

together in conjunction with the report by Professor W E Waters and others (12 November, p 1442) and one wonders why these authors are so emphatic about the absence of an increased risk of dying in the women aged 45-64 who had had headache and migraine in 1967.

Their report says that 86% of the intended population cooperated. This is a creditable rate, but it implies that about 477 women did not cooperate. If the proportion aged 45 and over was the same as in the cooperative women shown in table I, about 214 women have been omitted from the comparisons in table II. If none had headache and migraine in 1967 and none had died, they would raise the survival rate of their group from 82.0% to $(301+214)/(367+214)$ —namely, 88.6%. Even if seven of them had died the rate would still be no worse than the average in the affected groups, as $(301+207)/(367+214)=87.4\%$, to be compared with $(292+291+241)/(338+326+279)=87.4\%$. These calculations could be elaborated to take account of age, smoking, and taking analgesics and are likely to upset the conclusions from table III. That is to say, a sufficient number of the uncooperative women may have been better risks than those who did cooperate for there to be more uncertainty in their results than they seem willing to grant. As their only reference to bias concerns less healthy women, one would like their report to have discussed this apparent possibility, as Bradford Hill recommends.

It is regrettable that many textbooks and courses on elementary medical statistics do not go beyond a warning that incomplete data may be biased. Nevertheless, some illustrative computations are given by Bradford Hill. As they require only elementary arithmetic, these kind of analyses could be given priority over significance tests and training in the calculation of such measures as the correlation coefficient, important these formulas may be in suitable contexts. Perhaps computer analysis packages should have a warning attached.

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¹ Bradford Hill A. *A short textbook of medical statistics*. London: Hodder and Stoughton, 1977.

*.*The authors reply below.—ED, *BMJ*.

SIR,—As Mr Tweedie points out, his first reference to Bradford Hill is concerned with losses to follow up.¹ We lost only one woman in the follow up period so this is not an important source of bias in our study.

Mr Tweedie is concerned with the likely unrepresentativeness of volunteers. Our survey was, as we stated, mainly haematological and was based on all women in the age range studied in a defined area of south Wales: over 86% cooperated. It is unlikely, though possible, that there were important differences in the prevalence of headache. Even if there was considerably more, or considerably less, headache in the non-responders, however, this would be important in considering the prognostic significance of headache only if the headaches in the non-responders had a different prognosis from those of the 86% who cooperated in the study. MacMahon and Pugh state that the true relation between "exposure" (here headache) and "outcome" (here death)

will be distorted only if the loss through inability to assign individuals to exposure categories is biased with respect to both exposure and outcome.² If the loss is biased with respect to only exposure—that is, if women without headache did not respond—or outcome—that is, none of the non-responders died—then the true relation between headache and mortality can still be estimated. Any bias with respect to outcome is likely to be other than that suggested by Mr Tweedie, as we pointed out when considering the standardised mortality ratio of the population, in that the less healthy (and thus more likely to die) women are likely to be omitted. If we assume that none of the non-responders had died this would reduce the overall standardised mortality ratio to about 92, and even allowing for seven deaths would bring it up to 94, hardly likely in the population we were studying.

In a short paper it is not possible to go through all possible alternative analysis. Guidelines for deciding whether a sample is representative of a population do not appear to us very suitable for a computer package. (Would it take the form: "If percentage non-responders greater than 10, print 'warning, sample unrepresentative?'") Each study should be considered on its merits. We are fully aware of the importance of the problem of selection. Mr Tweedie refers to Bradford Hill page 261, where one of the examples cited is a study on migraine, published by one of us.¹

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² MacMahon B, Pugh T. *Epidemiology. Principles and methods*. Boston: Little, Brown and Company, 1970:218.

SIR,—Professor W E Waters and others (12 November, p 1442) put forward two possible explanations for their finding of lower mortality in women aged 45-64 years with headaches or migraine compared with controls: earlier diagnosis and treatment of hypertension in the group with headaches, and more advanced arterial disease in the control group. We would like to suggest a third possibility.

