LETTERS

Should thyroxine tablets be refrigerated? Have we got it wrong in Australia?

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TO THE EDITOR: In May 2004, Sigma, the sole Australian supplier of L-thyroxine sodium, instructed pharmacists that thyroxine tablets should be stored refrigerated, both in pharmacies and after dispensing. Thyroxine bottles now carry explicit labels: "keep refrigerated" or "refrigerate at all times". This instruction seems to have been accepted by health professionals, but patient-support groups immediately questioned the refrigeration directive. In response, Sigma conceded that thyroxine tablets can be stored at room temperature (< 25° C) for up to 4 weeks, with refrigeration still the preferred option.

There are major unresolved issues about the potency, stability and bioavailability of various thyroxine preparations that are marketed competitively in the United States.[1] With a single supplier in Australia, we can avoid between-preparation variations, provided that stability and consistency are maintained.

The instruction to refrigerate thyroxine tablets seems to be uniquely Australian. None of my co-authors of the website <www.thyroidmanager.org>[2] is aware of a refrigeration directive in any other country. The local instruction seems to have followed interaction between the Therapeutic Goods Administration and the manufacturer, so that unopened bottles could be marketed with a longer shelf life.

Is the rest of the world missing out on something important? Is there something peculiar about the Australian formulation that makes it unstable at room temperature? Could this directive be without firm basis, or even dangerous?

There is currently no evidence on whether thyroxine in already-opened, unsealed bottles is more or less stable at 4° C than at room temperature, but the need to keep the tablets dry has been widely emphasised.[3] Consider the condensation that will occur during 200 daily openings of a refrigerated glass bottle, whatever it contains. If damp tablets lose potency, this would lead to apparent under-treatment. In the months since refrigerated storage was recommended in Australia, preliminary observations suggest that apparent under-dosage (ie, unexpected rises in serum TSH) may indeed occur in previously compliant patients (personal observation). If dosage were increased, the adjustment could result in over-treatment after a change to a fresh preparation. Thyroxine has a narrow therapeutic window, and excessive dosage can have serious effects, especially if there is associated cardiac ischaemia.

While refrigeration of sealed bottles of thyroxine might extend the shelf life, the instruction to refrigerate unsealed bottles seems ill-advised. When an existing formulation is modified, it is generally the obligation of a manufacturer to demonstrate safety. The stability of tablets in sealed bottles and those in current use are quite separate issues. To establish how tablets in current use are influenced by refrigeration, it is necessary to measure the thyroxine content of remaining tablets from bottles of 200, opened and used daily for up to 6 months. Without such data, it is preferable to instruct patients *not* to store currently used bottles of thyroxine at refrigerator temperature.

1 American Association of Clinical Endocrinologists, The Endocrine Society and American Thyroid Association. Joint statement on the use and interchangeability of thyroxine products. January 2005. Available at: http://www.thyroid.org/professionals/advocacy/04_12_08_thyroxine.html (accessed May 2005).
2 Thyroid disease manager [website]. Available at: http://www.thyroidmanager.org (accessed May 2005).
3 Roberts GW. Taking care of thyroxine. *Aust Prescriber* 2004; 27: 75-76. ❑

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IN REPLY: Sigma Australia acquired Oroxine (thyroxine sodium) from the original manufacturer in 1999, and launched Eutroxsig, an identical product, in 2002. During 2002–03, as a result of advances in analytical technology for some pharmaceutical products, product specifications, including shelf life and storage conditions, were updated, so that the product's quality, safety and efficacy could be maximised or maintained throughout the claimed shelf life.

For Oroxine and Eutroxsig, the new stability data showed a loss of up to 10% of thyroxine sodium in the first 6 months when stored below 25° C, with some plateauing thereafter. As an interim measure, Sigma, in agreement with the Therapeutic Goods Administration (TGA), decided to immediately reduce the shelf life from 24 to 12 months ("store below 25° C") and set the lower release to 98.0% (up from 92.5%), while investigating reasons behind the loss in potency.

The manufacturing process was confirmed to consistently yield tablets with very reproducible chemical and physical attributes in accordance with the release criteria. During manufacturing, however, about 2% of the thyroxine sodium is lost, with a corresponding similar increase in degradants.

