tioner (GP) for "catch-up" vaccinations after referral from the emergency department.

Parents were asked to recall their child's vaccination status, which was verified by the Child Health Record (if available) from the parents. Fifty-six undervaccinated children were included in the survey. Of the eight children not included in the survey, four parents refused any further vaccination, two had a medical contraindication to vaccination, and two were currently being updated by their GP and were not due for further update for some time.

Reasons given by parents for not properly vaccinating their child included: the child was generally unwell (50%), the parent forgot or disagreed with vaccination (of these, four parents agreed to return to their GP to discuss vaccination) (each, 13%), fever (11%), medical contraindication (8%), egg allergy (2%), and Hib missed as not part of immunisation schedule when the child was initially vaccinated (5%). Of interest, the Child Health Record was brought to the emergency department in only 10% of children aged up to 18 months.

Undervaccinated children were referred back to their GP with a letter indicating the missing vaccinations. Parents were then randomised into two groups: Group A parents were asked to take their child to their GP within the next three weeks with the letter; Group B parents were identical, except that they were told that the hospital would also post out a letter to their GP advising him/her that the child was undervaccinated and would present in the next three weeks for updating.

Overall, approximately one-third of the children returned to their GP for "catch-up" vaccinations in the three weeks after referral. Although more parents in group B returned their child to their GP than group A, this difference was not statistically significant. When the children were divided into three groups (less than three months, three to six months, and more than six months overdue), the proportions presenting for "catch-up" vaccinations were 57%, 50% and 8%, respectively.

Jones et al. reported that 83% of parents of undervaccinated children presenting to their hospital emergency department would have agreed to "on-the-spot" vaccination if it were available.[1] Burgess et al. reported that in an emergency department that offered "on-the-spot" vaccination only 30% of undervaccinated children actually received it.[2]

Our results show that "on-the-spot" vaccination should be actively encouraged in hospital emergency departments because:

- less than one-third of undervaccinated children will return to their GP for "catch-up" vaccinations
- letters from hospital emergency departments do not increase rates of presenting to a GP for "catch-up" vaccinations
- once their vaccinations are at least six months overdue, underimmunised children are unlikely to return to their GP to have it updated.

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Ecstasy, serotonin syndrome and the treatment of hyperpyrexia

Peter K Gillman
Psychiatrist, PO Box 8183, Mount Pleasant, QLD 4740

To the Editor: The Journal has published several contributions on "ecstasy" (MDMA; 3,4-methylenedioxymethamphetamine) intoxication, hyperpyrexia and the possible use of dantrolene sodium as a treatment.[1-3]

The potentially fatal serotonin syndrome can result from ingesting a combination of drugs which raise intrasynaptic 5-hydroxytryptamine (5-HT), producing both the characteristic behavioural syndrome (altered mental state, hyperkinesia, hyperreflexia, clonus) and hyperpyrexia. The greater the elevation of intrasynaptic 5-HT concentration, the more severe the symptoms.[4] Ecstasy induces a massive release of 5-HT from the presynaptic terminals (acutely raising intrasynaptic 5-HT), after which total brain serotonin is depleted by about 80% within four hours of a single injection. Therefore, the mechanism of ecstasy intoxication produces the serotonin syndrome and hyperpyrexia is just one component of it.[5]

Denborough and Hopkinson's interesting preliminary work,[2] which indicated that ecstasy raised myoplasmic calcium levels (which are reduced by dantrolene), must be interpreted with caution. It seems unlikely that the many drugs which are implicated in serotonin syndrome all have a second primary mechanism acting through calcium changes and causing hyperthermia. Even if this were so, dantrolene would not treat the hyperactivity syndrome, which can be clinically important and problematic, nor presumably would it affect delayed neurotoxicity (which may be peculiar to serotonin syndrome when caused by ecstasy ingestion).[5]

A further problem occurs when the differential diagnosis of hyperpyrexia is doubtful. Dantrolene may not be effective in serotonin syndrome (including ecstasy toxicity), and bromocriptine, which has been used in hyperpyrexia caused by neuroleptic malignant syndrome, is serotomimetic and may aggravate serotonin syndrome. The differentiation of neuroleptic malignant syndrome from serotonin syndrome is important because there have been cases where treatment with bromocriptine for presumed neuroleptic malignant syndrome (when the correct diagnosis was probably serotonin syndrome) has led to the rapid demise of patients.[6] If hyperpyrexia is secondary to serotonin syndrome, it may be wise to avoid bromocriptine.

As noted by Dowsett,[1] it should be emphasised that conservative measures for the treatment of hyperpyrexia may be sufficient. If not, the non-specific 5-HT receptor antagonists cyproheptadine[7] and chlorpromazine[8] are the available choices according to current evidence.

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Adverse reactions to digoxin in four patients with normal or low serum digoxin levels

Geoffrey Mitchell

Senior Lecturer in General Practice, Department of Social and Preventive Medicine, University of Queensland Medical School, Herston, QLD 4006

To the Editor: Digoxin is used in the management of congestive cardiac failure and supraventricular arrhythmias. Early adverse reactions typically involve gastrointestinal symptoms; serious cardiac arrhythmias occur more frequently as the serum digoxin level rises.[1]

Although adverse reactions to digoxin usually correlate with raised serum digoxin levels, there have been reports of adverse reactions in the presence of levels within the normal therapeutic range (0.6–2.6 ng/mL).[2] From 1991 to 1996, 65 patients have been treated with digoxin in my average-sized general practice.[3] Of these, four patients appear to have had adverse reactions to digoxin in the presence of normal or low serum digoxin levels. The Box shows the drug dose, duration of treatment and serum digoxin levels for all four patients.

Three of the four patients had symptoms related to the gastrointestinal tract, all suggestive of major bowel disease. The fourth patient had tiredness and bradycardia. Symptoms were present in each patient for a minimum of several weeks. This is not consistent with the product information, which states that gastrointestinal side effects of digoxin are of acute onset, transient and usually related to a transient rise in the serum digoxin level.[4] Within a week of cessation of the drug, all four patients had fully recovered.

Factors contributing to elevation of serum digoxin levels include elevated serum creatinine levels, age greater than 80 years, a daily dose of digoxin equal to or greater than 0.25 mg, and the use of other antiarrhythmic drugs, including quinidine and verapamil.[2] Two patients had been taking concomitant verapamil and digoxin for many years; one patient had been taking quinidine for three months before commencing digoxin.

Low serum potassium levels sensitise patients to digoxin, but none of the patients had abnormal serum potassium levels, serum creatinine levels or liver function tests.

Intestinal ischaemia or intestinal necrosis has been reported to occur with digoxin therapy, not related to serum digoxin levels, and may be a cause of gastrointestinal symptoms in patients taking digoxin.[4]

The return of symptoms with a rechallenge of the suspected drug would be strong evidence of drug toxicity but difficult to justify in a general practice, non-trial setting. In my four patients, the prompt cessation of symptoms with the cessation of digoxin was suggestive of drug toxicity. Therefore, patients with long-standing symptoms and normal serum digoxin levels may benefit from withdrawal of digoxin.

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Patients with adverse reactions to digoxin, and normal serum digoxin levels

	Patient 1	Patient 2	Patient 3	Patient 4
Age, sex	73, Female	71, Male	59, Female	71, Female
Digoxin dose per day	0.25 mg	0.5 mg	0.25 mg	0.125 mg
Duration of treatment	>2 years	> 2 years	> 2 years	> 2 years
Reason for digoxin treatment	SVT	AF	SVT	SVT
Serum digoxin level on presentation* (range of serum digoxin over the past 2 years)	0.9 ng/mL (0.5–0.9 ng/mL)	0.8 ng/mL (0.8–1.4 ng/mL)	0.5 ng/mL (0.5–0.6 ng/mL)	1.0 ng/mL (0.9–1.1 ng/mL)
Adverse reactions	Tiredness (several weeks)	Anorexia, weight loss (several months)	Nausea, abdominal discomfort (several weeks)	Diarrhoea (12 months)
Concomitant drugs	Sotolol	Frusemide, amiloride	Thyroxine, verapamil	Verapamil, quinidine

* Normal (therapeutic) range: 0.6–2.6 ng/mL.
SVT = Supraventricular tachycardia. AF = atrial fibrillation.

An intractable error in MEDLINE

Mani Rajagopalan,* Bishakha Rajagopalan†

* Psychiatrist, † Dermatologist, Ballarat Base Hospital, Ballarat, VIC 3350

To the Editor: Intractable, meaning "refractory/obstinate/resistant to cure", arises from the Latin *in* = not, *tractabilis* = manageable.[1] While referencing a paper on treatment resistance, we conducted a search of the MEDLINE database[2] using the text word "intractable". The search produced 5856 references for the period 1976–1997 (January). Following this, we tried the wrong spelling "intractible" (as we had initially disagreed on how the word was spelled) and, surprisingly, came up with 15 documents from the same period. These journals were spread across all specialties and no journal appeared more than once. None of these 15 articles turned up in the earlier survey using the correct spelling. While the error is small (of the order of 0.3%), the significance of missing a major study cannot be overemphasised.

Previous studies have highlighted deficiencies in MEDLINE in the indexing of articles; sometimes complete issues of journals have been reported as missed.[3,4] While complete reliance on a few text words or Medical Subject Headings (MeSH terms) is certainly not recommended, our experience suggests a need to try out alternative (and possibly wrong) spellings for less commonly used words to increase the sensitivity of the search.

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3. Adams CE, Power A, Frederick K, Lefebvre C. An investigation of the adequacy of MEDLINE searches for randomised controlled trials (RCTs) of the effects of mental health care. *Psychol Med* 1994; 24: 741-748.
4. Silagy C. Developing a register of randomised controlled trials in primary care. *BMJ* 1993; 306: 897-900.

Lois Ann Colaianni

Associate Director, Library Operations, National Library of Medicine, Bethesda, Maryland, USA 20894

Comment: The United States National Library of Medicine, which produces the MEDLINE database, is aware of the importance of accuracy in citing the published literature and welcomes information by users of any errors which they encounter. We do have a number of validation processes in place to ensure a high level of quality.

The complete MEDLINE database, covering about nine million records from 1966 through to March 1997, contains 16 occur-