It has been suggested that migraine is a disorder of platelet function.¹ Women are most affected by migraine during their fertile years, and indeed both migrainous and non-migrainous headaches are generally worse around the time of menstruation.² We have therefore compared ex vivo platelet aggregation with various concentrations of serotonin in the postmenstrual (days 7-10) and premenstrual (days 25-28) phases of the cycle in eight women suffering from menstrual migraine and in a control group of nine women. Preliminary results show that the rate of aggregation is significantly reduced in those with migraine (mean (SEM):12.5(2.82)mm/min) compared with controls (mean(SEM):21.78(2.95)mm/min) in the premenstrual phase (Student's *t* test, $p < 0.05$) using low concentrations of serotonin (0.5 $\mu\text{mol/l}$ (88 $\mu\text{g/l}$). This difference was not detected with higher concentrations of the aggregating agent (2, 5, 10, and 20 $\mu\text{mol/l}$ (352, 881, 1762, and 3524 $\mu\text{g/l}$)), and the postmenstrual results were similar in the two groups.

These results were unexpected in view of reports of increased platelet aggregation in migraine,^{1,3} but strict comparison is difficult for a variety of reasons. Firstly, we were studying menstrual migraine specifically and at well defined times in the cycle; secondly, previous data were based on the aggregation response to 20 $\mu\text{mol/l}$ (3524 $\mu\text{g/l}$) of serotonin only; and thirdly, aggregation to serotonin was significantly increased only in classical migraine, no difference being found in common migraine.¹ Anovulatory doses of subcutaneous oestradiol implants are successful in treatment of both menstrual migraine and the headaches commonly associated with the premenstrual syndrome,^{4,5} as they remove any biochemical change that normally occurs between the follicular and luteal phases of the ovarian cycle.

Our results of reduced platelet aggregability in women suffering from migraine raise the possibility that this protects them to some extent against heart disease and strokes. Both conditions are associated with increased spontaneous platelet aggregation,⁶ and platelets play an important part in the pathogenesis of atherosclerosis. We now intend to extend our study to postmenopausal women who complain of headaches and migraine.

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¹ Hanington E, Jones RJ, Amess JAL, Wachowicz B. Migraine: a platelet disorder. *Lancet* 1981;ii:720-3.

² Somerville BW. The influence of progesterone and oestradiol upon migraine. *Headache* 1972;12:93-102.

³ Hilton BP, Cummings JN. 5-Hydroxytryptamine levels and platelet aggregation responses in subjects with acute migraine headaches. *J Neurol Neurosurg Psychiatry* 1972;35:505-9.

⁴ Magos AL, Zilkha KJ, Studd JWW. Treatment of menstrual migraine by oestradiol implants. *J Neurol Neurosurg Psychiatry* (in press).

⁵ Magos AL, Collins WP, Studd JWW. Management of the premenstrual syndrome by subcutaneous implants of oestradiol. *Proceedings of the 3rd International Congress on the Menopause, Antwerp 1983* (in press).

⁶ Wu KK, Hoak JC. A new method for the quantitative detection of platelet aggregates in patients with arterial insufficiency. *Lancet* 1974;iii:924-6.

A new treatment for asthma: promotional expediency versus pharmaceutical responsibility

SIR,—For the past 12 years I have enjoyed a close association with Allen and Hanburys Limited. This arose in the course of studies that I carried out to assess the value of beclomethasone dipropionate aerosol and micronised powder in the treatment of asthma.^{1,2} Having developed a high regard for the company's research division at Ware and also for the responsible and ethical manner in which Becotide was introduced and promoted, I was sad to learn of the recent introduction of Ventide, a compound aerosol containing salbutamol and beclomethasone dipropionate.

Last year I was one of several clinicians with particular experience of the use of beclomethasone dipropionate whose opinions were sought by the company concerning its proposal to develop and market Ventide. In a carefully considered report I strongly advised against it, and I know that at least one of the other clinicians gave a similar opinion. The compelling reasons for disregarding this impartial advice are not difficult to surmise and they have nothing to do with improving the

treatment of asthma. Indeed, it became clear in the course of discussion that the company itself had anticipated many of the objections to the compound aerosol and it tacitly acknowledged that the proposed development was related to the imminent expiry of the patent applying to Ventolin.