To limit the degradants responsible for the reduction in potency of thyroxine at room temperature, it was agreed with the TGA that thyroxine should be stored at 2°–8° C ("Refrigerate. Do not freeze"), based on good stability data generated at this temperature. Consumer Medicine Information (CMI) and Product Information (PI) were updated in May/June 2004 to reflect this change.

The new stability studies support the storage of Oroxine and Eutroxsig in the refrigerator; however, repeated in-use handling may result in an increase in condensation and microbial contamination. This may lead to changes in the physical characteristics of these products, including the growth of mould. There may be a further increase in condensation if the lid is not tightly closed. One possible solution is for patients to place up to 4 weeks' supply of tablets in a spare, previously used, Oroxine or Eutroxsig amber-coloured bottle and store out of the fridge (below 25° C) for current use, while keeping the remaining stock in the fridge. Sigma is looking at options to improve the packaging so that the above problems are minimised or eliminated.

Oroxine and Eutroxsig, manufactured by Sigma, are sold in Australia only. Sigma does not have access to formulation details, stability results and justification for the storage conditions used in other countries; therefore, we are unable to comment on such issues. As an Australian company, we are obliged to follow the regulatory guidelines of the *Therapeutic Goods Act 1989* (Cwlth).

Sigma recommends that the label instructions regarding storage conditions after opening be strictly followed to maximise the quality, safety and efficacy of the product. ❑

Staphylococcal toxic shock syndrome: still a problem

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To the Editor: We report a recent case of toxic shock syndrome associated with menstruation which illustrates that this syndrome still occurs, even when tampons are used appropriately. A potential diagnostic test for the syndrome is also discussed.

An 18-year-old woman presented with a 1-day history of fever, chills and severe back pain, with no other focal symptoms. On examination, she was febrile with a blood pressure of 75/40 mmHg, and had begun vomiting.

She was treated empirically with intravenous ceftriaxone and flucloxacillin and resuscitated with intravenous fluids. Over several hours, the back pain resolved, and a widespread erythrodermic rash developed, centred mainly on the trunk. Further questioning revealed that the patient had removed a tampon shortly before presentation, as she had just ceased menstruating. Renal ultrasound examination, chest x-ray and blood cultures were non-diagnostic. She was treated with intravenous antibiotics for 4 days and discharged home with a further 10-day course of oral amoxycillin and clavulanic acid. At outpatient follow-up 3 weeks after admission, she reported desquamation of the skin of her palms and soles.

Toxic shock syndrome was first described in 1978,[1] and a strong association with *Staphylococcus aureus*, menstruation and tampon use was established in 1980.[2] Toxic shock syndrome toxin-1 (TSST-1), a protein secreted by *S. aureus*, was the first of many toxins associated with the syndrome to be identified. The term "superantigen" was adopted to describe the ability of these toxins to cause a remarkable expansion of T lymphocytes displaying specific β chain variable regions of the T-cell antigen receptor. Superantigens bypass normal antigen presentation and can stimulate over 20% of all T cells, whereas a conventional antigen stimulates only in the order of 1 in 10 000 T cells. The signature feature of superantigen activity is the expansion of lymphocyte populations bearing the particular V_β chains that bind the superantigen. In the case of TSST-1, this is $V_\beta 2$.[3]

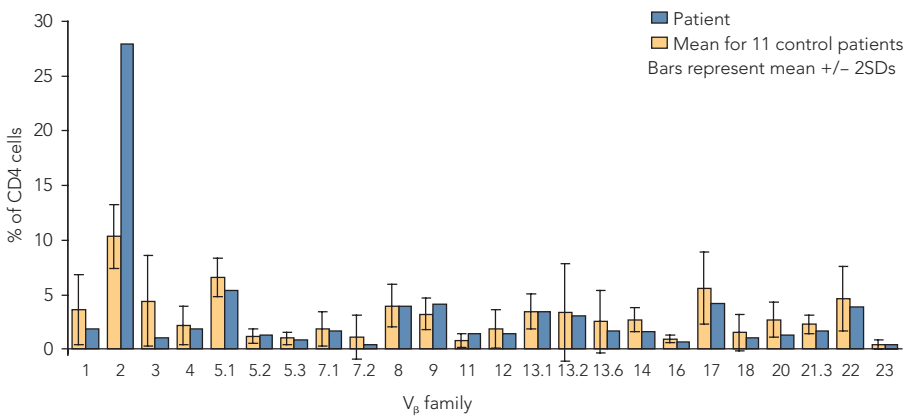
Our patient consented to blood being sampled to investigate the V_β profile of her T cells at follow-up. This investigation was part of a broader study on superantigens in sepsis that was approved by the Ethics Committee of the Royal Melbourne Hospital. The blood was stained with monoclonal antibodies against 24 V_β families[4] and analysed by flow cytometry. This showed a massive expansion of $V_\beta 2$ cells, which accounted for 28% of all CD4 lymphocytes (Box).

