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We may return unduly long letters to the author for shortening so that we can offer readers as wide a selection as possible. We receive so many letters each week that we have to omit some of them. Letters should be typed with double spacing between lines and must be signed personally by all their authors, who should include their degrees. Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue.

The Dobbing workshop and SWOP

SIR,—Your kind review of the publication of my most recent workshop (27 August, p 605) shared the same issue very comfortably with several letters from prominent medical men prepared to join Professor Tony Mitchell's proposed new campaign, SWOP (Speakers Who Oppose Publication) (27 August, p 615). I too, presumably along with dozens of others, would like to be a founder member of SWOP, for the same reasons as those expressed by Professor R M Hardisty and Professor Roy Meadow and by Mr Bryan N Brooke. Unfortunately, the suggested option for invited speakers to decline the invitation whenever a manuscript is demanded for a chapter usually leads to the organisers finding someone else, and the original chap may lose a free trip to a nice place. Thus my own practice is to weigh the chore of writing a chapter against my liking for the locality in which the meeting is held and the prospects of taking my wife. Since there seems to be a law that the nicer the occasion the more likely is a chapter to be required, I (thankfully) travel much less than I used to.

One of the reasons for inventing the Dobbing workshop was to help overcome some of the problem by restricting attendance to the "speakers," and then preventing them from speaking, except in genuine discussion of their precirculated position.

Although infinitely flexible, I still resist Dr Tony Smith's suggestion that the discussion should be published, except as at present in the form of carefully considered statements by those taking part in the discussion in the light of the hammer and tongs argument which takes place. The workshop itself, without any audience, is designed to produce final position, personal, and constructive statements for publication, and I can assure Tony Smith that nothing of the actual discussion is lost by

this procedure. If you read the three resulting books so far¹⁻³ you will not find watered down, agreed common denominators, but often considerably outspoken disagreement, without the usual anodyne wrappings.

Still more would I resist asking "a journalist to . . . attempt to produce an objective report of the talk." Some of my best friends are journalists, but their role in life is not (however much they may think it is) to summarise argument so that major medical puzzles can more nearly approach solution. That is the job of the practising scientist and the purpose of the Dobbing workshop.

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¹ Dobbing J, ed. *Maternal nutrition in pregnancy—eating for two?* London: Academic Press, 1981.

² Dobbing J, ed. *Prevention of spina bifida and other neural tube defects.* London: Academic Press, 1983.

³ Dobbing J, ed. *Scientific studies in mental retardation.* London: McMillan and The Royal Society of Medicine (In press).

SWOP (Speakers Who Oppose Publication)

SIR,—It would perhaps be interesting to draw up some conditions of membership for SWOP (Speakers Who Oppose Publication).

(1) At the rostrum they will be not only amusing but so splendid with reference to imparting both information and ideas that once we have heard what they say we will never forget it (or them).

(2) They will believe that no profit should be made from publishing.

(3) They will refuse to speak at section meetings at the Royal Society of Medicine.

SWOP members will, of course, share certain group characteristics, the most con-

sistent of which will be that their own curricula vitae will be so nicely tied up as to be considered totally satisfactory by those who really believe that curricula vitae help in some way to judge a man or woman's worth and mark. The more I think about the psychology of protest, the more sure I am that Shakespeare got it right. As an editor responsible for publishing proceedings that have ranged from those I would like to mention to those I would rather forget, I also quite like to check what people actually admit to having said at the rostrum from time to time, however embarrassed they may be about it all later.

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British Journal of Clinical Practice,
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Prevention of coronary heart disease

SIR,—In her article on the primary prevention of heart disease (3 September, p 651) Dr Chandra Patel introduces this brief but potent sentence: "Low oestrogen contraceptives are preferred, and patients are advised to interrupt pill use every three to four years."

