LETTERS

Cost of hepatitis A vaccine: $70. Mounting your own antibody response to hepatitis A before your overseas holiday: priceless

Jake Shortt, Denis Spelman and Erica M Wood

To the Editor: Human normal immunoglobulin (NIG) has historically been used to provide passive immunity against hepatitis A infection for susceptible travellers to areas where the virus is endemic.[1] The introduction of effective hepatitis A vaccines in recent years (which result in active, long-term immunity to the virus) should have largely replaced the use of NIG for travel prophylaxis.[2] However, the Australian Red Cross Blood Service still receives requests to supply NIG for travellers, even though the intended recipients have no contraindications to vaccination.

Requests for use of NIG for this purpose appear in many cases to be a consequence of the "out-of-pocket" cost to the patient of the hepatitis A vaccine, which is about $70–$100 (depending on the formulation used and the private dispensing fee charged). In contrast, NIG is provided free of charge to the recipient, but the community still incurs substantial costs related to blood collection and fractionation of plasma products. There is also the concern of unnecessary exposure of a healthy traveller to a pooled plasma product, which, despite blood donor screening, dedicated viral inactivation steps, and an excellent safety record in Australia, may theoretically transmit infectious agents. In addition, even if a small amount of NIG is used for this purpose, the plasma source would be better used for production of greater amounts of other scarce plasma-derived products (such as intravenous immunoglobulin).

While NIG can effectively prevent hepatitis A infection from developing in susceptible contacts, immunity is short-lived and likely to be inferior to the results of active vaccination.[1-3] Accordingly, NIG is only indicated for at-risk people who have a contraindication to vaccination, or in whom there is insufficient time to mount an endogenous antibody response (active immunity develops within 7–10 days of vaccination,[3] and vaccination may also prevent hepatitis A infection even when the vaccine has been administered up to a week after exposure[4]). Use of NIG is also appropriate where at-risk contacts may be unable to mount a protective antibody response because they have a congenital or acquired immune deficiency.

Although the extent of NIG use for travellers appears to be limited, we wish to highlight that, in the absence of contraindications to vaccination, it can no longer be advocated as best practice, and it is certainly not an appropriate cost-saving measure.

Jake Shortt, Haematology Registrar, Transfusion Medical Services[1]
Denis Spelman, Head of Microbiology and Deputy Director[2]
Erica M Wood, Transfusion Medicine Specialist[1]
1 Australian Red Cross Blood Service, Melbourne, VIC.
2 Infectious Diseases Unit, The Alfred Hospital, Melbourne, VIC.
jshortt@ausdoctors.net

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Intradermal rabies vaccine

Anthony Gherardin and Sonny Lau

To the Editor: Rabies vaccine is recommended for pre-exposure prophylaxis in travellers over 1 year old who intend to travel to predominantly developing countries where canine rabies is endemic. The incidence of dog bites in such countries is relatively high, being more common among travellers than typhoid fever.[1] Post-exposure rabies treatment of pre-immunised travellers is simpler, cheaper and safer than treatment of those who have not been immunised.

Rabies vaccines currently available in Australia are given intramuscularly as three doses of 1.0 mL on Days 0, 7, and 21–28, but are relatively expensive at more than $100 per dose. Some travellers will choose not to be vaccinated because of this cost. For at-risk travellers who might choose to decline vaccination because of the cost, and to facilitate use of pre-exposure vaccination in poorer countries, the World Health Organization approves the intradermal route of vaccination, where 0.1 mL of vaccine is administered, also on Days 0, 7 and 21–28.[2]

However, the intradermal technique is technically more difficult, may result in lower antibody levels that decline more quickly, and may be interfered with by concurrent administration of chloroquine or immunosuppressants. The *Australian immunisation handbook* therefore recommends that this technique be performed by vaccinators experienced in the technique, and that satisfactory antibody production is confirmed after vaccination.[3] Antibody levels of at least 0.5 IU/mL are considered protective, and the commercial enzyme immunoassay, available under Medicare, has been shown to correlate well with the gold-standard virus neutralisation test.[4]

We have been using the intradermal method for over 10 years for travellers considered at high risk, but who decline vaccine on cost alone; we use imported human diploid cell vaccine of potency of at least 2.5 IU/mL. As several travellers can be vaccinated from the same vial, costs are $30–$40 per dose, and vials can be stored and reused within 7 days under aseptic conditions. However, travellers must be vaccinated 7–8 weeks before departure to enable antibody testing and a booster vaccination if required.