Currently, there is no diagnostic test for toxic shock syndrome. Toxin production from cultured organisms can be established *in vitro* by some laboratories, but does not confirm toxin production *in vivo*. Detection of a "skewed" V_β repertoire is a potential diagnostic test. Clearly, the sensitivity and specificity of the assay would need to be established before general application. To date, we have found skewed V_β T-cell profiles in six independent cases of toxic shock syndrome.

This patient had used tampons appropriately, including replacing tampons at least every 4 hours and not using them overnight, but nevertheless developed a life-threatening disease. The incidence of toxic shock syndrome peaked in the United States in 1980 and has since fallen substantially, as a result of factors including changed tampon absorbency. However, the incidence may be now increasing.[5] Our case serves to remind us all to be vigilant for toxic shock syndrome in association with menstruation, and to consider the diagnosis in all patients with severe sepsis.

1 Todd J, Fishaut M, Kapral F, et al. Toxic-shock syndrome associated with phage-group-I staphylococci. *Lancet* 1978; 2: 1116-1118.
2 Davis JP, Chesney PJ, Wand PJ, et al. Toxic-shock syndrome: epidemiologic features, recurrence, risk factors, and prevention. *N Engl J Med* 1980; 303: 1429-1435.
3 Marrack P, Kappler J. The staphylococcal enterotoxins and their relatives. *Science* 1990; 248: 1066.
4 MacIsaac C, Curtis N, Cade J, et al. Rapid analysis of the Vbeta repertoire of CD4 and CD8 T lymphocytes in whole blood. *J Immunol Methods* 2003; 283: 9-15.
5 Schlievert PM, Tripp TJ, Peterson ML. Reemergence of staphylococcal toxic shock syndrome in Minneapolis-St Paul, Minnesota, during the 2000-2003 Surveillance Period. *J Clin Microbiol* 2004; 42: 2875-2876. ❑

V_β profile of the T-cell antigen receptor of CD4 lymphocytes in a patient with toxic shock syndrome



V_β profile of CD4 cells from a patient 21 days after onset of toxic shock syndrome compared with the mean profile from 11 adult intensive-care patients with no evidence of infection. Note the massive expansion of cells carrying $V_\beta 2$, for which toxic shock syndrome toxin-1 has known affinity.

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Comment: As noted by MacIsaac et al above, my colleagues and I recently reported an increase in the incidence of staphylococcal toxic shock syndrome (TSS) in Minneapolis–St Paul in the United States, from 0.8 per 100 000 (in January 2000) to 3.4 per 100 000 (in December 2003).[1] We noted that physicians across the United States were reporting TSS cases in increasing frequency.

There are two major categories of staphylococcal TSS, menstrual and non-menstrual.[2,3] Menstrual TSS is defined as occurring during menstruation or within the 2 days preceding its onset or the 2 days following its cessation; the illness is primarily, but not exclusively, associated with tampon use. Menstrual TSS is nearly always

caused by the superantigen exotoxin, TSS toxin-1 (TSST-1).[4] Superantigens significantly overactivate the human immune system to release cytokines that cause the clinical features of TSS (interleukin-1β [endogenous pyrogen]; tumor necrosis factor-α and β [capillary leak]; and interferon-γ and interleukin-2 [rash]).[5] Non-menstrual TSS may occur in anyone, young or old, male or female, and today commonly follows superinfection of the upper respiratory tract after viral infection. Non-menstrual TSS is caused by TSST-1 (50%) or by staphylococcal enterotoxin B or C (together nearly 50%).

