Post-conference thoughts from Malawi

Sir—I have just returned from an international conference on children’s cancers. Parallel sessions were held for doctors and nurses, and many esoteric as well as practical issues were discussed. It was held on African soil, but most of the 900 delegates were from Europe—perhaps not surprisingly, since cancer treatment is expensive and low on the agenda of poorly resourced countries overwhelmed by other diseases.

The nurses held a workshop on palliative care, and because we now have a palliative care team in our children’s wards, I went to see what I could learn. I arrived late and the discussion was around whether nurses should attend a child’s funeral and if so how many should go. How long after the death should an anniversary card be sent to the family? The Belgians favoured 5 years, the Swedes and Dutch did not have a policy on this. I sat quietly, feeling rather omitted. We have so many deaths, not only from cancer. We try to show how sad it makes us, we try to ease a child’s and family’s physical and emotional pains. Often we send them home to die, armed with as much appropriate medicine as we can provide.

But as I sat there I remembered Simone. Simone was 6 years old when he developed Burkitt’s lymphoma of the jaw. He was on our ward for 3 months of treatment. And like all cancer therapy it involved needles—for taking blood, giving medicines, giving fluids, and giving blood. He put up with it all bravely. He and his mother came from far away and so they stayed the full 3 months with us. Simone became bosom pals with Antoine—an 8-year-old with a similar problem. Both of them were fascinated by my car keys which opened the door from a distance and made the lights flash. They would follow me around the hospital hoping for a chance to use the remote control.

Simone did well and went home, but within 4 months the tumour was back; in the same place but bigger and nastier. More treatment failed and after a while we explained to him and his mother that there was no more we could do and that she shouldn’t waste money travelling to town but try to get help from the nearest clinic. She took a letter for the clinic with her, which explained the problems.

On duty over Easter, I found Simone and his Mum had returned. He was conscious but very ill, a large mass in his mouth and cheek, which distorted his eye and made speech difficult. I asked Simone’s mother what she hoped that we could do. “Nothing”, she replied, “but he asked to be brought to you”. I felt wretched; did Simone think we had something special that would make him better?

Crouched beside his bed where he lay, we talked. Would he like some nice milk and porridge to make him strong? We would find something for his sore mouth and a syrup for his aching head.

On Easter Sunday I was walking down the long, main, hospital corridor and found a procession slowly coming towards me from the children’s ward. A nurse was pulling a trolley on which a small bundle lay, covered by a white cloth stitched with a red cross. Behind the trolley came Simone’s mother and surrounding her and stretching far behind, came 30 or more women from the wards, most with their sick children on their backs. They were all singing. I stood aside as they passed, moved to tears.

Here was a hospital community sharing a mother’s grief and supporting her in the difficult business of taking her little son’s body home.

Palliative care is neither new nor the same everywhere. The miserable side of signs and symptoms needs careful management, and palliative programmes that have developed in the west teach us a lot about all that. But the warmth and support that surrounded Simone’s last few days showed how much can be done with little but hands, and hearts, and voices.

Elizabeth Molyneux
Paediatric Department, College of Medicine, Box 360, Blantyre, Malawi
(e-mail: emolyneux@malawi.net)

Selective decontamination of digestive tract in intensive care

Sir—Evert de Jonge and colleagues (Sept 27, p 1011)1 believe they have proven that selective decontamination of the digestive tract (SDD) of patients in intensive care units (ICUs) significantly improves hospital survival, and lowers the rate of acquisition of resistant gram-negative aerobic bacteria. Unfortunately, the design and execution of the study do not allow such conclusions to be drawn.

