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

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 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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² Jungman, E, et al, *Diabetologia*, 1975, **11**, 353.

³ Scholhamer, C, et al, *Clinical Research*, 1971, **19**, 736.

⁴ Ablad, B, et al, *Acta Pharmacologica et Toxicologica*, 1975, **36**, suppl 5, p 85.

⁵ Waal-Manning, H J, *Drugs*, 1976, **11**, suppl 1, p 121.

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 shown² that while maximal gastric secretion is correlated with weight a better correlation is obtained with height. Furthermore, we have recently shown³ 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.

³ Hobsley, M, et al, *Lancet*, 1975, **2**, 101.

SIR,—In an earlier study Lam and Sircus¹ 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 Sørensen 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 observations¹ 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, we³ (and, incidentally, Dr Sørensen and his colleagues⁴) 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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² Fox, J, and Care, A D, in *Calcified Tissues*, 1975, p 147. Copenhagen, FADL's Forlag, 1976.

³ Kanis, J A, et al. To be published.

⁴ Tougaard, L, et al, *Lancet*, 1976, **1**, 1044.

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

retarded skeletal growth in our diabetic rats may have led us to fallacious interpretations. They suggest that the reduction in the nerve fibre size of diabetic rats that we demonstrated may have been the result of a failure of growth of the animals causing a failure of normal maturation of nerve fibre size rather than representing a true reduction in fibre diameter.

When we designed our experiments we did consider the significance of weight and maturation. As to the weight problem, we decided to include a group of rats on reduced diet resulting in a weight loss comparable to that of the diabetic rats. It appeared that the fibre size was normal in this control group. These results are included in detailed reports to be published in the near future.

As to the problem of growth and maturation we chose the age of 19-20 weeks on the basis of information in the literature. According to the results published by Schlaepfer and Myers² the dimensions of nerve fibres are related to skeletal growth. After 16 weeks the leg length of rats remains constant and so do also internodal length and fibre size (internodal thickness). The statement made by Professor Thomas and Dr Sharma that "fibre size is known to increase progressively in rats, at least throughout the first year of life" is not supported by their own results.³ We have tried to see if four weeks of diabetes affects the tibial length of rats made diabetic at the age of 20 weeks. This was not the case, the mean tibial length of 10 diabetic rats being 42.5 ± 1.0 (SD) mm and that of 10 age-matched non-diabetic rats 42.7 ± 0.7 mm.

In our more detailed reports¹ we have shown that the normal stable relation between internodal length and fibre thickness, confirmed in so many studies, is changed in experimental diabetes. Studying large fibres we found that internodal length was normal, while fibre thickness was reduced. This is an important point, we think, in establishing a morphological basis for the reduction of conduction velocity in diabetes.

Another point, mentioned but not commented upon by our critics is our demonstration of the predominant shrinkage of the axon, suggesting a new concept of diabetic neuropathy.

The new results from consecutive studies mentioned by Professor Thomas and Dr Sharma are interesting but difficult to evaluate without further details.

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¹ Jakobsen, J. and Lundbaek, K. *Diabetologia*. In press.
² Schlaepfer, W. W., and Myers, F. K. *Journal of Comparative Neurology*, 1973, **147**, 255.
³ Sharma, A. K., and Thomas, P. K. *Journal of the Neurological Sciences*, 1974, **23**, 1.

Urinary retention in women

SIR,—Mr R Hole (28 August, p 524) should not be surprised that I have failed to encounter "female prostatic" (bladder neck) obstruction. It is a rare event as confirmed by Turner-Warwick.¹ Mr Hole claims to see one case a year; I should like to know the total female population that he sees with retention or a slow stream each year.

While a good history and examination are mandatory, it has been shown² that a history and examination are not always reliable. In

addition Emmett and Love³ and many other authors have shown convincingly that vertebral disc protrusion can produce bladder disturbances without neurological signs.

In answer to Dr G J Jarvis (28 August, p 524) I find it difficult to accept that patients with chronic retention may be divided into different aetiological groups according to the amount of residual urine and whether or not they have evidence of urinary infection or hysterical personality traits. I accept the spectrum of conditions covered by the term chronic urinary retention. The basic features seem to be a residual urine accompanied either by symptoms of a slow stream, straining to void, and incomplete emptying or complete retention. A further group should be included—namely, those patients with an asymptomatic residual urine. The aetiology, as has been noted previously, is varied. One compounding problem is the failure to recognise retention once it has occurred, so allowing the bladder to remain overdistended, which in some cases results in a failure to recover its contractility.

