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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 being received that the omission of some is inevitable. Letters should be signed personally by all their authors.

When is significant not significant?

SIR,—Professor Hugh Dudley (2 July, p 47) is wrong to fear that if we dismiss a statistically significant correlation as being due to chance we shall "destroy the logic of practical statistical inference." In fact the converse is true: over-slavish adherence to rigid criteria of statistical significance is a fault as serious as the fault of ignoring the possibility that chance alone has generated a certain effect.

In our recent paper (4 June, p 1433) we examined 400 different correlations between particular occupations and particular causes of death and of course found a couple of dozen "statistically significant" associations. We suggested that some of these were genuine and some the artefacts of chance; moreover, we suggested that some of the non-significant positive associations were also genuine.

Professor Dudley's suggestion that we should have accepted as true all associations that were statistically significant is unwise. Associations that are *extremely* ($P < 0.001$) significant should very rarely be doubted, but *moderate* statistical significance (such as $P < 0.05$) often does arise as an artefact of chance. For example, the probability of getting double-six when a pair of dice are rolled once only is one in 36, which is about 0.03. Thus if we ever see someone roll double-six at his first throw of a particular pair of dice that is "statistically significant ($P < 0.05$) evidence" that those dice are biased, but it would clearly be foolish to believe this on all such occasions (and, in bad company, it might be quite an

expensive error to conclude that failure to roll double-six first time proved the dice to be unbiased!). It would be even more foolish, if 400 different pairs of dice were rolled and double-six arose about a dozen times, to believe that all pairs which rolled double-six were loaded, although the analogy between this and what Professor Dudley expects us to do is quite close.

Conversely, if, for example, in our study two radiologists died of cancers which were actually directly caused by their jobs, this would probably not suffice to make the death rate statistically significantly high; so *lack* of statistical significance can, unfortunately, often exist when there really is a true association present.

In summary, we hope Professor Dudley achieves his expressed wish of immortality, but we hope that his "tenet . . . that given a certain probability level we will *believe* . . ." will perish.

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SIR,—Professor Hugh Dudley (2 July, p 47) writes trenchantly against the statistical logic of Sir Richard Doll and Mr Richard Peto (4 June, p 1433). I do not feel that Professor Dudley deserves the annihilation which he suggests is a possibility, but I think that he is

making a serious error. This is a prevalent error and so it has implications far beyond the particular issue of the work of Professor Doll and Mr Peto.

Professor Dudley claims that these two workers wish to have their statistical cake and also to eat it. This is just not so. Inferential statistics are there to guide one's formation of belief but not to determine it, and it would be only the naive person who would, before an experiment, commit himself absolutely to believing or not believing something as true or false, or due to chance or not due to chance, simply because of a particular probability level. Such a person would be making himself a slave to statistical methods rather than the appropriate way round—namely, allowing himself to use statistical methods as a servant to proper decision-making needs. Whether one decides to believe that something is almost certainly true or almost certainly false is determined by many matters, not least of which is the importance of the findings in terms of how these affect people and their welfare etc. In many cases, whatever the *P* value, an open mind is surely the necessary prerequisite to a good scientific worker and even more important to someone who has other peoples' welfare at stake.

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Comparison of treatment with fast neutrons and photons

SIR,—We are grateful to Dr W M Ross (9 July, p 128) for drawing attention to the disadvantage that the majority of the patients treated with photons in the MRC trial (25 June, p 1642)

were not treated at Hammersmith Hospital. This feature of the trial arose from the collaboration with other hospitals to ensure an adequate total intake. When a patient, first seen at another hospital, was allocated at random to receive conventional treatment it was often difficult to justify giving that treatment at Hammersmith rather than at the hospital of origin.

A comparison of the response of patients treated with photons at Hammersmith with those patients in the neutron series who would have received their treatment at Hammersmith, whichever form of treatment had been selected, was included in the first report on the trial.¹ The findings in this subtrial at September 1976 were as shown in the accompanying table. The findings in the subtrial are similar

Findings in subtrial of neutron and photon treatment at September 1976

	Neutron series (n = 20)	Photon series (n = 25)
Local control of tumour:		
No with continued complete regression	18	5
No with complete regression followed by recurrence		8
No with no or incomplete regression	2	12
Survival:		
% alive at 1 year (actuarial)	54	38
Additional treatment for suspected residual disease:		
No given radiotherapy		3
No treated surgically		3
No with severe complications in larynx or pharynx	3	1
Mean time-dose factor (TDF)	118	108

to those for the whole trial. The difference between the numbers with persisting local control is significant at the 0.1% level; the difference in mortality rates is not significant. In the subtrial the average time-dose factor (TDF) was about 10% higher for patients in the neutron series than for those in the photon series (compared with about 20% in the whole trial¹). Nevertheless, as the reports of both trials indicate, persistent local control of the tumour among subgroups of patients who were receiving equivalent doses of the two types of radiation was much more frequent among the neutron-treated patients.

We hope that many of the difficulties of a multicentre trial will be avoided in the new trials which will be undertaken with the cyclotron which has recently been installed at the Western General Hospital, Edinburgh.

Finally, we would like to correct a misprint in the table in our more recent article (25 June, p 1642). Ten, not 16, neutron patients received supplementary surgery for suspected residual disease.

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¹ Catterall, M, Sutherland, I, and Bewley, D K, *British Medical Journal*, 1975, 2, 653.