Recent analysis of 1532 non-immunosuppressed travellers (aged between 9 and 77 years; 55% female) who received three intradermal doses of 0.1 mL rabies vaccine on Days 0, 7, and 21–28 in our Melbourne clinic showed that only seven (0.46%) failed to reach the protective antibody level of 0.5 IU/mL on testing 2–4 weeks after the third dose, with readings of 0.4 IU/mL (in four), 0.3 IU/mL (in two) and 0.2 IU/mL (in one). None had undetectable antibody levels. All seven were advised to receive an intramuscular booster dose of 1.0 mL.

These data support the contention that the intradermal method is appropriate for use in travellers who may otherwise decline pre-exposure rabies vaccination, when the vaccine is administered by vaccinators with relevant experience.[5]

Recipients of intradermal rabies vaccine who have satisfactory antibody levels may be considered fully vaccinated in the post-exposure situation and managed accordingly.

Anthony Gherardin, National Medical Advisor
Sonny Lau, Medical Director, Melbourne Clinic
The Travel Doctor (TMVC), Melbourne, VIC.
tony.gherardin@hfi.com.au

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Spontaneous intracranial hypotension: an easily treated headache

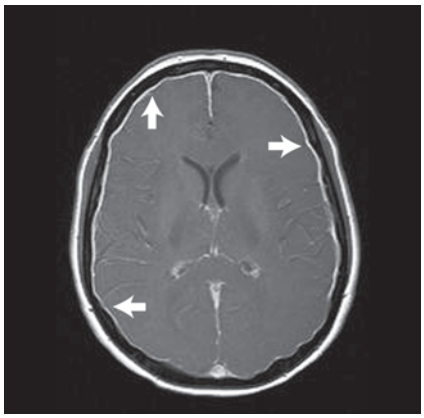
Mohamed Asif Chinnaratha, Ronald A Criddle and Paul J Graziotti

To the Editor: We report a patient with spontaneous intracranial hypotension (SIH), which is now an increasingly recognised syndrome. Orthostatic headache with typical findings on magnetic resonance imaging (MRI) are the keys to diagnosis. When correctly diagnosed, SIH management is easy and highly effective in most cases.

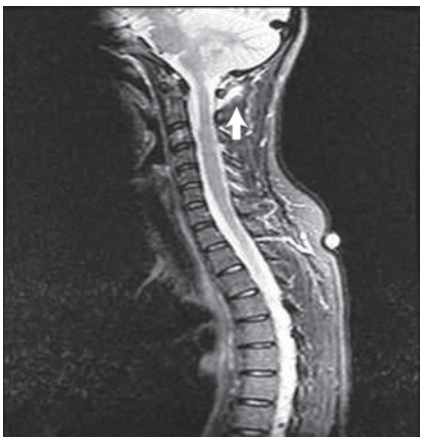
A 38-year-old woman presented to our hospital after having daily headaches for 3 weeks. The acute onset of severe headache occurred initially when she bent down and tried to lift her 16-month-old child. The headache began as a sharp pain over the right side of her occiput and rapidly spread to her frontal area. The headache was particularly bad in the morning and while standing, and was relieved by assuming a recumbent posture. Apart from nausea, she had no other associated symptoms. General and systemic examination findings were normal.

MRI of the brain showed diffuse dural enhancement and smooth thickening of the dura (Box, A) and a total spinal magnetic resonance image showed fluid in the posterior soft tissues at C1/C2 level (Box, B). These findings confirmed the leak of cerebrospinal fluid that accounted for the intracranial hypotension and orthostatic headache. Initial treatment with bed rest, increased fluid intake and non-steroidal anti-inflammatory drugs relieved her symptoms marginally. After a failed lumbar epidural blood patch, 10 mL of autologous blood was injected at the site of the cervical level leak. The patient's symptoms resolved, and she was asymptomatic and had had no recurrence at follow-up at 4 months.

Magnetic resonance images of the patient's brain and cervical spine



A: Diffuse dural enhancement and smooth thickening of the pachymeninges.



