they use could kill their children.—We are, etc.,

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Camphor Poisoning in Children

SIR,—I should like to support Dr. J. R. Sibert's comments on camphor poisoning in children (31 March, p. 803). Our experience with this substance at this hospital is in fact less than that in Newcastle, amounting to only two cases out of a total of 260 children admitted after ingesting various kinds of poison over the same period as that reviewed by Dr. Sibert (1970-2). This year, however, up to the end of March we have so far admitted two children who had ingested camphorated oil out of a total of 34 cases.

As pointed out by Dr. Sibert, camphorated oil is said to be lethally dangerous, fatalities having occurred after swallowing one teaspoonful. It seems incredible to me that such a substance should be so freely available to the public; and neither can one blame parents for taking few precautions to prevent its being handled by children when it is often sold specifically for rubbing into babies' chests and has even been smeared on their lips to prevent chapping. Surely it would not be too difficult to prevent the sale over the counter of this substance, which is both highly dangerous and of doubtful medical value.—I am, etc.,

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Duration of Action of Beta-blocking Drugs

SIR,—The observations of Drs. P. D. Nigam and A. S. Malhotra (24 March, p. 742) on the prolonged action of pindolol in the management of angina pectoris are of great interest.

Despite their established place and wide use in clinical medicine, little information is available about the duration of action of beta-adrenergic blocking drugs. Propranolol has been shown to have a pharmacological half-life of 11 hours as judged by inhibition of an isoprenaline tachycardia[1] and, although the plasma half-life of practolol is reported as 10 hours,[2] its pharmacological half-life has not been determined. Recently 5 mg of pindolol given orally has been shown to act for significantly longer than 100 mg of propranolol.[3] Knowledge of the duration of action is of vital importance in determining the dose frequency and effectiveness of any drug.

We have recently carried out observations on the duration of action of several beta-blocking drugs in normal volunteers using a standardized exercise test to produce a marked increase in heart rate as a result of increased sympathetic stimulation of the heart. Exercise was performed before and at intervals after the oral administration of alprenolol, sotalol, and practolol. The effect of each drug has been presented as a percentage reduction in the exercise tachycardia present before drug administration (table I). In the subjects who received practolol plasma levels and urinary excretion of the drug were determined.

TABLE I—*Effect of Beta-blocking Drugs on Exercise Tachycardia*

Drug	Dose (mg)	No. of Subjects	Reduction in Exercise Tacyhcardia (%)						
			2-3 hr	7-8 hr	24 hr	36 hr	48 hr	72 hr	96 hr
Placebo ..		6	0	0	0	—	0	0	—
Alprenolol ..	100	3	16·4	8·0	0	—	—	—	—
Alprenolol ..	400	3	26·8	25·0	10·1	7·4	—	—	—
Sotalol ..	100	3	16·1	13·8	10·6	—	—	—	—
Sotalol ..	400	3	27·4	24·8	23·4	17·2	23·1	6·5	11·8
Practolol ..	100	3	23·1	—	13·5	—	—	—	—
Practolol ..	200	3	26·4	—	19·1	—	—	—	—
Practolol ..	400	6	25·7	24·3	21·7	—	14·5	9·9	2·3
Practolol ..	800	3	27·5	—	22·1	—	—	—	—

TABLE II—*Relation of Reduction in Exercise Tachycardia to Blood Practolol Level*

	0 hr	3 hr	7 hr	24 hr	48 hr	72 hr	96 hr
Reduction in exercise tachycardia (%) ..	0	25·7	24·3	21·7	14·5	9·9	2·3
Blood practolol level (μg/ml)	0	3·5	3·1	1·2	0·45	0·15	0

Several conclusions may be drawn from these results. Firstly, maximum blockade of an exercise tachycardia was not produced by 100 mg of alprenolol or sotalol but was produced by this dose of practolol. Secondly, alprenolol, sotalol, and practolol in doses of 400 mg were equally effective initially, but sotalol and practolol continued to produce blockade of 20% or greater at 24 hours, at which time the effect of alprenolol had diminished to 10%. This dose of sotalol and practolol had some effect on an exercise tachycardia for up to 72-96 hours. This effect did not result from the subject becoming accustomed to the repeated periods of exercise as there was no change in an exercise tachycardia after administration of a placebo. Thirdly, increasing the dose of practolol from 100 to 800 mg did not produce greater maximum reduction in the exercise tachycardia, but it did increase the duration of effective blockade.

