

## A controlled trial of dietary modification in migraine

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### *Introduction*

The present study grew out of the experience of two of the authors (R. H. L. and A. R. S.) with dietary investigation of migraine patients at the Royal Prince Alfred Hospital allergy clinic. The principal interest of this clinic had been in the investigation of patients with chronic idiopathic urticaria and angioedema, a condition that involves histamine release from cutaneous mast cells by non-immunological mechanisms. Aspirin, food additives and other dietary triggering factors have long been recognized in certain patients, but systematic dietary investigation has only been carried out in large numbers over the past 10 to 15 years. Based on an extensive analysis of naturally occurring salicylate in foods<sup>1</sup> we developed an elimination diet which, when adhered to rigidly, resulted in complete remission of chronic urticaria in 50–60% of cases. Blind challenge with encapsulated food chemicals, additives and extracts provoked recurrences of urticaria in over 95% of these patients, most of whom could subsequently control their symptoms by following an appropriately modified diet<sup>2</sup>.

In some patients with a coincidental history of migraine as well as chronic urticaria it was found that dietary restriction could also result in the disappearance of headaches, and that these could be provoked, with or without urticaria, by a similar range of substances. To study the role of food chemicals in patients with migraine alone the allergy clinic challenge protocol was modified to include biogenic amines, MSG and nitrates, with starch and sucrose as placebos. Forty-eight per cent of 237 patients presenting with long-standing migrainous headaches improved subjectively on a stringent elimination diet over a 2- to 6-week period, and underwent double-blind challenge. All patients reacted to at least one active challenge, the commonest being nitrates, preservatives, salicylates, amines (tyramine and/or phenylethylamine), MSG, and tartrazine<sup>3</sup>. A follow-up questionnaire administered up to 4 years after presentation indicated that over 60% of the respondents had continued to follow a restricted diet and considered themselves to be substantially improved.

Since patients attending an allergy clinic known for its interest in the investigation of food intolerance are unlikely to be representative of migraine sufferers at large, it was decided to extend our studies to patients attending a neurology clinic. Furthermore, we wished to determine whether long-term dietary modification could be shown to be effective under controlled conditions, using objective criteria. For this purpose a prospective double-blind cross-over protocol was devised, using an individually tailored therapeutic and control diet based on the results of double-blind oral challenges.

### *Patients and methods*

The nature of a prospective double-blind crossover study of dietary modification was

explained to migrainous patients attending a neurology clinic at the Prince of Wales Hospital. The trial was approved by the ethics committee of the Hospital, and each patient signed a detailed consent form.

Of 95 patients who agreed to undertake the trial, 75 (78%) were female and 21 (22%) were male with an age range of 7–66 years (mean 38 years). History and physical examination were recorded by a resident medical officer or the supervising neurologist (MA or JW) and the diagnosis of migraine made on standard criteria<sup>4</sup>. Of the 95 patients, 19 suffered predominantly from migraine with aura (“classical migraine”), 68 from migraine without aura (“common migraine”), and eight from both forms. The history of headache extended for 1–15 years (mean 6 years) and the frequency of headache was 4–12 per month for most patients. Six stated that the frequency of headaches had increased to second daily or “almost every day” at the time of entry to the trial but were included because the headaches were unilateral (four), associated with nausea (five), photophobia (four), and fortification spectra (one) or unilateral paraesthesiae (one). Patients taking prophylactic medication were not excluded if they continued to have at least four headaches per month. Patients with a past history of asthma, urticaria, eczema or irritable bowel syndrome were not accepted into the study. Of the 95 patients, 26 considered that their headaches could be precipitated by specific foods, 14 by alcohol and 10 by both.

The protocol consisted of three stages (Fig. 1). As an initial screening procedure, patients were placed on a standard elimination diet which excluded wheat, dairy