The important question is what accounts for the fourfold rise in TSS that was reported in our 2004 study? We proposed several hypotheses. First, the increase in incidence partly results from the emergence of three strains of methicillin-resistant *Staphylococcus aureus* (MRSA), at least two of which are emerging worldwide. These strains are termed (by Centers for Disease Control [CDC] nomenclature) USA 1100 (TSST-1 positive), USA 400 (SEB/SEC, Panton–Valentine leukocidin [PVL] positive), and USA 300 (positive for an unknown superantigen as well as PVL).

In our studies, USA 1100 strains currently comprise 20% of submitted isolates, compared with none before the year 2000. These isolates may produce 10 to 100 times more TSST-1 *in vitro* than their methicillin-sensitive *S. aureus* counterparts matched by pulsed-field gel electrophoresis profile. Thus, these organisms rapidly produce high levels of TSST-1, leading to TSS even when lower-absorbency tampons are used. In addition, the USA 400 and USA 300 strains are also emerging and are associated with increases in non-menstrual TSS. These latter isolates also produce more superantigens than their methicillin-susceptible counterparts.

Secondly, in our 2004 study, physicians who submitted cultures to our laboratory defined cases of TSS based on patient presentation and the presence of an *S. aureus* strain producing one of the three causative exotoxins. Our TSS definition is likely to be broader than the strict CDC definition.

Finally, we also noted that it is possible that women are beginning to menstruate and to use tampons at earlier ages. In addition, teenagers are bombarded with media advice that TSS is no longer a problem; failure to recognise the illness may lead to it becoming more severe before presentation. These lifestyle and awareness changes, combined with the emergence of high-toxin-producing strains and the expanded definition of TSS, may account for the observed increase in TSS. The increase does not appear to be caused by changes in tampon composition or absorbency.

1 Schlievert PM, Tripp TJ, Peterson ML. Reemergence of staphylococcal toxic shock syndrome in Minneapolis-St. Paul, Minnesota, during the 2000-2003 surveillance period. *J Clin Microbiol* 2004; 42: 2875-2876.

2 Reingold AL, Hargrett NT, Dan BB, et al. Nonmenstrual toxic shock syndrome: a review of 130 cases. *Ann Intern Med* 1982; 96: 871-874.

3 Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. *N Engl J Med* 1980; 303: 1436-1442.

4 Schlievert PM. Staphylococcal enterotoxin B and toxic-shock syndrome toxin-1 are significantly associated with non-menstrual TSS. *Lancet* 1986; 1: 1149-1150.

5 McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. *Annu Rev Microbiol* 2001; 55: 77-104. ❑

Weight gain and diabetes with "second-generation" antipsychotic drugs

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To the Editor: Emerging evidence suggests that the so-called second-generation antipsychotics (SGAs), especially olanzapine and clozapine, can cause abnormal weight gain and increase the risk of diabetes mellitus.[1-3] In Australia, there are calls for a prospective multicentre trial to compare the rates of weight gain and diabetes between SGAs.[4,5] The Australian data presented here underline the pressing need for such a study.

Data were examined for the 10-year period January 1994 to December 2003 for:

- Total prescriptions dispensed by the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme for 12 antipsychotic drugs; and
- Reactions reported in the same period to the Adverse Drug Reactions Advisory Committee (ADRAC) for each of these drugs, involving excessive weight gain or obesity, and diabetes mellitus or hyperglycaemic reactions. Reports were included in the survey only when it was considered that no other drug could be responsible.

As clozapine is dispensed and recorded differently from other SGAs in Australia, complete data on numbers of prescriptions dispensed were not available. However, total Australian expenditure was available for each tablet strength of clozapine for the full 10-year study period, along with number of prescriptions dispensed and costs for the private hospital sector for the 4 years July 2000 to June 2004. Therefore, I calculated the average script cost for each tablet strength, and extrapolated the script numbers for the 10-year period, as shown in Box 1.

Box 2 shows the "report rate" for each SGA for the side effects of weight gain or obesity, and diabetes or hyperglycaemia. The report rate for side effects was greater for clozapine than for any other SGA. Unfortunately, the true situation may be still worse. Clozapine is usually prescribed a month at a time, while the other drugs are prescribed for up to 6 months. Adjusting for this would widen the gap further. Moreover, as ADRAC promotes reporting for new drugs, the report rates for the five drugs introduced during the study period are probably inflated. Clozapine is not one of them.

