamouring for recognition or upgrading, they would be wrong to spend funds in this way; if the country requires a forensic pathology service, it is up to the Government to provide it, or at least pay for it.

However, as is well known, the Government has so far made no provisions for a co-ordinated forensic pathology service. The extent of its participation has been to approve certain pathologists as competent to undertake major medico-legal cases and recommend these Home Office Pathologists, so-called, to coroners and police as the best people to be contacted when faced with a death under criminal circumstances. This is the cheapest way that the Government can discharge its obligations. There are no salaries to be paid; the pathologists might accept a small retaining fee but their principal remuneration comes from the fees charged for each case. There are no buildings to be kept up; the pathologists are already housed in hospital laboratories or in university premises. There are no secretaries and technicians to pay; their work is done by the staff of the hospitals or universities. There are no mortuaries to be provided and staffed; these are the concern of the local authorities. Nevertheless the cheapness of the service is more apparent than real; the present arrangements cost a fair amount of money but by allowing others to pay, the Government has little to find from its own coffers.

One might ask where the drawbacks lie. What matter that the cost is spread provided a good service is furnished? To answer this, one must ask what kind of service the country needs. There are, it seems, about 80,000 coroner's autopsies carried out every year. Over half of these are sudden natural deaths, some others are accidents and rather less are suicides. Homicides form a relatively small proportion. The majority of cases, it has been argued, can be undertaken by consultant pathologists working in the National Health Service but there are still a sizeable number of difficult or criminal cases which require pathologists with special forensic training and with time to devote to court work. This view has been practically unanimously propounded in the last two years; the deliberations of the

* M.D., M.C.Path., State Pathologist, Northern Ireland.

Broderick Committee have stimulated all interested bodies to discuss this very matter and the British Association in Forensic Medicine, the British Medical Association, the College of Pathologists and the Association of Clinical Pathologists have, in their independent recommendations, come out firmly in favour of a two-tier structure whereby the routine coroner's work is undertaken by hospital pathologists and the more serious medico-legal cases by those specially trained in forensic medicine.

If this is the best way of organising a medico-legal service, how far short do the present arrangements fall? There is no real problem with the ordinary work; there are probably enough volunteers among the hospital pathologists since the fees, which are additional to their salaries, provide a useful stimulus. Any shortcomings at present in training and experience could easily be rectified by the professional organisations. What causes alarm amongst those working in the field is the present dearth of trainees for the specialist tier and the difficulty which will soon arise when, with the retirement of the older men, new specialists have to be provided. *This is the crux of the present problem which has now reached the stage of an emergency. Unfortunately it is an emergency which is difficult to impress on administrators and legislators not directly concerned with the actual practice of forensic pathology.*

When the matter has been aired in the past, the main point—new arrangements for the continued supply of sufficient experts—has been lost in the confusion with other related, but subsidiary, matters such as the decline in status of university forensic medicine departments. The gradual atrophy of academic forensic medicine is certainly to be regretted, but the practical importance of the extinction of university departments is the effect it has on the provision of specialists. There is no other place in which young doctors can receive training. Without a supply of specialists from the university departments, the country will have to rely on hospital pathologists, experienced in other fields, but largely self-taught in forensic matters. Even their own organisations, by advocating the two-tier system, infer that they should not shoulder major medico-legal work.

The urgent need to train some new specialists is intimately connected with the need for a recognised service in which they can work once they are trained. There is none at the moment. In the past the universities have provided a niche for them, but if these departments disappear there is no alternative. Consequently, at present, a would-be recruit would be ill-advised to enter the speciality, as he cannot be guaranteed a career. A number who have undertaken some training have already emigrated or changed to another field of medicine due to lack of prospects in the future. There is now the position in England where there is but a handful of trained specialists and next to no young recruits. If present policy is maintained, forensic pathologists will become fewer, until fairly soon, as the Editorial put it so graphically, the police are "going to find themselves standing alone in that muddy field."

A solution must be found, and in this context the arrangements recently made for forensic pathology in Northern Ireland might be of interest. The provision of a service to coroners in Northern Ireland posed problems similar to those in England, but they were tackled by the Northern Ireland Government in a fundamental fashion, and the resulting system has much to commend it.

The opportunity to make radical improvements came in 1959 with the introduction of a new Coroners Act. There are sixteen part-time coroners, seven doctors and nine solicitors, dealing with about 1,800 cases a year. The Act limited all future coronerships to practising lawyers, but this necessitated the provision of a forensic pathology service. This was instituted by the appointment of a State Pathologist in 1958 whilst the Coroners Bill was going through its draft stages. The appointment was made jointly by the Ministry of Home Affairs, the University and the Northern Ireland Hospitals Authority, the University offering the holder a lectureship in the Department of Pathology, and the position of consultant was offered by the Hospitals Authority. The University undertook to deal with the day-to-day administration. The State Pathologist was paid by the University on the scale applying to lecturers with special responsibility, but the University only contributed a quarter of the salary itself; half the salary was recouped from the Ministry and the other quarter from the Hospitals Authority. The University provided office and laboratory

accommodation in the Institute of Pathology, but the secretary and technician were paid through the University by the Ministry. This arrangement worked very well. The Ministry met the bulk of the cost, but with the day-to-day control in the hands of the University, the State Pathologist obtained an overt independence of police and state.

Since those early days, the work has increased. The number of autopsies has risen to about 1,300 a year, lectures are now given to medical students (thirty lectures), dental students (six lectures), law students (six lectures) and a variable number at medical postgraduate courses, to nurses in training and at courses organised by the Royal College of Nursing. A good liaison has been developed with the hospital, and it is not uncommon for clinicians to request an examination of an injured patient from a medico-legal viewpoint. This extra work has required more staff. Three more pathologists have been appointed, together with two more secretaries and two more technicians. Plans are now afoot for building a new public mortuary, forensic pathology laboratories and offices in University grounds within the Hospital complex.

All the staff are now paid by the Ministry of Home Affairs through the University. The appointments held by the pathologists have recently been revised, and the grading and salary scales chosen were those of the Health Service.

The salary of the State Pathologist is now that of a consultant in the Health Service. His University appointment has become that of a part-time Senior Lecturer, for which he receives an honorarium. His consultant appointment in the hospitals service is now entirely honorary. The status of the Deputy State Pathologist has also been accepted as of consultant rank, but his salary scale has been fixed at slightly less than that of a consultant so as to produce a differential between it and the State Pathologist's scale. This is a standard civil service manoeuvre, though one which has not been accepted without strong protest. He, too, receives an honorarium from the University, having been appointed a part-time Lecturer, and he holds an honorary consultant post in the Hospitals Authority.

The two remaining posts, for trainees, received careful consideration. The Ministry agreed that if good graduates were to be recruited to these posts it was necessary that they were given a salary which had a sufficiently high maximum to satisfy them once they had been trained. Otherwise the same situation as at present in England would exist; potential recruits would be diverted to other specialities due to lack of a career future after the period of training. Consequently these two posts were given salary scales starting at that of Senior House Officer and rising through the Registrar and Senior Registrar salaries to the maximum of the Medical Assistant. Once this had been decided and a settled future had been provided, there was no difficulty in filling the posts.

This team of four is now likely to be the definitive one for some time. The members are full-time salaried people. This enables them to investigate their cases adequately and it abolishes their dependence on the good will of coroners for their income. One hears reports that some English coroners would oppose having to employ a state pathology service because, by not being able to choose their own pathologist, they would lose control over his proficiency, his competency as a witness and of the service he provides. These fears are groundless; in a full-time service considerable thought is given to the choice of entrants and their training is supervised, systematic and thorough. There is no reason why English coroners should not find it entirely satisfactory.

The forensic pathology service in Northern Ireland is exclusively for coroners and is available at all hours, every day. The number of autopsies is not too great and so the service deals with the whole range from natural deaths to homicides. Some hospital deaths reported to coroners are investigated by the hospital pathologists but their number is less than 10 per cent. of the total coroners' autopsy work. Because coroners are part-time and now mainly non-medical, the investigations carried out by the forensic pathologist are intended to give information to the coroner, not only about the *cause* of death but *on all the medical aspects* of the case. In order to do this the pathologist might visit the scene of death, interview relatives, witnesses, doctors and nurses, consult hospital case notes and statements made to the police. No charge is made for the investigation and the expenses of travelling and subsistence are borne by the Government.

The way in which our system works in practice is best appreciated by following step by step the course of events after a sudden or violent death has occurred. In about 30 per cent. of these cases, the coroner is satisfied by a doctor that the cause of death is known and that it is natural; he can then close his inquiries by issuing a burial order and sending the necessary particulars to the Registrar of Births and Deaths. In 70 per cent. of these cases, however, he asks the police to investigate and orders an autopsy.

