This hepatotoxic effect of busulphan therapy appears to be rare and in this case was associated with prolonged therapy. However, we suggest that jaundice in patients under treatment for chronic granulocytic leukaemia may be attributable to busulphan therapy rather than severe leukaemic infiltration of the liver.—We are, etc.,

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- 1 Wintrobe, M. M., *Clinical Hematology* 6th edn. 1967, London, Kimpton, p. 1060.
- 2 Galton, D. A. G., Till, M., and Wiltshaw, E., *Annals of the New York Academy of Sciences*, 1958, 68, 967.
- 3 Havhoe, F. G. J., and Kok, D'A., *British Medical Journal*, 1957, 2, 1468.
- 4 Fähränder, H., Huber, F., and Gloor, F. *Gastroenterology*, 1964, 47, 590.

Aerosols in Asthma

SIR,—We feel that the paper by Dr. L. H. Harris (5 December, p. 579) on the effects of isoprenaline plus phenylephrine given by pressurized aerosol requires comment. The final sentence of the summary is misleading. On the test day only 13 of the 23 patients showed any significant bronchodilatation, which does not support the statement that the combination aerosol has a satisfactory bronchodilator effect. This relative ineffectiveness of the combination aerosol as a bronchodilator has also been found by Pflug *et al.*¹ In their study Medihaler-duo was given to 13 patients with chronic airway obstruction, and in six of these there was either no change or an actual fall in FEV₁. Recent pharmacological studies (Simonsson, B. G., personal communication; Price, F. J., personal communication) have demonstrated that there may be alpha receptors in human bronchial muscle. Thus the addition of an alpha stimulant, phenylephrine, to an isoprenaline aerosol may well reduce its effectiveness as a bronchodilator.

Dr. Harris also claims in the summary of his paper that the aerosol is, "additionally safe if used by a severely hypoxic patient unaware of the seriousness of his condition." We believe that there is no aerosol that can be safely used by such a patient, if one defines safety in terms of avoiding a fall in arterial oxygen tension. It is of interest that in Dr. Harris's series of the three patients with the lowest oxygen tensions there was a slight fall in arterial oxygen tension in two of the subjects following Medihaler-duo. In addition, in the study previously quoted, by Pflug *et al.*,¹ nine out of the 13 patients showed a fall in arterial oxygen tension, following inhalation of Medihaler-duo and in five of these the fall was greater than 5 mm Hg.

We would not agree that a comparative trial with isoprenaline was unnecessary. We think that the effects of isoprenaline, and isoprenaline plus phenylephrine, should be compared in the same patients. All of the previous studies quoted for isoprenaline except that of Waddell *et al.*² were done either with wet aerosol isoprenaline (estimated doses being much higher than that contained in Medihaler-duo) or with intravenous isoprenaline. The study of Waddell *et al.* is the only study in which isoprenaline was administered by a

pressurized aerosol and we would estimate that oxygen tension fell by more than 5 mm Hg in only one out of 12 patients, and this would not be statistically different from the results that the author reports with Medihaler-duo. Similarly, under the results quoted for orciprenaline, two of the studies were performed with subcutaneous orciprenaline and one with a wet aerosol of orciprenaline, and only the study of Meisner and Hugh-Jones³ looked at the effects of a pressurized aerosol of orciprenaline, and in this study no patient showed a fall in arterial oxygen tension. Thus the grouping together of several papers to obtain average changes is really quite unjustified in view of the differences in diagnoses, doses of drug administered, route of drug administration, time of sampling of arterial blood, and degree of hypoxaemia in the different patients.

We would once again emphasize the danger of suggesting that any aerosol is safe in severely hypoxic patients. There is still no scientific evidence to suggest that any available bronchodilator aerosol has an additional margin of safety as regards changes in arterial oxygen tension. We would make a plea for future studies on this important topic to be carried out in a properly controlled manner, and in particular against the use of such data in advertising material.—We are, etc.,

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Brompton Hospital,
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- 1 Pflug, A. E., Cheney, F. W., and Butler J., *American Review of Respiratory Diseases*, 1970, 101, 710.
- 2 Waddell, J. A., Emerson, P. A., and Gunstone, R. F., *British Medical Journal*, 1967, 2, 402.
- 3 Meisner, F., and Hugh-Jones, F., *British Medical Journal*, 1968, 1, 470.

