LETTERS TO THE EDITOR

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Sweat chloride and conductivity 1

EDITOR,—As a principal author of the sweat testing document published by National Committee for Clinical Laboratory Standards (NCCLS) and consultant to the Cystic Fibrosis Foundation (CFF) (USA), I write to address an inaccuracy in the article by Heeley *et al*.[1] The authors misrepresent the NCCLS document on the role of conductivity analysis. Nowhere does the NCCLS document refer to the current conductivity methods described in the paper as unreliable; it does restate the widely accepted fact that some older conductivity methods are subject to evaporation error. The NCCLS document goes on to state that the CFF has approved the use of newer conductivity analysers for the screening of cystic fibrosis (CF) at community hospitals, using a decision level of 50 mmol/l.[2] This decision level is supported by the data presented in the Heeley article. The data presented in the article concerning equivocal patients also support the US reference interval for sweat chloride as normal below 40 mmol/l.[3 4] Patients with chloride values greater than 40 mmol/l should be further evaluated.

The reluctance of many to accept the use of sweat conductivity in place of sweat chloride for confirming a diagnosis of CF is based on the fact that chloride determinations directly reflect the genetic mutation of the disease. Conductivity is a property of all the charged species in a sample—for example, sodium, potassium, chloride, lactate, bicarbonate, etc. As the authors point out, chloride provides greater discrimination than sweat sodium—that is, less overlap between diagnostic categories. It would seem logical then, that combining sodium with chloride in a conductivity measurement would effectively cancel out the discrimination advantage of chloride alone. Referring to the data presented in table 2, there were twice as many patients with equivocal conductivity concentrations as with chloride (albeit a very limited sample size). Additionally, there exists a paucity of data in the scientific literature comparing conductivity and chloride values in CF and non-CF individuals. Even the scientists publishing such research support the conclusion that conductivity is appropriate for initial screening and chloride for confirmatory diagnosis.[5]

Heeley *et al*'s article attempts to provide relevant data, however it is most unfortunate that the authors failed to include in their analysis a linear regression plot of chloride versus conductivity along with a bias plot of the data so that the reader could assess the correlation. More studies need to be published comparing conductivity with chloride, particularly in patients with results in the equivocal range, before the conclusion can be made that sweat conductivity is as effective as chloride measurement for the diagnosis of CF.

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1 Heeley ME, Woolf DA, Heeley AF. Indirect measurements of sweat electrolyte concentration in the laboratory diagnosis of cystic fibrosis. *Arch Dis Child* 2000;**82**:420–4.
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Dr Heeley et al respond

EDITOR,—As the principal author of the NCCLS guideline on sweat testing methodology, Dr LeGrys should be better informed of its content. It includes the clear statement that when sweat test results are obtained by conductivity measurement "the patient should be referred for quantitative sweat electrolyte testing". In our paper we refer to this statement as implying that sweat conductivity measurement should be regarded as "unreliable for diagnostic purposes". This surely cannot be conceived as misrepresenting the NCCLS position, as claimed by Dr LeGrys. Although the NCCLS does, by reference, attribute this advice to Cystic Fibrosis Foundation (CFF) (USA) policy, by including it in their guideline without comment or qualification, the NCCLS authors are actively promoting it.

The medical politics of the USA do not concern us, but rather the question as to whether there is any scientific evidence underpinning this advice which the NCCLS upholds. The result of our study suggests there is none.

Dr LeGrys quotes research findings which support the conclusion that sweat conductivity measurement is appropriate only for initial screening purposes.[1] We contend that there is no data presented in this otherwise excellent paper which provide scientific justification for that conclusion.

Dr LeGrys is of the opinion that the conclusion we draw from our own study should have been supported by appropriate linear regression and bias plots of the data. The *Archives*' professional statistical adviser reviewing our manuscript, which included such data analysis, thought otherwise and requested us to remove it.

It is rather ironic that Dr LeGrys should now be pleading for more studies to be carried out to resolve the issue of the diagnostic equivalence of indirect and direct sweat electrolyte measurement, focusing on patients who produce results which are equivocal. Considering the relative rarity of such patients in general paediatric practice, if the problem revolves around these cases, why did the NCCLS guideline not clearly state this in the first place? In reality, the final diagnosis of cystic fibrosis in these cases is likely to be resolved by the results of investigations other than the sweat test.

