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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1 Chamberlain, D. A., White, R. J., Howard, M. R., and Smith, T. W., *British Medical Journal*, 1970, 3, 429.
2 Shaw, T. R. D., Howard, M. R., and Hamer, J., *Lancet*, 1972, 2, 303.

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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1 Fowler, P. B. S., and Swale, J., *Lancet*, 1967, 1, 1077.
2 Fowler, P. B. S., Swale, J., and Andrews, H., *Lancet*, 1970, 2, 488.
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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.

Laboratories, Dr. Brian Scales), the usual therapeutic level being about 1·5 μg/ml.[1] To our knowledge these are the highest values reported in man so far.

Possibly any beta-blocker may cause heart failure in a patient whose myocardial performance depends critically on sympathetic drive. However, practolol seems to be less dangerous than others in this respect, and in normal therapeutic doses causes only modest reduction of cardiac output.[2] Practolol has been shown to possess some sympathomimetic activity. Its positive chronotropic activity may explain why the pulse rate fell relatively little and definite bradycardia did not occur in the case presented here. This may explain, partly at least, why the patient's heart condition did not deteriorate. Another possible explanation could be the less pronounced effect of practolol on myocardial contractility.

This case illustrates the low toxicity of practolol and its modest cardiodepressive effect which has proved valuable in the treatment of patients with supraventricular arrhythmias and rapid ventricular rates after myocardial infarction and cardiac surgery. —We are, etc.,

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1 Fitzgerald, J. D. F., and Scales, B., *International Journal of Clinical Pharmacology*, 1968, 1, 467.
2 Sowton, E., Balcon, R., Cross, D., and Frick, H., *British Medical Journal*, 1968, 1, 215.

Intestinal Motility and Absorption

SIR,—I was interested in the study by Dr. J. Nimmo and others (10 March, p. 587) demonstrating impaired absorption of paracetamol after the administration of propantheline and enhanced absorption after metoclopramide, especially as this apparently conflicts with a recent report from Helsinki[1] that the absorption of digoxin is decreased by metoclopramide and increased by propantheline. Unfortunately the techniques of the two studies are dissimilar and it is difficult to make valid comparisons.

I am beginning to suspect that absorption from the gut of a normal person is decreased by drugs which either increase or decrease motility and that the individual's normal gut motility gives optimal absorption. In Dr. Nimmo's study the highest plasma levels of paracetamol were in the convalescent volunteers. When they were given propantheline absorption of paracetamol decreased. The second group of subjects was chosen because they were known to have abnormal and slow gastric emptying. When given metoclopramide intravenously absorption of paracetamol increased—I suspect because motility was returned towards normal.

In a study of the absorption of xylose in patients with normal gastrointestinal function[2] I found that 20 mg of metoclopramide reduced absorption in eight out of 10 subjects, the mean decrease in xylose excretion in the urine being 15·9% ($P < 0.0125$). After an intravenous injection of 0·6 mg of atropine nine of 12 subjects had a decreased absorption, the mean decrease in xylose excreted in the urine being 18·7% ($P < 0.001$). These studies, though crude and simple, tend to confirm that normal motility gives optimal absorption. Other results suggest, however, that in disease states these drugs, if they alter motility towards normal, enhance absorption. In five of a group of 11 myxoedematous patients the absorption of xylose was increased by metoclopramide, and in one patient with carcinoid syndrome 15 mg of propantheline given intramuscularly increased the xylose excretion in the urine from 0·86 to 1·35 g.—I am etc.,

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1 Manninen, V., Apajalahti, A., Melin, J., and Karesoja, M., *Lancet*, 1973, 1, 398.
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Early Diagnosis of Nephroblastoma

SIR,—In your leading article on this topic (10 March, p. 567) you state that it is important to identify the group of neonatal renal tumours which have been called fibrosarcoma or congenital mesonephric nephroma, and you continue: "The importance of identifying this group is to prevent the infant from receiving radiotherapy and chemotherapy." The implication is that if a true nephroblastoma (Wilms's tumour) is diagnosed in early infancy it is reasonable to include radiotherapy and chemotherapy as part of the management.

It would be a pity if this impression were not corrected, for now there must be few teams dealing with embryonal tumours who would recommend in infants under one year of age any treatment other than surgery. The exception must be made of those unusual cases in which there is undoubted spread, local or distant, at the time of operation.—I am, etc.,

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Ultrasonic Detection of Deep Vein Thrombosis

SIR,—As experienced users of the ultrasonic Doppler technique for the detection of deep vein thrombosis, who have performed tests on over 650 patients in the past 2½ years, we should like to make two comments on the paper by Mr. O. B. Williams and others (3 March, p. 517).

(1) The authors state that the high frequency (10 MHz) focused ultrasonic beam of the Parks Model 802 or 806 instrument has several advantages over "other models used in similar studies." Our experience of both the Park Model 806 and the Sonicaid Model D205 have led us to believe that the broad beam and lower frequency (2 MHz) of the Sonicaid is the more useful. Inclusion of the relevant vein in the broad beam is almost automatic if the Doppler signal from the adjacent artery is located. The test thus becomes much easier to perform for even the comparatively inexperienced user and false positive results arising from failure to include the vein in the beam are avoided. The greater penetration of the lower frequency of the ultrasound beam also enables the test to be performed routinely up to the level of the iliac veins.

(2) The results reported appear to contradict the author's own statement that "The experienced observer using the 806 directional machine can diagnose thrombotic lesions of the calf veins." It is our opinion that the existence of the plexus of veins in the calf results in transfer of blood through collateral pathways when individual veins in the calf are thrombosed. Consequently the flow at the level of the popliteal or femoral veins resulting from a calf squeeze will not usually be affected by a single occluded calf vein. Only widespread occlusion of the calf veins or occlusion at the level of the popliteal vein can be detected with any certainty.—We are, etc.,

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Cubital Tunnel External Compression Syndrome

SIR,—The paper by Messrs. T. G. Wadsworth and J. R. Williams (17 March, p. 662) prompts me to warn orthopaedic surgeons to be cautious before making this diagnosis on an immigrant from a country where leprosy is endemic. The ulnar nerve is the commonest peripheral nerve to suffer damage in leprosy. The patient may present with what may seem to be a typical entrapment neuropathy even in the absence of skin lesions, and the diagnosis will be missed if thickening of the nerve in the upper arm, immediately proximal to the cubital tunnel, is not noted.

As leprous changes are within the nerve, surgical transposition is unlikely to prove of value. On the basis that repeated trauma will aggravate such changes, however, it has been suggested[1] that this operation will benefit a small minority, who can be selected on the following criteria: (1) presence of a small interval between the olecranon and the medial epicondyle of the humerus (25 mm or less with the elbow extended), and (2) increase of this interval by more than 50% with the elbow fully flexed.—I am, etc.,

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1 Srinivasan, H., and Namasivayam, P. R., *Indian Journal of Medical Research*, 1971, 59, 1385.

Injury on the Football Field

SIR,—The present laws of rugby football permit the use of replacements in matches in which a national representative side is playing, "only when, in the opinion of a medical practitioner, the player is so injured that he should not continue playing in the match." Even at international level the emphasis seems to be whether the player can return, rather than whether it is advisable in the immediate and ultimate interest of the same player. In recent weeks, I have seen several match incidents in which players have returned to play and faced the likelihood of more grievous injury because substitutes are not yet permitted in county championship and other richly competitive games. The pressure is always on the injured player—self-applied, maybe, but inculcated by long tradition—to return to the field of play, given half a chance by medical