Practolol in Angina

SIR,—I wish to report briefly a double-blind trial of practolol (Eraldin) in angina pectoris. Practolol is a beta-receptor antagonist which is cardioselective and is therefore preferable to other beta-blockers in patients with obstructive airways disease. It lacks the "quinidine-like" or membrane-stabilizing action of propranolol, it has intrinsic sympathomimetic activity, and is less liable than other beta-blockers to produce or exacerbate cardiac failure. Results of controlled trials of practolol in angina have varied, suggesting that it is less effective in relieving angina than propranolol. George, Nagle, and Pentecost¹ found practolol almost as effective as propranolol, while Prichard, Lionel, and Richardson² demonstrated only slight relief of angina by practolol in oral doses up to 2.4 g daily. Westerlund³ found no reduction in the number of anginal attacks although there was improvement in the work performance with exercise tests. In addition, Atkins, Blomqvist, and Cohen⁴ have found recently that practolol was more effective than propranolol in improving exercise tolerance measured by bicycle ergometry.

Twenty-eight patients with stable angina pectoris which had been present for a minimum of 3 months (mean 3 years 8 months) were studied. These were 20 men and 8 women, with mean age of 59.5 years. The trial started with a run-in period of

one to three months, during which the dose of practolol was increased until subjective improvement of angina occurred. No patient was rejected owing to lack of improvement in this open part of the trial. The patients then entered the double-blind phase of the trial, consisting of two four-week periods in which they took either practolol or placebo in random order, later crossing over to the alternative preparation. The dose of practolol was that established in the open trial (range 200-800 mg/day, average 447 mg). Patients were seen at fortnightly intervals throughout the trial and the frequency and severity of angina, trinitrin consumption, and effort tolerance were recorded. A summary of the patient preferences in the 28 patients follows:

Better in practolol period	10
Better in placebo period	3
Improved in both periods	12
Worse or unchanged in both periods	3

Side effects were not troublesome. One patient, who was worse in both periods, could not take more than 200 mg practolol daily because of nausea.

These patient preferences—10 improved on practolol compared to three improved in control periods—are statistically significant at the 5% level. The order of the practolol and control periods did not influence drug preference. The large number of patients improving in both periods, 12 out of 28, may well be a feature of trials of effective drugs in angina, and is not seen in trials of inert drugs.⁵ The run-in period on practolol might well produce an improvement in exercise tolerance with improvement of cardiovascular reserve by increased exercise, which might persist into the control period.

I am most grateful to Dr. B. Nebenzahl, Dr. R. B. Royds, and Dr. R. A. Wiseman for help with this trial.

—I am, etc.,

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St. Albans City Hospital,
St. Albans, Herts

- 1 George, C. F., Nagle, R. E., and Pentecost, B. L., *British Medical Journal*, 1970, 2, 402.
- 2 Prichard, B. N. C., Lionel, N. D. W., and Richardson, G. A., *Postgraduate Medical Journal Suppl.* 1971, 47, 59.
- 3 Westerlund A., *Postgraduate Medical Journal Suppl.* 1971, 47, 64.
- 4 Atkins, J. M., Blomqvist, C. G., and Cohen, L. S., *Circulation*, 1970, 42, Suppl. No. 3, p. 132.
- 5 Phear, D. N., *British Medical Journal*, 1968, 2, 740.

Long-acting Phenothiazines

SIR,—We would like to compliment you on your concise leading article on long-acting phenothiazines in schizophrenia (23 January, p. 189). The effect on hospital admission rates is demonstrated by our retrospective study of 212 chronic schizophrenic outpatients attending St. Clement's Hospital in which each patient was acting as his own control. A total of 103 patients fulfilled the criteria of this study, in that they had a follow up period of 12 months or more and a previous history of fully documented hospital admissions prior to receiving injections of long-acting fluphenazine. The remaining patients were excluded because they had received their injections for less than 12 months or had incomplete records. The number and duration of hospital admissions in the follow up period was compared with the number

and duration of admissions during a corresponding period of equal length before starting therapy with long-acting phenothiazines. All patients received their first injection during a period of psychiatric relapse, but only 50 were admitted to hospital.

The follow up period ranged from 12 to 40 months, with an average of 24.8 months. All other necessary therapy remained constant throughout both retrospective and follow up periods. The Table summarizes our findings

	Admissions	Duration in Days
Prior to Receiving Long-acting Fluphenazine ..	241	10,048
After Long-acting Fluphenazine	50	1,335

A more detailed analysis of the causes of the admissions during the follow up period is shown below.

Psychiatric relapse	34	Duration	1022 days
Side effects	5	"	70 days
Default in attendance for injections with psychiatric relapse	11	"	243 days

In our series hospital admissions have been reduced from 241 to 50, and in patient time by 8,713 days. We feel that our findings substantiate the claims made in your leading article.