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Sweat chloride and conductivity 2

EDITOR,—As I understand the Scientific Method, a statement purporting to be factual, either in a scientific article or in a discussion with peers, must be supported by cited evidence that may be publicly examined for its scientific veracity.

The paper by Heeley *et al*[1] provides data to illustrate the equivalence of conductivity and chloride in cystic fibrosis (CF) diagnosis, and therefore corroborates the findings of an earlier clinical trial by Hammond *et al*.[2] Further, a statistical comparison of the extensive published sweat chloride data of Shwachman *et al* with the conductivity data of Hammond shows that the two are of equal discriminatory power in CF diagnosis.[3]

Despite this evidence, Dr LeGrys has authored a document[4] that contains a number of assertions on this subject and on other aspects of sweat testing, that are not supported by any published results of original work of which I am aware. No clinical trial data exist which show that conductivity should only be used as a screen, that it is in any way inferior to chloride as a reliable diagnostic discriminator, or that conductivity readings of 50 mmol/l are positive for CF. Dr LeGrys' call for more studies on this matter may be seen as an evasion of the true issue. I suggest that the time has come, albeit belatedly, for her to substantiate her case, not with opinions, but by providing proper citations for relevant experimentally obtained data to support her contentions in the said document.

In a separate article[5] Dr LeGrys refers to conductivity as a "qualitative" assay, appearing to infer that it is less reliable than chloride analysis. The term "quantitative", used in the pad-absorption method merely indicates that

gravimetric means are used to measure the obtained sweat. It is obvious that this must be done to allow measurement of chloride concentration since elution of collecting pads is involved. The conductivity method is unequivocally quantitative because it measures a solution property in a micro cell of defined geometry. The inference is therefore absurd and irrelevant.

LeGrys, in her letter makes the incredible statement that since sodium is not as reliable as chloride as a discriminator it would seem "logical" (sic), that because conductivity measures both, the discriminatory advantage of chloride would be cancelled out. The logic of this is difficult to comprehend. Increase in sweat chloride due to functional aberration of the chloride channel must be compensated by increase of one or another of the available cation species—for example, potassium, sodium, or ammonium, in order to satisfy the Law of Electrical Equivalence. Such an increase in chloride will therefore be reflected by a proportionate increase in the total electrolyte concentration, which is the basis of analysis by electrical conductivity.

It is regrettable that lack of proper attention to basic scientific principles has persisted in the NCCLS guidelines for sweat testing for a considerable time without correction and has produced increasing confusion among medical technologists, particularly in the United States. It is sincerely hoped that the author of this document will see fit to amend it appropriately by substituting scientific accuracy for prejudice.

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Dipstrip examination for urinary tract infection

EDITOR,—We read with interest the letter by Thayyil-Sudhan and Gupta reporting their study on the role of dipsticks in the detection of urinary tract infection in children.[1] We believe that this is a very important subject and wish to comment on the report and their conclusions in the light of our published study.[2]

We note that as 188 urine samples were not sent for culture, it is not possible to determine the number of true and false negative dipstick tests (if any). Without these data, calculation of sensitivity and specificity of dipstick testing becomes impossible.[3] Because of the above we believe that the data presented are skewed secondary to a flawed experimental design. Consequently, the statement of the authors that urinary tract infection in children cannot be excluded by a negative nitrite or leukocyte esterase reaction is difficult to justify. Furthermore, there is no information to indicate whether children who were being treated with antibiotics at or immediately before admission were included in the study. If this is the case, the possibility of false negative culture results cannot be excluded and this will add further bias to the results. No data are provided for the number of infants included in the study. It has been reported that negative dipstick tests have a higher false negative rate in infants or in cases of urinary frequency because decreased bladder incubation time diminishes in vivo bacterial multiplication.[4] We are not told about the percentage of the samples, which were collected by pads, as compared to midstream specimens as this may further add to the inaccuracy of the culture results.