The participation of the police is a statutory one under the Coroners Act. They must make inquiries and furnish the coroner with a report. In actual fact the police have a wider administrative role. They take charge of the body and supervise its removal to the mortuary; they notify the pathologist and other interested parties; they attend the autopsy; they inform the coroner of the provisional diagnosis; they pay the mortuary assistant. The ease with which the pathologist's investigation is conducted in areas remote from Belfast depends on the efficiency with which the local police make these arrangements.

When the coroner requests an autopsy, the police notify the State Pathologist's Department in Belfast or if after office hours, one of the pathologists at his home. At about 10 a.m. each morning the work in hand is shared out and unless there are more than a dozen widely spread cases, it is rare that the work cannot be completed that day. About half the work is in Belfast; of the rest, about two-thirds is within a forty-mile radius of the city. The one disadvantage with Northern Ireland is that Belfast lies on the periphery and outlying mortuaries are less easily served than they would be if our base were near the centre of the area. However, this is to some extent offset by the ease of travelling by car; it is possible to average forty miles an hour on long journeys so that our farthest mortuary at Enniskillen, eighty miles from Belfast, can be reached in two hours. Nevertheless, travelling is a major consideration and in 1967 we travelled a total of 50,000 miles. It has been suggested that the bodies might be brought to the pathologists but the relatives dislike the bodies being taken far, and since there are advantages in carrying out the investigation in the locality the pathologists have not pressed for it.

Good work cannot be done in poor mortuaries as exist in many parts of England. To overcome this problem in Northern Ireland, coroners' autopsies are restricted to mortuaries approved by the Ministry. There is statutory power to use any suitable mortuary and since the hospital mortuaries are generally very good, sixteen were approved for the work outside Belfast. There is at least one in each coroner's area. Belfast has its own public mortuary and there are also mortuaries of approved standard in four Belfast hospitals. The various hospitals undertake to provide a mortuary assistant and he is paid by the Ministry a fee of thirty shillings per autopsy. He receives this in addition to his usual wages and whether or not the autopsy is done inside or out of his normal working hours. The assistants seem satisfied with this and there is rarely difficulty in obtaining help at any hour of any day.

No autopsy is started before a satisfactory history of the case is available. For this purpose a police officer attends every autopsy and gives the pathologist the known facts. He then identifies the body and waits to answer any questions which might arise during the examination. Later, he might have to collect further information for the pathologist. Whilst in the mortuary the policeman is given the job of writing down the draft of the autopsy report at the pathologist's dictation; this enables a full and accurate account of the findings to be recorded during the examination.

During the course of the autopsy, material is retained for laboratory investigation. Histology is carried out more or less routinely; it is essential when the state of a tissue is in doubt yet equally important in other cases to confirm and record naked-eye findings. Blood alcohol is estimated in the victims of all traffic accidents, in suicides and in most other types of unnatural death. Analyses for other poisons are carried out in all cases of suspected poisoning and whenever the pathologist is not entirely happy about a natural cause. As a result, some form of chemical analysis is performed in 50 per cent. of cases. This work is done entirely free of charge at the request of the pathologist by the Forensic Science Laboratory set up by the Government in Belfast. This laboratory also undertakes, without charge, other forms of scientific investigation

at the request of the pathologist, coroner or police.

When the autopsy is completed and the necessary specimens retained, the pathologist issues a certificate informing the coroner that he has finished with the body. The coroner can then permit the disposal of the body without waiting for the definitive cause of death. This has been of considerable help to the pathologists by allowing them time to complete their work properly.

In some parts of England, undue haste is an undesirable feature of coroners' post-mortem work, the pathologist sometimes being expected to provide opinions at an inquest held immediately after the autopsy. On many such occasions the pathologist can do no more than state the cause of death; sometimes it is only his best guess. The arrangement in Northern Ireland whereby the body can be buried once the autopsy has been carried out allows the pathologist as much time as he needs to complete his investigations. He has time to collect more history from the relatives, family doctor and hospital case notes; to confirm the presence of disease processes; to clarify the nature of injuries; to detect the presence of alcohol and other drugs or exclude poisons. He has time to decide what part the various diseases, injuries or drugs played in the death or whether the victim of an accident had a normal expectation of life and he can think out carefully the terms in which he wishes to report his opinions.

All this takes time, of course. On average, an autopsy report is not in the coroner's hands for ten days. When the body can be buried this is no problem. Cremation is still uncommon in Northern Ireland but when it is the method of disposal, it is usually possible to give a cause of death sufficient to satisfy the medical referee without prejudice to some rewording in the final report to the coroner. The delay in furnishing the autopsy report means that inquests are rarely held within ten days of the death. However, there is no reason to believe that they are any less valuable than inquests held sooner. The delay gives the police time to complete their inquiries. Witnesses do not forget vivid events in the interval; in fact, having had time to recover from the shock, they often state things more clearly.

The autopsy report is completed only when the results of all the ancillary investigations are at hand. It ends with a Commentary which summarises in layman's terms the findings in the case, interprets them in the light of the history and answers those questions which the pathologist knows from experience might be put to him by the coroner or by a solicitor interested in subsequent litigation. The writing of a full Commentary is frequently a salutary demonstration of the difficulties of interpreting post-mortem findings and of how personal many interpretations are. The working out of one's data in this way provides a final measure of satisfaction which is not felt when coroners ask only for a likely cause of death obtained from an autopsy carried out only hours beforehand, unsupported by ancillary investigations and unrelated to the history of the deceased.

The Northern Ireland forensic pathology service has now been developing for ten years. It provides the pathologist with a settled career, reasonable remuneration and a satisfying role in the medico-legal investigation. It provides coroners and police with a specialist investigation service such as is needed for the top of the two-tier system now widely advocated for England. Northern Ireland has demonstrated the practicability of setting up, under the aegis of a university, a pathology service paid for principally by the central Government in such a way that both the academic and practical sides of the subject flourish. In England there are at present forensic pathology units in seven universities which could be developed with Government blessing into an integrated service with a much needed career structure for the participants. There is no doubt that the universities would co-operate provided the Government made available the necessary funds. With the Broderick Committee soon to report on coroners and death certification, this would seem to be the very time to organise English forensic pathology in such a way.

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Litigation Management Office, 4th Floor, Bostock House, RVH – Tel: [redacted]

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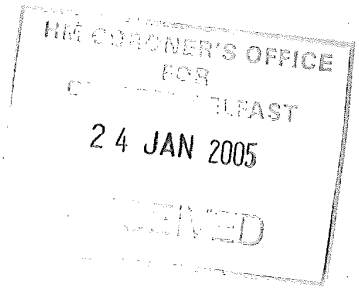
18th January 2005



Mr J L Leckey
H M Coroner
Coroner's Office
Courthouse
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80 Victoria Street
BELFAST BT1 3GL

Dear John

Re: Hyponatraemia and Intravenous Fluids

I mentioned to you recently that the choice of intravenous fluids for children remains a prominent issue and I enclose a copy of the Lancet article I referred to together with letters published in response.

Yours sincerely

A P Walby FRCS Ed
Associate Medical Director

Enc,

Viewpoint

Intravenous fluids for seriously ill children: time to reconsider

Trevor Duke, Elizabeth M Molyneux

Intravenous (iv) fluids are used for many sick and injured children. Such fluids generally used are 0·18% or 0·2% saline with 5% dextrose. These fluids are often given at maintenance rates—100 mL/kg for the first 10 kg of bodyweight, 50 mlL/kg for the next 10 kg, and 20 mL/kg for bodyweight exceeding 20 kg.[1] Some standard paediatric texts caution the need to modify maintenance requirements according to disease states, but this specification has been lost in some recent empirical recommendations: for example, WHO now suggests full maintenance fluids for the routine treatment of bacterial meningitis (albeit with a caution about cerebral oedema), with an emphasis on glucose but not sodium content.[2] This is partly based on concerns about dehydration, but there is no strong evidence that this advice is ideal.[3,4] Hypotonic iv fluids given at maintenance rates might be unsafe, especially in hospitals in developing countries where serum sodium concentration often cannot be measured.

The traditional use of hypotonic maintenance fluid in paediatric medicine is based on requirements of normal physiology—eg, if an infant weighing 6 kg receives 0·18% saline fluid for 24 h, they will receive 3 mmol/kg sodium chloride, 100 mL/kg water, and 3·5 mg/kg per minute glucose. These are the amounts of (1) sodium and chloride needed for normal metabolism and growth; (2) water needed by the kidneys to excrete nitrogenous wastes in urine with similar osmolarity to plasma (so that the kidneys do not need to excessively concentrate or dilute urine); and (3) glucose needed to avoid hypoglycaemia and glycogen breakdown. This sounds ideal, but is it? Most healthy people do not drink this much water each day (average for adults is 2·5–3 L), so their kidneys usually concentrate, or if they drink more than usual dilute, their urine. Healthy people are able to excrete large amounts of free water. This is not the case for many children after surgery, or with serious infections.