B: Fluid in the posterior soft tissues at C1/C2 level. ◆

Also known as Schaltenbrand syndrome, SIH is very rare, with a prevalence of about 1 in 50 000 population, and a female preponderance of 3:1.[1] Patients with connective tissue diseases[2] or Chiari malformation may be more susceptible to SIH. Orthostatic headache is the cardinal feature of this syndrome. Headache is usually holocranial, although it might be localised to the frontal or occipital regions. Patients may have other symptoms such as diplopia and photophobia. MRI with gadolinium is critical in diagnosing this syndrome. The condition of most patients improves with conservative therapy (bed rest, increased fluid intake and caffeine). Epidural autologous blood patch is effective in relieving low intracranial pressure headaches.[3] Surgical repair of the leak is rarely used and should be used only if medical therapy fails.[4]

Mohamed Asif Chinnaratha, Resident Medical Officer
Ronald A Criddle, Physician
Paul J Graziotti, Pain Management Physician
St John of God Hospital, Perth, WA.
drmohamedasif@hotmail.com

1 Blank SC, Shakir RA, Bindoff LA, Bradley N. Spontaneous intracranial hypotension: clinical and magnetic resonance imaging characteristics. *Clin Neurol Neurosurg* 1997; 99: 199-204.
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Australian children and adolescents with type 1 diabetes have low vitamin D levels

Ristan M Greer, Meredith A Rogers, Francis G Bowling, Helen M Buntain, Mark Harris, Gary M Leong and Andrew M Cotterill

To the Editor: Recent studies provide evidence that having a low serum vitamin D level is a risk factor for autoimmune disease, including type 1 diabetes mellitus (T1DM).[1,2] Available data come from northern hemisphere countries where sunlight exposure levels and the genetic background of the population are different from those in Australia. We compared vitamin D levels in stored serum from Brisbane children and adolescents with T1DM who attended the Mater Children's Hospital clinic with local historical control data from a previous study.[3]

Levels of 25-hydroxyvitamin D (25-OHD; the major circulating form of vitamin D) were lower in those with T1DM than in the control group, with no difference in levels of 1,25-dihydroxyvitamin D (1,25-$[OH]_2D$; the biologically active form). Children and adolescents with T1DM were more than three times as likely to have vitamin D deficiency[4] as those in the control group. There was a trend towards seasonal variation in 25-OHD levels, with mean levels (95% CI) being 53.8 nmol/L (47.0–60.6 nmol/L) in summer, 61.4 nmol/L (54.9–67.9 nmol/L) in autumn, 56.4 nmol/L (51.7–61.0 nmol/L) in winter and 64.7 nmol/L (58.8–70.6 nmol/L) in spring

Comparison of clinical characteristics and vitamin D levels in healthy children and adolescents and those with type 1 diabetes mellitus

Variable	Control group	Type 1 diabetes mellitus group	*P*
No. of children and adolescents	94	47	
Age (range)	13.2 years (12.5–13.8 years)	13.6 years (12.6–14.6 years)	0.47*
No. of males/females	44/50	21/26	0.81†
Mean duration of diabetes (95% CI)	—	4.7 years (3.9–5.5 years)	
Sample collection period	July 2000 – December 2001	June 2001 – July 2006	
Mean 25-OHD level (95%CI)‡	64.6 nmol/L (61.3–67.9 nmol/L)	54.7 nmol/L (50.3–58.9 nmol/L)	0.0005*
Mean 1,25-$(OH)_2$D level (95% CI)‡	126.7 pmol/L (115.8–137.6 pmol/L)§	127.6 pmol/L (114.8–140.4 pmol/L)	0.92*
Proportion 25-OHD-deficient (≤ 50 nmol/L)	18% (17/94)	43% (20/47)	0.002† (OR,¶ 3.4; 95% CI, 1.5–7.3)
Proportion with 1,25-$(OH)_2$D level below reference range (40–150 pmol/L)	0 (0/84)	4% (2/47)	0.13** (OR,¶ 9.3; 95% CI, 0.4–197.6)

* *t* test. † χ^2 test. ‡ DiaSorin radioimmunoassay double antibody assay (DiaSorin Inc, Stillwater, Minn, USA), performed by Queensland Health Pathology Services. § 84 controls; insufficient serum for analysis in 10. ¶ Odds ratio for deficiency in type 1 diabetes mellitus. ** Fisher's exact test.
25-OHD = 25-hydroxyvitamin D. 1,25-$(OH)_2$D = 1,25-dihydroxyvitamin D. ◆

($P = 0.06$), but no difference in seasonal variation between T1DM and control groups ($P = 0.73$). There was no difference in the ages or proportions of males and females in the two groups (Box). There were no differences in vitamin D levels between the sexes in either T1DM or control groups, nor any correlation with duration of diabetes.