In our prospective study of 325 children in whom urinary tract infection was a clinical possibility, all urine was sent for laboratory examination.[2] The laboratory was unaware of the results of the dipstick tests until the end of the study. Analysis of our data showed that the combination of negative dipstick tests for nitrite and leucocyte esterase gave a negative predictive value for urinary tract infection of 96.9%, with a specificity of 98.7%. The figures for infants were 96.7% and 99.2%, respectively. A positive nitrite and/or leucocyte esterase had a positive predictive value of 60% and a sensitivity of 54.6%, compared with 50% and 20.0% respectively in infants. In our series we found that there were four false negative and six false positive nitrite tests.

The dipstick tests are most likely to be useful as a screening test to exclude urinary tract infection in children but may be less suitable for infants. They should not be used to diagnose urinary tract infection. We therefore disagree with Thayyil-Sudan and Gupta in their view that if nitrites are positive, starting empirical treatment for urinary tract infection seems to be reasonable until cultures are reported.

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Dr Thayyil-Sudhan and Dr Gupta comment:

Our study involved a selected group of children who were at an increased risk of having urinary tract infection.[1] The inclusion criteria were the presence of any of the following: firstly, clinical suspicion of urinary tract infection; secondly, history of previous urinary tract infections or renal anomalies; thirdly, children needing antibiotics (urine culture was sent before starting antibiotics); and finally, any of the dipstick tests (nitrites, protein, leukocyte esterase, or blood) being abnormal.

Out of the 500 children admitted to the hospital during the study period, only 312 met the above criteria and were included in the study. Urine culture was done for all these children, which reflects the local practice at our hospital of sending urine for culture. We wanted to see if a change in practice to urine culture being done only if nitrites or leukocyte esterase were positive would be effective in reducing the number of urine cultures.

The inclusion criteria for Sharief and colleague's study[2] was a clinical suspicion of urinary tract infection, when urine cultures were sent and dipstick testing was done. We found that urinary tract infection could easily be missed if urine culture is undertaken only if nitrites or leukocyte esterase are positive. Surprisingly, the results of both our study and theirs are similar: sensitivity was 34.4% *v* 20.0% and specificity was 90.7% *v* 99.2% in our study and Sharief's study respectively. Negative predictive value was 92.4% in our study and 96.7% in Sharief's study. Only the interpretation of the results is different.

A test with such a low sensitivity cannot be recommended as a screening test to exclude urinary tract infection. Urinary tract infection may result in irreversible renal damage in infants and therefore most care should be given to the detection of this infection in this age group. Unfortunately, this is the age group where sensitivity of dipstick testing is the lowest (20%). I agree with Sharief and colleague's study[3] that because of its high negative predictive value, dipstick testing may have some role as a screening test for urinary tract infection in situations where the incidence is very low. Positive nitrites have a high specificity for urinary tract infections, which was the basis of our suggestion that if nitrites are positive, especially in a febrile infant, empirical treatment with antibiotics may be considered until the result of urine culture is obtained. However, it should not be the whole criterion for diagnosing this infection.

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2 Sharief N, Hameed M, Petts D. Use of rapid dipstick tests to exclude urinary tract infection in children. *Br J Biomed Sci* 1998;**55**:242–6.

Should repeat lumbar punctures be routinely done in neonates with bacterial meningitis? Results of a survey into clinical practice

EDITOR,—Neonatal meningitis remains a very important cause of morbidity and mortality, with 30% death or handicap rate reported in a recent study.[1] In common with other clinical situations, the evidence base for some of the management recommendations for good clinical practice is hard to find. One particular aspect of the management of neonatal bacterial meningitis is whether or not a repeat lumbar puncture should be undertaken routinely. Several standard textbooks of neonatology[2 3] recommend repeating the lumbar puncture routinely in the course of neonatal bacterial meningitis, to ensure that "meningitis" continues to improve. This recommendation is based on past practice, and current evidence in favour or against repeating the lumbar puncture in neonatal bacterial meningitis is lacking.