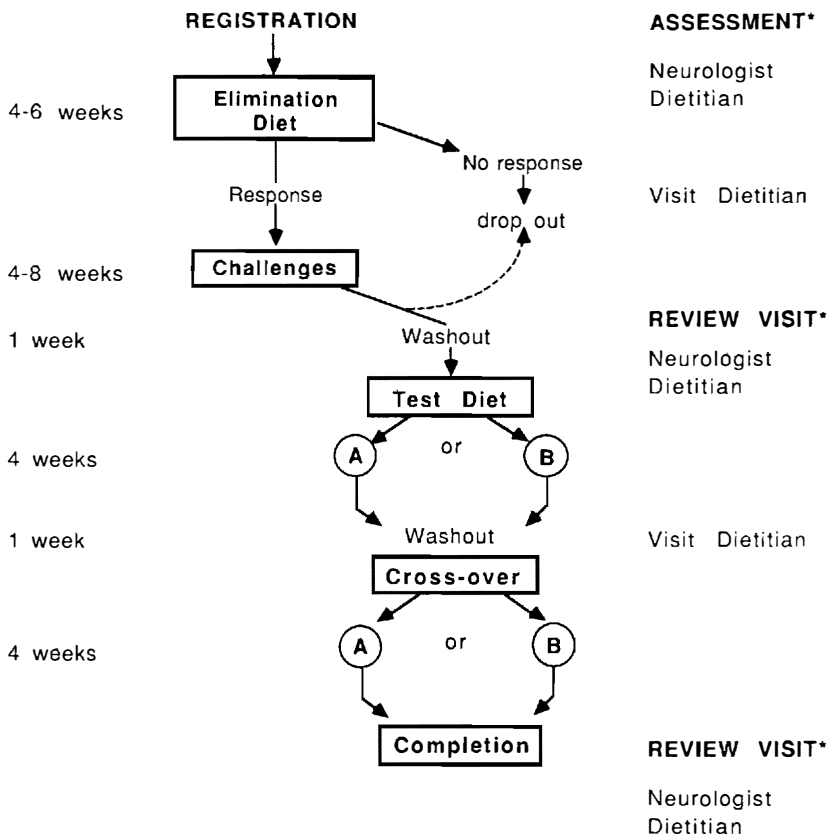


Fig. 1. Experimental protocol.

products, natural salicylates, amines, MSG and all food additives<sup>5</sup>. They were also advised to avoid coloured medications and those containing aspirin, as well as strong-smelling perfumes, sprays and household cleaning agents. Patients kept a daily diary of food intake, symptoms and medications. If headache frequency and severity was reduced to less than half of that previously experienced over a 4- to 6-week period the patients was presumed “food-sensitive” and proceeded to the challenge stage. Those who failed to improve after 6 weeks were considered unlikely to be food-sensitive and were advised to resume their normal eating pattern.

Before commencing double-blind challenges wheat and milk were tried as open challenges, and if tolerated were added to the baseline diet. Test substances and placebos<sup>5</sup> were packaged in opaque ferric oxide-coated gelatine capsules and were given to each patient as a coded set in random order to be taken at 48-h intervals. If a headache occurred within 48 h further challenges were deferred until the subject had been free of symptoms for 3 days. When the challenges were completed, a dietitian (J. McQ.) reviewed the patients’s diary to determine which challenges were followed by headache. This information was conveyed by telephone to an independent dietitian (A. R. S.) who decoded the results and designed an “appropriate” (therapeutic) diet and an “inappropriate” (control) diet undividually tailored for each patient. The “appropriate” diet excluded foods containing substances to which the patient had reacted, and the “inappropriate” diet was designed to include these foods.

The third stage began with randomization of each patient to receive either the therapeutic or control diets, administered double-blind by the dietitian (J. McQ.). This diet was followed for 4 weeks, after which the patient was crossed over to the alternate diet. A 1 week washout on the strict elimination diet was allowed for before the commencement of each diet. Headache severity was scored as: 3+ if patients were confined to bed; 2+ if they were prevented from working or undertaking other activities; 1+ if they were able to continue their normal routine.

### Results

Of the 95 patients who entered the study, 36 dropped out during the first 6 weeks, 22 followed the elimination diet for the required period without significant improvement, and 37 became free of headache for at least 2 weeks. Of the latter group only 19 (20% of

Table 1. Response to double-blind challenges.

<i>Challenge substance</i>	<i>Positive reactions (%)</i>	
	<i>Allergy Clinic</i> ( <i>n</i> =109)	<i>Neurology Clinic</i> ( <i>n</i> =95)
Salicylate	51	48
Amines	52	32
Monosodium glutamate	54	58
Preservatives	51	21
Colouring agents	43	32
Nitrates	58	42
Antioxidants	33	26
Propionate	32	37
Lactose	11	47
Gluten	7	ND
Sucrose	7	21
Starch	8	32

Sucrose and starch are considered placebo challenges. Note that many patients developed headache after more than one challenge. The dose regimen is described in<sup>5</sup>.

those entering the study) completed the challenges and went on to the test diets. Double-blind challenge results are shown in Table 1.

When the 19 patients were given an appropriate diet (with the provoking agents removed), three became virtually headache-free, six were significantly improved (less than half the frequency and severity of headache), six were unchanged, and four were worse compared with their symptom score in the control (inappropriate) diet (Table 2). The number of patients in each category who had stated that their headaches had often been precipitated by taking certain foods was 1, 0, 2 and 3, respectively. Six of the patients were known to have broken their diet on at least one occasion during the cross-over study, two in the “half-improved”, three in the “unchanged” and one in the “worse” category.

Table 2. Headache ratings of 19 patients in double-blind cross-over trial of therapeutic and control test diets.