By contrast with their statement, the study was neither randomised nor well controlled. They essentially compared the performance (ie, the rates of hospital mortality and resistance acquisition) of two separate ICUs—in one of which, SDD was introduced for 2–3 years, whereas in the other it was not. Since de Jonge and colleagues elected not to switch the SDD regimen from one ICU to the other somewhere through their observation period, it is very difficult to ascribe differences in outcomes to the use of the SDD regimen alone. The ICU unit applying SDD already had a 10% lower rate of hospital mortality than the control ICU in the 2 years preceding the start of the study. The 95% CI of this 10% difference in mortality was 0·7–1·1. During the study, de Jonge and colleagues observed a 24% lower hospital mortality rate in the SDD-using ICU than in the other—a difference that clearly falls within this CI, indicating that the true a-priori performance of the ICU unit applying SDD might already have been much better.

The similarity in baseline characteristics between the two cohorts of patients treated does not correct for the performance bias built into the design of the study. Infection and mortality rates differ greatly between various ICUs within and between hospitals—differences that cannot solely be explained by differences in the average severity of illness of patients at the time of admission.2 Intensive care is critically dependent on the skills of and care delivered by a heterogeneous,
multidisciplinary team of experts in medicine, surgery, supporting specialties, and by specially trained nursing staff. de Jonge and colleagues do not control for the crucial influence of the ICU team on patients’ outcome. Indeed, by its design, the study has added to the a-priori performance difference between the two ICUs since patients in the unit applying SDD were better observed and cared for as a consequence of the need to apply the SDD medication.

Finally, de Jonge and colleagues did not properly examine the risk of the emergence of antibiotic resistance due to SDD. They took samples for systematic culture only during patients’ stay in the ICU. Since application of large quantities of antimicrobial agents to mucosal surfaces will eradicate much of the aerobic microbial flora, and might well mask the selection or acquisition of resistance clones as long as SDD is given, the true risk of fostering resistance emergence should have been assessed by using special, SDD-neutralising media for culture while patients were on SDD, and by monitoring the recolonisation of the patients’ digestive tracts after they were discharged from the ICU and the hospital.

Although de Jonge and colleagues do not exclude the possibility that the performance differences seen between the ICUs were due to differences in care, they believe that this cannot account for the differences in outcomes. I believe it can, and would rather not have to believe one way or the other, but know for sure.

Henri A Verbrugh
Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Centre, 3015 GD Rotterdam, Netherlands (e-mail: h.a.verbrugh@erasmusmc.nl)


Our most significant concern is the open-label design of the study. Patients enrolled were admitted to one of two units, the SDD unit and the control unit, and medical staff did not mix between the two. de Jonge and colleagues selected objective endpoints such as inhospital mortality to keep bias to a minimum. However, unrecognised bias might have influenced the results of this study, considering the possible differences in ward environments and medical staff between the two treatment groups. The decrease in mortality in the SDD unit could also be explained by the possibility that SDD might have reduced bacterial or fungal infections. We would be interested to see detailed information on the ward environments, including incidence of nosocomial infections, patients’ outcomes, and causes of death.

Sung-Won Kim, *Masahiro Kami, Kazuhiro Kobayashi, Yolchi Takaue, Osamu Honda
*Hematopoietic Stem Cell Transplantation Unit, Tokyo 104-0045, Japan (e-mail: mkami@ncc.go.jp)

In conclusion, we believe the issue of reduced mortality with SDD can only truly be resolved through a large, randomised, double-blind, placebo-controlled trial.

* Martin E Stryjewski, Keyur Patel
Divisions of *Infectious Diseases (MES) and Gastroenterology (KP), Duke Clinical Research Institute, Duke University Medical Center, PO Box 17969, Durham, NC 27715, USA (e-mail: stryj001@mc.duke.edu)

Sir—Evert de Jonge and co-workers’ report that SDD confers an astonishingly strong benefit in terms of survival for patients in ICUs. In fact, the point estimate of the effect is beyond the 95% confidence limits of several meta-analyses on this subject. de Jonge and colleagues claim that the design of their study can explain this finding, and we agree. However, we do have some questions about the design and execution of the study and about current practices in the hospital.