However, we have observed that day to day clinical practice appears to have changed and fewer repeat lumbar punctures are being done. To investigate this we performed a simple questionnaire survey across the north

Table 1 Results of the questionnaire survey

Question: Do you routinely repeat LP in proven neonatal meningitis?
172 (100%) surveys posted
112 (65%) responded
3 (1.5%) were invalid (incompletely filled)
Answer: YES, 20 (18%) do routinely repeat LP because:
It helps in deciding duration of treatment—14 (70%)
It reassures that infant is improving—10 (50%)
It is recommended in textbooks—9 (45%)
Answer: NO, 89 (82%) do not routinely repeat LP and will only repeat if clinically indicated, because:
It will not help in deciding the duration of therapy—63 (70%)
Clinical improvement is more important—61 (68%)
It is unnecessary trauma—35 (39%)

LP, lumbar puncture.

Table 2 Breakdown of those who responded

	Registrars	*Consultants*	*<10 years experience*	*>10 years experience*	*DGH*	*Tertiary centres*
Routinely repeat LP	3.6%	14.6%	5.5%	12.8%	14.6%	3.6%
Do not routinely repeat LP	38.5%	43.2%	47.7%	33.9%	54.1%	27.5%

DGH, district general hospital; LP, lumbar puncture.

west of England to determine the opinion of currently practising/trainee paediatricians and neonatologists. Table 1 shows the results of the survey.

The response rate of 65% is a representative response for this type of survey. There was a good mix of experience—58% consultants and 42% trainees in paediatrics/neonatology; 47% had more than 10 years neonatal experience (table 2).

Many textbooks reflect past practices, especially when there is little new published evidence to support a change, yet in some circumstances day to day clinical practice is quite different from that promulgated in the standard texts. In an era of a demand for evidence based practice and an ever increasing level of litigation it is clearly important that current practice based on experience is reflected appropriately. This study shows that there is a widely held and practised view that routinely repeating lumbar punctures in neonates with bacterial meningitis is not appropriate and that a selective approach to repeating the lumbar puncture based on the clinical situation is the preferred option. This opinion was reflected by both those with long experience and in the teaching hospitals as well as by those practising in district general hospitals and trainees in paediatrics/neonatology. A national clinical survey of the outcome for infants with meningitis under different management practices should be carried out.

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We need the full picture on both smacking and vaccinations

EDITOR,—Dr Elliman is noted for his careful methodological analysis of vaccination studies,[1] but is not so careful in his recent analysis of physical punishment.[2]

The American Academy of Pediatrics's co-sponsored scientific consensus conference on corporal punishment used a more scientific approach than the Elliman-Lynch summary. First, it carefully defined spanking as a subset of corporal punishment. Second, it incorporated a range of scientifically validated perspectives into summary statements that were more balanced than the Elliman-Lynch perspective. Third, it solicited the first systematic review of child outcomes of non-abusive or customary physical punishment by parents,[3] which was recently updated.[4]

Both reviews concluded that non-abusive smacking had consistently beneficial child outcomes in the most causally conclusive studies—for example, randomised trials. Both non-compliance and fighting decreased in 2–6 year olds after non-abusive smacking was used to back up milder disciplinary tactics, such as reasoning or time out.

Causal evidence of detrimental effects of customary physical punishment was less conclusive and limited to overly frequent smacking—for example, three times weekly for 6–9 year olds. In head-to-head comparisons, the effects of non-abusive or customary smacking rarely compared unfavourably with any disciplinary alternative, whereas its effects were significantly better than six alternative disciplinary tactics, mostly in 2–6 year olds.

My updated review considered all 92 studies included in the unpublished 1999 Gershoff review cited by Elliman and Lynch. Most (76) of her studies were excluded from my review for reasons that Elliman would use to discount vaccination studies—for example, inappropriate measures, cross sectional designs.

Ellison and Lynch also presented a one sided summary of Swedish statistics since their 1979 smacking ban. Additional information on this issue and other related issues can be found at http://people.biola.edu/faculty/paulp/. The issues are complex, requiring the same careful analysis given to concerns about vaccination.

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Oral steroids and inflammatory markers in asthma

EDITOR,—We thank Dr Grigg for his interest in our work.[1] We agree that the asthma attacks may have resolved spontaneously in some cases, which was precisely why we stated that the markers fell in association with steroid therapy, and nowhere implied causality. Nevertheless, the statistical analysis suggests that the chances this occurred at random are extremely low.