<i>Patient Number</i>	<i>Test Diet</i>	
	<i>Therapeutic</i>	<i>Control</i>
<i>Virtually headache-free (3)</i>		
1	0	6
2	1	25
3	2	12
<i>50% better (6)</i>		
4	3	7
5	3	10
6	12	23
7	6	14
8	6	13
9	4	14
<i>Unchanged (6)</i>		
10	9	12
11	19	34
12	13	16
13	16	18
14	14	20
15	10	11
<i>Worse (4)</i>		
16	9	6
17	20	5
18	19	7
19	6	2

Before the cross-over code was broken each patient was asked to express their subjective preference for one or other diet. Fourteen preferred the “appropriate” diet, two chose the control (“inappropriate”) diet, and three were undecided.

### *Discussion*

The relationship between migraine and allergy, in particular food allergy, has been a matter of speculation and controversy for well over 50 years. In the latter half of the 19th century migraine was linked with hay fever, asthma, eczema and other conditions as a manifestation of the “exudative diathesis”. After the turn of the century, when anaphylactic phenomena were shown to have an immunological basis, further attention was paid to migraine as an allergic manifestation by numerous authors<sup>6-10</sup> Confusion soon arose for several reasons, and this has persisted to the present day. When skin tests for “reaginic” (IgE) antibodies were popularized following the careful

studies of Schloss<sup>11</sup>, most clinicians did not appreciate that around 30% of the population has a genetic predisposition to produce IgE, but at least half such individuals will never develop symptomatic allergic disease. Furthermore, in the euphoria which followed the discovery of allergic mechanisms capable of explaining a wide range of previously mysterious conditions, it was not recognized that non-immunological mechanisms could produce indistinguishable clinical symptoms such as urticaria, angioedema, asthma and rhinitis. Compounding this was a failure to appreciate the importance of selection bias in making disease associations, the need for blinding of patients and observers when testing therapeutic measures, and the power of placebo and other confounding effects.

In this climate of confusion, well summarized by May<sup>12</sup>, it is easy to see how misconceptions about the role of allergy arose, particularly in a common condition such as migraine where dietary triggers are suspected by as many as 25% of patients<sup>13</sup>. Systematic studies over the past 20 years have established that migraine is not part of the atopic diathesis<sup>14-16</sup>, although it is generally accepted that in some patients allergic reactions may act as a trigger factor. However, the role of specific foods or food constituents as triggers remains controversial. The issues have unfortunately been obscured by a more general confusion about food allergy and intolerance, and the polarization of allergists into an “orthodox” (scientific) school and an “unorthodox” (clinical ecology) school<sup>17</sup>. Amongst the latter, publications by Grant<sup>18</sup>, and Monro *et al.*<sup>19,20</sup> have been strongly criticized on methodological grounds, casting considerable doubt on their conclusion that specific food allergies, mediated by IgE, are responsible for “dietary migraine”<sup>21-28</sup>.

There are only two well controlled studies suggesting an allergic aetiology for migraine. One is that of Egger *et al.*<sup>29</sup> based on the response of children with migraine to an “oligoantigenic” diet and double-blind food challenge. However, it should be noted that there was a poor correlation between food challenges and measurements of specific IgE. Even so, Egger *et al.* considered it likely that some other immunological mechanism might be involved, a view which we have criticized in another context<sup>30</sup>. In another recent study by Mansfield *et al.*, seven selected patients who had responded subjectively to an elimination diet underwent double-blind challenge with foods identified by positive skin prick tests<sup>31</sup>. Five developed headache after challenge with some, though not all, of the relevant foods with no reaction to placebo, and in two patients headaches were accompanied by a rise in plasma histamine. Although the results of this study suggest that IgE-mediated food reactions might have been responsible for provoking headache, no challenges were reported with foods which gave negative skin test results, nor were the 27 skin test-negative patients (presumed not to have dietary migraine) given any food challenges. It is therefore not possible to determine the sensitivity, specificity or predictive value of skin testing in such patients, or to draw definite conclusions about the role of IgE. In contrast to these two studies, Medina and Diamond<sup>32</sup> and Merrett *et al.*<sup>33</sup> found no abnormalities in IgE levels in migrainous patients, nor any difference in IgG4 food antibodies amongst patients with dietary or non-dietary migraine<sup>33</sup>.