Values for the percentage reduction in an exercise tachycardia and the blood practolol levels in six subjects given 400 mg of practolol orally are shown in table II. It will be seen that the decay of the blockade curve appears to be less rapid than that of the blood practolol level. Thus although the plasma half-life of practolol is about 10-11 hours, the pharmacological half-life appears to be of the order of 40-50 hours. As all but 10-30 mg of this dose of practolol had been excreted in the urine in the first 48 hours, it would appear that it may be bound to the tissues, and that this accounts, at least partially, for the long duration of action.

These results, together with those of other studies currently in progress in this department, indicate that the maximum reduction of an exercise tachycardia produced in normal subjects with practolol given either orally or parenterally depends upon the achievement of a blood practolol level of 1·0 μg/ml. As long as the blood practolol level is maintained above this value, an exercise tachycardia will be reduced by at least 20%. It is shown in table II that, on this basis, an oral dose of 400 mg of practolol need only be taken once daily; we would predict from studies at present in progress that 800 mg of practolol would be effective for 48 hours, as the blood practolol level is about 3·0 μg/ml 24 hours after such a dose.

The prolonged effect of pindolol observed by Drs. Nigam and Malhotra may also be explained on this basis. A 10-mg dose of pindolol maintains complete blockade at 24 hours[4] and has been shown to be about 40 times more active than propranolol in inhibiting an isoprenaline tachycardia.[3] Therefore the dose of pindolol (5 mg four times daily) had about five times the activity of the dose of propranolol (40 mg four times daily) and in addition was about twice the dose required for a maximum effect. It is possible that after four weeks on such a regimen blood levels of pindolol had been achieved in excess of those required and may have been maintained for much of the first week after cessation of therapy above the level required for a blocking effect.

Little attention has been focused on this important area of the clinical pharmacology of beta-blocking drugs. Studies on these drugs have often been terminated within eight hours, thus failing to obtain much vital information. It is our contention that rationalization of dosage regimens is long overdue, even with drugs like propranolol and practolol which have now been in clinical use for more than five years.—We are, etc.,

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Biological Availability of Digoxin

SIR,—The comparative study of "new" and "old" Lanoxin by Dr. D. Falch and others (24 March, p. 695) seems to perpetuate some misconceptions with regard to the significance of plasma levels of dixogin.

The action of digoxin is not closely related to the plasma level but depends on the relatively slow uptake of the drug on the active

sites in the myocardium. A delay of two to three hours between peak plasma level and maximal effect seems likely. The fall from peak plasma levels is due to this process in addition to the effects of "excretion and metabolization."

The attribution to toxicity of the nausea noted soon after an oral dose of 0·5 mg of "new" Lanoxin is unfortunate, as the associated plasma levels were relatively low and any adverse effect on the myocardium seems unlikely.

When considering the dose of "new" Lanoxin it must be borne in mind that traditional regimens were based on tablets of similar properties which were in general use up to 1970. Comparison of the plasma levels obtained with the same radioimmunoassay technique in 1970[1] and 1972[2] confirms that the less well-absorbed preparation described as "old" Lanoxin was in use between 1970 and 1972 only.

Patients differ considerably in their response to variations in the biological availability of digoxin. Although some subjects show little difference in plasma levels when changed from the "old" to the "new" preparation, those who absorb digoxin relatively poorly will show a very great increase. No general rules of dose equivalence for the two preparations can be given; each patient must be assessed individually.—We are, etc.,

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Grades of Hypothyroidism

SIR,—We were interested in the article on grades of hypothyroidism by Dr. D. C. Evered and others (17 March, p. 657). Since we first described preclinical hypothyroidism in 1967[1] on the basis of thyroid antibodies and the hypercholesterolaemia that may occur in this condition, accurate thyroid stimulating hormone (T.S.H.) measurements have clearly defined the stages of thyroid failure in autoimmune thyroiditis. Our classification[2] of the stages of thyroid failure, which we made in 1970, is only semantically different from that proposed by Dr. Evered and his colleagues. Our experience suggests that after many years in the stage of preclinical hypothyroidism progression to hypothyroidism occurs rather rapidly over six months to a year. Twenty-two of our first 50 patients progressed in this way to hyperthyroidism in a comparatively short time.

Dr. Evered and his colleagues used 10 IU of TSH for assessing the thyroid reserve. We found this test superstimulatory and occasionally not without danger in patients with ischaemic heart disease. We measured the thyroid reserve using 2·5 IU doses of TSH by the method described by Hobbs *et al.*[3] Tests for thyroid reserve were compared with TSH estimations kindly done by Professor R. Hall and his colleagues. Patients with preclinical hypothyroidism and raised TSH levels all had reduced thyroid reserves. In patients with suspected preclinical hypothyroidism and normal TSH levels the thyroid reserve was sometimes reduced (unpublished). This suggests either that measurement of the thyroid reserve is more sensitive than the TSH level or it is less discriminatory.