These observations support previous reports. One found low 25-OHD levels in 459 Swedish patients aged between 15 and 34 years who were newly diagnosed with T1DM compared with age-matched and place-matched controls.[1] Another found low 25-OHD levels in 88 newly diagnosed children and adolescents.[2] Understanding the nature of low vitamin D levels in people with diabetes is important because it potentially clarifies the mechanisms of autoimmune β-cell destruction, and may lead to interventions for preventing or delaying insulin dependence by using vitamin D or its analogues. Vitamin D probably acts by modifying the autoimmune response, as 1,25-$(OH)_2$D modulates dendritic cell function to promote tolerogenic T cells. It may be relevant that we have recently found low blood dendritic cell counts in children and adolescents with T1DM.[5]

Vitamin D levels in our Queensland sample of children and adolescents were lower overall than those found in the subjects of the Swedish study, (mean 25-OHD levels [± SEM] were 96.7 ± 2.7 nmol/L for the control group and 82.5 ± 1.3 nmol/L for those with T1DM); this is unexpected given Brisbane's latitude (29° S) compared with that of Sweden (about 55–65° N). These differences might be explained by differences in dietary intake, sun avoidance behaviours promoted in Queensland, or differences in the assays used, as the Swedish group used the Nichols chemiluminescence assay (Nichols Institute, San Juan Capistrano, Calif, USA) and we used the DiaSorin radioimmunoassay (DiaSorin Inc, Stillwater, Minn, USA). The observation in the Swedish study that the deficit in 25-OHD level did not resolve over time after diagnosis concurs with our finding of low levels in children and adolescents several years after diagnosis.

While our pilot data cannot support causal inference, and is limited by being retrospective and our lack of information about history of sunlight exposure, dietary vitamin D intake, cultural factors such as sun avoidance or veiling, skin tone, and not having contemporaneous controls, it strongly supports the case for prospective clinical studies of vitamin D in T1DM.

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Ristan M Greer, Lecturer, Paediatrics and Child Health[1]
Meredith A Rogers, Research Assistant, Paediatric Endocrinology and Diabetes[2]
Francis G Bowling, Professor of Medical Biochemistry and Director of Biochemical Diseases[2]
Helen M Buntain, Respiratory Physician[3]
Mark Harris, Paediatric Endocrinologist[2]
Gary M Leong, NHMRC Senior Research Officer, Institute for Molecular Bioscience,[1] and Paediatric Endocrinologist[2]
Andrew M Cotterill, Associate Professor, Paediatrics and Child Health,[1] and Director, Paediatric Endocrinology and Diabetes[3]
1 University of Queensland, Brisbane, QLD.
2 Mater Children's Hospital, Brisbane, QLD.
3 Royal Children's Hospital, Brisbane, QLD.
r.greer@uq.edu.au

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Revisiting the metabolic syndrome

Tomi-Pekka Tuomainen

To the Editor: I read with interest the excellent review article on the metabolic syndrome by Chew et al in the 16 October 2006 issue of the Journal.[1] In their article the authors claim there is a lack of data about the relationship between hyperinsulinaemia and changes in free testosterone levels.

As part of the Kuopio Ischaemic Heart Disease (KIHD) Risk Factor Study, an ongoing prospective epidemiological study of 2682 middle-aged Finnish men investigating risk factors for chronic disease, our research group has shown an association between the presence of metabolic syndrome at baseline and a change in sex hormone levels at follow-up after 11 years.[2] In our study, men who met the World Health Organization criteria for metabolic syndrome both at baseline and at 11-year follow-up were at 2.6-fold increased risk of developing hypogonadism (serum total testosterone concentration < 11 nmol/L) during the study period compared with men who did not have metabolic syndrome. There was also a non-significant trend for men with metabolic syndrome to develop hypogonadism as defined by calculated free testosterone levels of < 225 pmol/L at 11-year follow-up.[2]