You mention the lack of double blind controlled studies of long-acting fluphenazine. This may be caused by the risk that substitution of a placebo in this vulnerable group of patients is very real and therefore poses ethical problems. We would like to bring to your attention two double blind controlled studies of fluphenazine enanthate. One is by Del Giudice *et al.*¹ who divided 63 hospitalized male schizophrenics into three groups on discharge. Group I (24 patients) received oral fluphenazine tablets. Group II (20 patients) received oral fluphenazine and were visited by a nurse every 15 days when a placebo injection of sesame oil was administered. Group III (19 patients) received oral placebo tablets and a visit from a nurse every 15 days when a fluphenazine enanthate injection was given. The efficacy of treatment was judged by the number of days out of hospital to the end of the follow up period or until readmission if any. The mean for Group I was 133 days. Group II 164 days, and Group III 287 days. Statistical comparisons between Group I and Group II was not significant; between Group II and Group III was significant to the level of $p < 0.001$; and between Group II and Group III was significant to the level of $p < 0.01$. Ravaris *et al.*² found 30 out of 34 hospitalized chronic schizophrenics developed regression with placebo.—We are, etc.,

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¹ Del Giudice, *et al.*, 7th Congress of the Collegium of International Neuro Psychopharmacologists, 1970, Prague.

² Ravaris, C. L., Weaver, L. A., and Brooks, G. H., *American Journal of Psychiatry*, 1967, 124, 248.

Representation of Regional Consultants

SIR,—The control of British medicine is moving rapidly from the hands of the individuals to central committees. The power of the Department of Health in monitoring and affecting our affairs is growing as is seen in the new proposals (see *Supplement*, 20 February, p. 47) for the Central Advisory Committee on Hospital Medical and Dental Staffing, which has an "overlord" control of hospital staff. In this an agglomeration of Department officials and our own inveterate politicians will decide the staffing structure.

We are now in the phase of a dwindling freedom to manage our own affairs in the periphery and must accept progressive central control. The regional consultants, comprising 70% of the total consultants,

hitherto more concerned with their clinical responsibilities, are now demanding greater representation in the central committees (*Supplement*, 4 July, p. 15).

The traditional control by the London-based consultants of the college and state committees is now seen as unacceptable. Active participation of consultants throughout the country is essential if their practical views are to be heard, and more to the point taken into account. The stampede of the Elephant and Castle to effect further control is now a major anxiety for British medicine.—I am, etc.,

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Smoking in Postgraduate Medical Centres

SIR,—The second report of the Royal College of Physicians re-emphasizes our profession's responsibilities in the matter of health education about the hazards of smoking. Unfortunately recent communications¹⁻⁵

ally (smoking is pollution); and it is bad medical psychology (the obligation of self-discipline is forgotten). Surely the time has come for all postgraduate medical centres to accept their anti-smoking and "clean air"

TABLE I

Date of Circular	Total Circulation	Replies Received	No Comment or Comment Incomplete	Questionnaires Analysed	Centres with "No Smoking" in Meetings
November 1967	228	170	24	146	19 (13%)
May 1969	228	183	9	174	35 (20%)

TABLE II

Smoking in Meetings 127	Smokers: Non-smokers at the various centres	↓ or less ↑-↑ Over ↑ Unknown	74 25 8 20
Smoking in the presence of patients 46			

have shown that medical students receive very inadequate anti-smoking instruction. Is it possible that our rapidly-improving postgraduate medical facilities are being used prophylactically to remedy the situation? To assess this possibility questionnaires had been circulated to all known postgraduate medical centres in England and Wales in November 1967, and again in May 1969. The quantitative responses are shown in Table I. Table II indicates the prevailing practices as recorded in November 1967 in 146 centres.

Table III shows the low priority accorded to reconsideration by postgraduate medical centres of their policy (regarding smoking in meetings) during the 18 months between the two questionnaires.

TABLE III

Reconsideration: Smoking prohibited ..	8
Reconsideration: Smoking permitted ..	16
No Reconsideration: Smoking prohibited ..	27
No Reconsideration: Smoking permitted ..	123

It is evident that during two-thirds of meetings at postgraduate medical centres two-thirds of the doctors did not smoke, yet four-fifths of the centres still permitted smoking. This paradoxical situation is trebly inappropriate: it is bad public relations

educatively (the patients and lay staff get to know); it is bad public health environment-responsibilities, and acknowledge that smoking is "sociable" only among consenting adults in private?—I am, etc.,

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Taunton, Somerset

¹ Bynner, T. M., *Medical Students Attitudes Towards Smoking*, 1967, London, H.M.S.O.

² Curran, A. P., *The Smoking Habits of Medical Students*, Paper to Society for Social Medicine, Glasgow, 1969.

³ Arva, O. P., and Bennett, F. J., *East African Medical Journal*, 1970, 47, 18.

⁴ Anderson, J. P., *British Medical Journal*, 1970, 4, 120.

⁵ Ball, K., *British Medical Journal*, 1970, 4, 367.

Independent Contractors

SIR,—Will someone explain how the profession managed to discharge its duties during the postal strike without instruction from all those Government and other pamphlets which tell us how to do our job? Very well, I guess. It will be interesting to see the morbidity and mortality statistics during the next few months.—I am, etc.,

CLIVE SHIELDS

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