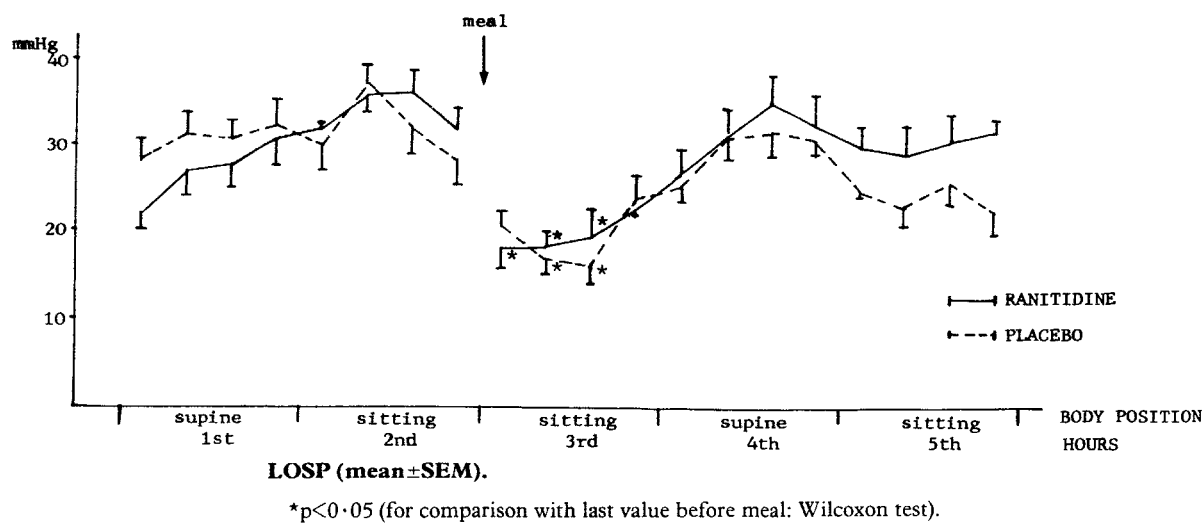




recorded at the gastric fundus, the LOS, and 5 and 10 cm above the LOS with a multilumen probe containing a sleeve sensor, perfused with a low compliance system. The pH was measured at 8 cm above the LOS with a combined glass electrode. The recordings began 1 h after the administration of the drug and continued for 5 h. The volunteer's body position (supine or sitting) was changed periodically and a standardised balanced meal (850 kcal) was given at the end of the second hour. The LOSP was assessed every minute, the fundic pressure being subtracted and relaxation phases being excluded. The peristaltic amplitude, duration, and propagation velocity were assessed every 5 min during wet swallows (5 ml of tap water). Gastro-oesophageal acid reflux was considered to be present when the oesophageal pH fell below 4 for at least 5 s; we evaluated the number of reflux episodes per hour and the proportion (%) of time with an oesophageal pH less than 4.

Neither LOSP (figure) nor motor function of the oesophagus (not shown) were affected by ranitidine; acid gastro-oesophageal reflux was almost abolished by the drug (table).

HOURLY REFLUX RATE AND TIME WITH OESOPHAGEAL pH <4

| Hour   | Refluxes (no/h) |            | Time (%) with pH <4 |            |
|--------|-----------------|------------|---------------------|------------|
|        | Placebo         | Ranitidine | Placebo             | Ranitidine |
| 1      | 1.2±0.5         | 0          | 0.3±0.1             | 0          |
| 2      | 1.7±0.6         | 0          | 1.0±0.5             | 0          |
| (Meal) |                 |            |                     |            |
| 3      | 3.0±0.5*        | 0          | 1.2±0.5*            | 0          |
| 4      | 1.0±0.2         | 0.2±0.1    | 3.0±1.7             | 0.1±0.1    |
| 5      | 2.0±0.7         | 0.7±0.4    | 1.9±0.9             | 0.1±0.1    |

Mean ± SEM. \*p<0.05 (for comparison with ranitidine figure; Wilcoxon test).