In the same cohort, we also reported a reverse association — that is, hypogonadism predicting metabolic syndrome.[3,4] However, as the question posed by Chew et al was whether hyperinsulinaemia affects free testosterone levels, I examined the KIHD data further for evidence of such an association. I found that subjects grouped in ascending baseline fasting serum insulin quartiles had baseline mean free testosterone levels of 316 pmol/L (SD, 72 pmol/L), 312 pmol/L (SD, 77 pmol/L), 299 pmol/L (SD, 74 pmol/L) and 271 pmol/L (SD, 79 pmol/L), respectively ($P < 0.001$ for trend). At 11-year follow-up, mean free testosterone levels for subjects in each quartile were 248 pmol/L (SD, 64 pmol/L), 242 pmol/L (SD, 68 pmol/L), 229 pmol/L (SD, 70 pmol/L) and 216 pmol/L (SD, 67 pmol/L), respectively ($P < 0.001$ for trend).

The proportional drop in free testosterone levels over 11 years was approximately the same in each quartile, ranging from 20% to 23%. On the basis of these data, it seems that hyperinsulinaemia is associated not only with a fall in serum total testosterone levels but also with a fall in free testosterone levels in a general population.

Tomi-Pekka Tuomainen, Professor of Epidemiology
School of Public Health and Clinical Nutrition, University of Kuopio, Kuopio, Finland.
tomipekka.tuomainen@uku.fi

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Gerard T Chew, Seng Khee Gan and Gerald F Watts

In reply: We thank Tuomainen for his interest in our review article, and for sharing with us his data showing an inverse association between fasting serum insulin levels and calculated serum free testosterone levels. We were cautious in our statement about the relationship between hyperinsulinaemia and free testosterone levels, as there are conflicting data in the literature regarding this,[1,2] and few studies that directly measure free or bioavailable testosterone. Moreover, there is ongoing controversy about the calculation of free testosterone levels using total testosterone and sex hormone-binding globulin concentrations, with the validity and assumptions of some of these widely used estimation equations being called into question.[3,4]

We also echo the concerns of Allan et al[5] about the potential pitfalls of diagnosing hypogonadism based on testosterone levels only. As the presence of low total (and even calculated free) testosterone in obese men may not necessarily reflect deficient androgen action, the diagnosis of androgen deficiency should only be made in the context of supportive clinical features. Furthermore, in abdominally obese men with the metabolic syndrome, levels of sex hormone-binding globulin and both total and calculated free testosterone can increase following weight loss,[6] thereby obviating the inappropriate use of testosterone supplementation in such patients.

Gerard T Chew, Endocrinologist and Postgraduate Research Scholar[1,2]
Seng Khee Gan, Endocrinologist and Senior Lecturer in Medicine[1,2]
Gerald F Watts, Consultant Physician and Professor of Medicine[1,2]
1 School of Medicine and Pharmacology, Royal Perth Hospital Unit, University of Western Australia, Perth, WA.
2 Department of Internal Medicine and Department of Endocrinology and Diabetes, Royal Perth Hospital, Perth, WA.
gwatts@meddent.uwa.edu.au

1 Andersson B, Marin P, Lissner L, et al. Testosterone concentrations in women and men with NIDDM. *Diabetes Care* 1994; 17: 405-411.
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Genotype and adverse drug reactions to warfarin

Keith A Byron and Anthony E Dear

To the Editor: The recent article by Miller and colleagues regarding adverse drug events (ADEs) in general practice highlights the high frequency and considerable morbidity associated with ADEs in the general community.[1] The authors identified recognised side effects, drug sensitivity, and allergy as responsible for most ADEs.

The contribution of the patient's genotype to drug response, via altered metabolism or responsiveness to pharmaceuticals, is increasingly recognised as potentially responsible for a significant proportion of ADEs.

The science of determination of the genetic contribution to an individual's response to drug action is referred to as pharmacogenomics,[2] and represents a potentially beneficial diagnostic tool to aid in the prevention of ADEs.