Large volumes of hypotonic fluid were generally given after surgery, until reports led to recognition that postoperative patients have reduced free-water clearance, and hypotonic saline solutions at maintenance rates or greater put patients at risk of hyponatraemia and encephalopathy—the syndrome of water intoxication.[5–8]

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Children with serious infections share similar pathophysiological mechanisms and risks of adverse neurological outcomes if given hypotonic iv solutions. We outline the pathophysiology of hyponatraemia in acute infections, and argue that the safest empirical iv fluid for most children with serious infections, who cannot take enteral fluids, is 0·9% sodium chloride with dextrose, at rates of infusion that take account of reduced free-water clearance.

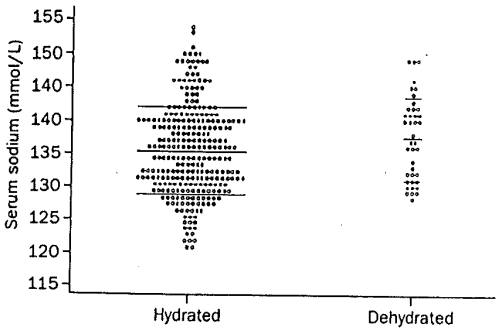
Impaired free-water excretion during severe infections

Antidiuresis during fever and sepsis has been known for over a century, especially in pneumonia and meningitis. Hippocrates' description of pneumonia included scanty and high-coloured urine. In a rhesus monkey model of pneumococcal sepsis, urine volume and free-water clearance decreased to 25% and 17% of baseline values, respectively, during the first 9 h of infection.[9] When 0·45% saline, equal to 105% of urine output in controls, was intravenously infused into septic monkeys, their bodyweight expanded by more than 10% during 9 h of experimental sepsis. Of note, serum sodium concentration or serum osmolarity did not change greatly. In a clinical investigation, 70% of infants with

Mechanism	Setting
Dilution of ECFV	
High ADH activity	Despite normal or expanded ECFV and hypo-osmolarity, so-called SIADH
	Because of hypovolaemia
	Other non-osmotic ADH stimuli[10,13]
	Pain
	Nausea
	Hypoxaemia
	Drugs
	Mechanical ventilation
Increased sensitivity of renal tubules to ADH	Drugs
	Severe illness
Increased intake of free water	Excessive enteral water intake
Iatrogenic administration of free water	iv administration of hypotonic solutions
Increased urinary sodium loss	
ECFV expansion	Retention of free-water from high ADH activity
	Unrestricted oral intake
	Iatrogenic administration
Natriuretic peptide activity (ANP/BNP)	Increased right atrial pressure
Cerebral 'salt wasting'	Described in tuberculous meningitis and traumatic brain injury
Diuretic administration	"
Corticosteroids	"
ADH	ADH may have a direct effect on increasing urinary sodium excretion

ECFV=extracellular fluid volume. ANP=atrial natriuretic peptide. BNP=brain natriuretic peptide. ADH=antidiuretic hormone. SIADH=syndrome of inappropriate ADH secretion.

Table 1: **Causes of hyponatraemia in severe childhood illness**



Serum sodium in well hydrated and dehydrated children with meningitis

p=0·03. Well hydrated, n=286; dehydrated, n=40. Horizontal lines represent mean (SD).

acute bronchiolitis had impaired free-water excretion; at recovery, free-water clearance was up to 15 times more than at the time of admission.[10]

Hyponatraemia in severe infections

Hyponatraemia arises in between 20% and 45% of children with meningitis,[11,12] pneumonia,[13] encephalitis,[14] septicaemia,[15] cerebral malaria,[16,17] and somewhat less often in those with bronchiolitis.[10] The pathophysiological basis is not fully understood, but many factors could be active in the same patient (table 1). Dilution of extracellular fluid because of impaired free-water excretion and increased urinary sodium losses seem to be the main mechanisms. Other mechanisms, including shifts of water from intracellular to extracellular spaces, have been shown in some models of sepsis,[20] but not in others, and are less likely to be important in practice.[21]

Antidiuretic hormone

High concentrations of antidiuretic hormone are seen in many acute febrile illnesses,[22] and are traditionally described as inappropriate. When applied generally, this term indicates our incomplete understanding of the potency of different stimuli to antidiuretic hormone release and suppression (table 1). Hypovolaemia might be a more potent stimulus for secretion of antidiuretic hormone than hypo-osmolarity is to its suppression. In a retrospective study of 300 children with meningitis, investigators noted that serum sodium was lower in those with dehydration than in those with normal hydration.[12] Conversely, a prospective investigation showed that serum sodium concentrations were lower in children with normal hydration than in those with clinical signs of dehydration (figure).[23] Such conflicting data suggest that hyponatraemia arises either as a result of an appropriate pathophysiological response of antidiuretic hormone to restore extracellular fluid volume at the expense of hypo-osmolarity, or as a result of hormonal activity that is inappropriate to both osmolarity and fluid volume status. Antidiuretic hormone also acts centrally, via aquaporin-4 water-transporting proteins expressed in astrocyte foot processes near capillaries and in ependymal cells lining ventricles, to increase brain water.[24,25] Administration of sodium results in a more rapid return to normal of antidiuretic hormone concentrations than does use of low sodium-containing fluid.[4]

Adverse effects of hyponatraemia

In the peripheral circulation, sodium moves freely throughout the extracellular fluid; the hydrostatic pressure gradient and oncotic pressure (predominantly made up of plasma proteins) are responsible for preventing the movement of water out of the vasculature. Cerebral circulation is different. Endothelial tight junctions prevent free movement of sodium across the intact blood-brain barrier, and therefore effective osmolarity is the major determinant of water movement into the brain interstitium or into brain cells.[18] When the blood-brain barrier is intact, an abrupt fall in effective serum osmolarity of 5·mmol/L decreases osmotic pressure difference between the capillary lumen and the brain interstitium by 95 mm Hg (17·5%), favouring water accumulation in the interstitium or brain cells.[26] Many case reports have described acute neurological deterioration in children with serious infections, associated with progressive hyponatraemia and hypotonic intravenous fluid administration (table 2). Researchers who examined the aetiology of extreme hyponatraemia (<115 mmol/L) in a tertiary children's hospital, reported iatrogenic administration of excessive free water as the most common cause.[31]

Investigation	Disease state	Reduction in serum [sodium] or value at time of complication (mmol/L)	Intravenous fluid type and volume	Adverse event	Comments
Cooke[27]	2-year-old girl with tuberculous meningitis	From 130 to 120	Not stated	Coma, seizures	
McJunkin[14]	La Crosse encephalitis (13 of 127 children had neurological deterioration while in hospital)	All children with adverse neurological deterioration had a reduction in sodium. From 138·2 to 134·2 (reduction in mean)	Not stated	Neurological deterioration including cerebral herniation, status epilepticus, and intracranial hypertension	27 children developed hyponatraemia while in hospital, of whom 13 had neurological deterioration
Mor[28]	Infant with pneumonia	107	0·18% saline at 150 mL/kg per day for 2 days	Seizures and cerebral oedema	
Potts[29]	17-month-old with minor burns	From 133 to 113	0·2% saline at 250 mL/kg/day	Seizures	Complications ascribed to SIADH but really represent iv free water intoxication
Jackson[30]	Two children: one with viral respiratory tract infection and one with *Streptococcus pneumoniae* meningitis	121 and 128, respectively, after administration of fluid	5% dextrose at 35–40 mL per kg	Seizures, cerebral oedema, and death	

Table 2: **Adverse events after progressive hyponatraemia induced by hypotonic solutions in children with serious infection or injury**

Fluid	Volume (mL/kg/day)	Volume per day (mL)	Urine output (mL)	Insensible losses (mL)	Total output (mL)	Total net water added (ICF/ECF) (mL)	Na+ added (mmol)	24-h serum [Na]*
0·18% saline	100	600	210	180	390	210 (84/126)	7·2	130·6
0·9% saline	75	450	210	180	390	60 (0/60)	13·5	137·5

Total body water=70% of bodyweight (35% ECF, 35% ICF. ICF=intracellular fluid. ECF=extracellular fluid. Free-water excretion reduced by 50% normal (urine volume from 70–35 mL/kg/day) due to increased activity antidiuretic hormone. Starting serum [Na] 135 mmol/L; total ECF Na=0·35×6×135=283·5 mmol.
*24-h serum [Na]=(pre-existing ECF [Na]+[Na] added)/(pre-existing ECF+ECF added).