What is required to elucidate this condition is an adequate amount of urodynamic data (cystometry, bladder pressure, and flow recordings—if able to void) and an accurate measurement of residual urine together with a reliable method of measuring urethral resistance—other than the urethral pressure profile. Only then can we say whether the lesion is due to decompensation of the detrusor or an increase in urethral outflow resistance or a combination of both. At that stage, I think the aetiological factors will become clearer.

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¹ Turner-Warwick, R. T., in *Urodynamics*, ed E Letzeyer and H Melchoir, p 245. Berlin, Springer, 1973.

² Bates, C. P., Loose, H., and Stanton, S. L. R., *Surgery, Gynecology and Obstetrics*, 1973, **136**, 17.

³ Emmett, J., and Love, J. G., *Journal of Urology*, 1971, **105**, 86.

Pets and asthma

SIR,—Your leading article (31 July, p 264) discusses the danger caused by pets to asthmatic children. Although your general conclusion is that pets should not be kept in a home with persons suffering from asthma, you included an opinion that in my view is frightening—that is, if the prick test gives no definite reaction an asthmatic family might keep a cat or a dog.

Skin tests map only cases of sensitisation that have already occurred. They do not help one to see into the future. Animal dust is one of the most potent allergens in the air we breathe. Practically speaking every one with an inherited predisposition to atopy develops respiratory tract allergy if exposed to animal dust for a long time. It is common knowledge that a fairly long exposure time is necessary before allergen dust causes the onset of the disease, generally $\frac{1}{2}$ -4 years. Lutsky and Neuman¹ studied 1293 animal keepers, of whom 14.7% developed respiratory tract allergy (allergic rhinitis and/or asthma). During three years of exposure 36 subjects became affected; the exposure time was 4-9 years for 11 persons before onset of the disease.

As a physician I would never dare give permission to an atopic family to keep a pet. The question of pets is a very sore point with us in

Finland. The number of registered dogs alone is 330 000 for a population of 4.6m. Approximately 60% of Finns with asthma develop the symptoms from animal dust. It should also be remembered that a person who gets allergic rhinitis or asthma from grass pollen, etc., and who has a cat or dog in his home may often, having got rid of animal dust, tolerate grass pollen without difficulty; pollen alone does not take him over the tolerance threshold. This makes the pet problem even more serious. Love of animals must not be allowed to undermine our health at home. Before a pet is adopted we should always find out whether there is a tendency to atopy in the family. A predisposition to atopy in just one member of the family is an absolute contraindication to adopting a pet.

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¹ Lutsky, I. I., and Neuman, I., *Annals of Allergy*, 1975, **35**, 201.

Breast-feeding advisory groups

SIR,—I wish to support Mrs Katherine M Lawler (18 September, p 704) in drawing attention to groups which advise mothers on breast-feeding, such as the La Leche League and the Breastfeeding Promotion Group of the National Childbirth Trust. Readers may wonder why there is any need for advice on this most natural function, but in fact the need arises from the *un-natural* impositions of hospital routines and out-dated advice from others.

In the natural state the baby would be put to the breast a few minutes after birth. Early suckling provides the threefold benefits of assisting uterine contractions, establishing sucking when the baby's sucking reflex is strongest, and stimulating lactation. Sometimes, of course, suckling may have to be delayed for medical reasons, but too often it is delayed for many hours purely for reasons of routine. There is also a tendency to consider that suckling before the milk "comes in" need only be half-hearted; whereas in fact the colostrum supplied during these days is of great value. Furthermore, if the neonatal intestine is more permeable to the gamma-globulins of the colostrum in these first few days, then surely the introduction of foreign protein in cow's milk at this early stage is to be deprecated.

This raises the whole question of test-weighing and complementary feeds. In a busy maternity ward it may happen that all babies are sent out for feeding at the same time, and by the time they are all collected back in the nursery, test-weighed, changed, and the complements prepared an hour or more may have passed. If a baby is then given a complement, which he may not even want, he will be sound asleep when it is time to go out to his mother again and will not be persuaded to suck. The mother then waits anxiously for the results of the test-weighing, only to be told that her baby "didn't get enough." He is eventually given another complement. Under these circumstances it is hardly surprising if breast-feeding fails.

Hence groups which promote breast-feeding advise mothers to request rooming-in or demand feeding and to insist that the baby is to be entirely breast-fed, including during the night. Mothers are also advised to feed more