We agree that corticosteroids do not inhibit, except at very high concentrations, degranulation of the eosinophils induced by incubation with opsonised particles, such as Sepharose beads in vitro.[2] However, there is overwhelming evidence that cytokines such as IL-5 prime eosinophils for increased release of granule proteins in this situation,[3 4] and that they inhibit cytokine-mediated prolongation of eosinophil survival.[5] These observations, coupled with the abundant evidence that corticosteroids reduce the expression of eosinophil-active cytokines, such as IL-5, provide a convincing chain of evidence linking the clinical use of corticosteroids with reduced release of eosinophil granule proteins in vivo.

With regard to the controls in this study the ratio of atopic to non-atopic asthmatics was 4:1 and of atopic to non-atopic controls was 3:1. These differences are not significant by chi-squared testing. Whilst we agree that more controls might have strengthened our conclusions, nonetheless the evidence of unresolved inflammation after an apparently clinically adequate course of prednisolone, as shown by the elevated levels of IL-5 and sCD25, remains strong.

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BOOK REVIEW

The Neurological Assessment of the Preterm and Full-term Newborn Infant. L Dubowitz. (Pp 167; £35.00). Cambridge University Press, 2000. ISBN 1898683158.

Progress in the management of disease in the newborn has carried with it a recognition of the substantial risk of injury to the immature nervous system. The aspiration to localise and prognosticate from neurological signs in the early newborn period is easily understood. The problem is that the signs available to be discerned are in themselves usually insufficient to allow precision. In addition, the child grows and develops, the range and complexity of skills are constantly changing, and the manifestations of the lesion(s) alters, or may become silent, often to reappear later as a different but nevertheless highly significant impairment.

The evaluation of the newborn nervous system was originally based upon concepts learnt from adult neurology. The baby was seen as demonstrating little or no cortical or cerebellar activity and the study of primary reflexes predominated. The approach of adult neurology, with emphasis on localisation of the lesion, becomes less applicable in the younger child. In the newborn period, focal insults to the brain will often give rise to generalised disturbances and, contrarily, generalised disturbances may show focal deviations. Recognition of these phenomena has led to a progression from the concept of a localisation based neurology to one which sees the infant displaying a neurological/behavioural repertoire. Over the past several decades Saint Anne Dargassies, Prechtl, Amiel Tison, Brazelton, Dubowitz, and others have, through meticulous study, done much to illuminate this area. Through these studies, awareness of the importance of the behavioural state of the baby, as well as the more detailed neurological items has evolved.

A second problem in this area, particularly in relation to research studies, has been the development of a systematic newborn neurological examination which is reliable and repeatable. This has been the subject of the two editions of this work. The first, published in 1981, gave a detailed, easily understood and applied system for the neonatal neurological examination. The current edition brings that work up to date. New material is presented, refinement of the scheme has occurred, and the examination is described. Items which were less discriminatory of pathology from the 1981 version have been withdrawn and, following the work of Prechtl, more emphasis is placed on the analysis of general movements. There is a further post neonatal to two year old infant neurological examination proforma presented briefly at the end of the text.

The text is essentially a manual on the application of this neurological examination scheme. It is easy to follow and the segments of the examination are presented clearly with excellent photographs and line drawings of each manoeuvre. There is also a useful addendum ("cautionary tales") to each section of the examination, giving guidance on possible pitfalls and sources of error. There is a lot of very useful information on the variations in findings in term and preterm infants, and particularly the changes in the neurological features of preterm infants as they grow towards term. There follows a section on the development of an optimality score from the observed items of the assessment. This section deals with the results of a survey of 224 normal term infants. In this study each item of the scheme was plotted, and centile values (and thereby optimality scores) were computed. This provides quantification of the assessment, a sense of the range of findings to be expected, and can be useful in correlating lesions observed on neuro imaging with clinical findings. Chapter six deals with the scheme in relation to findings in infants with recognised brain lesions.

The book is not designed to be a text of neonatal neurology and readers looking for discussion of neurological disease states will be disappointed. As a description of a comprehensive and easily applied system of neonatal neurological examination the new edition succeeds admirably.

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Sweat chloride and conductivity 1

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Notes