It is difficult to imagine a more concise expression of false information. It would be seriously damaging to our patients' interests if translated into clinical practice. Firstly, there is substantial evidence that it is the progestogen component in the combined pill that is associated with the increased risk of vascular side effects.¹⁻⁴ Emphasis should, therefore, be placed on using the brands with low progestogen activity and I personally can find no clinical indication for a preparation which contains more than 150 µg of levonorgestrel or desogestrel or 1 mg of norethisterone acetate. Secondly, Dr Patel seems to assume that a relationship has been demonstrated with duration of use. Indeed, in our

paper on mortality⁵ published in 1977, which she quotes, there did appear to be a significantly increased risk after five years of use. This article was superseded, however, by the publication in 1981⁶ of a paper based on a larger database, which failed to show any evidence of an effect of duration.

There is thus now no convincing evidence that duration of use has an important influence on the excess risk of vascular disease associated with oral contraceptive use. This statement needs a minor qualification. There is tentative evidence from a study of perimenopausal former users that their current risk of myocardial infarction became materially related to former use of oral contraceptives longer than 10 years.⁷ Our own analysis of vascular morbidity⁸ (fatal and non-fatal disease) suggested a possible relationship of cerebrovascular disease to duration of use, but the trend was not statistically significant. In the absence of sound statistical guidance I would personally consider critically the situation of a woman who had been using oral contraceptives for longer than 10 years. Even here, in the absence of any other risk factors for vascular disease and a marked preference for continuing oral contraceptives, I would be inclined to do so. There has never been any evidence that periodic rests from oral contraceptive use are beneficial, and I would have thought that the attendant substantial risks of an unwanted pregnancy were obvious.

Finally, although Dr Patel rightly draws attention to the increased risk of pill use for a woman over the age of 35 who smokes cigarettes, she fails to make the point that a comparable risk for a non-smoker is not reached until the woman is well into her fifth decade. The relevant data are presented in our 1981 mortality analysis,⁹ which, because it contains more good than bad news for pill users, has never received the publicity I believe it deserves.

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¹ Royal College of General Practitioners' Oral Contraception Study. Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. *Lancet* 1977;ii:624.

² Khaw K-T, Peart WS. Blood pressure and contraceptive use. *Br Med J* 1982;285:403-7.

³ Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 30- μ g oestrogen preparations. *Br Med J* 1980;280:1157-61.

⁴ Kay CR. Progestogens and arterial disease—Evidence from the Royal College of General Practitioners' study. *Am J Obstet Gynecol* 1982;142:762-5.

⁵ Royal College of General Practitioners' Oral Contraception Study. Mortality among oral contraceptive users. *Lancet* 1977;ii:727-31.

⁶ Royal College of General Practitioners' Oral Contraception Study. Further analyses of mortality in oral contraceptive users. *Lancet* 1981;ii:541-6.

⁷ Stone D, Shapiro S, Kaufman DW, et al. Risk of myocardial infarction in relation to current and discontinued oral contraceptive use. *N Engl J Med* 1981;305:420-4.

⁸ Royal College of General Practitioners' Oral Contraception Study. Incidence of arterial disease among oral contraceptive users. *JRCGP* 1983;33:75-82.

Mechanism of antihypertensive action of ketanserin in man

SIR,—In a letter to the *Lancet*¹ and, more recently, in your pages (6 August, p 381) Dr I W Reimann and Professor J C Fröhlich offer evidence of an α_1 adrenergic effect of ketanserin administered intravenously to five normal subjects. Animal and in vitro studies leave little doubt that this drug exhibits

α_1 antagonist activity, and it is not surprising that such action can be shown at certain dose levels in man. Demonstration of α_1 antagonist properties does not, however, exclude other actions of the drug in contributing to blood pressure reduction. The pharmacological profile of the drug makes its initial designation as a 5-hydroxytryptamine type 2 antagonist appropriate, though of course this property may not be relevant necessarily to the antihypertensive effect. If, nevertheless, blockade of 5-hydroxytryptamine type 2 receptors does lower blood pressure, this could have important implications in understanding the mechanisms underlying hypertension; conversely, a lack of any such effect would also be important.