Treatment with warfarin, one of the most frequently prescribed drugs in Australia, has been estimated to account for up to15.1% of all severe ADEs, manifest as minor and major bleeding.[3]

We have recently determined the presence, frequency and laboratory sequelae of genetic variants (single nucleotide polymorphisms) in two genes responsible for the metabolism (cytochrome P450 2C9 [*CYP2C9*]) and

potency (vitamin K epoxide reductase complex, subunit 1 [*VKORC1*]) of warfarin[4] in an Australian population. In our study of 120 patients in an anticoagulation clinic, the frequencies of allelic variants of the *CYP2C9* and *VKORC1* genes responsible for altered warfarin activity were 31%[5] and 59% (unpublished data), respectively, in keeping with previously published studies.[4] Detection of these variants was associated with increased induction international normalised ratio (INR) readings compared with controls, and reduced overall warfarin requirements.[6] These findings support previous studies,[7] and suggest that genotype determination may be of benefit in identification of patients with increased sensitivity to empiric induction phase warfarin dosing schedules. This may allow for a reduction of induction doses of warfarin, decreasing the risk of excessive INR and bleeding sequelae, commonly observed with induction of warfarin treatment. Furthermore these benefits may aid in reduced time to stabilisation.

Additional cost–benefit analysis[8,9] will enable determination of the economic viability of genotype determination as an adjunct to management of warfarin dosing.

The high population frequency of genetic variants associated with warfarin response emphasises the significant contribution genetic factors can play in patient reaction to drugs and highlights their involvement as potential causes of ADEs.

Keith A Byron, Chief Scientist[1]
Anthony E Dear, Senior Research Officer[2]
1 Molecular Diagnostics, Gribbles Pathology, Melbourne, VIC.
2 Department of Medicine, Monash University, Melbourne, VIC.
keith.byron@gribbles.com.au

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Lack of consistency in safe-sleeping messages to parents

Roger W Byard, Glenda Cains, Helen Noblet and Maxine Weber

To the Editor: V-shaped pillows ("tri-pillows") may cause suffocation of an infant left to sleep between the two arms of the pillow when he or she slips into the crevice between the arms, or beneath the pillow. The deaths of two infants who died in this manner were reported in South Australia in 1997, and a third death was the subject of a coronial inquiry.[1,2] In 1998, the SA State Coroner recommended that "a public warning be issued against the use of tri- or U-shaped pillows by infants under two years of age for sleeping".[2] This message has also been issued in subsequent safe-sleeping campaigns, with a statement in the SIDS and Kids national "Safe sleeping" brochure[3] that "tri-pillows are too soft and can cover baby's face", and a statement on the SA Child and Youth Health website that "... babies should not be left in these pillows while they are sleeping".[4] Despite these clear messages, deaths continue to occur in SA,[5] and V-shaped pillows are still being sold in the foyer of a local obstetric hospital. Although the pillows are being promoted to assist breastfeeding, infants who have been left to sleep on them will be exposed to the risk of suffocation.

Deaths of infants in shared sleeping situations may also occur due to suffocation from "overlaying". However, parents are still being advised by health advice telephone enquiry services to sleep in the same bed with their children. This was the unequivocal message given to one of the authors (GC) when she recently telephoned for advice following the birth of her first child. No mention was made of the potential danger of suffocation if parents are physically large, intoxicated, sedated, or simply exhausted, or if the infant is placed between the parents under bedcovers.

It appears, despite clear evidence that certain sleeping situations are potentially dangerous for infants, as well as the widespread dissemination of this information in safe-sleeping literature, that certain organisations or individuals continue to give a contrary message. What hope do parents have of understanding these issues and making informed decisions to optimise the safety of their infant's sleeping environment if they are exposed to such conflicting messages and advice? Perhaps another question to ask is, "What responsibility do organisations and employees bear if an infant dies as a result of parents following such advice or purchasing equipment such as a V-shaped pillow?"

