From the Editor’s Desk

MENTORS AND MENTORING

More than 100 years ago, a medical student at John Hopkins Medical School nervously approached the amphitheatre where Dr Osler, the professor of medicine, was to conduct his weekly clinic. He watched with envy as senior students, residents and physicians took their places. By tradition, junior students were not welcome, or, on the occasion when there was room, banished to the back.

“Just before I got to the entrance of the amphitheater, some one came up and ran his arm through mine and asked where I was going. I looked up, and, behold, there was Dr Osler! I told him I had started toward the pathologic laboratory, and he said, ‘Why go there? I thought you might be coming to my clinic.’ I said, ‘Dr Osler, I’m not yet a third year medical student.’

“All the better. Come along with me.” Whereupon Osler directed him to a chair in the front row as he began his clinic. Afterwards, Osler extended an open invitation to the student to attend his clinics.*

This particular student was to become one of the foremost medical consultants in the US, physician to President Franklin Roosevelt, and a leader of American medicine at the highest level.

This story resonates with most of us. We have all been influenced by mentors who have inspired and supported us, and invested effort and time on our behalf. They have freely taught, counselled, criticised and comforted us on our professional journeys.

All this takes time, continuity of contact, and a “giving” culture. Unfortunately, such precious mentoring is slowly disappearing from our time-poor, fragmented and dehumanised health systems, and perhaps even from our medical schools.

The future does not augur well for mentors and mentoring.

Martin B Van Der Weyden

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. 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> 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. 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.

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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 blood cultures were non-diagnostic. 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 Vβ chains that bind the superantigen. In the case of TSST-1, this is Vβ2.3

Our patient consented to blood being sampled to investigate the Vβ profile of her T cells at follow-up. We saw an increase in the mean profile from 11 adult intensive-care patients with no evidence of infection. Note the massive expansion of cells carrying Vβ2, for which toxic shock syndrome toxin-1 has known affinity. 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 confirmed toxin production in vivo. Detection of a “skewed” Vβ 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 Vβ 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.


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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-1\(\beta\) [endogenous pyrogen]; tumor necrosis factor-\(\alpha\) and \(\beta\) [capillary leak]; and interferon-\(\gamma\) and interleukin-2 [rash]).\(^3\) 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 \(S. aureus\) (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 \(\text{i}v\text{o}\) 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.


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 numbers of prescriptions dispensed and costs for the private hospital sector for the 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 new 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

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<tr>
<th>Tablet strength (mg)</th>
<th>Total clozapine used (Jul 1994–Jun 2004)</th>
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<tr>
<td></td>
<td>Cost ($)</td>
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<tr>
<td>25</td>
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<td>463131</td>
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<tr>
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and diabetes much more often than the older antipsychotic agents.

These data accord with previously published studies¹ 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.

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 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 ourselves² and others.³ ⁴


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.

We agree that a rash is not an isolated phenomenon. In recent months, rash has been associated with a number of syndromes that are being classified as part of a wider range of disorders affecting patients in methadone clinics. We believe that the next step is to alert the wider medical community to the emergence of these syndromes, so that the diagnosis and treatment of these conditions can be improved.

In summary, we agree with the authors that the rash described in the patients described in this paper is “adverse effects of methadone”. However, we believe that the rash is not a side effect of methadone, but rather an adverse effect of the presence of methadone in the blood. We therefore believe that further investigation of this syndrome is warranted.

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

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In supporting the diagnosis of pancreatitis, serum lipase level remains the best biochemical test and is more specific than amylase level.

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.

We appreciate the opportunity to reply to the self-diagnosis of pancreatitis. However, we believe that such a diagnosis is not appropriate in this case.

In summary, we believe that the diagnosis of pancreatitis in this case is not appropriate and that further investigation is required.

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To the Editor: The interesting article by Gordon et al 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 294-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 calcium 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. 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.

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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 osteoclastic suppression, would be of little value other than in precipitating hypocalcaemia. Thus, expectant management as outlined by the authors would be sufficient to achieve normocalcaemia.

As bisphosphonates are not without adverse effects, they should only be used after a clear diagnosis of hypercalcaemia has been made.


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 H2-receptor antagonists in pregnancy. While there is no current evidence of teratogenicity in almost 900 cases of exposure, 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.

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 H2-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.

Thus we see, 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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REFERENCES