First, the study was a randomised controlled trial with patients assigned to one of the two treatment groups. de Jonge and colleagues state that “unless beds were available in one unit only, patients were allocated to one of the IC-units”. In the SDD unit, patients had a median ICU stay of 6·8 days compared with a median stay of 8·5 days in the control ward. Therefore patients in the SDD ward had a 20% shorter ICU stay, and one would expect that more beds would have come available in that ward. Yet, the total number of patients in both wards was identical. An average of 2 days for 466 patients would have resulted in 932 extra bed-days available, which could have been occupied by 137 patients with an average stay of 6–8 days. We are not sure how this difference in length of stay resulted in equal number of patients allocated to the wards. We therefore wondered how many patients were really randomly allocated to one of the two ICUs. Although de Jonge and colleagues’ table 1 suggests that relevant characteristics for both patient groups were comparable, randomisation in this unblinded study is crucial to avoid bias.

Second, there was a tendency towards better hospital survival in the ward assigned SDD (relative risk 0·9 [95% CI 0·7–1·1]) in the 2 years before
the study. Since the differences in the SDD trial were higher for ICU mortality than hospital mortality, the same could apply for the prestudy period. We would therefore be interested to know ICU mortality rates in both wards in the prestudy period. Absolute mortality figures would also be of interest to see whether there was an improvement in survival during trial execution in both wards.

Third, colonisation with resistant bacteria occurred more frequently in the control ward. Was there any evidence of clonal spread of these bacteria? In other words, if there were an outbreak, the actual number of patients colonised could be quite high owing to only a single event. It is important to clarify the clonal distribution of resistant pathogens on both wards.

Fourth, for generalisability, antibiotic use must be expressed in standard units—ie, number of defined daily doses (DDDs) per 1000 patient-days. Unfortunately, de Jonge and colleagues provide only total DDDs, which makes comparison of antibiotic use between ICUs impossible.

Jacob M Puliyel
Department of Pediatrics, St Stephens Hospital, Tis Hazari, Delhi 110054, India (e-mail: puliyel@vsnl.com)


Authors’ reply

Sir—Several coauthors suggest that treating SDD and control patients on separate units might have introduced major bias because improved survival in SDD-treated patients might be caused by differences in care other than the use of SDD. We do not think that this scenario is very likely. Both units were part of the same ICU, used the same treatment protocols, and had the same physicians taking care of the patients. The only difference was the nursing staff, and we do not think that this difference can account for the major effect on mortality in the SDD group. Henri Verbrugh suggests that SDD patients were better observed and cared for as a consequence of the application of SDD four times daily. However, this possibility is not very realistic. ICU nurses spend virtually all of their time at the bedside of the patient,1 and a patient’s observation will not be improved by the application of SDD to the mouth and gastric tube.

We deliberately chose a non-crossover design with separate units. The alternative—mixing SDD and control patients in close contact on the same unit—would lead to cross-colonisation of patients, making it impossible to determine the true effects of SDD on mortality and particularly on the emergence of resistance. Furthermore, because the effects of SDD on the bacterial flora in the environment could be present for long periods, washout periods of many months would be necessary in a crossover design.

Sung-Won Kim and coauthors and Martin Stryjewski and Keyur Patel ask for information about nosocomial infections and causes of death. Because unequivocal definitions for these endpoints are lacking, we preferred not to include them in our study. Owing to the non-blinded design, we preferred to have only solid endpoints—ie, mortality and resistance to antibiotics.

Martin Stryjewski and Keyur Patel argue that a two-sided α error should be used for sample size calculation if an intervention might lead to either increased or decreased bacterial resistance rates. We agree. However, at the time our study was designed, it was generally believed that SDD could lead to increased but not to decreased resistance.2 We agree that lower resistance might be explained by a more rational use of antibiotics. In fact, we think that SDD itself can be regarded as a more rational use of antibiotics. We analysed the influence of SDD on mortality depending on the presence of pre-existing infection. Documented pre-existing infection was present in 69 (14·8%) of SDD patients and in 84 (17·9%) of control patients. The relative risk of death in SDD-treated patients was 0·79 (95% CI 0·62–1·00) in patients without pre-existing infection and 0·81 (0·53–1·26) in patients with pre-existing infection.