I have no means of knowing whether the company's medical division attempted to persuade those responsible for developing Ventide that its introduction would be as undesirable as it was unnecessary: if any attempt was made, it did not prevail. Consequently, some special pleading has been made to justify Ventide's introduction. It has been claimed that it will "improve compliance, especially with the Becotide component" on the ground that some patients who have been prescribed beclomethasone dipropionate alone "stop taking it or use it only intermittently because it does not have an instant effect."³

There are better ways to solve this problem than by misleading patients into believing that beclomethasone dipropionate, the more important of Ventide's two constituents, confers immediate benefit. While I do not wish to imply that Allen and Hanburys regarded this as a commercially attractive aspect in the marketing of Ventide, I cannot believe that the company did not foresee the likely consequences of confusion among patients, particularly with the precedent of Intal Compound. At the time of the introduction of Intal Compound, however, there appeared to be valid reasons for combining cromoglycate with isoprenaline to facilitate inhalation. No such justification can be offered for combining beclomethasone dipropionate with salbutamol. In the first place, a more rapidly acting beta agonist would have been a more logical choice than salbutamol and, secondly, it was shown in a recent trial that the inhalation of salbutamol either 10 minutes before or after beclomethasone dipropionate made no difference to the overall control of asthma.⁴

The data sheet describing Ventide states that the compound aerosol has been "specially provided for those patients who require regular doses of both drugs." Yet the principal objection to it (which applies to all compound preparations) is that it permits no flexibility of dosage of its individual constituents. Hence, 600-800 µg of salbutamol per day must be taken in order to attain the conventional daily dose of 300-400 µg of beclomethasone dipropionate. The conventional dose of beclomethasone dipropionate, however, often proves inadequate to control asthma during exacerbations, and in some patients a higher dose is permanently required.

In few other diseases is it as important as in asthma to instruct patients about the action and purpose of whatever treatment they have been advised to take. If all doctors invariably give a clear explanation about the purpose of beclomethasone dipropionate and emphasised that it does not give rise to any immediately perceived relief, non-compliance, which Ventide has been claimed to prevent, would become much less frequent.

It is ironic that at the very time it has marketed Ventide Allen and Hanburys is about to embark on educational programmes for general practitioners in the management of asthma. The findings from some of my own research studies (which it gives me pleasure to acknowledge have received generous support from Allen and Hanburys) suggest that improved management of asthma in general practice will come about only when treatment is prescribed on a rational basis. This depends on a full assessment of the patient and of the prevailing circumstances, then making inferences about the mechanisms responsible for airflow limitation. This procedure will suggest the form of treatment that is most appropriate.

I would hope that the educational programmes planned by Allen and Hanburys will endorse this principle of rational treatment. If so, their sales force will have an unenviably difficult task in promoting Ventide and it will be interesting to see whether their representatives perform it with the same probity

and responsibility as they showed over the promotion of Becotide.

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¹ Gregg I. The place of beclomethasone dipropionate aerosol in the treatment of asthma. *Drugs* 1975;10:161-5.

² Gregg I. Experience of the use of beclomethasone dipropionate aerosol in general practice. *Br J Clin Pharmacol* 1977;4:275-80(S).

³ Anonymous. New combined inhaler for chronic asthmatics. Editorial. *General Practitioner* 1983 Oct 21:71.

⁴ Mackay AD, Dyson AJ. How important is the sequence of administration of inhaled beclomethasone dipropionate and salbutamol in asthma? *Br J Dis Chest* 1981;75:273-6.

* * * Allen and Hanburys reply below.—ED, *BMJ*.

SIR,—The many factors that affect the decision to market a new product—albeit in this case a combination of two well established compounds—are extremely complex. They include pharmaceutical, pharmacological, medical, and commercial principles, and advice on all these aspects is taken from a large number of experts, both from within the company and externally. We are grateful to Dr Gregg for his help and counsel but should emphasise that his view was one of a wide variety of clinical opinions that were expressed.

The commercial considerations were of minor importance. Contrary to Dr Gregg's assertion, the patent on Ventolin has still a number of years to run. Allen and Hanburys is concerned with and has a major interest in the sound management of patients with asthma. We therefore agree with all that Dr Gregg says regarding the importance of a rational approach to treatment.

Ventide is formulated to provide the most commonly used maintenance doses of Ventolin and Becotide in one inhaler and is primarily for use by those patients who have previously been stabilised with Ventolin and Becotide in this dose ratio. Our promotion of the product, an example of which is appearing in the *BMJ*, reinforces this message and is not aimed at misleading either doctors or patients.