The limitations of ADRAC data are well known.[4] Nevertheless, these are currently our best Australian data and strongly suggest that SGAs, of which risperidone has the most favourable profile, cause weight gain

1 Estimation of the total number of clozapine scripts in Australia

Tablet strength (mg)	Private hospitals data (Jul 2000–Jun 2004)			Total clozapine used (Jul 1994–Jun 2004)	
	Total prescriptions	Cost ($)	Average cost/ prescription ($)	Cost ($)	Estimated total prescriptions
25	3 650	230 929	63.27	9 636 814	152 313
50	25	1 443	57.72	85 980	1 490
100	21 057	6 632 499	314.98	153 276 771	486 624
200	69	24 392	353.51	463 131	1 310
Total	**24 801**	**6 889 263**	–	**163 462 696**	**641 737**

2 Report rates for side effects of antipsychotic drugs

	No. of years*	No. of prescriptions dispensed	No. of ADRAC reports		Report rate (per million prescriptions dispensed)	
			Weight gain†	Diabetes‡	Weight gain†	Diabetes‡
Chlorpromazine	10	950 221	0	0	0	0
Fluphenazine	10	327 126	0	0	0	0
Trifluoperazine	10	937 605	1	0	1.07	0
Pericyazine	10	657 514	0	0	0	0
Thioridazine	10	1 983 915	1	3	0.50	1.51
Haloperidol	10	1 499 254	2	0	1.33	0
Flupenthixol	9	121 132	0	0	0	0
Zuclopenthixol	8	93 839	0	1	0	10.66
Olanzapine	6	2 786 334	47	19	16.87	6.82
Quetiapine	4	271 957	1	4	3.68	14.70
Risperidone	9	1 298 156	6	2	4.62	1.53
Clozapine	10	641 737§	41	61	63.89	95.05

ADRAC = Adverse Drug Reactions Advisory Committee.* Number of years with data available (as some drugs were introduced only after the start of the 10-year period). † Weight gain or obesity. ‡ Diabetes mellitus or hyperglycaemia. § Estimated number (see Box 1).

and diabetes much more often than the older antipsychotic agents.

These data accord with previously published studies[1] and support the US advice to avoid olanzapine and clozapine if possible. Recent PBS approval in Australia for use of olanzapine in bipolar disorder further underlines the urgent need for a prospective multicentre study to compare weight gain and glucose metabolism in patients taking antipsychotic drugs.

Meanwhile, I suggest that:

- Patients who have abnormal weight gain with an SGA might be treated with chlorpromazine, trifluoperazine or haloperidol.
- PBS regulation of clozapine might be amended, to discourage its prescription until after failure of a "first-generation" as well as a second-generation antipsychotic drug.

1 American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27: 596-601.

2 Graham KA, Perkins DO, Edwards LJ, et al. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry* 2005; 162: 118-123.

3 Holzer L, Paiva G, Halfon O. Quetiapine-induced weight gain and escitalopram. *Am J Psychiatry* 2005; 162: 201-202.

4 Lambert TJR, Chapman LH, on behalf of the Consensus Working Group. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. *Med J Aust* 2004; 181: 544-548.

5 Firestone A. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement [letter]. *Med J Aust* 2004; 182: 310. ❑

A syndromic rash in patients attending methadone clinics in New South Wales

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To the Editor: The interesting case report by Currie and colleagues describes a variable cutaneous eruption of uncertain aetiology in a cluster of methadone-dependent patients.[1] The rash was described as including pruritic, exanthematous, purpuric and eventually desquamative components, and typically as involving the trunk and extremities, particularly palms and soles.

Secondary syphilis classically presents in a similar fashion, but no mention was made as to whether this had been excluded by serological testing. Indeed, the histology of the rash (perivascular inflammation, including plasma cell infiltrate, progressing to endarteritis) is similar to that seen in skin biopsies from methadone patients with secondary syphilis. However, an allergic or toxic cause appears to be implicated, in view of previous, well documented reports of hallucinogenic or other drug-related vasculitis published by ourselves[2] and others.[3-5]

1 Currie JN, Wallman L, Chien J, et al. A syndromic rash in patients attending methadone clinics in New South Wales. *Med J Aust* 2005; 182: 73-75.

