Epidemic	Antigen	Geometric Mean of Antibody Titres		X-fold Rise in Mean Titre	Proportion of Cases with ≥4-fold Rise in Titres
		Acute Phase Sera	Convalescent Phase Sera		
1968-9	Hong Kong/8/68	6	213	36	20/20
	MRC-2	6	30	5	14/20
	MRC-10	6	19	3	10/20
	Finland/1/74	6	15	2·5	10/20
1969-70	Hong Kong/8/68	7	411	59	10/10
	MRC-2	7	59	8	8/10
	MRC-10	6	26	4	7/10
	Finland/1/74	6	19	3	5/10
1971-2	Hong Kong/8/68	6	245	41	20/20
	MRC-2	6	46	8	17/20
	MRC-10	6	24	4	15/20
	Finland/1/74	6	19	3	13/20
1972-3	Hong Kong/8/68	17	220	13	24/25
	MRC-2	9	227	25	25/25
	MRC-10	6	138	23	25/25
	Finland/1/74	6	162	27	25/25
1974	Hong Kong/8/68	26	244	9	40/43
	MRC-2	18	214	12	38/43
	MRC-10	7	143	20	42/43
	Finland/1/74	7	229	33	43/43

Titres of <12 are regarded as 6.

and the convalescent sera in the 11-26th day. The treatment of sera and the HI tests were done as described previously.[4] With the exception of A/Finland/1/74 the strains used for preparation of antigens were obtained, through the courtesy of Dr. G. C. Schild, from the World Influenza Centre. The recombinant strain, MRC-2, is antigenically identical with A/England/42/72 and the MRC-10 strain with A/Port Chalmers/1/73. The results from the five epidemics are summarized in the table.

Comparatively high antibody titres to A/Finland/1/74 were evoked by A/England/42/72 infections during the 1972-3 epidemic. In contrast, the sera collected during the previous years did not attain the fourfold increase in the geometric mean titre with A/Finland/1/74, though about half of the cases showed a significant increase of A/Finland/1/74 antibodies (usually from <12 to 24). The highest increase was from <12 to 96 in two cases out of 50 Hong Kong patients. In the earlier convalescent sera a titre of ⩾ 48 was present in only nine cases. These findings suggest that vaccines containing the original Hong Kong virus are unlikely to raise HI antibodies against strains like A/Finland/1/74 to a level consistent with immunity.

A preliminary survey of HI antibodies to A/Finland/1/74 in June 1974 suggests that in spite of the recent epidemic the immune status in the beginning of the next epidemic season in Finland will be even poorer than in autumn 1973.—We are, etc.,

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1 *Weekly Epidemiological Record*, 1974, **49**, 107.
2 *Weekly Epidemiological Record*, 1974, **49**, 176.
3 Pereira, M. A., *et al.*, *British Medical Journal*, 1972, **4**, 701.
4 Pyhälä, R., and Kleemola, M., *Scandinavian Journal of Infectious Diseases*, 1973, **5**, 273.

Serum Calcitonin and Thyroid Carcinoma

SIR,—The suggestion in your leading article (1 June, p. 461) that the finding of a raised serum calcitonin level in a member of a family with a high incidence of medullary carcinoma is an indication for total thyroidectomy is based on several assumptions.

Firstly, it assumes that hypercalcitoninaemia in these families is always due to excessive production of calcitonin by thyroid C cells. Hypercalcitoninaemia has been reported in a number of conditions other than medullary carcinoma[1-3] and we have found that it occurs frequently in patients with non-thyroid tumours.[4] The recent account of production by oat cell carcinomas of the lung[5] draws attention to extra-thyroidal sources of calcitonin.

The second assumption is that hypercalcitoninaemia identifies a malignant or premalignant state of the thyroid C cells. Individual members of these families who have had a thyroidectomy on the basis of hypercalcitoninaemia have shown histological changes which are consistent with increased numbers and activity of thyroid C cells.[6-8] Though it appears that the level of calcitonin progressively increases in members who have only hyperplastic changes it remains to be seen if this condition inevitably progresses to a malignant one.