Our results, with ranitidine at the oral dose usual for the treatment of peptic ulcer, confirm the absence of any effect of ranitidine on the motor function of the oesophagus, before or after a meal. However, ranitidine virtually abolished the physiological acid gastro-oesophageal reflux. This effect, if confirmed in patients with pathological reflux, would provide a rationale for the use of this drug in the treatment of gastro-oesophageal reflux disease.

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ADDITION OF RETINOIDS TO PUVA FOR PSORIASIS

SIR,—We were surprised to read that etretinate/psoralen-ultra-violet-A (PUVA) has become an established treatment for severe psoriasis in Vienna (Jan. 29, p. 236) because our experience in double-blind placebo controlled trials (unpublished) of etretinate/PUVA has not been that encouraging; we did find a significant benefit in the treatment of psoriasis of palms and soles but in patients with ordinary chronic plaque psoriasis, although more responded and there was a reduction in total dose and time taken to clear, these differences were small and insignificant (table).

In contrast to the patients in Vienna ours did not find the side effects of etretinate acceptable. 13 of the 15 patients had cheilitis and 3 had severe hair loss; 4 of the 10 patients who received etretinate for palm and sole psoriasis also had severe hair loss. We did not find changes in serum lipids but others have.<sup>1</sup>

CHRONIC PLAQUE PSORIASIS

| Treatment              | No. of patients cleared | Total UVA dose (J/cm <sup>2</sup> ) to clear | Duration of PUVA treatment to clear (days) |
|------------------------|-------------------------|----------------------------------------------|--------------------------------------------|
| Etretinate-PUVA (n=15) | 14                      | 62.1± 8.9                                    | 40.3±4.3                                   |
| Placebo-PUVA (n=13*)   | 9                       | 77.3±15.8                                    | 49.4±6.7                                   |

\*Excludes 2 patients who withdrew due to intercurrent illness.

One possible explanation of these differences is that we were using an unnecessarily high dose of UVA with the etretinate although this was not apparent from the day-to-day erythematous response. Another is procedural: our study differed from that of Dr Honigsmann and Dr Wolff in Vienna in that it was confined to ordinary plaque psoriasis, the dose of etretinate was 0.7 mg/kg, and it was started two weeks before PUVA which was given thrice weekly;<sup>2</sup> we also studied fewer patients but they were allocated at random to etretinate-PUVA and placebo-PUVA groups. Until the reason for the difference is explained and the magnitude of the effects which are to be expected in different groups is elucidated, the use of retinoids with PUVA should be experimental and provisional rather than finalised as an established treatment. Nor would we wish to use the less teratogenic isotretinoin routinely with PUVA because of its effects on serum lipids.<sup>3</sup>

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SPECIFIC IgE ANTIBODY TESTS IN ALLERGY DIAGNOSIS

SIR,—The wealth of information generated by Dr Thompson and Dr Bird's thorough study (Jan. 22, p. 169), designed to assess the usefulness of a laboratory allergy service, confirms our own findings and the data accumulated internationally over the past decade. There were, however, some aspects of the report which deserve comment.

While we agree that laboratory allergy tests are an adjunct to, and cannot replace sound clinical judgment and careful history taking,

1. Ellis CN, Swanson NA, Grekin RC, Goldstein NG, Bassett DR, Anderson TF, Voorhees JJ. Etretinate therapy causes increases in serum lipids in patients with psoriasis. *Arch Dermatol* 1982; **118**: 559-62.  
2. Rogers S, Marks J, Shuster S, Briffa DV, Warin A, Greaves M. Comparison of photochemotherapy with dithranol in the treatment of chronic plaque psoriasis. *Lancet* 1979; **1**: 454-58.  
3. Marsden JR, Shuster S, Laker MF. Isotretinoin and serum lipids. *Lancet* 1983; **i**: 134

laboratories do receive many samples accompanied by insufficient information to allow rational selection of allergens for testing. In these circumstances, some form of screening system is helpful. The scheme suggested by Thompson and Bird is essentially sound, but it has a critical weakness in that it relies heavily on the total serum IgE as an initial discriminator. Our experience, culled from several studies, indicates that up to 6% of subjects with clinically significant sensitivities have serum IgE levels within the currently accepted "normal range" (<25 kU/l). IgE screening with cut-off levels of more than 50 kU/l is of little use. Indeed, in our experience IgE screening with an upper limit of normal of 100 kU/l offers only a 50% chance of identifying atopic individuals. The data presented showed that more than 30% of patients classified as having a low or normal IgE level (<200 kU/l for adults in this study) had one or more specific sensitivities detected by radioallergen sorbent test (RAST). The IgE level was, in some cases, supported by skin test results, but these may not always be available. In our view, the IgE level should not be used as a screening test, but should be used to complement specific IgE results obtained by RAST.