Marc Bonten and coauthors suggest that more patients should have been enrolled in the SDD group as a result of a reduced length of stay in SDD treated patients. However, the numbers enrolled were not different between the groups because about 75% of all patients on both units were not enrolled in the study as a result of the inclusion and exclusion criteria. The patients enrolled in the study, about 90% were actually included.

It is not true that the ICU unit applying SDD had a lower mortality rate in the 2 years preceding the study, as suggested by Marc Bonten and coauthors and by Henri Verbrugh. On the basis of the 95% CI of 0·7–1·1, no difference in hospital mortality was found. The relative risk of ICU mortality was also not different between both units before the study (relative risk 0·9 [95% CI 0·7–1·1]).
During the study period, there were two outbreaks with resistant bacteria—one with \textit{Enterobacter cloacae}, which was resistant to tobramycin and ciprofloxacin, and one with \textit{Acinetobacter sp}, which was resistant to tobramycin, ciprofloxacin, and imipenem; both were on the control unit. Of the 104 patients in the control group who were colonized with resistant gram-negative bacteria, 14 were involved in one of these outbreaks.

We agree that it is almost impossible to compare antibiotic use in our study with that in other ICUs. To make comparisons, it is necessary to correct for the case-mix of patients, the prevalence of antibiotic resistance in the population, and for factors influencing the length of stay of patients, such as the availability of medium care facilities.

Henri Verbrugh is concerned that antibiotics applied in SDD-treated patients do not lead to false-negative cultures and an underestimation of the resistance rates in these patients. Since cultures from the ICU environment, where no antibiotics were present, showed differences in resistance similar to those from patients, this suggestion is unlikely. Nevertheless, we cannot exclude this hypothesis and we agree that monitoring of recolonisation after ICU discharge could be very informative. Our intention is to make this the subject of future research.

Finally, Mohit Sahni and coauthors comment on the fact that patients who did not give consent were treated with or without SDD depending on the unit they were admitted to. In those patients, no investigational cultures were taken and they were not included in the study. However, we do not agree that we have set a new ethical standard because, for many years, both SDD and non-SDD have been regarded as standard therapy in the Netherlands. Patients who declined consent were fully informed about their treatment with or without SDD.

**Paulesco: science and political views**

Sir—Gérard Slama (Oct 25, p 1422) raises an important issue in his letter about the alluded antisemitic past of the Romanian scientist Nicolae Paulesco: should unacceptable political ideas obscure a recognised scientific achievement?

The International Diabetes Federation (IDF) was confronted with this issue at its 2003 Congress in Paris in the circumstances described by Slama. We would like to present here the press release issued by the IDF on August 26, 2003: "In view of the controversy raised in \textit{Le Monde} of August 26th 2003 about the Romanian scientist Nicolae Paulesco, and in the absence of additional information as to the truthfulness of facts, the Organizing Committee of the 18th Congress of the International Federation, in agreement with the International Diabetes Federation, decided to cancel the session on August 28th at which a Prize was to be awarded in memory of Mr Paulesco."

The IDF is now collecting the appropriate writings of Paulesco. These will be scrutinised by an independent committee. The IDF does not wish to mix science and politics. But more information is needed before we can internationally laud an individual who has undoubtedly made a major scientific contribution, but who might have espoused a morally unacceptable position later in life.