Relative activity of atenolol and metoprolol

SIR,—With the increasing interest in the clinical use of cardioselective β -adrenergic

antagonists it is of fundamental importance that the relative potency of the individual compounds be established. Using propranolol as the reference substance, it has been shown that the ratio between equipotent doses of atenolol and propranolol¹ is 1:0.7 and that of metoprolol and propranolol² 1:0.8. These results would suggest that identical doses of the two selective β_1 -receptor antagonists, atenolol and metoprolol, would give the same degree of β -blockade.

To test this hypothesis we have compared the β -blocking effects of the two drugs in a group of seven hypertensive patients who, after one week's placebo treatment, were given in random order, one week's treatment with atenolol 100 mg daily, atenolol 200 mg daily, metoprolol 100 mg daily, and metoprolol 200 mg daily. At the end of each treatment period an exercise test on a bicycle ergometer (5 min at 75 W) was carried out two hours after tablet administration, heart rate and blood pressure recordings being taken before, during, and after exercise.

Mean results on placebo showed a resting heart rate of 98/min and a resting blood pressure of 170/105 mm Hg rising to 145/min and 221/111 mm Hg at the end of exercise. The respective values after atenolol 100 mg were 59/min, 161/99 mm Hg, 96/min, and 188/106 mm Hg and after metoprolol 100 mg they were 61/min, 161/102 mm Hg, 97/min, and 195/110 mm Hg. After atenolol 200 mg the respective values were 63/min, 161/97 mm Hg, 92/min, and 191/105 mm Hg and after metoprolol 200 mg they were 62/min, 163/97 mm Hg, 93/min, and 189/104 mm Hg. This similar degree in the inhibition of exercise tachycardia following both 100 mg and 200 mg administration suggests the equipotency of these two compounds. It is also interesting that no significant difference was observed in the hypotensive effects of these compounds at rest and on cessation of exercise.

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¹ De Plaen, J F, Amery, A, and Reybrouck, T, *European Journal of Clinical Pharmacology*, 1976, 10, 297.
² Bengtsson, C, *Acta Medica Scandinavica*, 1976, 199, 71.

Poisoning with maprotiline and mianserin

SIR,—Since the introduction of tricyclic antidepressant drugs into clinical practice 20 years ago they have become an increasingly popular agent for suicide and self-poisoning. In 1974, the latest year for which figures are available, there were 323 deaths attributed to these drugs,¹ and this number has probably increased since then. In order to ascertain the incidence of serious toxicity from overdose we have followed up all cases of antidepressant poisoning referred to this unit in the year starting April 1976. Although analysis of this study is not yet complete, the report by Drs J Park and A T Proudfoot (18 June, p 1573) prompts us to report our experience of overdose with the two newly introduced quadricyclic antidepressants, maprotiline (Ludiomil) and mianserin (Bolidon; Norval). Follow-up was achieved on 41 cases (36 in adults and five in children) of maprotiline poisoning and 20 cases (19 in adults and one in a child) of mianserin poisoning.

Of the adults taking maprotiline, 17 had ingested more than 1 g and 10 less than 1 g, and in nine cases the amount ingested was not known; 10 patients had taken additional drugs. All but two of these patients developed symptoms. These, in order of frequency, were: drowsiness in 24 cases, convulsions in eight, coma in seven, anticholinergic signs in five, tachycardia in five, bradycardia in three, cardiac arrest in three, hypotension in two, and hypertension in one. Two of the patients died, but their deaths were not directly attributable to the overdose; one died of a massive pulmonary embolus after making a full recovery from the overdose and the other died from a fall following the overdose. Two of the five children who took maprotiline developed symptoms. One was just drowsy, while the other, a girl of 4, had repeated convulsions after the ingestion of 525 mg of the drug.

The symptoms reported in the 19 adults who ingested mianserin were drowsiness in 13 cases, hypertension in three, coma in two, tachycardia in two, and hypotension in one. There were no reports of cardiac arrhythmias or convulsions. The two patients who were in coma had taken additional sedative drugs. There was one death. This patient, a woman of 72, had threatened suicide previously. She was admitted deeply unconscious having ingested about 600 mg of mianserin and an unknown quantity of lorazepam. She did not regain consciousness and died the next day. Necropsy revealed bronchopneumonia. Toxicological analysis confirmed that only these two drugs had been ingested. The plasma mianserin concentration on admission was 110 μ g/l and that of lorazepam 500 μ g/l.

From our as yet limited experience it would appear that the clinical features of poisoning with these two compounds differ. Overdose of maprotiline causes symptoms similar to those produced by the more conventional tricyclic antidepressants² and our findings are in accord with those reported by Drs Park and Proudfoot. Overdose of mianserin commonly causes drowsiness but the more serious complications of tricyclic antidepressant poisoning (convulsions and cardiac arrhythmias) were not reported. It is possible that if these patients had taken larger quantities of mianserin they would have exhibited more serious symptoms. The absence of anticholinergic effects with mianserin would suggest that physostigmine or other cholinesterase inhibitors should not be used in therapy.

We would like to thank all those physicians who completed our questionnaires and Dr Ian Bradbrook for the mianserin estimations.

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¹ Office of Population Censuses and Surveys, *Deaths from Poisoning by Solid and Liquid Substances, 1974*, London, OPCS, 1976.

² Noble, J, and Mathew, H, *Clinical Toxicology*, 1969, 2, 403.

Whooping-cough immunisation

SIR,—As stated in your leading article (2 July, p 5), there have been differences in the estimates of the risks which may be associated with whooping-cough vaccine. As I have previously pointed out, in evaluating the vaccines available today "it is not acceptable to extrapolate from data collected from studies with other vaccines and different schedules, or from