The third and most important assumption is that asymptomatic hypercalcitoninaemic members will benefit by total thyroidectomy. Even if hypercalcitoninaemia was shown to be due to a potentially or frankly malignant disease of the C cells the operation would be justified only if it served to prevent the development of illness. In some individuals the disease may be quite occult; one member of a large family was found to have medullary carcinoma incidentally at necropsy in his 79th year.[9] Furthermore, the finding of a high incidence of cervical lymph node metastases in young adults,[6] the failure of total thyroidectomy to produce undetectable levels of serum calcitonin in members shown to have medullary carcinoma[6] or C-cell hyperplasia,[7] and the early recurrence of hypercalcitoninaemia following total thyroidectomy in one member[6] raise the question of adequacy and timing of this operation. Calcitonin is not confined to the thyroid C cells in man[10] and the developmental history of the C cells[11] suggests the possibility of multifocal extra-thyroidal as well as intra-thyroidal[12] origin of the tumour, especially in these families.

The measurement of serum calcitonin helps to define those members in whom there is a relatively greater risk of developing symptoms due to medullary carcinoma or phaeochromocytoma. In addition, it is useful in following the extent and activity of the C-cell system. Other clinical and laboratory[13] findings may prove of value in further selection of individuals at risk. Decisions regarding the type of treatment, especially of asymptomatic members, by procedures having finite risks should be made only after careful consideration of the likely natural history of the "disease" and the "illness" in the individual concerned.—We are, etc.,

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1 Sizemore, G. W., *et al.*, *New England Journal of Medicine*, 1973, **288**, 641.
2 Deftos, L. J., *et al.*, *Journal of Clinical Investigation*, 1973, **52**, 3109.
3 Milhaud, G., *et al.*, *Lancet*, 1974, **1**, 462.
4 Coombes, R. C., *et al.*, *Lancet*, 1974, **1**, 1080.
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6 Melvin, K. E. W., Tashjian, A. H., and Miller, H. H., *Recent Progress in Hormone Research*, 1972, **28**, 399.
7 Wolfe, H. J., *et al.*, *New England Journal of Medicine*, 1973, **289**, 437.
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9 Ljungberg. O., *Acta Pathologica et Microbiologica Scandinavica*, 1972, Suppl. no. 231. p. 10.
10 Galante, L., *et al.*, *Lancet*, 1968, **2**, 537.
11 Carvalheira, A. F., and Pearse, A. G. E., in *Calcitonin*, ed. S. Taylor, p. 122. London, Heinemann, 1968.
12 Ljungberg, O., Cederquist, E., and Studnitz, W. von, *British Medical Journal*, 1967, **1**, 279.
13 Li., F. P., *et al.*, *Journal of the National Cancer Institute*, 1974, **52**, 285.

Toxic Reaction to Phenytoin

SIR,—In the light of the paper by Drs. D. L. McLellan and M. Swash (27 April, p. 204) we should like to report the following case recently under our care.

The patient originally presented at the age of 11 months with febrile convulsions. Her birth was normal and there was no family history of epilepsy. She was started on phenobarbitone but two months later had a second series of convulsions and phenytoin was added. Over the next three years she was admitted to hospital on six occasions for further convulsions and was treated with various combinations of phenytoin, ethoxusimide, chlorpromazine, and beclamide with little success. Her E.E.G. showed some abnormal spike activity and her I.Q. progressively fell from 75 on the Wechsler scale in 1967 to 51 in 1971. Extensive investigation revealed no definite aetiology and she was thought to be suffering from some degenerative condition of the brain. In February 1974, aged 11 years, she was moderately controlled on phenytoin 400 mg and primidone 500 mg daily when she suddenly developed choreoathetoid movements of all her limbs and jerking movements of her tongue and facial muscles. She rapidly became uncontrollable and was sedated with intravenous diazepam. The serum phenytoin level was 42 μg/ml. The drug was reduced to 240 mg daily and the dyskinetic movements disappeared. However, her convulsions became worse and after discharge from hospital the phenytoin was increased again to 400 mg daily. She was readmitted two weeks later with a recurrence of the choreoathetosis. It was concluded that this was a toxic reaction to phenytoin. She was taken off this and started on carbamazepine. The dyskinetic movements rapidly ceased and the patient became generally easier to control and more orientated. Her convulsions remain in satisfactory control.

