me is to produce a non-encephalitogenic and attenuated but still efficacious and immunogenic vaccine for use in the final stages of the WHO smallpox eradication campaign and for a safety period of 2-3 years thereafter, assuming that in this interim period no smallpox variant is detected anywhere in wildlife.[1]

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Posts in clinical rheumatology

SIR,—Professor W Watson Buchanan and his colleagues have produced a most interesting paper (11 September, p 628) but unfortunately, while making wide-ranging recommendations about the future of rheumatology, have failed to define the clinical scope of the specialty.

The two definitions of rheumatology cited by Dixon,[1] "the study of rheumatoid arthritis and diseases which resemble it" and "rheumatology is that branch of medicine concerned with rheumatic complaints and includes systemic disorders of connective tissue, inflammatory arthritis, osteoarthrosis, back troubles and soft tissue or non-articular rheumatism," express nicely the views of those at either end of the rheumatology spectrum.

Defining the clinical scope of the specialty is essential to any discussion about the future of rheumatology because the size of the problem to be tackled and the relationship of the specialty to other disciplines depend on it. Certainly "rheumatic diseases are a major medical and socioeconomic problem in the Western World," but to fail to stress that it is the degenerative/mechanical rheumatic disorders that account for the greater part of this problem is surely to mislead by omission. If only a minority of new patients with "rheumatic complaints" attending a district general hospital have a general condition such as rheumatoid arthritis, and if the rheumatologist would expect to see a substantial number of these, then the need for a close link with general medicine becomes less pressing and the relationship to orthopaedics more apparent.

It is also somewhat mischievous of the authors to suggest, albeit indirectly, that there is anything like the need for one rheumatologist per 20 000 people when these figures are clearly based on an overestimate of the prevalence of clinically significant rheumatoid arthritis,[2] of which they themselves are well aware.[3]

The future of rheumatology certainly needs debate, but before Professor Buchanan tells us how many beds we need in a district general hospital he surely must tell us what kind of patient is to occupy them.

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[1] Dixon, A St J, *Rheumatology and Rehabilitation*, 1973, **4**, 165.
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Once-daily treatment of hypertension

SIR,—Studies have shown that patients on antihypertensive treatment are still often unsatisfactorily controlled.[1] It is also known that a simple dose regimen is important if the patient is going to take his medicine regularly.[2] Earlier studies with propranolol have shown a discrepancy between the biological effect and serum concentration.[3] Against this background we felt it important to study the effect of propranolol in a once-daily regimen.

Nineteen patients with moderate hypertension, previously controlled with propranolol twice daily (mean daily dose 227 mg), were advised to take the whole daily dose in the morning. Ten were men and nine women, and their mean age was 49 (33-72) years. On once-daily treatment the blood pressure was measured at the same time during the day and always at least 24 h after the last tablets. In seven patients the serum concentration of propranolol was measured 12 h after the last dose on the twice-daily regimen (mean 220 (range 44-524) nmol/l (55 (11-131) ng/ml)) and 24 h after the last dose on the once-daily regimen (mean 68 (range 8-180) nmol/l (17 (2-45) ng/ml)).

The mean supine blood pressure and heart rate for the 19 patients before treatment, after treatment with propranolol twice daily, and after 15 weeks on once-daily treatment are shown in the table. There was no significant difference in blood pressure control between the two regimens in spite of the fact that a few patients misunderstood the instructions and took only their previous morning dose. This brought the mean daily dose on once-daily treatment down to 199 mg. All patients preferred the once-daily regimen and no new side effects occurred.

	Before treatment	Propranolol twice daily	Propranolol once daily
Blood pressure (mm Hg) ..	171/104	138/87	139/90
Heart rate (/min)	77	63	66

Thus once-daily treatment with propranolol seems to be useful in most cases, maintaining blood pressure control of the same order as with more complicated dose regimens. In this study all patients were transferred from a twice-daily regimen, but preliminary results indicate that it is also possible to start treatment with propranolol once daily.

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[1] Wilhelmsen, L, Tibblin, G, and Werkö, L, *Preventive Medicine*, 1972, **1**, 153.
[2] Malahy, B, *American Journal of Hospital Pharmacy*, 1966, **23**, 283.
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SIR,—The interest in the possibilities of once-daily treatment of hypertension with beta-blockers is increasing, as reflected by recent papers and letters (Drs A P Douglas-Jones and J M Cruickshank, 24 April, p 990; Dr E M M Bestman, 5 June, p 1403; Drs M J Kendall and R A Yates, 5 June, p 1404; and Dr T O Morgan, 24 July, p 235). These comments reinforce the extensive Swedish experience with pindolol[1-4] that many patients with mild to moderate hypertension can be successfully treated with certain beta-blockers once daily.