2 Heazlewood VJ, Bochner F, Craswell PW. Hallucinogenic drug-induced vasculitis. *Med J Aust* 1981; 1: 359-360.

3 Matick H, Anderson D, Brumlik J. Cerebral vasculitis associated with oral amphetamine overdose. *Arch Neurol* 1983; 40: 253-254.

4 Kaye BR, Fainstat M. Cerebral vasculitis associated with cocaine abuse. *JAMA* 1987; 258: 2104-2106.

5 ten Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; 36: 130-147. ❑

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To the Editor: As a Victorian always on the lookout for something new, I read with interest the report by Currie and colleagues of a syndromic rash in patients attending methadone clinics in New South Wales.[1] From the title I expected to read about a rash occurring as part of a syndrome, yet no group of concurrent symptoms was described. In fact, there was a long list with each patient of negative findings. I also had trouble deciding whether the four patients described indeed had the same rash. While the "lumpers" among us may consider it pedantic to split "rash" into more than one category, some doctors make an occupation of it quite successfully.

For example, Patient 1 had petechiae and purpura, but no erythema and no involvement of the palms and soles. No photo, but nevertheless a nice description of vasculitis — common among intravenous drug users. Patient 2 had, from the look of the photo, a toxic erythema that resolved with desquamation of the palms and soles. No petechiae or purpura. Therefore, must be a different rash to Patient 1. Patient 3 is described as having " a prominent purpuric rash involving both lower limbs". However, the photo shows a macular erythema with some associated purpura that looks almost certainly to be an incidental manifestation of dependency. Difficult to say from a photo, as touch is so important in the diagnosis of true purpura. Of course, a 2 mm punch biopsy of the skin could resolve this almost instantly. Again, it is not clear whether this rash is similar to that seen in either Patient 1 or Patient 2.

Patient 4 is described as having a red and itchy rash (erythematous and pruritic), but, from the photograph, we can clearly see that the rash is urticarial. This raises the possibility of urticaria, or urticarial vasculitis, or even erythema multiforme. Again, a skin biopsy would be very useful. The severe

palmar peeling almost seems incongruous, but it does give me faith that buried in this report there might actually be a new desquamating rash associated with methadone use.

In summary, I am still not clear whether the four patients described had the same rash, but I concur with the authors that several of these patients might warrant specialist assessment. Let's hope they get it.

1 Currie JN, Wallman L, Chien J, et al. A syndromic rash in patients attending methadone clinics in New South Wales. *Med J Aust* 2005; 182: 73-75. ❑

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In reply: The purpose of our report[1] was to alert the wider medical community to the recent outbreak of a "syndrome" ("a group of symptoms and signs, which, when considered together, are known or presumed to characterise a disease or lesion"[2]) that included the development of various forms of rash in patients taking methadone syrup. Our report included four cases illustrating the different types of rash encountered to date.

From October 2004, over 400 cases were reported from methadone clinics in New South Wales, although very few new cases have been reported since February 2005, presumably reflecting the success of preventive measures instituted by the NSW Health department. To date, the cause of this methadone-associated syndrome has not been elucidated.

Skin biopsies of rash lesions have been performed in a number of our patients. All have shown chronic perivascular inflammation, with most demonstrating hyperkeratosis. A small number of patients have had a true leukocytoclastic vasculitis. As Heazlewood has commented, both secondary syphilis and illicit drugs such as amphetamines and cocaine have been reported to cause vasculitic rashes. However, none of the more than 50 patients in whom we have performed syphilis serological testing has had positive results, and few of our affected methadone patients have had urine drug-test results positive for amphetamine or cocaine use. We therefore believe that the syndrome we have described remains specific to the patients' current use of methadone syrup.

We are unaware of a rash that is "an incidental manifestation of dependency", as suggested by Sinclair, but we would assure him that specialists from a wide variety of fields, including dermatology, immunology, immunopathology, infectious diseases, addiction medicine and epidemiology, have all been involved in the assessment and treatment of patients with this syndrome, and in the wider investigation of its pathogenesis.

1 Currie JN, Wallman L, Chien J, et al. A syndromic rash in patients attending methadone clinics in New South Wales. *Med J Aust* 2005; 182: 73-75.
2 Blakiston's Gould medical dictionary. 4th ed: abridged. New York: McGraw-Hill, 1979. ❑

Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy

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To the Editor: The interesting article by Gordon et al[1] warrants further discussion with regard to the hypophosphataemia, "inappropriately" high level of serum 25-hydroxyvitamin D, biochemical diagnosis of pancreatitis and management of hypercalcaemia.