Initially we were cautious about calling this phenytoin toxicity in view of the lack of such descriptions in the literature. However, the diagnosis later became obvious when the symptoms were abolished by reducing the dose of phenytoin and then returned on increasing it. As in the cases described by Drs. McLellan and Swash our patient was on a combination of phenytoin and primidone. When high doses are required it is often a question of which is less

acceptable—the convulsions or the toxic effects. If extrapyramidal movements do in fact represent toxic damage to the cerebellum it would seem advisable to us to discontinue phenytoin in such a case and substitute one of the other drugs in the steadily expanding anticonvulsant armamentarium.—We are, etc.,

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Pharaoh's Ants in Hospitals

SIR,—Further to Mr. P. L. G. Bateman's letter (18 May, p. 383) I have found the most successful means of getting rid of ants is just to pour boiling water down their point of entry, whether it be a hole or crack. After one or two applications there is no more trouble.—I am, etc.,

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Tunnel Tactics

SIR,—It was with interest that I read your leading article on carpal tunnel syndrome (15 June, p. 573). In particular, I note the reference to the presence of forearm and upper arm symptoms in nearly 60% of Cherrington's cases.[1] Later, the statement that "coincident clinical and radiographic evidence of cervical spondylosis is common" is made and symptoms caused by root irritation are said to be distinguishable from those of carpal tunnel syndrome on the clinical grounds of difference in pain distribution and a relationship to head and neck movement. Such a distinction may not always be possible.

Upton and McComas[2] propose that an insult to peripheral nerves occurring both in the neck and at the wrist might predispose to the development of carpal tunnel syndrome by a "double crush" mechanism. They provide electro-physiological evidence that 70% of their 115 patients with carpal tunnel syndrome also had cervical root lesions. Patients had deliberately not been excluded from their series on the basis of neck or upper arm pain. The work of Crymble[3] again suggests that carpal tunnel syndrome and cervical root lesions cannot be clearly distinguished on the basis of pain distribution. Patients with prominent proximal symptoms at least merit a complete electro-physiological investigation if not decompression at both the neck and wrist.—I am, etc.,

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1 Cherington, M., *Archives of Surgery*, 1974, **108**, 69.
2 Upton, A. R. M., and McComas, A. J., *Lancet*, 1973, **2**, 359.
3 Crymble, B., *British Medical Journal*, 1968, **3**, 470.

Hypotension with Intravenous Salbutamol in Premature Labour

SIR,—During the course of administering salbutamol intravenously in patients with premature labour[1] we came across a side effect not previously noted.[2] A total of 32 patients have been treated so far. Salbutamol 25 mg was administered in 500 ml of 5% dextrose starting at 10 drops per minute using an ordinary intravenous infusion set. The dose was increased by 10 drops per minute every 10 minutes till 40 drops per minute was reached or the patient's pulse rate increased to 140 per minute or the contractions ceased, whichever occurred earlier.

The results so far are similar to those of Liggins and his colleagues[2] with one exception. Among the side effects noted was a drop in systolic blood pressure of over 30 mm Hg in three patients. In two patients this was controlled by stopping the drip and running in about 500 ml 5% dextrose in the course of half an hour. In the third patient the blood pressure had dropped to 90/60 mm Hg from an initial 126/80 mm Hg and the drip was continued under close supervision. There was an associated tachycardia of 120 per minute. Within half an hour the blood pressure rose gradually to 110/70 mm Hg and the drip was therefore not discontinued. All three patients were healthy, between the ages of 20 and 26, para 2 or 3, between 32 and 36 weeks' gestation, and with an initial cervical dilatation of 3 to 4 cm.

Liggins *et al.*[2] noted that the vasomotor side effects of salbutamol occur only at high doses. They used a Palmer pump to obtain an accurate, controlled dose. However, most clinical units throughout the world will only have recourse to simpler, inexpensive, but less accurate standard intravenous infusion sets, and it seems therefore that while using this technique for arresting premature onset of labour a close check on the blood pressure is advisable at least for the first hour. Despite the associated fetal tachycardia[2] the fetus appears in no way compromised, and certainly when the initial drop in blood pressure is not too great the drip can be continued under close supervision.