**George Alberti,** *Pierre Lefèbvre*

International Diabetes Federation, Avenue Emile De Môt 19, B-1000 Bruxelles, Belgium
(e-mail: pierre.lefebvre@ulg.ac.be)


**Contract for UK consultants**

Sir—William Jeffcoate’s Commentary (Nov 1, p 1432) combines inaccuracies with basic statistical errors. He argues that only 44% of consultants supported the new contract. In fact, almost 70% of English consultants turned out to vote and 60% of them voted "yes". We are unaware of any research that assumes that unknown variables have a particular value; it is simply poor science to pretend that those who did not vote were against the contract. Such a turnout, and such a high "yes" vote, is a very firm endorsement in any democratic process, and should be seen as particularly conclusive, in view of the large "no" vote a year ago (66%).

There is no vagueness about the number of ballot papers sent out: 30 518 to consultants and 8733 to specialist registrars in England, and there was no impression in the ballot process which was done by the Electoral Reform Society. That a very small proportion did not receive a ballot paper is inevitable, given that all consultants and specialist registrars were balloted, not just members of the British Medical Association (BMA), and that maintaining up-to-date addresses is often difficult for a mobile workforce.

However, the use of advertisements in the medical press and the BMA website, as well as telephone and internet voting, should have meant that all had a chance to vote.

Furthermore, the ballot result was not—as Jeffcoate implies—announced in the pages of the \textit{Guardian} newspaper, but was placed on the BMA website within minutes of the announcement. An e-mail was sent to all consultants who had registered for such information (about 10 000), and a letter was posted to all those eligible to vote, both on the day of the ballot result.

The ballot question for consultants, “Do you want to have the option to take up the new 2003 national contract negotiated between the BMA and Department of Health in England?” was not intended to encourage a “yes”, but simply to reflect the situation.

Finally, Jeffcoate argues that we should not have conveyed the Government’s threat of local deals and that the medical profession should have made a stand. To do the former would have been undemocratic, and in fact the BMA led a very successful stand against local implementation of the (unrevised) contract.

In summary, the criticisms raised by Jeffcoate have little value other than conveying his disappointment in a “yes” vote. We agree with him that clinical services need more resources and that provision of quality care is the most important thing for most consultants. Far from being sidelined, the BMA is actively lobbying for more resources and better quality in the National Health Service, at every level.

**Nizam Mamode, Paul Miller**

BMA Central Consultants and Specialists Committee, BMA House, Tavistock Square, London WC1H 9JP, UK
(e-mail: ftranza@bma.org.uk)

The selection of doctors

Nearly 30 years ago I suggested that three top-grade science A-levels (examinations taken at age 18 years in the UK) were a poor prognostication of success in a medical career, and that other skills and qualities were much more important. That article struck a chord; it prompted a flood of letters of agreement from specialists, general practitioners (GPs), surgeons, and medical schools everywhere. Sadly, changes have been slow. Some medical schools have given more weight to interviews, and some consider candidates with high grades in arts subjects, provided they undertake a premedical conversion course. Few selectors have been brave enough to wonder what their patients hope for in GPs and consultants.

A surgeon needs to have diagnostic skills, a detailed knowledge of anatomy, and a cool head in a crisis. Judgment and a sharp eye are vital, as is a real concern for patients and assistants. How A-grades in mathematics or physics nurture these attributes is not clear. Yet hundreds of good potential doctors have been turned down because of weak grades in those subjects, which most of them will never need again. So how might we look out for the essential attributes of a surgeon?

Anything that tests the powers of detailed and systematic observation could give a better clue as to diagnostic skills than academic qualifications: a first-class ability to identify birds at all ages, of both sexes, and different times of the year might reveal unusual potential. Anatomy? Either the present biology syllabus should give more insight into anatomy, or there should be a separate paper stressing the medical and anatomical parts of the subject, as in the newly proposed biomedical paper.

