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Correspondents are urged to write briefly so that readers may be offered as wide a selection of letters as possible. So many are now being received that the omission of some is inevitable. Letters should be signed personally by all their authors.

An Easy Death—An Uneasy Argument

SIR,—Dr. S. L. Henderson Smith (3 May, p. 276) may be right in stressing that excellent hospice-type care of the dying may not render all discussion of the issues of euthanasia quite obsolete, even though it might greatly decrease the number of instances in which the question might arise. It is unfortunate, to some extent, that the issues of good terminal care and active euthanasia should have become muddled in some minds to the point that they may begin to appear as alternatives. Doctors and laymen may justifiably disagree on questions of "assisted suicide" or "arranging dying" (the number of circumlocutions this debate is spawning is awesome). But we should not disagree on the importance of drastically improving the standards of terminal care received by the majority of dying patients, nor should we allow the euthanasia debate, however spirited or sincere, to interfere with the attempt to achieve this more universally applicable objective.

Dr. Smith would also be advised to avoid seriously misleading abuse of statistics, lest the rest of his arguments be regarded as similarly ill-founded. The "continuing occurrence of suicides in those suffering from terminal conditions" does, verily, continue; but in the experience of most of those associated with the care of the dying it is an uncommon event and seldom seen in the context of optimal terminal care. That 18% of "successful" suicides are associated with organic illness is barely relevant, unless Dr. Smith wishes to equate organic illness with terminal illness, surely an excessively gloomy attitude. The proportion of the population of completed suicides

suffering from what would generally be acknowledged as a terminal illness is uncertain, but available data suggest that it is low. The majority of the 18% so glibly quoted would be suffering from such conditions as rheumatoid arthritis, peptic ulcer, or asthma.—I am, etc.,

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Paradoxical Effect of Pindolol

SIR,—Clinical experience has shown that for some beta-blockers there seems to be a dosage ceiling beyond which further increase in dosage is unprofitable.¹

In the case of pindolol increase in dosage may actually cause a rise in blood pressure. We first noted this in a man aged 56 with malignant hypertension. He responded well initially to cyclopenthiatide and a small dose

of pindolol (rising to 15 mg daily), but when the dose was further increased to 25 mg daily in an attempt to achieve completely normal blood pressure the pressure in fact rose. Reduction in the dose of pindolol led once again to a fall in blood pressure.

Subsequently we looked for this phenomenon in patients with poorly controlled blood pressure (in this case >160/110 mm Hg lying) on relatively high pindolol dosages. While taking a high dose of pindolol nine patients had a morning test, during which five lying and standing blood pressure and pulse readings were taken by trained technicians. The dose of pindolol was then reduced and a further morning test was done after an interval of 1-4 weeks. In all nine patients the blood pressure fell (see table); the pulse rate did not alter significantly.

Pindolol has a considerable sympathomimetic effect,² but its beta-blocking effect is so powerful that it is usually used at a low dosage compared with most other beta-blockers. The sympathomimetic effect is thus usually not excessive. However, it may be that in some patients the sympathomimetic effect tends to predominate when the dose rises above a certain level. Collins and King³ found a rise in blood pressure in 8% of patients treated with pindolol in a multi-centre study (dosage in these cases was not

Effect of Lowering Dosage of Pindolol in Nine Patients

	Pindolol High Dose	Pindolol Reduced Dose	Change
Mean dose (mg/24 h)	48	19	
Range (mg/24 h)	27.5-67.5	7.5-30	
Lying:			
Systolic B.P. (mm Hg)	196	179	-17*
Diastolic B.P. (mm Hg)	120	108	-12†
Pulse (/min)	76	75	-1
Standing:			
Systolic B.P. (mm Hg)	176	160	-16*
Diastolic B.P. (mm Hg)	115	106	-9†
Pulse (/min)	79	76	-3

*P<0.002. †P<0.01. ‡P<0.05.

stated) and Morgan *et al.*⁴ also noted a rise in blood pressure in a few cases. Thorpe⁵ reported a rise in blood pressure (to 240/140 mm Hg) in a patient who took about 500 mg of pindolol in a suicide attempt.