We wish to acknowledge the continuing help of Glaxo Holdings Ltd.—We are, etc.,

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1 Sen, D. K., and Ng, K. H., *Medical Journal of Malaysia*, 1974, **28**. 191.
2 Liggins, G. C., and Vaughan, G. S., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1973, **80**, 29.

Duration of Action of β-Adrenergic Blocking Drugs

SIR,—Drs. P. D. Nigam and A. S. Malhotra (24 March 1973, p. 742) have reported a clinical study designed to evaluate the response of angina to pindolol. Their results suggested a carry-over effect that might be explained by a long duration of action of pindolol. Dr. S. G. Carruthers and others (21 April 1973, p. 177) presented data on the duration of action of some β-blocking drugs (alprenolol, practolol, and sotalol) and stated that more information was necessary to enable more accurate dosage schedules to be recommended. We recently supervised a study aimed at determining the oral antiarrhythmic response of sotalol (DL-4-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide hydrochloride) and also administered ^{3}H-sotalol (100 μg) to two patients to determine its metabolic profile. Information is also available concerning the distribution of sotalol in animals.[1]

Sixteen patients suffering from cardiac arrhythmias were given 100 mg of sotalol, 100 mg of alprenolol, and placebo tablets four times a day for four successive weeks under double-blind cross-over conditions. The results indicated that sotalol had an anti-arrhythmic profile similar to those of other β-blocking drugs. There was no evidence of a carry-over effect.

Sotalol has a long duration of action and Dr. Carruthers and his colleagues have shown that maximum β-blockage is not obtained with 400 mg of sotalol. This single dose level produces 11·8% protection against exercise-induced tachycardia 96 hours after administration. A single 100 mg dose (that used four times a day in this study) provides 10·6% protection 24 hours after administration, and Svedmyr *et al.*[2] have shown that after single oral doses of 40 mg of sotalol and propranolol both drugs had the same β-blocking effect against isoprenaline-induced tachycardia four hours after administration. After 24 hours sotalol still showed 50-60% protection while propranolol had no effect at this time. If these responses were related to plasma levels it is possible that over a four-week treatment period there would be evidence of accumulation. Plasma samples were accordingly taken at two-weekly intervals and the results (range at two weeks 1·14-4·05 μg/ml and at four weeks 0·83-2·47 μg/ml) indicated that plasma sotalol levels did not increase during treatment.

Tritiated sotalol (100 mg) was administered as a single dose to two patients and provided peak plasma levels of 0·1 and 0·065 mg/100 ml respectively 2-3 hours after administration. The decay was biphasic—an initial rapid reduction to 0·067 and 0·043 mg/100 ml after 5½ hours and a slower reduction to 0·015 and 0·0075 mg/100 ml after 24 hours. Administration of tritiated sotalol to dogs (1·5 mg/kg and 15 mg/kg) and rats (5 mg/kg and 50 mg/kg) showed no evidence of storage in liver, kidney, heart, lung, brain, spleen, adrenals, or gonads. The amount of ^{3}H-sotalol present in muscle and fat 24 hours after treatment was less than 1 μg/g. In vitro experiments showed that sotalol is not bound to plasma proteins and the red blood cells—the plasma partition coefficient is unity.

Clinical objective data showed that 100 mg of sotalol four times a day for four weeks significantly reduced the incidence of arrhythmias and plasma analysis demonstrated that accumulation did not occur.—We are, etc.,

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1 Martin, L. E. Personal communication, 1973.
2 Svedmyr, N., Jakobsson, B., and Malmberg, R., *European Journal of Pharmacology*, 1969, **8**, 79.

Folic Acid Supplements for Pregnant Epileptics

SIR,—Dr. Marion H. Hall's (22 June, p. 661) admirably concise account of anaemia in pregnancy raises two points which deserve comment. One is academic and merely a matter of setting the record straight—the attribution to us of the suggestion that the normal fall in serum folate in pregnancy is "principally" due to increased renal excretion of folate. Our paper[1] indicated only that the increased excretion, if it occurs in the presence of folate deficiency, could