identifying the thrombus can all be used as diagnostic criteria. Since heparin might interfere with the incorporation of fibrinogen into a thrombus, the fibrinogen-uptake study may not be reliable in patients already receiving heparin. 27 of our patients (54%) were already receiving anticoagulants when they were investigated. Also, since a long-established clot will incorporate ^{99m}Tc-labelled fibrinogen only poorly,[33] the investigation needs to be done soon after the onset of symptoms.

When a definitive report of positive or negative was required, the accuracy of venoscan was only 80%. When equivocal images were excluded from analysis, the accuracy was 97%, with no false-negative and one false-positive result (table II). However, only 68% of venoscans could be reported as unequivocal. Venoscan is, therefore, not a suitable method for the definitive diagnosis of deep-vein thrombosis. It may be useful as a screening test. One approach would be to use the venoscan as the initial investigation and reserve X-ray venography for patients with equivocal scans. In this way no case of deep-vein thrombosis would have been missed, one ruptured Baker's cyst would have been diagnosed mistakenly as deep-vein thrombosis, and only a third of patients would have required X-ray venography in our study.

Although X-ray venography is the "gold standard" test in the diagnosis of deep-vein thrombosis, we found that the reporting of venography is fallible. Others have reached similar conclusions.[29,30] A further potential difficulty with X-ray venography is that it may not visualise small thrombi in calf-vein sinusoids. In such cases, the venoscan may correctly diagnose clots which would remain undiagnosed by X-ray venogram. If venography is taken as the gold standard this possibility is untestable.

We saw no major complications of venography, although venous thrombosis as a consequence of venography was not investigated. X-ray venography is contraindicated, for example, in allergy to contrast media, myeloma, and conditions in which the risk of venous insufficiency is likely to be high (eg, recent obliteration of superficial veins in patients with varicose veins). The venoscan may prove a useful alternative in such patients.

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REFERENCES

1. Hull R, Hirsh J, Sackett DL, Stoddart G. Cost effectiveness of clinical diagnosis, venography and non invasive testing in patients with symptomatic deep vein thrombosis. *N Engl J Med* 1981; **304:** 1561–67.
2. Simpson FG, Robinson PJ, Bark M, Losowsky MS. Prospective study of thrombophlebitis and "Pseudothrombophlebitis". *Lancet* 1980; i: 331–33.
3. Peyman MA. The significance of haemorrhage during the treatment of patients with the coumarin anticoagulants. *Acta Med Scand* 1958; **1** (suppl): 1–62.
4. Mant JM, O'Brien BD, Thong KL, Hammond GW, Birtwhistle RV, Grace MG. Haemorrhagic complications of heparin therapy. *Lancet* 1977; i: 1133–35.
5. Williams WJ. Venography. *Circulation* 1973; **47:** 220–21.
6. Browse NL. Diagnosis of deep vein thrombosis. *Br Med Bull* 1978; **34:** 163–67.
7. Albrechtsson U, Olsson CG. Thrombotic side-effects of lower limb venography. *Lancet* 1976; i: 723–24.
8. Martin JF, Blake GM. A new method giving a two criteria diagnosis of venous occlusion using isotope imaging of ^{99m}Tc labelled fibrinogen. *Eur J Nucl Med* 1983; **8:** 281–83.
9. Lee Nix M, Barnes RW. Non invasive peripheral vascular laboratory diagnostic techniques. Virginia: Medical College of Virginia, 1980.
10. Mullick SC, Wheeler HB, Sonster GP. Diagnosis of DVT by measurement of electrical impedance. *Am J Surg* 1970; **119:** 417–22.

References continued at foot of next column

MIGRAINE IS A FOOD-ALLERGIC DISEASE

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Summary Foods which provoked migraine in 9 patients with severe migraine refractory to drug therapy were identified. The patients were then given either sodium cromoglycate or placebo orally in a double-blind manner, with foods previously identified as provocants. Sodium cromoglycate exerted a protective effect, thus confirming that it can prevent a hypersensitivity mechanism as well as the symptoms of migraine. Immune complexes were not produced in those patients who were protected by sodium cromoglycate. These observations confirm that a food-allergic reaction is the cause of migraine in this group of patients.

D. A. SANDLER AND OTHERS: REFERENCES—*continued*

11. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972; **104:** 134–44.
12. Spitzer RL, Cohen J, Fleiss JL, Endicott J. Quantification of agreement in psychiatric diagnosis. *Arch Gen Psychiatry* 1967; **17:** 83–87.
13. Gray HW, Pearson DW, