in the hope that a ground swell of resistance will cause the politicians to think again.

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Torsade de pointes induced by sotalol

SIR,—Drs R Krapf and M Gertsch (15 June, p 1784) make an important point about the arrhythmogenicity of the β blocking drug sotalol, which has additional class III (Vaughan Williams) antiarrhythmic properties. They concluded that the arrhythmogenic effect may be due to a prolonged QT interval and that clinicians should be aware of sotalol's arrhythmogenicity when QT prolongation occurs. Therefore they suggest strict and early control of the QT interval when starting treatment.

In a recent study on patients with coronary artery disease and arrhythmias induced by exercise we observed an increase in the number and severity (assessed by the Lown score) of ventricular premature beats. After a pretreatment stress test (without any antiarrhythmic medication) 25 patients received sotalol by mouth 160 mg twice daily; they were reinvestigated at a further stress test two weeks later. Although two thirds of our patients made outstanding improvements at the second stress test, in three ventricular arrhythmias worsened (a twofold to fourfold increase in the numbers of ventricular premature beats). Two also showed a deterioration in the Lown score without demonstrable electrocardiographic changes.

The degree of deterioration agrees well with the percentage of aggravation described by Lown's group for any antiarrhythmic drug in clinical application.[1] Worsening of arrhythmias was recorded in 15% of those given propranolol and 7% of those given metroprolol. Only six out of 20 patients who deteriorated on quinidine also had prolongation of the QT interval; and out of the 722 patients studied by Velebit *et al* only these six had aggravation of ventricular premature beats corresponding to electrocardiographic changes.[1]

Clinicians should therefore be aware of drug induced arrhythmogenicity (including potentially fatal complications) in about 10-15% of patients receiving any antiarrhythmic drug, even when the QT interval is normal.

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1 Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. *Circulation* 1982;65:886-94.

SIR,—In the patient described by Dr R Krapf and Professor M Gertsch (15 June, p 1784) torsade de pointes was induced by sotalol despite therapeutic sotalol concentrations. The patient was also receiving maprotiline 75 mg daily throughout. The authors state that "the temporal association indicates that digoxin and maprotiline did not have a role."

Tricyclic antiaepressants are known possible causes of prolonged QT syndrome and torsade de pointes,[1] and it seems logical that sotalol should not be given in combination with such agents. Although maprotiline (Ludiomil) is not a tricyclic but a tetracyclic antidepressant, it has a similar mode of action and, to quote the *Physician's Desk Reference*, "its pharmacological similarity to tricyclic anti-depressants requires that each reaction be considered when administering Ludiomil."[2] *Martindale: The Extra Pharmacopoeia* states that maprotiline requires similar precautions to those of amitriptyline, which "should be used with caution in patients with cardiovascular disease."[3] It would therefore seem that the concomitant treatment with maprotiline may have played an important part in the genesis of torsade de pointes in the patient described. As far as can be ascertained in published reports there has been only one case of torsade de pointes induced by sotalol in the absence of any other factor prolonging the QT interval.[4]

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Relation between recurrence of cancer of the colon and blood transfusion

SIR,—Professor Neil Blumberg and colleagues (6 April, p 1037) showed a significant association between recurrence of colorectal cancer and perioperative blood transfusion. We reviewed 109 patients who underwent resection of carcinoma of the colon and rectum in 1977-84 without adjuvant treatment. Sixty patients (55%) had received transfusions. There was no significant difference in the age, sex, stage of disease, degree of tumour differentiation, or length of follow up between these patients and those who had not received transfusions. Of the 55 patients with right sided (caecum, ascending, and transverse colon) carcinomas, 37 (67%) had received transfusions whereas only 26 of 54 patients (48%) with left sided tumours had received blood ($\chi^2=4{\cdot}08$, 1 df, $p<0{\cdot}05$).

Recurrent disease was diagnosed in 29 patients (27%), 18 of 63 (28%) who had received transfusions and 11 of 46 (24%) who had not ($\chi^2=0{\cdot}29$, 1 df, $p>0{\cdot}5$). Cumulative percentages of patients surviving without recurrence were calculated by a life table method.[1] Although there was no significant difference at any interval of follow up, patients who had not received transfusions had a marginal disease free survival advantage (table).

Cumulative percentages of patients free from disease after resection of carcinoma

	Time after operation (years)				
	1	2	3	4	5
Patients given transfusions	85·4	66·2	58·6	56·3	49·6
Patients not given transfusions	91·1	77·0	71·8	61·6	55·9

No significant association was found between transfusions and recurrence for any stage of disease or location of tumour, but each analysis consistently showed a slightly longer interval free from disease for patients who had not received transfusions.

Blood transfusions given before transplantation resulted in significant prolongation of renal allograft survival, probably as a consequence of immune suppression induced by transfusion. Conclusions from transplant studies, however, may not necessarily apply to cancer: tumours, which are often antigenic, have been present in patients with cancer for some time before transfusion, whereas transplant recipients are given transfusions before receiving the antigenic stimulus of a renal allograft. Although allogeneic blood given before transplantation of an immunogenic tumour significantly accelerates tumour growth in rats,[2] our recent studies in mice show that transfusions given at the time of or after tumour transplantation are not associated with increased tumour growth (unpublished data).

An association between recurrence of cancer and blood transfusions could be due to immunological manipulation or may be fortuitous. For example, Blumberg's patients who had received transfusions were more likely ($p<0{\cdot}05$) to have received cytoreductive treatment, presumably for residual and perhaps more aggressive disease. Thus blood transfusion could be simply an index of either less successful or more difficult surgery or the biological behaviour of malignant tumours, a variable that is not measured adequately by histopathological staging.

Our retrospective review was of a small number of patients and may be subject to a type II error,[3] obscuring a significant difference between those who had received transfusions and those who had not. Further studies are required to verify the existence of an association between cancer recurrence and transfusions and to identify the determinants of such an association.

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Intranasal calcitonin and plasma calcium concentrations

SIR,—We were as puzzled as Dr J C Stevenson (6 July, p 54) when reading the paper by Dr A E Pontiroli and colleagues (11 May, p 1390) that healthy volunteers could have plasma ionised calcium concentrations anywhere in the range of 2·0-2·5 mmol/l (8-10 mg/100 ml). We were less surprised about their ability to find a slight yet significant effect from intravenous human calcitonin on serum calcium concentrations.

Blanc *et al* found, in 15 volunteers, a small but significant decrease in serum calcium concentrations (0·05 (SD 0·02) mmol/l (0·2 (0·08) mg/100 ml)) six hours after intramuscular injection of 100 U of salmon calcitonin,[1] and Gennari *et al* obtained, in 10 volunteers, a dose dependent decrease of serum calcium concentrations after intravenous administration of the three most widely used types of calcitonin (porcine, salmon, and human). For human calcitonin this was significant between 10 and 120 minutes—that is, the duration of the study—with 0·5 mg and between five and 120 minutes with 1·0 mg intravenously.[2]

The magnitude of the decrease of serum calcium concentration in controls is such that it has always been a controversial point, and many authors have not found any significant decrease at all (admittedly, usually with smaller series). It therefore seemed inappropriate to test the effectiveness of an intranasal spray in volunteers using this variable. It appeared more logical to test the hourly urinary excretion of electrolytes since calcitonin is a potent natriuretic hormone,[3] and thereby a calciuretic hormone as well. We therefore studied an intranasal spray of salmon calcitonin in this way and found that it induced significant excretion of sodium, chloride, calcium, and potassium when 200 U was administered intranasally.[4] This dose was less potent, however, than 100 U of salmon calcitonin given intramuscularly, but it did not