Table 3: **Expected changes after 24 h of fluid administration to an infant weighing 6 kg**

Avoidance of hyponatraemia is essential, but not sufficient, to prevent adverse events associated with iv fluid in all children. Fluid overload occurs in children with impaired free-water clearance who receive 100% or more of maintenance fluid. In a randomised trial of fluid management in bacterial meningitis, facial oedema developed 48 h after admission in 45 of 176 (25·6%) children who received 100% of maintenance fluids using 0·45% saline. The relative risk of death or severe neurological sequelae when facial oedema was present was 2·5 (95% CI 1·4–4·8), despite the absence of differences in serum sodium or osmolarity (Duke T, unpublished). This finding suggests that fluid overload, even without progressive hyponatraemia, can contribute to adverse neurological events, which might be explained by disruptions to the blood-brain barrier in children with meningitis. Thus, generation of cerebral oedema in severe infections is multifactorial: the effective osmolar gradient, administered fluid volume, and a direct effect of antidiuretic hormone on aquaporin proteins are each important.

Table 3 shows the estimated effect of two types of fluid management regimens on serum sodium and volume status in an infant weighing 6 kg, with impaired free-water excretion. Renal function was assumed to be otherwise normal. After use of 0·18% saline at 100 mL/kg per day, serum sodium would be expected to fall from 135 mmol/L to 131 mmol/L within 24 h, associated with a 5% increase in total body water. With 0·9% saline at 75 mL/kg per day, serum sodium would increase by 2 mmol/L and total body water by 1·5%, with no increase in intracellular water. These are the initial changes; secondary effects might include part correction of the fall in serum sodium in those receiving 0·18% saline, because of intracellular water shifts, but increased urinary sodium losses because of expansion of the extracellular fluid.

Few clinical trials have assessed these differences. A non-randomised comparison of 0·18% and 0·9% saline in 24 postoperative patients, showed a similar biochemical effect to our predicted result. Adults receiving 0·18% saline at 3 L per 24 h had a median fall in serum sodium at 24 h and 48 h of 5·4 mmol/L and 7·1 mmol/L, respectively, but serum sodium did not change in those receiving 0·9% saline.[22] In patients in whom renal clearance of free water is reduced by more than 50%, maintenance fluid will need to be considerably less than 75% of normal maintenance volumes to avoid oedema. This approach is not fluid restriction, as it is sometimes interpreted: restriction of fluids to the point of dehydration in the hope of avoiding cerebral oedema is dangerous, and will result in worse outcomes.[23]

Potential pitfalls

Use of an isotonic, rather than hypotonic, solution does not mean that progressive hyponatraemia would not take place, but that it is much less likely. Although use of high-sodium-containing solutions in children with meningitis in the first 24 h was not associated with development of hypernatraemia,[9] during the later phases of illness there is a theoretical risk of hypernatraemia if isotonic saline is used. Diuresis and low urine osmolarity is a feature of the convalescent phase of childhood infections. However, during this phase of illness iv fluid rates are reduced, and enteral feeding reintroduced. Children with severe infections, who are not taking enteral feeds, are at risk of hypoglycaemia; isotonic saline should always have glucose added (5–10%) when given as maintenance fluid. Early correction of clinical signs of severe dehydration or shock is essential.[23]

In renal failure there is no safe substitute for measurement of urine output and serum sodium, and adjustment of water and solute intake accordingly. Severe hyponatraemia should be corrected slowly to avoid the demyelinating syndrome.[23] Although there is no evidence that correction of moderate hyponatraemia in children with isotonic saline causes a large risk of this syndrome, to increase sodium by no more than 1 mmol/L every 2 h, seems sensible when this can be measured. Isotonic saline has a pH of 5–6. When it is used in large volumes for children in shock, metabolic acidosis can persist, and in some circumstances bicarbonate or other buffer might be needed.

Possible solution

We postulate that 0·9% saline (with 5% dextrose) at less than standard maintenance volumes results in a lower frequency of hyponatraemia, seizures, and adverse neurological events than do hypotonic solutions (0·18%–0·3% saline), in acutely unwell children with brain injury of any type (meningitis, encephalitis, cerebral malaria, febrile seizures); serum sodium less than 138 mmol/L;[10] or severe infection associated with greatly impaired free-water excretion.

Ideal testing of this hypothesis would be done in a large randomised controlled trial of hypotonic versus isotonic saline in children with severe infections, stratified for types of infections. However, we think it would be unethical to include some infections, particularly encephalitis and meningitis, because there is already substantial experience of harm from hypotonic solutions and pathophysiological plausibility of the cause of such harm. Such infections also have a much higher risk than do other infections of cerebral oedema and adverse outcomes if hyponatraemia occurs.

An alternative approach, in hospitals in which hypotonic fluids at maintenance volumes are the routine standard of care, would be to change the policy such that isotonic saline at reduced infusion rates (60–70% of maintenance) becomes the standard iv fluid for seriously ill children. Although not as robust as a randomised control trial, this approach might allow for a detailed before-and-after analysis. Outcomes could include differences in the proportions of children who have neurological events associated with progressive falls in serum sodium. Assessment of harm could include differences in frequencies of severe hypernatraemia, or neurological complications associated with rapidly rising serum sodium.

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Intravenous fluids for seriously ill children

Sir—Trevor Duke and Elizabeth Molyneux (Oct 18, p 1320)[1] once again call attention to a serious clinical problem—hospital-induced hyponatraemia. However, their Viewpoint contains errors of fact and recommendations that are counter to established principles of fluid therapy. The article, like another,[2] inappropriately proposes that isotonic saline be used as maintenance therapy. This strategy poses risks of hypernatraemia and other consequences of sodium overload.[3] These proposals mark a tendency to conflate maintenance therapy with rehydration or restoration therapy—two very separate functions of fluid therapy.

Rehydration or restoration therapy is the first priority of fluid therapy. Rapidly infused isotonic saline, resulting in the restoration of extracellular fluid, is essential in the recovery of adults with cholera and infants with diarrhoeal dehydration. Isotonic saline has been used to treat burn shock since the 1960s. The idea is to temporarily overexpand extracellular fluid to restore circulation.[4] Once accomplished, renal regulation of salt and water balance are also restored. The excess extracellular fluid is mobilised and excreted as urine. Isotonic saline given for these purposes is indexed to bodyweight.

Maintenance therapy, introduced in the 1950s, is replacement of physiological insensible and renal water losses by use of hypotonic saline; these losses vary according to metabolic rate, which is readily estimated from bodyweight, but not to bodyweight itself. The average amount required is 100 mL per 100 kcal (419 kJ) per day; adjustment to that average is appropriate when projected losses differ from average.[5]

We have accumulated evidence that children admitted to hospital because of acute illness or scheduled for surgery are often mildly hypovolaemic; concentrations of plasma antidiuretic hormone are increased, inhibiting free water excretion. Administration of maintenance fluids as hypotonic saline in that setting risks hyponatraemia. Rapid expansion of the extracellular fluid of these patients with 20–40 mL/kg isotonic saline before maintenance therapy is started, and limiting of maintenance therapy to that recommended in the original 1957 protocol outlined above[5] greatly reduces this risk (unpublished data).

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1 Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003; 362: 1320–23.
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Sir—Trevor Duke and Elizabeth Molyneux[1] underscore the critical role of appropriately or inappropriately secreted antidiuretic hormone in the development of hyponatraemia in children with severe infections. They claim that centrally acting antidiuretic hormone contributes to intracellular water accumulation in the brain by increasing water transport across aquaporin-4, the water-channel protein predominantly expressed in the perivascular astrocyte endfoot processes and in subpopulations of ependymal cells. In support of this contention, they refer to our publication[2] about the effects of intraventricular administration of arginine vasopressin and atrial natriuretic peptide on the brain water content and its localisation into the intracellular and extracellular space in rats with experimentally induced hyponatraemia. In fact, the regulation of brain-specific aquaporin-4 is not yet fully explored, but the involvement of antidiuretic hormone in this process is not substantiated by experimental evidence.