For manual dexterity, some people can deal with inaccessible screws; others, with similar tools, intelligence, and lighting, find it impossible. Given the choice between being operated on by a master of calculus or an expert fly tier, chicken carver, puppet maker, or cellist, the one with the sharp eye and neat fingers will win my vote every time. There will always be a call for some top academics to advance the frontiers of medical science, but exceptional academic achievement is not necessary for most. Personal qualities and relationships with patients and nurses are of supreme importance. Not all doctors really listen to the patient. How difficult it is to hit the right balance between truth and reassurance—a proper confidence and a recognition of the possibility that one might be wrong. School reports should be vital in this regard, but unfortunately are unreliable. Headmasters, trained to fight for league positions, and to compete for the number of places secured at prestigious institutions, turn their ugly ducklings into swans. As a rule, only the best schools openly express reservations about their candidates' weaknesses.

Now that the school day finishes so early, there is very little contact between teachers and pupils outside the classroom. Heads no longer know what kind of pets their pupils keep, their individual hobbies, and whether their younger sisters have recovered from measles. It is, however, in these spheres, together with evidence of motivation, that the vital clues lie.

GPs should be more broadly based. The 18-year-old A-grade stars are not always those who get first-class degrees at age 22, or become brilliant doctors. They are just as liable to take to drugs or drink, to prefer personal indulgence to duty, to be unreliable in their personal relationships, and to imagine that they have no more to learn. Schools must be taught to give truly detailed and relevant reports to the medical schools to enable them to select deeply committed, kindly people; those appreciated and respected by others; and those who are careful, dextrous, observant, humble, and keen to keep on learning.

Logie Bruce-Lockhart
Mead Barn, New Road, Blakeney, Norfolk NR25 7PA, UK


Primary prevention of stroke

Sir—Charles Warlow and colleagues begin their comprehensive Seminar on stroke (Oct 11, p 1211) by drawing attention to the major public-health burden of stroke and to the need for prevention programmes. However, they focus on secondary prevention and not primary prevention—ie, prevention of first stroke. Primary prevention is an imperative, since first stroke is still often fatal or causes major disability. Additionally, as Warlow and colleagues point out, a second stroke can follow soon after the first, leaving little time for secondary prevention.

There is good evidence that risk of a first stroke can be reduced with interventions including lowering of blood pressure and lipids, use of antithrombotic therapy in patients with non-valvular atrial fibrillation, and antiplalet therapy in patients with myocardial infarction. Additionally, observational studies indicate risk reduction with lifestyle modification (smoking cessation, regular physical activity, healthy diet, and abandonment of heavy alcohol consumption),

But who are the candidates for primary prevention of stroke? Clearly, individuals with established coronary heart disease or peripheral arterial disease are at high risk of stroke. Also, asymptomatic men and women with a high risk of cardiovascular disease can be identified. Several charts, scores, and algorithms are available for risk estimation. Most of these prediction tools have been developed with data from the Framingham Heart Study and use information on risk factors such as age, sex, blood pressure, serum cholesterol concentration, smoking status, and diabetes. A chart for cardiovascular risk prediction based on data from 12 European cohort studies has been published this year and is used in the new European guidelines on cardiovascular disease prevention issued by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention. As reflected in these and in numerous other guidelines, there has been a paradigm shift in blood pressure and lipid management away from fixed treatment thresholds towards differential recommendations according to absolute risk of developing cardiovascular disease.

The overall effect of preventive measures on first stroke can be substantial. For example, a recent study estimated that combinations of different personal and non-personal health interventions for reduction of high cholesterol concentrations and blood pressure (eg, individual treatment and education, population-wide reduction in salt intake, or health education through mass media) are cost effective and might be able to lower the global incidence of cardiovascular events by as much as 50%. Apart from such interventions, adoption of healthier lifestyles by large groups of the population is pivotal. Further research is needed to better identify not only specific risk factors for stroke, including detrimental health behaviours, but also possible reasons for the difficulty in changing them. Such information would enable us to better tailor preventive measures to specific risk profiles.