The convenience of one inhaler for maintenance treatment should improve compliance and ensure that patients actually take their beclomethasone dipropionate. It is well recognised that when patients have to use both Ventolin and Becotide inhalers regularly there is a tendency to default on one. It is usually Becotide that is missed out, sometimes with serious consequences. By combining both drugs in one inhaler we hope that this problem will be avoided.

Beclomethasone dipropionate is an important therapeutic agent for those patients with chronic forms of asthma, and we believe that Ventide will make a positive contribution to patient management.

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Vaginal discharge

SIR,—Professor Michael W Adler's ABC of vaginal discharge (19 November, p 1529) puts *Gardnerella vaginalis* sixth in a list of pathological causes and goes on to describe the clinical and diagnostic features of this infection.

Our experience with this organism differs in several aspects. Firstly, we find that *G vaginalis* rarely occurs on its own in non-candidal, non-trichomonal vaginal infection, large numbers of anaerobic bacteria being an almost invariable accompaniment.^{1 2} It was for this reason (among others) that a more descriptive and microbiologically accurate name, anaerobic vaginosis has been proposed.^{3 3} Secondly, we feel that the long held view of *Candida* as the most common cause of vaginal infection may need to be revised. In 1982 we saw 2860 women with anaerobic vaginosis, 2337 women with candidiasis, and 1074 women with trichomoniasis. Anaerobic vaginosis may be underdiagnosed elsewhere. On the exceptionally rare occasions that *G vaginalis* is found alone, the vaginal pH may not be raised but the amine test is always negative.²

The suggestion that, when only limited culture facilities are available, investigation for chlamydial infection should be restricted to contacts of men with non-specific urethritis or gonorrhoea is topsy turvy. It is widespread practice to treat the former with antichlamydial antibiotics anyway and the latter are known to have a high incidence of positive isolations.⁴ Surely the group to be investigated are those with no history of contact, for whom the lack of a diagnosis may give rise to complications both social and clinical?⁵

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¹ Taylor E, Blackwell AL, Barlow D, Phillips I. *Gardnerella vaginalis*, anaerobes and vaginal discharge. *Lancet* 1982;i:1376-9.

² Blackwell A, Fox A, Phillips I, Barlow D. Anaerobic vaginosis (non-specific vaginitis): clinical, microbiological and therapeutic findings. *Lancet* (in press).

³ Blackwell A, Barlow D. Clinic diagnosis of anaerobic vaginosis (non-specific vaginitis): a practical guide. *Br J Vener Dis* 1982;58:387-93.

⁴ Richmond SJ, Oriel JD. Recognition and management of genital chlamydial infection. *Br Med J* 1978;iii:480-3.

⁵ Willcox JR, Fisk PG, Barrow J, Barlow D. The need for a Chlamydia Culture Service. *Br J Vener Dis* 1979;55:281-5.

Gliadin antibody levels in screening tests for coeliac disease

SIR,—Dr Cliona O'Farrelly and others claim that an enzyme linked immunosorbent assay test using purified α gliadin rather than crude gliadin (containing α, β, γ and ω gliadins) improves discrimination between untreated patients with coeliac disease and control subjects.

We performed essentially similar studies some time ago, and our results point to a different conclusion. In our enzyme linked immunosorbent assay test, we coated the wells overnight at 4°C with wheat protein at a concentration of 20 µg/ml in 60% ethanol/water, but otherwise the methods were similar.¹ We compared three different wheat protein preparations, each derived from the wheat variety known as Flander's. α Gliadin (preparation 1) was prepared as described by Patey and Evans²; crude gliadin contaminated with wheat albumins and globulins was prepared by direct extraction of flour with 70% ethanol (preparation 2); and crude gliadin free of albumins and globulins (preparation 3) was prepared by salt precipitation (1.5% sodium chloride) of preparation 2. The preparations were carefully characterised by polyacrylamide gel electrophoresis in aluminium lactate buffer pH 3.1.³

We first tested serum from 16 adults (mean age 47.5 years) with coeliac disease proved on biopsy, 32 adults (mean age 43 years) with miscellaneous