Treatment of cultured rat astrocytes with the protein kinase C (PKC) activator phorbol ester has been shown to cause a rapid time-dependent and dose-dependent decrease in expression of aquaporin-4 mRNA.[3] Inhibition of mRNA concentrations was not related to their stability nor to de-novo protein synthesis, indicating that regulation of aquaporin-4 mRNA via PKC activation could be at the transcriptional level. The water-channel activity of aquaporin-4 has also be been shown to be regulated by phorbol-ester-dependent protein phosphorylation via the PKC pathway, as shown by the presence of typical consensus sites for phosphorylation in the aquaporin-4 protein and by the striking reduction of aquaporin-4 protein concentrations by phorbol diesters.[4]

Moreover, in cultured cells with features of renal medullary collecting ducts, aquaporin-4 expression can be downregulated not only by PKC but also by dopamine.[5] Dopaminergic regulation of brain-specific aquaporin-4, therefore, should be considered as a possible mechanism in the control of brain water metabolism.

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1 Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003; 362: 1320–23.
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Author's reply

Sir—I agree with Malcolm Holliday and colleagues that use of only hypotonic saline as maintenance fluid increases the risk of hyponatraemia. There are several strategies to avoid this outcome, and the most practical might depend on the setting and resources available. Giving normal saline as extracellular fluid expansion followed by 0·18% sodium chloride at volumes that take account of the strikingly reduced free water excretion that occurs in serious infections or after surgery will be safe for many seriously ill children.

Our article was not designed to address the issue of adequate volume resuscitation, which should use isotonic fluid. The alternative approach we suggested to maintenance fluid considered that recommendations often suggest giving too much water (100 mL per kg per day).[1] In many hospitals in developing countries, the fluid management suggested by Holliday (use of two types of intravenous fluid and regular monitoring of serum sodium) is unavailable. Even in developed countries, deciding on the maintenance fluid rate is often difficult and results in overestimation.

I recently cared for an 8-week-old infant with streptococcal meningitis who presented to an outside hospital with poor perfusion and a serum sodium concentration of 137 mmol/L. She was resuscitated with 50 mL/kg 0·9% saline. The infant was alert and interactive, and had a normal neurological examination and normal hydration when transferred to our hospital. She then received 0·18% saline intravenously at 69 mL/kg per h. 9 h later she developed seizures and a dilated right pupil. The serum sodium concentration was 131 mmol/L, and a CT scan showed extensive bilateral cerebral oedema. Although the clinical course of meningitis might have had a role in the child's deterioration, iatrogenic hyponatraemia due to hypotonic fluid administration, despite initial appropriate normal saline bolus resuscitation, is the most likely cause of the extensive cerebral oedema.

We proposed that for children with meningitis, other brain injury, or serious illness associated with reduced free water excretion, administration of reduced volumes of isotonic saline plus dextrose (after adequate volume expansion) might be a practical approach. No empirical strategy will be ideal for all children: in renal failure, cardiac disease, or severe malnutrition, the risk of salt retention and water overload might be greater if isotonic saline is used. Although I think that dangerous levels of hypernatraemia are less likely to occur with the strategy we proposed than are dangerous levels of hyponatraemia if 0·18% saline is used, this hypothesis should be tested. Empirical fluid strategies should be assessed in various acute clinical conditions for their effects on serum sodium, body water (measurable by very accurate serial bodyweight), and urinary sodium excretion.

The reference we cited by Vajda and colleagues[2] supports the statement that antidiuretic hormone can act centrally to increase water permeability of the cerebral vasculature and intracellular brain water, and other research by them[3] suggest that aquaporin-4 receptors mediate increases in intracellular brain water. However, Vajda and colleagues are right to correct us that there is no good evidence of a link between these two processes.

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Sir—Trevor Duke and Elizabeth Molyneux's article[1] on the fluid management of severely ill children is an important step in the reassessment of the current recommendations for fluid management in critically ill children in tropical settings. However, we believe that three issues deserve further emphasis. First, in many children, iatrogenic hyponatraemia can be averted by avoiding the unnecessary use of intravenous fluids: in most disorders that lead to hospital admission in tropical countries, including respiratory distress, children are able to take fluid orally after initial management. Second, as Duke and Molyneux's title suggests, their recommendations are for "seriously ill children"—a group that includes malnourished children, in whom WHO currently recommends the avoidance of sodium-rich resuscitation fluids, for fear of salt overload and cardiogenic failure. Finally, many seriously ill children also present in hypovolaemic shock and require resuscitation, often with large boluses of isotonic solutions.

The emergency triage assessment and treatment guidelines, developed by WHO for use in developing countries, define shock on the basis of a delayed capillary refill time (dCRT; >3 s), cold hands, and a weak, fast pulse.[2] However, studies in Brazil[3] and Malawi[4] suggest that these criteria are insensitive, since in both studies shock was rarely diagnosed (<0·5%), although the case fatality rate in those defined as shock approached 100%. In our hospital on the coast of Kenya, clinical assessment for shock has been part of our routine admission practice for several years. A review of data from children admitted to our paediatric ward during the past 12 months shows that dCRT was present in 8% (case fatality rate 24%), a temperature gradient in 4% (12%), and a weak pulse volume in 3% (23%; unpublished data). Mortality in children without any of these features was 2·6%, suggesting that these signs are useful in identifying

	Sodium concentration (mmol/L)				Total
	<125	125–135	135–144	≥145	
Number of children	26 (5%)	257 (50%)	212 (42%)	17 (3%)	512 (100%)
Age (median [IQR], months)	28 (8–74)	23 (10–44)	25 (11–52)	19 (7–37)	24 (10–47)
MUAC <12 cm	12 (46%)	54 (21%)	38 (18%)	7 (41%)	111 (22%)
Falciparum-positive	9 (35%)	172 (66%)	111 (52%)	8 (47%)	300 (59%)
Respiratory distress	16 (62%)	74 (29%)	79 (37%)	8 (47%)	177 (35%)
Impaired consciousness	13 (50%)	170 (66%)	143 (68%)	14 (82%)	327 (64%)
Coma	7 (27%)	102 (40%)	89 (42%)	11 (65%)	203 (40%)
CRT ≥3 s	10/26 (39%)	78/236 (33%)	51/185 (28%)	7/16 (44%)	146/463 (32%)
Hypotension*	6/25 (24%)	33/234 (14%)	16/191 (8%)	2/14 (14%)	57/464 (12%)
Seizures before or at admission	7 (27%)	145 (56%)	116 (55%)	9 (53%)	277 (54%)
Inpatient seizures					
Non-malarial	2 (14%)	20 (24%)	21 (24%)	3 (33%)	46 (23%)
Falciparum-positive	3 (33%)	36 (21%)	47 (43%)	4 (56%)	90 (31%)
Mortality	8 (31%)	40 (16%)	46 (22%)	6 (35%)	100 (20%)

MUAC=mid-upper-arm circumference. CRT=capillary refill time. *Systolic blood pressure <70 mm Hg if younger than 1 year and <80 mm Hg if older than 1 year.

Clinical characteristics of all children older than 1 month admitted to high-dependency unit

Queen's University Belfast

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Mr J L Leckey
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80 Victoria Street
BELFAST
BT1 3GL

5th January 2004

Dear Mr Leckey

Hyponatraemia in Children

When I gave evidence at the inquest last year into the death of Rachel Ferguson, you asked me to consider how best the dangers of hyponatraemia in children could be brought to the attention of medical colleagues.

Following this, together with two other colleagues, I prepared a short outline of the dangers of this condition and this has now been published in the Ulster Medical Journal.

I am attaching a copy of the paper and I hope you will find this of some interest.
It is our hope that this will bring this important condition to the attention of medical colleagues in Northern Ireland and further afield.

With best wishes.

Yours sincerely

Dr John Jenkins MD FRCP FRCPCH FRCPI
Senior Lecturer in Child Health & Consultant Paediatrician

Enc.

The Ulster Medical Journal, Volume 72, No. 2, pp. 69-72, November 2003.

Editorial

Prevention of hyponatraemia in children receiving fluid therapy

Severe hyponatraemia (serum sodium <130 mmol/1) has become increasingly recognised in recent years as a potential complication of fluid therapy in children,[1] and at least two children in Northern Ireland have died in recent years as a result. Worldwide, death or neurological morbidity related to this condition has recently been reported in more than 50 children.[2] Hyponatraemia has also been reported in as many as 5% of adults undergoing elective surgery[3] and in 25% of children following spinal fusion.[4] It has been suggested that menstruant women and prepubertal children are particularly at risk of brain damage in this situation.[5] Although risk factors include vomiting, pain, anxiety, disturbances of the central nervous system and metabolic and endocrine disorders, it has become recognised that any child receiving intravenous fluids or oral rehydration is potentially at risk. The particular risks associated with the post-operative period were highlighted by Arieff who pointed out that plasma levels of vasopressin (antidiuretic hormone, ADH) are elevated in virtually every child in the post-operative period.[5] If such children are given fluids containing less than 140 mmol/1 of sodium there will always be a tendency towards post-operative hyponatraemia.