Fibroblast growth factor-23 (FGF-23) is a recently described 254-amino-acid peptide that has been shown to have significant phosphaturic effect. It probably plays a major role in phosphate metabolism and homeostasis by rising after an oral phosphate load and falling after dietary phosphate restriction. In the patient discussed by Gordon et al, elevated FGF-23 level may, hypothetically, have been a major contributing factor to the low serum phosphate level. Although the understanding of this factor is still in its infancy, measuring the serum level of FGF-23 in the patient might have shed more light on the role of FGF-23 in phosphate homeostasis. However, FGF-23 levels do not correlate directly with serum phosphate levels, suggesting that FGF-23 exercises control via renal tubular cells, regulation of calcitriol levels or intestinal phosphate absorption. FGF-23 levels are also markedly elevated in chronic renal failure, partly in response to the chronic hyperphosphataemia and partly because of reduced renal clearance.[2] Its action is independent of the traditional and better understood regulators of phosphate level, including parathyroid hormone and parathyroid hormone-related protein.

The triad of high vitamin D level, hypercalcaemia and hypophosphataemia points strongly to a diagnosis of vitamin D intoxication, despite a patient history to the contrary. An alternative explanation is an inaccurate vitamin D assay from the supporting laboratory. This issue, which has been highlighted recently, has therapeutic relevance in monitoring vitamin D replacement therapy.[3]

In supporting the diagnosis of pancreatitis, serum lipase level remains the best biochemical test and is more specific than amylase level.[4] The practice of dual amylase and lipase ordering in the investigation of such conditions is excessive, confusing and costly to the community and should be discouraged.

The indication for bisphosphonate treatment in milk-alkali syndrome remains unclear and contradicts the underlying pathogenesis, which is believed to be that of excessive calcium ingestion. In the patient in question, excessive calcium ingestion overwhelmed the calcium homeostatic mechanism, resulting in severe hypercalcaemia. In such a milieu, osteoclasts would be heavily suppressed and inhibited, and thus the use of a bisphosphonate, whose major action is also by osteoclastic suppression, would be of little value other than in precipitating hypocalcaemia.[5] Thus, expectant management as outlined by the authors would be sufficient to achieve normocalcaemia. As bisphosphonates are not without adverse effects,[6] they should only be used after a clear diagnosis of hypercalcaemia has been made.

1 Gordon MV, Hamblin PS, McMahon LP. Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy. *Med J Aust* 2005; 182: 350-351.
2 Ferrari SL, Bonjour J-P, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. *J Clin Endocrinol Metab* 2005; 90: 1519-1524.
3 Hollis BW. The determination of circulating 25-hydroxyvitamin D: no easy task [editorial]. *J Clin Endocrinol Metab* 2004; 89: 3149-3151.
4 Treacy J, Williams A, Bais R, et al. Evaluation of amylase and lipase in the diagnosis of acute pancreatitis. *ANZ J Surg* 2001; 71: 577-582.
5 Raisz LG, Kream BE, Lorenzo JA. Metabolic bone disease. In: Larsen PR, Kronenberg MH, Melmed S, Polonsky SK, editors. Williams textbook of endocrinology. 10th ed. Philadelphia, Pa: Saunders, 2003: 1378.
6 Carter G, Goss AN, Doecke C. Bisphosphonates and avascular necrosis of the jaw: a possible association. *Med J Aust* 2005; 182: 417-418. ❑

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TO THE EDITOR: I read with interest the *Lessons from Practice* article on milk-alkali syndrome during pregnancy.[1] I would like to offer the following comments.

The patient's alkalosis was in fact more impressive than presented, as the authors used the reference range for serum bicarbonate in *non*-pregnant patients. During pregnancy, serum bicarbonate levels typically fall by about 4 mmol/L to compensate for the respiratory alkalosis caused by elevated progesterone levels stimulating respiratory drive.

Given the patient's life-threatening calcium level on presentation, I am interested to know whether calcitonin treatment or even dialysis was considered while waiting for the pamidronate to take effect.