The choice of allergens for testing often presents a problem. Unless specific allergens are requested by the clinician, the laboratory usually submits the serum sample to a screening panel comprising the most common environmental allergens (a grass, house dust mite, cat or dog dander, and a mould; and, in samples from children, food allergens such as egg white or cow's milk may be included). Such limited screening panels are effective in both identifying atopic subjects and revealing some of the relevant allergens, but a significant number of specific sensitivities are missed.

The ten-allergen panel chosen for the study was fairly comprehensive and included three different moulds. Not surprisingly there were 53 positive mould RASTs among the 192 patients with one or more positive tests. Many of these would not have been revealed by a more limited panel including only one mould. On the other hand, the panel included only one species of grass, and, while most grass pollens share allergens and cross-sensitise, about 5% of grass-pollen sensitive patients react to one or two species only and a confusing negative result will be obtained if the grass pollen used for RAST is from a different species. Other factors restricting the effectiveness of the panel in identifying all relevant sensitivities include the absence of dog dander, weed pollen, and tree pollen. Larger panels reveal more sensitivities but may prove too expensive for routine screening purposes.

This problem has largely been solved by the recent introduction of mixed allergen discs for 'Phadebas RAST'. These can test a patient's serum against eight grasses, ten trees, six weeds, four animal epithelia, four moulds, and house dust at a fraction of the cost of individual RASTs. Positive results to the mixes may be followed by specific tests if required.

On the question of the "necessity" or usefulness of specific IgE antibody tests in allergy diagnosis, the answer is provided through the testimony of the clinicians involved in the study. Ear-nose-and-throat surgeons found the RAST results helpful in 40% of cases and paediatricians in 45% of cases referred for consultant opinion. However, the burden of caring for most allergy sufferers falls on the general practitioner whose time and involvement may not allow extensive investigation and whose facilities for, and experience of, skin testing may be severely limited. In this situation the provision of an effective laboratory testing service to GPs has proven to be of great value, influencing and improving management in a large proportion of cases, whilst saving time and overall costs.<sup>1</sup>

We would submit that the more widespread use of phadebas RAST has been of value in improving patient management and in helping to substitute rational treatment for therapeutic trial. This is not only beneficial to patients but increases the cost effectiveness of primary care.

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## REMOVAL OF COBALAMIN ANALOGUE IN BILE BY ENTEROHEPATIC CIRCULATION OF VITAMIN B<sub>12</sub>

SIR,—Microorganisms, the ultimate source of all vitamin B<sub>12</sub> (cobalamins), also synthesise other corrinoids (analogues of vitamin B<sub>12</sub>). Analogues are absorbed much more poorly by the intrinsic factor mechanism than is cyanocobalamin. Analogues have been found in vitamin pills:<sup>1</sup> some have anti-vitamin-B<sub>12</sub> action and could be harmful<sup>2,3</sup> while others may have vitamin B<sub>12</sub> activity.<sup>4</sup> Kolhouse et al.<sup>5</sup> presented evidence that about 30% of the corrinoids in human serum were non-cobalamin analogues, and we have found evidence for analogues in human liver and, in much lower quantities, in brain and red cells.<sup>6</sup>

There is a major enterohepatic circulation of vitamin B<sub>12</sub>, involving 0.5–6 µg daily, thus often supplying each day more vitamin B<sub>12</sub> for absorption than is supplied in food.<sup>7</sup> However, the assays used were microbiological, and microorganisms grow not only on cobalamin but also on corrinoid analogues, not all of which are cobalamins. On the basis of radioassays to differentiate cobalamins from other corrinoids we suggest that the main purpose of the enterohepatic circulation of vitamin B<sub>12</sub> may be to filter into the stool analogues of this vitamin.