The complex inter-relationships between multiple factors influencing decisions regarding fluid and electrolyte management in children are described in standard texts. These result in difficulty in establishing simple guidelines for fluid administration in children. A solution containing 0.18% sodium chloride in 4% glucose has commonly been used in paediatric practice and is generally held to be isotonic. However, in the catabolic child the glucose is metabolised rapidly causing the fluid to become hypotonic in vivo, with the potential for significant fluid shifts. If the child is in the post-operative period or in any other situation where there is a high level of circulating vasopressin a situation can arise where excess free water is retained within the circulation. This can be compounded by water effectively administered in the intravenous fluids. This condition has been called "dilutional hyponatraemia" because the "free" water component of the serum has increased, causing dilution of the major cation, sodium. This "free" water will pass rapidly and unhindered across cell membranes with the particular risk of development of cerebral oedema. Children may be at particular risk of brain damage due to increase in intracranial pressure in this situation.[2]

GUIDANCE AND ADVICE

A Working Group in Northern Ireland has developed guidelines (figure), which have been published by the Department of Health, Social Services and Public Safety, and can be downloaded from the internet.[6] These guidelines emphasise that every child receiving intravenous fluids requires a thorough baseline assessment, that fluid requirements should be assessed by a doctor competent in determining a child's fluid requirement, and fluid balance be rigorously monitored. They emphasise the value of accurate measurement of body weight and monitoring of serum urea and electrolytes in any child requiring prescribed fluids after 12 hours, together with the importance of assessment of fluid balance and prescription at least every 12 hours by an experienced member of clinical staff. This assessment needs to take account of all oral and intravenous intake, together with the measurement and recording of all losses (including urine, vomiting, diarrhoea, etc.) as accurately as possible.

While general guidance can be given regarding *maintenance* fluid requirements in children of different weights, these must be assessed in the clinical context of each individual child. Requirements for water and electrolytes should be considered separately and an appropriate solution chosen. Although the baseline maintenance requirement for 2 to 3 mmol/kg/day of sodium can be applied to children of all ages, the amount of water needed varies with weight. It will readily be apparent that this means that the concentration of sodium in the maintenance fluid has to be different for children of different ages and weights. For example, an infant of 5 kg requires 150 ml/kg/day of water, so the daily sodium requirement will be provided by a fluid

any CHILD RECEIVING PRESCRIBED FLUIDS is AT RISK OF HYPONATRAEMIA

INTRODUCTION

- **Any child on IV fluids or oral rehydration is potentially at risk of hyponatraemia.**
- Hyponatraemia is potentially extremely serious, a rapid fall in sodium leading to cerebral oedema, seizures and death. Warning signs of hyponatraemia may be non-specific and include nausea, malaise and headache.
- Hyponatraemia most often reflects failure to excrete water. Stress, pain and nausea are all potent stimulators of anti-diuretic hormone (ADH), which inhibits water excretion.
- Complications of hyponatraemia most often occur due to the administration of excess or inappropriate fluid to a sick child, usually intravenously.
- Hyponatraemia may also occur in a child receiving excess or inappropriate oral rehydration fluids.
- Hyponatraemia can occur in a variety of clinical situations, even in a child who is not overtly "sick". Particular risks include:
  - Post-operative patients
  - CNS injuries
  - Bronchiolitis
  - Burns
  - Vomiting

BASELINE ASSESSMENT

Before starting IV fluids, the following must be measured and recorded:

- **Weight:** accurately in kg. [In a bed-bound child use best estimate.] Plot on centile chart or refer to normal range.
- **U&E:** take serum sodium into consideration.

FLUID REQUIREMENTS

Fluid needs should be assessed by a doctor competent in determining a child's fluid requirement. Accurate calculation is essential and includes:

Maintenance Fluid

- 100mls/kg for first 10kg body wt, plus
- 50mls/kg for the next 10kg, plus
- 20mls/kg for each kg thereafter, up to max of 70kg [This provides the total 24 hr calculation; divide by 24 to get the mls/hr].

Replacement Fluid

- Must always be considered and prescribed separately.
- Must reflect fluid loss in both volume and composition (lab analysis of the sodium content of fluid loss may be helpful).

CHOICE OF FLUID

- **Maintenance fluids** must in all instances be dictated by the anticipated sodium and potassium requirements. The glucose requirements, particularly of very young children, must also be met.
- **Replacement fluids** must reflect fluid lost. In most situations this implies a minimum sodium content of 130mmol/l.
- **When resuscitating** a child with clinical signs of shock, if a decision is made to administer a crystalloid, normal (0.9%) saline is an appropriate choice, while awaiting the serum sodium.
- The composition of oral rehydration fluids should also be carefully considered in light of the U&E analysis.

Hyponatraemia may occur in any child receiving any IV fluids or oral rehydration. Vigilance is needed for all children receiving fluids.

MONITOR

- **Clinical state:** including hydrational status. Pain, vomiting and general well-being should be documented.
- **Fluid balance:** must be assessed at least every 12 hours by an experienced member of clinical staff.

  Intake: All oral fluids (including medicines) must be recorded and IV intake reduced by equivalent amount.

  Output: Measure and record all losses (urine, vomiting, diarrhoea, etc.) as accurately as possible.

  If a child still needs prescribed fluids after 12 hours of starting, their requirements should be reassessed by a senior member of medical staff.
- **Biochemistry:** Blood sampling for U&E is essential at least once a day - more often if there are significant fluid losses or if clinical course is not as expected.

  The rate at which sodium falls is as important as the plasma level. A sodium that falls quickly may be accompanied by rapid fluid shifts with major clinical consequences.

  Consider using an indwelling heparinised cannula to facilitate repeat U&Es.

  Do not take samples from the same limb as the IV infusion.

  Capillary samples are adequate if venous sampling is not practical.

  Urine osmolarity/sodium: Very useful in hyponatraemia. Compare to plasma osmolarity and consult a senior Paediatrician or a Chemical Pathologist in interpreting results.

SEEK ADVICE

Advice and clinical input should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist

- In the event of problems that cannot be resolved locally, help should be sought from Consultant Paediatricians/ Anaesthetists at the PICU, RBHSC.

The Department Of Health, Social Services And Public Safety. Guidance is also available on the Departmental website : www.dhsspsni.gov.uk

containing 15 to 20 mmol/1 of sodium. The standard 0.18% saline solution contains 30 mmol/1 and so will adequately provide for this requirement. On the other hand, a child of 40 kg requires 50ml/kg/day, so a solution containing 3 times as much sodium will be needed to provide adequate maintenance sodium. A solution containing 0.18% saline will thus not provide adequate sodium to maintain the normal plasma level in the older child unless there are clinical reasons to limit sodium intake. This would require instead a solution containing 40 to 60 mmol/1. Half normal saline contains 75 mmol/1 of sodium.

Replacement fluids must reflect fluid loss, and in most situations this will imply a minimum sodium content of 130 mmol/1. This must be considered and prescribed separately, reflecting the fluid loss in both volume and composition. In some situations laboratory analysis of the electrolyte content of the fluid lost may be helpful.

It is important to remember that, while children receiving intravenous fluids are at particular risk, children receiving oral rehydrating fluids may also be at risk as these are invariably hypotonic. Vigilance is therefore required for all children receiving fluids. Medical and nursing staff need to be aware of risks in this situation, and of early signs of developing cerebral oedema such as vomiting, deteriorating level of consciousness or headache before more serious symptoms such as seizures occur, as deterioration to this extent is associated with significant morbidity and mortality.

Particular attention needs to be given to fluid management in specific situations such as diabetic ketoacidosis, renal failure and in the newborn, but attention to detail in assessment and management of intravenous and oral fluids in all children where these are required for medical or surgical reasons is essential to minimise the risks associated with hyponatraemia. It must be clearly recognized that prevention is quite different from treatment of hyponatraemia. All those working with children must be familiar with good practice to *prevent* hyponatraemia but not all will have the necessary expertise in *treating* a child with hyponatraemia which can be extremely complex. If concern is raised regarding clinical deterioration or biochemical abnormality then advice and clinical input should be obtained from a senior member of medical staff, for example a Consultant Paediatrician, Consultant Anaesthetist or Consultant Chemical Pathologist.

We recommend that complications and critical incidents related to intravenous fluids are reported to the Medicines Control Agency (MCA) in the same way as drug side-effects, by using the "yellow card" system. Fluids are included in the British National Formulary and are under the regulatory authority of the MCA. This will permit a nationwide analysis of the problem and also direct information to clinicians. When one of the deaths locally was reported to the MCA the Agency was asked to consider issuing a "hazard warning" about the use of a solution containing 0.18% sodium chloride in 4% glucose in children following surgery. After due consideration the MCA replied that electrolyte imbalance is a risk with the use of all intravenous solutions. The MCA Working Group on Paediatric Medicines advised that there should be no amendments to product information (personal communication).