For beta-blockers with a high intrinsic sympathicomimetic effect, such as pindolol, the possibility of a paradoxical effect in about 5% of cases has been suggested[5] when high doses of the drug are used, although it is not clear whether this rise is more than a random variation in a few patients. However, as experience with pindolol in once-daily dosage in hypertension has been extended it has been shown that the blood pressure can be controlled in many cases with a single dose not exceeding 20 mg daily, with an average of 15 mg. At such a dose level any theoretical possibilities of a paradoxical effect of pindolol are certainly negligible.

Experience with pindolol has shown that with doses above 20 mg it is beneficial to combine the treatment with a dose of a long-acting diuretic given at the same time rather than increasing the dose of beta-blocker.[4] In such a way the benefits of once-daily administration can be maintained for the hypertensive patient.

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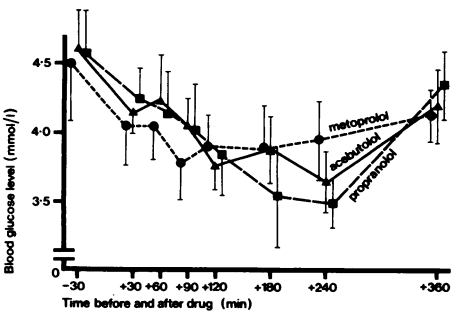
Blood sugar and beta-blockers

SIR,—The possible interactions between relatively selective and non-selective beta-adrenergic blocking drugs and glucose homoeostasis are extremely complicated. We were therefore very interested in the study by Dr Raymond J Newman (21 August, p 447) carried out on human volunteers, from which potentially clinically important conclusions can be drawn. He found that three different beta-adrenergic blocking drugs, acebutolol, metoprolol, and propranolol, all potentiated and prolonged the hypoglycaemic response to insulin administration but that the effect was least marked with the relatively selective drug acebutolol and most marked with the non-selective drug propranolol. In all subjects the control experiment was performed first and no placebo tablets appear to have been taken. This may make interpretation of the data a little difficult since subjects attending for the first time were presumably aware that it was the control experiment. This may well have influenced their attitudes, their circulating catecholamine levels, and therefore their blood sugar concentrations.

We would like to present our own data from a double-blind study on eight healthy males in which the drugs were given in random order and which to some extent supports Dr Newman's work. These results were obtained during a study of the effects of beta-blocking drugs on respiratory function. The subjects attended after a light breakfast and performed near-maximal exercise for three minutes on a bicycle ergometer at half-hourly intervals before and for six hours after an intravenous dose of the three active drugs or normal saline. The doses used were propranolol 0·15 mg/kg body weight, metoprolol 0·3 mg/kg, and acebutolol 1 mg/kg. Heart rates were measured from an electrocardiographic strip at the end of the exercise period and blood was taken from an indwelling cannula for sugar estimation. The figure shows the blood sugar curves for the three active drugs. In all cases exercise resulted in a fall in blood sugar, recovering



Blood sugar levels (means and standard errors) after acebutolol, metoprolol, and propranolol given intravenously.

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

after lunch (taken after 240 minutes). Acebutolol and metoprolol values closely followed the curve for placebo (omitted for clarity), whereas the results for propranolol were lower at three and four hours after drug administration, although these differences do not achieve statistical significance. The areas bounded by the mean blood sugar curves and the horizontal lines drawn through the mean control values for each drug were: placebo 121, metoprolol 186, acebutolol 236, and propranolol 251. These figures may be used as a guide to the degree of hypoglycaemia while on these drugs.

Our results taken together with those of Dr Newman do suggest that the relatively selective beta-adrenergic blocking drugs are less likely to produce hypoglycaemia and are therefore potentially safer in diabetics or during starvation. The reason for this is that normally during exercise muscle glycogenolysis is increased, peripheral glucose utilisation is reduced, and lipolysis occurs to provide an alternative source of energy. Propranolol inhibits these processes thereby reducing the blood sugar level.[1-3] Metoprolol is less likely to cause hypoglycaemia since it causes less interference with glycogenolysis and lipolysis.[4] These drugs also reduce the secretion of insulin in response to glucose administration and can impair the carbohydrate tolerance of diabetics. This also seems to be mediated by a B_2 receptor since carbohydrate tolerance improves and insulin secretion increases when diabetics are changed from a non-selective drug to metoprolol.[5]

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[1] Gothelf, B, and Ellis, S, *Proceedings of the Society for Experimental Biology and Medicine*, 1974, **147**, 259.
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[3] Scholhamer, C, *et al*, *Clinical Research*, 1971, **19**, 736.
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Two populations with duodenal ulcer?