An important aspect that the authors did not discuss in relation to this case is the reassuring data on the safety of both proton-pump inhibitors and H_2-receptor antagonists in pregnancy. While there is more experience with the latter, two recent studies found no evidence of teratogenicity in almost 900 cases of exposure to proton-pump inhibitors in the first trimester.[2,3] Clinicians should feel comfortable about prescribing these medications in pregnancy.

After reporting a similar case,[4] I wrote to Walco, the manufacturers of Quick-Eze, who subsequently changed their product labelling to include a warning about the number of tablets that could be safely taken each day. Disappointingly, they did not include a warning about ingestion during pregnancy, as I suggested.

1 Gordon MV, McMahon LP, Hamblin PS. Life-threatening milk-alkali syndrome resulting from antacid ingestion during pregnancy. *Med J Aust* 2005; 182: 350-351.
2 Diav-Citrin O, Arnon J, Shechtman S, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. *Aliment Pharmacol Ther* 2005; 21: 269-275.
3 Nikfar S, Abdollahi M, Moretti ME, et al. Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002; 47: 1526-1529.
4 Morton A. Milk-alkali syndrome in pregnancy, associated with elevated levels of parathyroid hormone-related protein. *Intern Med J* 2002; 32: 492-493. ❑

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IN REPLY: Our case appears to be consistent with typical milk-alkali syndrome. While measuring fibroblast growth factor-23 (FGF-23) level might have been of hypothetical interest, it is unlikely that it would have influenced management. Vitamin D intoxication was considered once the 25-hydroxyvitamin D results became available, and we closely questioned our patient in relation to this possibility. She was insistent that she had not taken any vitamin D supplements. It is possible either that the patient did not wish to admit to taking vitamin D or that the assay was misleading, as suggested by Tran. We agree that bisphosphonate therapy should not be advocated when the diagnosis of milk-alkali syndrome is clear. In this case, however, the patient was drowsy and very ill; the full history relating to antacid ingestion was not obtained until after the bisphosphonate therapy had been given.

With regard to Morton's comments, the hypercalcaemia settled promptly, so fortunately calcitonin treatment and other measures did not need to be considered. Drug safety in pregnancy is a difficult issue, as the effects of fetal or neonatal damage may carry lifelong implications, and even relatively rare associations need to be considered with care. In addition, many pregnant women are uncomfortable about taking prescription medications during pregnancy, even though their doctors may have a more relaxed view. Currently, over-the-counter antacids are classed as category A drugs for pregnancy, whereas H_2-receptor antagonists and proton-pump inhibitors are category B1 and B3, respectively. Cimetidine has been associated rarely with neonatal hepatic abnormalities,[1] and it is still too early to state with confidence that proton-pump inhibitors are "safe", despite promising initial analyses. Ironically, the potential dangers of over-the-counter calcium-containing antacids, as demonstrated in this case report and others, are not currently adequately acknowledged. We have written to the manufacturers of Rennie tablets requesting a package label warning advising consumers not to exceed six tablets a day.

1 Glade G, Saccar CL, Pereira GR. Cimetidine in pregnancy: apparent transient liver impairment in the newborn. *Am J Dis Child* 1980; 134: 87-88. ❑

THIS YEAR marks the 60th anniversary of the end of World War II. The following poem pays tribute to those who carry the legacy of that war.

Thus we see

The memories of war are embodied forever. I wrote this poem some months after a 65-year-old man consulted me in the mid-1980s complaining of a band of chest pain that two cardiologists had investigated without diagnosis. As a Polish prisoner-of-war in World War II, he had been enslaved in a German coalmine, starved and inadequately clothed. He described to me how, as winter progressed, he and his fellow prisoners would wire the decaying pieces of their clothes together. His shirt was reduced to a band of fabric around the middle of his chest. His current chest pain was in the same anatomical zone as that covered 45 years before by the remnants of his shirt.

Thus we see and sew and save
the triangular, square or without form,
coloured bits of fabric
that keep us warm.

Thus we see
the landscape under snow,
"the infected winter of our condition",
and in seeing, know.

Thus we sew,
as freezing prisoners of war,
the remnants of the clothes we wear,
Dole. Too rough:
thread of repair is not enough
to make us whole.

Thus we save,
as lining for our trap,
flotsam rescued from the wave,
the storm, from life's enthralling
compromise —
worn and wet rags
to fill the gap —
we have only man's eyes.

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