Roger W Byard, George Richard Marks Professor of Pathology[1]
Glenda Cains, Mortuary Team Leader[2]
Helen Noblet, Executive Officer[3]
Maxine Weber, Executive Director[4]
1 Discipline of Pathology, University of Adelaide, Adelaide, SA.
2 Forensic Science SA, Adelaide, SA.
3 Kidsafe SA, Women's and Children's Hospital, Adelaide, SA.
4 SIDS and Kids, Adelaide, SA.
roger.byard@adelaide.edu.au

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Mycobacterium ulcerans infection: an eponymous ulcer

Derek H Meyers

To the editor: Bairnsdale ulcer is known by the eponyms Buruli in Uganda, Kakerifu in Zaire, Kumusi in New Guinea, and was formerly referred to as Searls' ulcer in Australia. In the original 1948 article describing the causative organism,[1] MacCallum and colleagues acknowledged assistance from Drs Alsop, Clay and Searls, in that (alphabetical) order. In sending material to Melbourne for examination, these doctors of the Bairnsdale Clinic described the ulcers, and also commented on the similarity of their appearance in the first three patients. JR Searls, after whom the ulcer was originally named, was regarded as an excellent general practitioner. He died in 1971.

Derek H Meyers, Retired Physician
Brisbane, QLD.
d&rmeyers@acenet.net.au

1 MacCallum P, Tolhurst JC, Buckle G, Sissons HA. A new mycobacterial infection in man. *J Pathol Bacteriol* 1948; 60: 93-122. ❑

Paul D R Johnson and John A Hayman

"What's in a name? That which we call a rose
By any other ***name*** *would smell as sweet."*

— William Shakespeare,
Romeo and Juliet; II, ii, 1-2; circa 1595

Comment: In 1948, MacCallum and colleagues published an article reporting a new mycobacterial infection in man,[1] and later named the causative organism *Mycobacterium ulcerans*. In their article, they described six patients, five of whom came from the Bairnsdale district in Gippsland, Victoria. Three Bairnsdale general practitioners, Drs Alsop, Clay and Searls, had initially recognised a novel disease in their region and submitted pathological specimens to Melbourne University for diagnosis.[2]

Subsequently, the same disease was described in many different areas, mostly in Africa ("Buruli ulcer"). Each new outbreak tended to give rise to a new name; of all these, perhaps the most colourful is "Sik belong Sepik", describing the infection as it occurs along the Sepik River in Papua New Guinea. In Victoria, where most Australian cases of *M. ulcerans* infection occur,[3] we have continued to use the term "Bairnsdale ulcer" even though the main endemic areas are now the Bellarine and Mornington Peninsulas near Melbourne.[3]

Medical eponyms have a place for diseases that are poorly understood or have unknown causes, but it could be argued that the terms "Bairnsdale ulcer" and "Buruli ulcer" now belong in the annals of medical history.

However, there are other considerations. In 1998, the World Health Organization launched the Global Buruli Ulcer Initiative.[4] This successful advocacy raised the profile of this neglected disease and facilitated major improvements in diagnosis and treatment.

For better or worse, "Buruli ulcer" has become the internationally recognised term for *M. ulcerans* infection, and we propose that we should now also adopt this name in Australia. While this should come as a relief to the good citizens of Bairnsdale and the Bellarine peninsula, what about those of Buruli in Uganda? Fortunately, their county has been renamed and is now known as the Nakasongola District.[5]

Paul D R Johnson, Deputy Director[1]
John A Hayman, Associate Professor[2]
1 Infectious Diseases Department, Austin Health, Melbourne, VIC.
2 Department of Anatomy and Cell Biology, Monash University, Melbourne, VIC.
Paul.Johnson@austin.org.au

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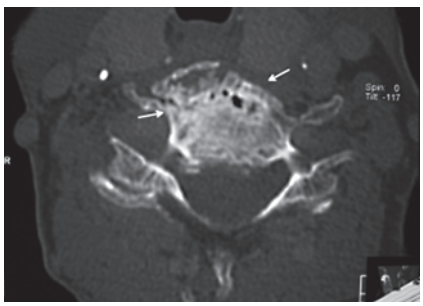
Mycobacterium ulcerans infection in Brazil

Vitorino M dos Santos, Flávio L Noronha, Érica C Vicentina and Camila C Lima

To the Editor: Recent articles in the Journal referred to clinical characteristics of lesions caused by *Mycobacterium ulcerans* in Australia, and to recommendations and challenges in their management.[1-3]