It is difficult to estimate exactly how often a hypertensive effect occurs, but our experience with 260 patients treated with pindolol suggests that it may occur in about 5% of cases. We believe that pindolol is a useful and effective drug but that the initial dosage should be low (for example, 2.5-5.0 mg twice daily) and that if dosages above 25-40 mg daily seem to be ineffective, then dose reduction should be tried. The blood pressure may then fall to satisfactory levels. If it remains unchanged, or if it falls but is still unsatisfactory, then some other drug should be added.—We are, etc.,

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1 Simpson, F. O., *Drugs*, 1974, 7, 85.

2 Saameli, K., *Heveta Physiologica et Pharmacologica Acta*, 1967, 25, CR 432.

3 Collins, I. S., and King, I. W., *Current Therapeutic Research*, 1972, 14, 185.

4 Morgan, T. O., *et al.*, *Medical Journal of Australia*, 1972, 2, 309.

5 Thorpe, P., *Medical Journal of Australia*, 1971, 1, 1242.

Gold Therapy in 1975

SIR,—Your leading article (26 April, p. 156) has attracted only two cynical letters. One does not deny that gold is a toxic drug, but equally its proved beneficial effects should not be decried. I would disagree with your interpretation of the results of three trials.

It should be stressed that in the E.R.C. trial, gold was given as a "course" for five months and in all parameters assessed, excluding radiological examination, "the gold-treated patients improved to a greater degree than the controls from the third month onwards, and this improvement was still apparent 12 months after the last injection was given." It is in the light of this limited course of injections that one should interpret the statement that "by month 30 most of the advantage seen in the gold-treated series at month 18 had disappeared." I should add that the next part of the above sentence reads "though by some criteria the gold-treated series still remained significantly better than the control series, albeit by only a slender margin." Gold, of course, is no longer given as a limited course, but is continued long-term on a maintenance basis.

Huskinson *et al.*¹ did not report "that penicillamine may be superior to gold." I quote from their summary: "in the first six months of a comparative study in patients with rheumatoid arthritis, penicillamine and gold were equally effective."

You claim that Currey *et al.*² (incidentally 1974, not 1973) "concluded that the immunosuppressive drugs were superior" (to gold). I quote again: "cyclophosphamide and azathioprine given relatively early in the course of rheumatoid arthritis produce clinical improvement over 18 months similar to that achieved with gold." They did claim, however, that "both azathioprine and cyclophosphamide showed advantages in reducing the rate of joint deterioration as seen radiologically and in steroid sparing not shared by gold."

When the results of properly conducted controlled trials are available, they should be quoted correctly.—I am, etc.,

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1 Huskinson, E. C., *et al.*, *Annals of the Rheumatic Diseases*, 1974, 33, 532.

2 Currey, H. L. F., *et al.*, *British Medical Journal*, 1974, 3, 763.

** When reviews such as leading articles are written it is always important to try to extract an all-embracing comment rather than quote isolated phrases which may or may not have a particular bias. For example, Huskinson *et al.* state further that "gold treatment had to be withdrawn much more frequently than penicillamine because of rashes which occurred in about one-third of cases." It is not unreasonable that a drug having no additional therapeutic benefit over another, yet having a greater incidence of side effects requiring termination of treatment should be considered inferior. Again, as Dr. Liyanage admits, Currey *et al.* concluded that azathioprine and cyclophosphamide had certain special therapeutic benefits that gold had not.

We cannot deny that gold is of benefit to some patients, but when looked at objectively these benefits are only marginal. The question is still whether a drug which causes the highest number of deaths per prescription¹ should be used to treat a condition in which its benefits are only marginal. We feel it is becoming increasingly important to weigh side effects against efficacy when making value judgements about various treatment for rheumatoid arthritis.—ED., *B.M.J.*

1 Girdwood, R. H., *British Medical Journal*, 1974, 1, 501.

Tolamolol in Treatment of Angina Pectoris

SIR,—We were interested to read the favourable report by Dr. Graham Jackson and his colleagues (29 March, p. 708) on tolamolol in angina pectoris. We have recently completed a similar study using higher doses given for longer and our results are similar.