We gave either placebo or ketanserin 10 mg intravenously, using a randomised double blind design, to nine supine patients with essential hypertension. Ketanserin caused a significant ($p < 0.01$) decrease in average blood pressure for the group, from 150 (2 SEM)/94 (1) mm Hg in the period before injection of the drug to 137 (3)/88 (2) mm Hg during the subsequent two hours; pressures were still significantly reduced ($p < 0.05$) two hours after injection of the drug (139 (8)/90 (5) mm Hg). Blood pressure (154 (5)/93 (3) mm Hg) did not change significantly after placebo.

Two hours after administration of the drug (or placebo) phenylephrine was infused intravenously in incremental rates² (fig 1). There was no evidence of any important degree of α_1 blockade (fig 1). Mean plasma concentration of ketanserin before infusion was 38.0 (2.4) μ g/l and 37.9 (2.8) μ g/l at the end of the infusion. We have reported similar findings in normal subjects.³

In a separate double blind study, seven normal

FIG 1—Change in mean arterial pressure with infusion of phenylephrine in patients with hypertension who had been given ketanserin or placebo.

FIG 2—Change in mean arterial pressure with infusion of phenylephrine in normal subjects who had been given ketanserin or placebo.

subjects were given placebo or ketanserin 40 mg twice daily (the dose likely to be used in the treatment of hypertension) for three days, and on the fourth day phenylephrine was infused. The dose response curve was shifted to the right (fig 2); the slope during drug treatment was significantly ($p < 0.025$) different from the slope in the placebo period. Mean (SEM) plasma ketanserin concentrations before and after infusion were 37.9 (2.5) and 33.7 (2.2) μ g/l.

Infusion of phenylephrine in normal subjects one hour after an oral dose of 1 mg prazosin, a well accepted α_1 antagonist, failed to cause a measurable rise in blood pressure until a rate of 2 μ g/kg/min was reached.

Drugs are not absolute in their specificity; the mechanisms by which many agents reduce pressure remain disputed. Ketanserin may act as an α_1 antagonist at the doses used by Dr Reimann and Professor Fröhlich in man. It seems from our findings and those of others,³ however, that this drug may lower blood pressure through mechanisms other than peripheral α_1 blockade. The characteristics of the drug suggest that this could be by antagonism of 5-hydroxytryptamine type 2 receptors. The development of more selective agents should help to clarify the mechanisms.

The relative contributions of at least these two and perhaps other mechanisms to the hypotensive effect of ketanserin during long term oral antihypertensive treatment remain to be determined.

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¹ Reimann IW, Fröhlich JC. Is ketanserin a D receptor antagonist? *Lancet* 1983;ii:703-4.

² Zoccali C, Zabludowski JR, Isles CG, et al. The effect of ketanserin, a serotonin type 2 antagonist, on blood pressure, the renin-angiotensin system and sympatho-adrenal function in normal subjects. *Br J Clin Pharmacol* (in press).

³ Wenting GJ, Man In't Veld AJ, Woittiez AJ, Boomsma F, Schalekamp MADH. Haemodynamic effects of ketanserin, a selective 5-hydroxytryptamine (serotonin) receptor antagonist, in essential hypertension. *Clin Sci* 1982;63:435-8s.

Myocardial infarction and the normal coronary arteriogram

SIR,—Dr Kim M Fox (13 August, p 446) discussed the importance of spontaneous thrombolysis and of coronary artery spasm in patients in whom the coronary arteriogram shows no abnormality. I would suggest that another condition should also be considered when faced with such patients—myocardial necrosis associated with cardiotrophic viruses such as Coxsackie virus B.

Results of a recent study from this department have suggested that some patients, diagnosed confidently as having non-transmural myocardial infarction, may in reality have viral myocarditis and might therefore reasonably be expected to have normal coronary arteriograms.¹ Our group of "non-transmural myocardial infarction" patients, although small, showed a relatively high incidence of recent Coxsackie virus infection (as judged by raised neutralisation titres) and a remarkably high proportion of women. Subsequently three of those patients with raised titres proved to have normal coronary arteriograms.

Following this study coronary arteriography has been carried out prospectively on a number of patients diagnosed as probable or definite cases of non-transmural myocardial