Bile from the postoperative T-tube drains of five patients who had had gallbladder surgery was divided into two parts one of which was dialysed against five changes of distilled water for 24 h at 4°C. Dialysis tubing of pore size 2.4 nm was used to remove assay inhibitors. Total corrinoid and cobalamin were assayed by a modified<sup>5</sup> coated charcoal method.<sup>8</sup> Purified hog intrinsic factor was used to bind cobalamin, and R-binder from human saliva was used to bind total corrinoids. Recoveries of cyanocobalamin added to undialysed bile were 1% by assay for total corrinoids and 0% by assay for cobalamin. Recovery of cyanocobalamin added to dialysed bile was 93% by each assay. Assays were therefore done on both undialysed and dialysed bile.

Analogues contributed 32% of total corrinoids in serum, but almost twice that proportion in bile (table). Measurable total corrinoids and cobalamin in bile were significantly increased after removal of inhibitors by dialysis. Thus in bile there was more analogue than cobalamin, whereas the reverse was true for serum.

Before assay we had removed factors in bile which can prevent cobalamin binding to intrinsic factor, dissociate the intrinsic-factor/cobalamin complex, and prevent cobalamin binding to charcoal. After dialysis both cobalamin and total corrinoids were significantly increased, while measurements in undialysed bile gave false low values (caused by false high counts of supernatants due to undialysed bile preventing free vitamin B<sub>12</sub> from binding to charcoal). Unsaturated cobalamin binding capacity was present before dialysis and, though reduced, afterwards, suggesting that most cobalamin and analogue were bound and that losses during dialysis were small.

For 24 h output of, say, 1 litre of bile the five patients excreted daily in bile about 0.89 µg of analogue and 0.65 µg of cobalamin. The primary purpose of the enterohepatic circulation of cobalamin may thus be to filter out of the body into the stool potentially noxious cobalamin analogues, which use the intrinsic factor

- Herbert V, Drivas G, Foscaldi R, et al. Multivitamin/mineral food supplements containing vitamin B<sub>12</sub> may also contain analogues of vitamin B<sub>12</sub>, not mentioned on the label. *N Engl J Med* 1982; **307**: 255–56.
- Kolhouse JF, Allen RH. Evidence for the existence of multiple mechanisms that prevent the absorption and tissue dissemination of naturally occurring cobalamin analogues. *J Clin Invest* 1977; **60**: 1381–92.
- Herbert V, Drivas G, Foscaldi R, Manusselis C. Are multivitamin/mineral preparations with vitamins B<sub>12</sub> harmless? They may degrade some B<sub>12</sub> to analogs. *Clin Res* 1981; **29**: 673A.
- Herbert V, Colman N. Evidence humans may use some analogues of B<sub>12</sub> as cobalamins (B<sub>12</sub>): pure intrinsic factor (IF) radioassay may "diagnose" clinical B<sub>12</sub> deficiency where it does not exist. *Clin Res* 1981; **29**: 571A.
- Kolhouse JF, Kondo H, Allen NC, Podell E, Allen RH. Cobalamin analogues are present in human plasma and can mask cobalamin deficiency because current radioisotope dilution assays are not specific for true cobalamin. *N Engl J Med* 1978; **299**: 785–92.
- Kanazawa S, Herbert V. Vitamin B<sub>12</sub> analogue content in human red cells, liver and brain. *Clin Res* 1982; **30**: 504A.
- Herbert V, Colman N, Jacob E. Folic acid and vitamin B<sub>12</sub>. In: Goodhart RS, Shils ME, eds. *Modern Nutrition in Health and Disease*. Philadelphia: Lea & Febiger, 1980: 229–59.
- Lau KS, Gottlieb C, Wasserman LR, Herbert V. Measurement of serum vitamin B<sub>12</sub> level using radioisotope dilution and coated charcoal. *Blood* 1965; **26**: 202–14.

<sup>1</sup> Parker JH, Moore RMA, Wilson RSE. Trial of a centralised IgE allergy service to general practitioners in a rural area. *J Roy Coll Gen Practit* 1981; **31**: 231–40