CONCLUSION

It is important that all doctors caring for children are aware of current literature and advice in relation to the rare but serious condition known as "Dilutional Hyponatraemia". A complex neuro-endocrine response in susceptible children can occur where the "free" water component of intravenous fluids can cause a sudden and unheralded decrease in the serum sodium concentration. Preventative measures to avoid this potentially fatal condition need to be instituted in all units caring for children.[7]

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Department of Health, Social Services & Public Safety
An Roinn Sláinte, Seirbhísí Sóisialta agus Sábháilteachta Poiblí

From The Deputy Chief Medical Officer:
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Mr John Leckey
Coroner's Office
80 Victoria Street
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23rd January 2004

Dear John

Please find enclosed a copy of an article published in last week's Lancet with regard intravenous fluids for seriously ill children.

I hope this is of interest.

Kind regards.

Yours sincerely

pp **DR IAN CARSON**
Deputy Chief Medical Officer

encl.

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Intravenous fluids for seriously ill children

Sir—Trevor Duke and Elizabeth Molyneux (Oct 18, p 1320)[1] once again call attention to a serious clinical problem—hospital-induced hyponatraemia. However, their Viewpoint contains errors of fact and recommendations that are counter to established principles of fluid therapy. The article, like another,[2] inappropriately proposes that isotonic saline be used as maintenance therapy. This strategy poses risks of hypernatraemia and other consequences of sodium overload.[3] These proposals mark a tendency to conflate maintenance therapy with rehydration or restoration therapy—two very separate functions of fluid therapy.

Rehydration or restoration therapy is the first priority of fluid therapy. Rapidly infused isotonic saline, resulting in the restoration of extracellular fluid, is essential in the recovery of adults with cholera and infants with diarrhoeal dehydration. Isotonic saline has been used to treat burn shock since the 1960s. The idea is to temporarily overexpand extracellular fluid to restore circulation.[4] Once accomplished, renal regulation of salt and water balance are also restored. The excess extracellular fluid is mobilised and excreted as urine. Isotonic saline given for these purposes is indexed to bodyweight.

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We have accumulated evidence that children admitted to hospital because of acute illness or scheduled for surgery are often mildly hypovolaemic; concentrations of plasma antidiuretic hormone are increased, inhibiting free water excretion. Administration of maintenance fluids as hypotonic saline in that setting risks hyponatraemia. Rapid expansion of the extracellular fluid of these patients with 20–40 mL/kg isotonic saline before maintenance therapy is started, and limiting of maintenance therapy to that recommended in the original 1957 protocol outlined above[5] greatly reduces this risk (unpublished data).

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1 Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. *Lancet* 2003; **362**: 1320–23.
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Sir—Trevor Duke and Elizabeth Molyneux[1] underscore the critical role of appropriately or inappropriately secreted antidiuretic hormone in the development of hyponatraemia in children with severe infections. They claim that centrally acting antidiuretic hormone contributes to intracellular water accumulation in the brain by increasing water transport across aquaporin-4, the water-channel protein predominantly expressed in the perivascular astrocyte endfoot processes and in subpopulations of ependymal cells. In support of this contention, they refer to our publication[2] about the effects of intraventricular administration of arginine vasopressin and atrial natriuretic peptide on the brain water content and its localisation into the intracellular and extracellular space in rats with experimentally induced hyponatraemia. In fact, the regulation of brain-specific aquaporin-4 is not yet fully explored, but the involvement of antidiuretic hormone in this process is not substantiated by experimental evidence.

Treatment of cultured rat astrocytes with the protein kinase C (PKC) activator phorbol ester has been shown to cause a rapid time-dependent and dose-dependent decrease in expression of aquaporin-4 mRNA.[3] Inhibition of mRNA concentrations was not related to their stability nor to de-novo protein synthesis, indicating that regulation of aquaporin-4 mRNA via PKC activation could be at the transcriptional level. The water-channel activity of aquaporin-4 has also be been shown to be regulated by phorbol-ester-dependent protein phosphorylation via the PKC pathway, as shown by the presence of typical consensus sites for phosphorylation in the aquaporin-4 protein and by the striking reduction of aquaporin-4 protein concentrations by phorbol diesters.[4]

Moreover, in cultured cells with features of renal medullary collecting ducts, aquaporin-4 expression can be downregulated not only by PKC but also by dopamine.[5] Dopaminergic regulation of brain-specific aquaporin-4, therefore, should be considered as a possible mechanism in the control of brain water metabolism.

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Author's reply

Sir—I agree with Malcolm Holliday and colleagues that use of only hypotonic saline as maintenance fluid increases the risk of hyponatraemia. There are several strategies to avoid this outcome, and the most practical might depend on the setting and resources available. Giving normal saline as extracellular fluid expansion followed by 0·18% sodium chloride at volumes that take account of the strikingly reduced free water excretion that occurs in serious infections or after surgery will be safe for many seriously ill children.

Our article was not designed to address the issue of adequate volume resuscitation, which should use isotonic fluid. The alternative approach we suggested to maintenance fluid considered that recommendations often suggest giving too much water (100 mL per kg per day).[1] In many hospitals in developing countries, the fluid management suggested by Holliday (use of two types of intravenous fluid and regular monitoring of serum sodium) is unavailable. Even in developed countries, deciding on the maintenance fluid rate is often difficult and results in overestimation.

I recently cared for an 8-week-old infant with streptococcal meningitis who presented to an outside hospital with poor perfusion and a serum sodium concentration of 137 mmol/L. She was resuscitated with 50 mL/kg 0·9% saline. The infant was alert and interactive, and had a normal neurological examination and normal hydration when transferred to our hospital. She then received 0·18% saline intravenously at 69 mL/kg per h. 9 h later she developed seizures and a dilated right pupil. The serum sodium concentration was 131 mmol/L, and a CT scan showed extensive bilateral cerebral oedema. Although the clinical course of meningitis might have had a role in the child's deterioration, iatrogenic hyponatraemia due to hypotonic fluid administration, despite initial appropriate normal saline bolus resuscitation, is the most likely cause of the extensive cerebral oedema.

We proposed that for children with meningitis, other brain injury, or serious illness associated with reduced free water excretion, administration of reduced volumes of isotonic saline plus dextrose (after adequate volume expansion) might be a practical approach. No empirical strategy will be ideal for all children: in renal failure, cardiac disease, or severe malnutrition, the risk of salt retention and water overload might be greater if isotonic saline is used. Although I think that dangerous levels of hypernatraemia are less likely to occur with the strategy we proposed than are dangerous levels of hyponatraemia if 0·18% saline is used, this hypothesis should be tested. Empirical fluid strategies should be assessed in various acute clinical conditions for their effects on serum sodium, body water (measurable by very accurate serial bodyweight), and urinary sodium excretion.

The reference we cited by Vajda and colleagues[2] supports the statement that antidiuretic hormone can act centrally to increase water permeability of the cerebral vasculature and intracellular brain water, and other research by them[3] suggest that aquaporin-4 receptors mediate increases in intracellular brain water. However, Vajda and colleagues are right to correct us that there is no good evidence of a link between these two processes.

Trevor Duke

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Sir—Trevor Duke and Elizabeth Molyneux's article[1] on the fluid management of severely ill children is an important step in the reassessment of the current recommendations for fluid management in critically ill children in tropical settings. However, we believe that three issues deserve further emphasis. First, in many children, iatrogenic hyponatraemia can be averted by avoiding the unnecessary use of intravenous fluids: in most disorders that lead to hospital admission in tropical countries, including respiratory distress, children are able to take fluid orally after initial management. Second, as Duke and Molyneux's title suggests, their recommendations are for "seriously ill children"—a group that includes malnourished children, in whom WHO currently recommends the avoidance of sodium-rich resuscitation fluids, for fear of salt overload and cardiogenic failure. Finally, many seriously ill children also present in hypovolaemic shock and require resuscitation, often with large boluses of isotonic solutions.