Sir,—We were interested to read the recent communication from Dr R J Prescott and others (18 September, p 677) in which they report that they were unable to confirm the results of their previous study of patients with duodenal ulcer.[1] We would like to comment on two points in their article.

Firstly, the secretion data in the study were expressed as maximal acid output per kg total body weight (presumably per hour but not stated). The reason stated for making the correction for weight was that such correction reduced the differences between the sexes. However, it has been shown[2] that while maximal gastric secretion is correlated with weight a better correlation is obtained with height. Furthermore, we have recently shown[3] by means of multiple linear regression analysis that after standardisation for height there is no longer a significant correlation between maximal secretion and weight and the difference between the sexes completely disappears.[2] We would therefore suggest that standardisation for height rather than just dividing the secretion data by weight would give a more useful correction.

Our second point regards the statistical analysis of the data and the comment on this analysis by the authors. The differences between the means of the secretion data of the various groups were tested by the *t*-test. Unfortunately gastric secretion data very rarely follow a normal distribution and unless they can be suitably corrected—for example, by means of logarithmic transformation—the *t*-test can give positively misleading results. In a recent letter (2 October, p 812) commenting on Dr T D V Swinscow's article on non-parametric tests (11 September, p 632) we made this very point; we suggested then, and reiterate here, that such dangers are removed by the use of non-parametric tests—for example, the Wilcoxon test. If Dr Prescott and his colleagues apply non-parametric tests to their secretion data we feel sure that they will cease to obtain spurious apparently significant results and will not have to resort to rejecting probabilities of between 1 in 20 and 1 in 1000.

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[1] Lam, S K, and Sircus, W, *Quarterly Journal of Medicine*, 1975, **44**, 369.
[2] Hassan, M A, and Hobsley, M, *British Journal of Surgery*, 1971, **58**, 171.
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Sir,—In an earlier study Lam and Sircus[1] had been able to divide duodenal ulcer patients into two types which differed significantly as regarded maximal acid output, ABO blood groups, and other variables. However, in a subsequent study (18 September, p 677) the same group was unable to confirm the previous findings and they state that "experience shows that the usually acceptable level of significance of 1 in 20 ($P < 0.05$) is often found in this field when a true association is shown later not to exist." In this way the authors imply that special laws of chance are at work in studies involving ABO blood grouping and it would seem reasonable to consider a different explanation.

All hypothesis testing is based on the assumption that the research process has this sequence: formulation of hypothesis—performance of study—significance testing of results. However, in large clinical surveys with many variables (including, for instance, ABO grouping) the sequence is often different. Firstly the study is performed, then the results are scrutinised, and finally the hypotheses are formulated and tested. This method invites type I errors because numerous correlations can be performed between variables in a study of this kind, 5% of which are probably significant at the 5% level, 1% at the 1% level, etc, and the research worker selects those correlations for significance testing which look and probably are significant.

Descriptive studies ought not to lead to significance tests at all but only to the generation of hypotheses which are then tested in a subsequent study. The two duodenal ulcer studies may be viewed in this light. First Lam and Sircus performed a descriptive or inductive study which led to a hypothesis (but should not have led to P values) and in a second study which represents typical hypothetico-deductive research they showed this hypothesis to be false. Therefore they have provided us with a textbook example of the way research should take place.

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Magnesium intoxication during 1-α-hydroxycholecalciferol treatment

Sir,—Dr E Sörensen and his colleagues (24 July, p 215) infer that treatment of patients with chronic renal failure using 1-α-hydroxycholecalciferol (1-α-HCC) may be associated with the risk of magnesium intoxication. But the case reported confirms other observations[1] that the same risk also occurs when the dietary intake of magnesium is excessive. It is possible, therefore, that the episode of hypermagnesaemia reported was not directly related to treatment with 1-α-HCC but was due to an increase in self-medication with magnesium.

The effects of vitamin D metabolites on the intestinal absorption of magnesium have not been fully investigated. However, in short-term studies on animals 1-α-HCC has produced no measureable effect on magnesium absorption despite considerable increases in absorption of calcium and phosphate.[2] Similarly, in two patients with chronic renal failure treatment with 1-α-HCC did not result in acute or long-term changes in magnesium balance despite increases in calcium retention.[3] Finally, during the long-term treatment of patients with chronic renal failure, we[3] (and, incidentally, Dr Sörensen and his colleagues[4]) have observed no consistent changes in mean plasma magnesium during extended treatment even at times of accidental overdose with 1-α-HCC. It seems likely, therefore, that 1-α-HCC does not normally result in appreciable changes in the intestinal absorption of magnesium in patients with chronic renal failure.

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Neuropathy in experimental diabetes

Sir,—Professor P K Thomas and Dr A K Sharma (21 August, p 478), discussing our paper on neuropathy in experimental diabetes (31 July, p 278), state that weight loss and