Now that it is at last being accepted that preclinical hypothyroidism does exist it is important to know how to find these cases. Dr. Evered and his colleagues, with the advantage of being able to do large batches of TSH estimations, have made a study of only 22 patients. Ten of the 22 were extracted from their "normal" controls accidentally found to have raised serum TSH concentrations. The next largest group were six patients who were found by "observation of a small goitre in relatives or friends visiting outpatients." We collected 50 patients with preclinical hypothyroidism in about a year, though they had been followed up for longer periods. Twenty-nine were patients with a past history of thyrotoxicosis or goitre but 10 presented with coronary artery disease.

One should always exclude preclinical hypothyroidism in a young woman with coronary artery disease, especially if the serum cholesterol is raised and there is no corneal arcus and also if there is a family history of specific autoimmune disease or coronary artery disease. Since our original 50 patients with preclinical hypothyroidism we have found many more each year. The serum cholesterol levels always fall with clofibrate, but probably thyroxine will be more effective than clofibrate in preventing the progression of the degenerative arterial disease.

Lastly, we agree with Dr. Evered and his colleagues that cytoplasmic antibodies are more important than antibodies to thyroglobulin. The Helsinki[4] survey which failed to find autoimmune thyroiditis a significant factor in the aetiology of coronary artery disease did not use the immunofluorescent techniques for their thyroid antibody studies.—We are, etc.,

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Postoperative Empyema and Survival in Lung Cancer

SIR,—Your leading article (3 March, p. 504) raised many points of interest. Contrary to your belief Le Roux[1] did not find an improved survival rate after empyema, nor have more recent, larger studies.[2] Nevertheless, the clinical impression is still held, as you state, that people surviving empyemas after lung resection for carcinoma do have an increased chance of surviving five years. You refer to Coley's work[3] as indicating that infection may have a beneficial effect in helping eradicate cancer. I would like to suggest that it is the pyrexia that accompanies infection which is the important factor.

Westermark in 1898[4] was perhaps the first person to use heat alone in tumour therapy, but more recently extensive investigation into the use of hyperthermia in the treatment of solid tumours has been undertaken. Selawry[5] showed that in tissue culture the growth of cells derived from human tumours could be inhibited by a temperature of 39-40°C. This is arguably an ideal treatment as it has a selective effect on malignant cells, and normal cells are unaffected. Muckle and Dickson[6] have admirably demonstrated in an animal model how effective a treatment hyperthermia can be. It has been used in man with demonstrable results both by regional perfusion of prewarmed blood[7] and total body hyperthermia,[8] and further clinical trials are being carried out.

It may be that surgery will remain the main treatment for malignant disease, but it is becoming apparent that further improvement in results will occur only when we learn to utilize other factors acting to eliminate malignant disease. These adjuvant forms of treatment may include chemotherapy, immunotherapy, and perhaps hyperthermia. The clinical beginning of hyperthermia at the end of the nineteenth century may yet bear fruition before the end of the twentieth.—I am, etc.,

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Suicidal Attempt with Practolol

SIR,—Tolerance to beta-adrenergic blocking agents varies considerably. There is also a definite difference in the cardiodepressive action of different beta-adrenergic drugs. We therefore think it of interest to report an attempted suicide with practolol in a patient with severe heart disease.

The patient, a man aged 39, had rheumatic mitral disease. In 1964 mitral commissurotomy was performed and in 1969 the mitral valve was replaced with an artificial ball-valve. Thereafter the patient's main problems were recurrent attacks of atrial fibrillation and flutter. He also had several periods of depression and was treated three times in a mental hospital. During the last year he had been taking digoxin (0·375 mg/day) and warfarin. For prevention of dysrhythmias he had been taking 200 mg of practolol twice a day.

During a depressive mood he took 90 tablets (9,000 mg) of practolol. Three hours later he was taken to hospital. On admission his general condition was good. The heart rate was 70 beats/min and the blood pressure 90/70 mm Hg. There were no signs of cardiac decompensation. During the next hour the heart rate dropped to 64/min, but within two hours it regained the previous value. The blood pressure rose simultaneously to 100/70 and later to 110/75 mm Hg, which was his usual level. The further course was uneventful and no special treatment was necessary at any time. Blood samples taken 4½ and 9½ hours after ingestion of practolol gave serum concentrations of 40 μg/ml, and 58·6 μg/ml respectively (I.C.I.