The emergency triage assessment and treatment guidelines, developed by WHO for use in developing countries, define shock on the basis of a delayed capillary refill time (dCRT; >3 s), cold hands, and a weak, fast pulse.[2] However, studies in Brazil[3] and Malawi[4] suggest that these criteria are insensitive, since in both studies shock was rarely diagnosed (<0·5%), although the case fatality rate in those defined as shock approached 100%. In our hospital on the coast of Kenya, clinical assessment for shock has been part of our routine admission practice for several years. A review of data from children admitted to our paediatric ward during the past 12 months shows that dCRT was present in 8% (case fatality rate 24%), a temperature gradient in 4% (12%), and a weak pulse volume in 3% (23%; unpublished data). Mortality in children without any of these features was 2·6%, suggesting that these signs are useful in identifying

	Sodium concentration (mmol/L)				Total
	<125	125–135	135–144	≥145	
Number of children	26 (5%)	257 (50%)	212 (42%)	17 (3%)	512 (100%)
Age (median [IQR], months)	28 (8–74)	23 (10–44)	25 (11–52)	19 (7–37)	24 (10–47)
MUAC <12 cm	12 (46%)	54 (21%)	38 (18%)	7 (41%)	111 (22%)
Falciparum-positive	9 (35%)	172 (66%)	111 (52%)	8 (47%)	300 (59%)
Respiratory distress	16 (62%)	74 (29%)	79 (37%)	8 (47%)	177 (35%)
Impaired consciousness	13 (50%)	170 (66%)	143 (68%)	14 (82%)	327 (64%)
Coma	7 (27%)	102 (40%)	89 (42%)	11 (65%)	203 (40%)
CRT ≥3 s	10/26 (39%)	78/236 (33%)	51/185 (28%)	7/16 (44%)	146/463 (32%)
Hypotension*	6/25 (24%)	33/234 (14%)	16/191 (8%)	2/14 (14%)	57/464 (12%)
Seizures before or at admission	7 (27%)	145 (56%)	116 (55%)	9 (53%)	277 (54%)
Inpatient seizures					
Non-malarial	2 (14%)	20 (24%)	21 (24%)	3 (33%)	46 (23%)
Falciparum-positive	3 (33%)	36 (21%)	47 (43%)	4 (56%)	90 (31%)
Mortality	8 (31%)	40 (16%)	46 (22%)	6 (35%)	100 (20%)

MUAC=mid-upper-arm circumference. CRT=capillary refill time. *Systolic blood pressure <70 mm Hg if younger than 1 year and <80 mm Hg if older than 1 year.

Clinical characteristics of all children older than 1 month admitted to high-dependency unit

children with a poor prognosis in whom volume expansion should be considered. In developing countries, a change in culture towards early recognition of compensated shock and implementation of rapid volume resuscitation might improve outcome irrespective of cause.

We agree that hyponatraemia commonly complicates many serious infections in children. Prompted by their article, we examined data from critically ill children older than 1 month admitted to our high-dependency unit between September, 1999, and December, 2000. Admission criteria included impaired consciousness—defined as prostration (inability to sit up) or coma (inability to localise pain)—and deep acidotic breathing.[5] Hyponatraemia was present in only 5%, being more common in children with respiratory distress, hypotension, and severe malnutrition (mid-upper-arm circumference <12 cm). It was not more frequent in those with impaired consciousness or seizures (table). Moreover, despite a higher case fatality rate in those with hyponatraemia, the clinical significance was less pronounced, since only eight of the 100 children who died were admitted with sodium concentrations of less than 125 mmol/L. Throughout this period, our routine fluid management for all children with impaired consciousness was intravenous maintenance with 0·18% saline and 4% dextrose at 4 mL/kg hourly. Boluses of normal saline were reserved for children with clinical features of shock or with metabolic acidosis (base deficit >8). In-hospital seizures were not more common in children who were already hyponatraemic on admission. These data are, however, inadequate to make any recommendations regarding fluid management and we acknowledge that this issue can only be addressed satisfactorily through prospective randomised trials.

We agree that reconsideration of the current WHO recommendations for fluid management is timely; however, we suggest that more basic research is needed to help define the "whole package". We suggest the formal assessment of a simple management plan for fluid administration that encompasses a broader range of children admitted to hospitals that are unable to measure electrolytes or renal function.

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HIVNET 012 and Petra

Sir—J Brooks Jackson and colleagues (Sept 13, p 859)[1] report 18-month follow-up data from their study of single-dose nevirapine for prevention of mother-to-child transmission of HIV-1. Although some people doubt the lasting relevance of their findings in terms of the regimen they used, there is no doubting the importance of HIVNET 012 as a "proof-of-principle" study of intrapartum intervention.

Jackson and colleagues are remiss, however, in not highlighting an apparent decline over time in postnatal transmission of HIV-1 in Kampala. This decrease might affect the relevance of their findings to other settings. Compared with the findings of the earlier Petra study,[2] which included their study hospital, transmission between 3 and 6 months was much lower (compare top of figure 2 from the recent HIVNET 012 paper[1] with the group C survival curve in figure 3B of Petra).

Why are the findings of HIVNET 012 and Petra so different? The magnitude of the difference will only be revealed if the two study teams do a combined analysis. However, discussion of the reason for the difference need not—and should not—wait for such an analysis. Both trials recruited over a lengthy period, but only Jackson and colleagues examined time as a covariate. Because they found no time-dependent effect, any change in postnatal transmission must have occurred during the lifetime of Petra, which started almost 18 months earlier, or result from a qualitative difference between the two trials—either recruitment bias or content of counselling. Jackson and colleagues should describe any differences in the counselling given in their study compared with the early stages of Petra.

By November, 1997, when HIVNET 012 started recruiting, there was growing acceptance of the findings of a paper published in 1993 showing a strong relation between sexual behaviour during pregnancy and mother-to-child transmission of HIV-1.[3] The interpretation of that study has never been fully resolved. However, the increasing recognition of HIV-1 superinfection[4] raises the possibility that sexual exposure to an HIV-1-infected partner contributes to mother-to-child transmission in women who are already HIV-1-infected. The increased postnatal transmission in Petra between 3 and 6 months coincides with resumption of sexual activity in many couples. Abstinence from sex with an HIV-1-infected partner is associated with diminution of CD8 responses and increased risk of infection.[5] There is no reason why the same should not be true of superinfection.

Although Jackson and colleagues might not be able to provide evidence for or against the above hypothesis, they can still get more out of their data. For example, there is no discussion of the importance of the timing of the paediatric dose in relation to the maternal dose. Reluctance of midwives to use the HIVNET 012 regimen could partly relate to the need to tailor the timing to each woman, especially when postnatal care will be by someone on the next nursing shift. Transmission rates in the nevirapine group should also be reported according to whether a maternal dose was given within 2 h of delivery or given well before delivery.

Chris P Hudson

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From the Chief Medical Officer
Dr Henrietta Campbell CB

Department of
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An Roinn
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Mr John L Leckey LLM
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Your Ref:
Our Ref:
Date: 28 June 2004

Dear John

CORRESPONDENCE FROM EDWARD SUMNER

We both received a copy of a letter sent by Ed Sumner to John Jenkins regarding fluid management. I thought it would be helpful to outline some of the initiatives we are taking forward.

We are organising a workshop for the early Autumn to raise awareness of the basics of fluid management. We are relatively confident that the paediatric community has embraced the essentials of good fluid management, however, this may not be the case with general surgical staff in all of our hospitals. The workshop will therefore focus on those staff who require greater training and awareness.

You will also be aware that the future shape of our hospitals as outlined in "Developing Better Services" will lead to a more specialised approach to the care of critically ill children. We are also looking at some of the learning points from the 'Hospital at Night' pilot projects in England. This will influence the range of services, and the professional skills, available at an acute hospital site on a 24 hour basis. This work will be taken forward urgently.

A further initiative, which is relevant to Ed's concerns, is the work being taken forward by the Health and Social Care Records Steering Group. This group, chaired by Ian Carson, has completed a review of records management in the HPSS, and issued guidance for consultation in May of this year. This guidance will form the basis of a new circular "Good Management, Good Records", and new Controls Assurance standards in records management, which will be issued in due course. It is expected that this will address shortcomings which you have alluded to in recent inquests.

I am copying this letter to both Ed Sumner and to John Jenkins.

Yours sincerely

Dr Henrietta Campbell

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26 July 2004

Dr H Campbell
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Dear Etta,

I am very much in sympathy with your concerns regarding good education practice in relation to the management of intravenous fluids, particularly in children.

The topic is taught and highlighted at several junctures throughout the undergraduate curriculum. The modern curriculum links physiology and clinical practice very early in the course. Again, in the 3rd year Nephrology attachment, this is a specific topic addressed by experts in the field. In the 4th year it is a core component of the Paediatric course, and we have a specific session in the final year in preparation for PRHO practice in relation to prescribing fluids.

I have no doubt that Jack McCluggage will make this a key component of PRHO training, both in the current structure and with the introduction of the 2-year foundation course.

Yours sincerely,

Maurice Savage

Professor Maurice Savage
Director, Institute of Medical Education

cc Dr J McCluggage, Post Graduate Dean
Professor Rod Hay, Dean, Faculty of Medicine