Ten patients completed our double-blind crossover trial. Diagnostic criteria for admission were identical with those of Dr. Jackson and his colleagues except that one of our patients had long-standing maturity-onset diabetes mellitus. After a run-in period to establish rapport and familiarity with the clinic and record cards each patient was seen every four weeks for 36 weeks. At each attendance records were made of the number of anginal attacks, trinitrin consumption, and each patient's subjective assessment of treatment. Clinical examination and resting electrocardiography were followed by standardized exercise on a treadmill (20% elevation) with continuous electrocardiography (V5 position) until an end-point was reached (angina, fatigue, breathlessness, or 1 mm ST depression). Patients received, in random order, capsules of identical appearance containing tolamolol 100 mg, propranolol 20 mg, or placebo, each given for three consecutive months using successively one, two, or three capsules thrice daily unless side effects prevented an increase in dose. Patient compliance was measured by counting returned capsules.

The same "blind" observer saw patients throughout the trial and he assessed which treatment appeared to give best overall response: six

patients were rated best on tolamolol, two on propranolol, and two on placebo. Formal statistical analyses were performed on the observations at the end of the last month of each treatment (that is, when on maximum dose). The number of attacks of angina (measured by mean consumption of trinitrin) during each active treatment period was less than during the placebo period but the difference was not statistically significant. The results of the exercise test in nine patients (one was excluded because he developed atrial fibrillation during the trial and required digitalization) were analysed as shown in the table.

Routine haematological, biochemical, and clinical observations each month did not detect any adverse effects other than the common minor side effects of beta-blockade. Six patients took tolamolol 300 mg thrice daily; four took only 200 mg thrice daily because of exertional dyspnoea, bradycardia, or diarrhoea. Similarly, six patients tolerated the maximum dose of propranolol (60 mg thrice daily).

We have shown that tolamolol is an effective treatment for angina but we place no importance on its greater apparent benefit compared with propranolol because this is probably entirely due to the doses selected. The results of Dr. Jackson and his colleagues show that we should have used double the dose of propranolol. Tolamolol may have an advantage of greater tolerability; in our patients 900 mg daily was equally acceptable to 180 mg of propranolol. We suggest that further studies should be undertaken to assess tolamolol in patients who require large doses of beta-blockers.

We are grateful to Pfizer Central Research for supplying tolamolol.

—We are, etc.,

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SIR,—In reply to Dr. S. Oram and his colleagues (21 June, p. 686) I am well aware that bradycardia is a well-documented side effect of beta-blockers. What I question is the sagacity of excluding from any further discussion four patients, three of whom subsequently died, who deteriorated during the trial—all during treatment with the test compound tolamolol (is this a coincidence?). No mention is made of these deaths in the summary. The authors in their letter have altered their statement to "our mortality was of the order of 4%" without an annual figure. From the figures in the original paper, ignoring the fact that all incidents occurred on tolamolol, three deaths among 47 patients each followed for 26 weeks (not 10 months) would give an annual mortality of 12.8%—three times the expected yearly mortality quoted. If one cannot do this arithmetic to obtain an annual figure, what was the purpose of the authors in quoting an annual figure and equating it with their results? Is the fact that these reactions (three leading to death) occurred on only tolamolol a coincidence or not? Surely further study with a large group of patients is required to clarify the point. If severe bradycardia is coupled with hypotension, also a side effect of beta-blockers, the resultant reduction in myocardial perfusion could precipitate angina or infarction or exacerbate concurrent infarction in susceptible individuals.

Dr. I. M. Graham and his colleagues (15 March, p. 626, and 14 June, p. 616) challenge the conclusions of Dr. K. M. Fox and his colleagues (18 January, p. 117) and point out