Hannelore K Neuhauser
Robert Koch-Institute, Department of Epidemiology and Health Reporting, D-13553 Berlin, Germany (e-mail: h.neuhauser@rki.de)
Effect of Estonian law on prospects for public health research

Sir—On Feb 12, 2003, with only 26 of its 101 members present, the Estonian Parliament (the Riigikogu) unanimously adopted a new law on data protection. The law that came into force on Oct 1, will inflict profound damage on public health research in a country where life expectancy at birth is almost 8 years less than in the European Union (EU), and which is highly respected internationally. Bureaucratic obstacles have already prevented the registry from linking to data from the national mortality database, so that about 5% of incident cases, for which the only primary information is from death certificates, are now lost. This gap clearly obscures real trends in incidence and thus gives a false impression of the health of the Estonian population. The use of personal identifiers in the national mortality database, maintained by the Statistical Office of Estonia, has been declared as violating privacy rules and their removal is now under discussion.

Those drawing up the EU directive on data protection were persuaded of the need for exemptions to the general right to privacy on grounds of public health when the dangers of failing to do so were brought to their attention,1 and although the implementation of the legislation has given rise to substantial confusion by over-zealous authorities in some countries,2 such uncertainty is now being given rise to substantial confusion by over-zealous authorities in some countries,3 such uncertainty is now being resolved in most. Yet as the Estonian decision shows, there is a need for continuing vigilance by the European public health community, who must continue to speak out in support of our colleagues who are struggling to understand the health of their populations.

*Mati Rahu, Martin McKee

*Department of Epidemiology and Biostatistics, National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia (MR); and European National Institute for Health Development, Hiiu 42, 11619 Tallinn, Estonia (MR); and European


A bad dose of the ‘flu

Sir—Cases of acute necrotising encephalopathy (ANE) have been reported mainly from Japan.1 D L Jardine and colleagues (Oct 11, p 1198)2 describe one case, and suggest that subtle antigenic changes to influenza virus might be the cause. However, if so, why in this era of large-scale global travel is ANE so rare among Western people?

First, ANE is seen not only in patients with influenza, but also in febrile patients with upper respiratory infections caused by other viruses. Mizuguchi and colleagues3 reported ANE cases with exanthema subitum, Coxackievirus A9 and B4 infection, herpes simplex, and measles, as well as influenza A and B.

Second, many doctors in Japan prescribe stronger antipyretics than aspirin (eg, diclofenac and mefenamic acid) to febrile children. In the national survey of 1998–99, correlation was noted between the use of antipyretics and death due to influenza-associated encephalopathy, including ANE. ANE seems to be caused by an exaggerated cytokine response resulting in vascular damage and breakdown of the blood-brain barrier.1 However, the causative agent is not necessarily the virus itself. Cytokine responses to drugs in the febrile state could have a major role. In Japan, the Ministry of Health and Welfare banned prescription of diclofenac in 2000, and mefenamic acid in 2001, for influenza. Whether cases of influenza-associated encephalopathy will decrease, remains to be seen.

Third, many Japanese doctors prescribe several drugs at once to febrile children with upper respiratory infections. In one report, a 3-year-old girl treated with cefdinir (an antimicrobial), procaterol (a β-adrenergic agent), ambroxol (an expectorant), alimemadine (an antihistamine), and acetaminophen succumbed to ANE; in addition, a 1-year-old boy prescribed erythromycin, tulobuterol (β-adrenergic agent), ambroxol, carbocisteine (expectorant), bromhexine (expectorant), and ephedrine also died of ANE.1 Although, in these two cases, too many drugs were used to clarify the cause-effect relation with ANE, the possibility that drugs induce influenza-associated encephalopathy, including ANE, should be kept in mind.

Masako Kondo

Department of Radiology, Keio University School of Medicine, 35 Shihanomachi, Shinjuku-ku, Tokyo 160, Japan (e-mail: kondo@rad.med.keio.ac.jp)