Another unresolved question is the role of tyramine and other dietary chemicals in triggering migraine<sup>34</sup>. Since the original observations of Hanington<sup>35</sup> other studies have produced conflicting results. For example, Medina and Diamond<sup>36</sup> reported that migrainous patients on a tyramine-free diet fared no better than those on a tyramine-rich diet. In reviewing the subject Glover *et al.*<sup>37,38</sup> point out that tyramine content does not correlate well with the frequency with which foods such as chocolate, cheese, citrus

fruits and wine are reported as precipitants. These authors have provided evidence of a reduction in phenolsulphotransferase (PST) activity in patients with dietary migraine, and have suggested that this may point to involvement of a much wider range of dietary phenols<sup>38</sup>. This enzyme system is widely distributed in the body, including platelets, intestine and central nervous system, and is responsible for metabolism of dietary as well as endogenous monoamines. A number of complex food phenols and certain food additives have also been shown to inhibit the activity of PST *in vitro*<sup>39</sup>. In a recent study the same group showed that red wine but not vodka was capable of triggering headache under controlled conditions<sup>40</sup>, arguing against the idea that alcohol itself is the trigger in such patients. In discussing the common observation that red wine more often provokes headache than white wine they point out that red wines contain very much higher concentrations of complex phenolic flavonoids, some of which may have noxious effects which are exaggerated in patients with low levels of PST.

Our experience of patients with food intolerance at the Royal Prince Alfred Hospital allergy clinic indicates that true food allergy (mediated by IgE) is largely confined to children with eczema, and that migraine is an uncommon feature in this setting. In adults the great majority of adverse food reactions appear to be due to chemical idiosyncrasies which can be identified by systematic dietary elimination and double-blind challenge<sup>3</sup>. Patients with dietary migraine are usually sensitive to several substances, including natural salicylates, amines, MSG and certain food additives, in varying combinations. Reactions are dose-dependent and may be delayed or cumulative. Since these substances are widely distributed in many different foods, it is not surprising that there has been considerable confusion about the role of diet in such patients.

There are several related but separate questions to be addressed regarding the role of diet in migraine. (1) Can dietary factors be shown objectively to act as triggers in migraine, and in what proportion of patients does this occur? (2) Which components of the diet are responsible and by what mechanisms do they act? (3) What implications might this have for understanding the pathogenesis of migraine? (4) Is long-term dietary restriction an effective means of management in patients with “dietary” migraine?

The present study was aimed at answering the last of these questions. Patients were screened and selected on the basis of dietary elimination and challenge tests, and were then randomized to have either an appropriate (test) diet or an inappropriate (control) diet based on the initial challenge results. After 1 month each patient was crossed over to the alternate diet. Neither the patient nor the dietitian was aware of which diet was which until the code was broken, and careful steps were taken to ensure that guessing was not possible. The results showed that of 19 patients completing the study less than half experienced a significant improvement on the appropriate diet, and only three were free of headache altogether.

In retrospect it was evident that there were several flaws in our study design which may have produced less clear-cut results than might have been expected. Firstly, there is some uncertainty about the accuracy of the challenge results as reflected by the high frequency of reactions to “placebo” substances. In situations where extraneous factors such as stress, infections and other triggers may be contributing it is normally our practice at the allergy clinic to repeat challenges if in doubt and to confirm both positive and negative responses with open food challenges, and we would normally expect a placebo response rate of approximately 10%<sup>3</sup>. Secondly, blinding of the dietitian was found to reduce significantly patients’ confidence and resulted in poorer dietary

compliance than expected. This may have been further exaggerated by the length of the protocol and the obvious difference in motivation of patients attending a neurology clinic compared with those attending an allergy clinic. Thirdly, it was found that the 1-week washout period was not always adequate, and patients were also reluctant to change their eating habits after crossing over. Finally, patients were given a list of foods allowed and foods to avoid without specific instructions about which foods they must eat, the timing and amounts. Thus there was no control over the dose of particular food substances ingested.

Despite these drawbacks it was concluded that even in patients in whom dietary triggers may have been identified by double-blind challenge, long-term avoidance of the relevant foods is likely to be effective as a prophylactic measure only in a minority of patients. This should not be taken to mean that patients who incriminate particular foods as triggers must be mistaken. The situation is comparable to that in asthmatics where it has become abundantly clear that some patients are sensitive to the effects of salicylates, MSG and sulphite preservatives. Large doses may sometimes precipitate acute attacks, but regular avoidance of foods containing these substances does not usually produce measurable clinical improvement in the long term<sup>41</sup>. No doubt, in asthma as in migraine, this reflects the multitude of other intrinsic and extrinsic factors involved in the triggering of symptoms in predisposed individuals.

It was also evident from the present study that patients attending an allergy clinic are not only unrepresentative of migraine patients as a whole, but that they are generally much more strongly motivated to explore dietary triggering factors and are therefore more likely to comply with long-term dietary modifications. To what extent reports of favourable results in such patients represent accurate identification and elimination of significant triggering factors on the one hand, and the perceptions of the patient and therapist on the other, remains to be determined. However, it was interesting to note that before the code was broken in our study a significant majority of the patients expressed a preference for the appropriate diet over the control diet. This may possibly have been due to a sense of well-being which is often experienced by food-sensitive patients once their diet has been appropriately modified<sup>3</sup>.

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