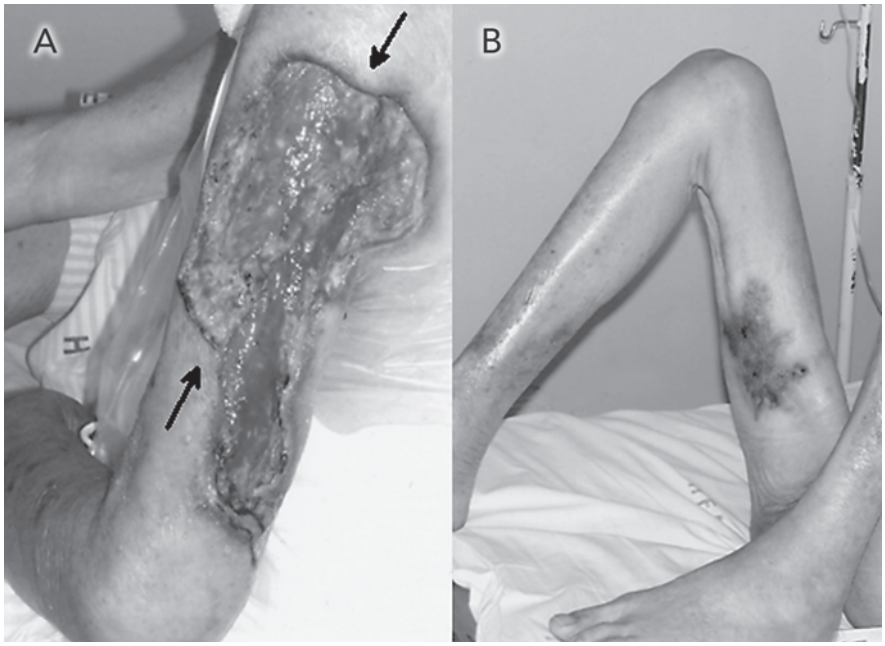


1: *X-ray image of osteomyelitis (arrows) affecting the body of the fourth cervical vertebra.* ◆

Brazil may also be an endemic area of this devastating neglected but treatable disease. In developing countries, cases of Bairnsdale or Buruli ulcer (BU) can be misdiagnosed or underreported because neither the general public nor health care workers have sufficient knowledge about the disease, and because affected people usually have little contact with the health care system, or do not seek prompt treatment.[4] Expensive tests like the polymerase chain reaction are not available to confirm all suspicious cases, and smears can give a low diagnostic yield; there are often minimal histopathological changes and absence of bacilli, particularly in patients with long-standing lesions previously treated with effective antimicrobial drugs.[4]

We report the case of a 65-year-old Brazilian woman with a 2-year history of BU in her extremities coexistent with osteomyelitis in the fourth cervical vertebra (Figure 1), and evidence of inadequate nutrition. Although she had received BCG vaccine as an infant, mycobacteria osteomyelitis developed in the site of an arthrodesis performed in 1998 to treat an accidental fracture.[4,5]

This patient had lived in a poor riverside rural area with a humid, hot climate. As in descriptions of Australian cases, our patient was much older than the age (5–15 years) at which most cases of *M. ulcerans* infection are reported in tropical and subtropical



*2: Extensive ulcer on the left arm (arrows; **A**) and brown pigmented scars on the inner right thigh (**B**).* ◆

regions.[1,2,4] Before her disease was characterised through positive cultures for *M. ulcerans* in samples from skin and bone lesions, the main differential diagnosis was ulcers resulting from fungal infection and leishmaniasis,[4] conditions that are frequently seen in the region where she lived. The earlier skin lesions had appeared in May 2004 as papules and nodules, and evolved as painless, chronic, indolent ulcers with undermined edges.[2,4] Despite treatment in another hospital that included surgery as well as medical therapy with rifamycin, aminoglycoside and quinolone antibiotics, the disease recurred. On admission to our hospital in August 2006, she had an extensive ulcer on her left arm in addition to scars on the right inner thigh (Figure 2).

After nearly 2 months of hospitalisation, the patient was discharged to continue antimicrobial therapy with outpatient follow-up. Despite this, the lesions are healing very slowly.

Vitorino M dos Santos, Preceptor[1] and Professor[2]
Flávio L Noronha, Internal Medicine Physician[1]
Érica C Vicentina, Internal Medicine Physician[1]
Camila C Lima, Internal Medicine Physician[1]
1 Department of Internal Medicine, Armed Forces Hospital, Brasilia, DF, Brazil.
2 Catholic University of Brasilia, Brasilia, DF, Brazil.
vitorinomodesto@gmail.com

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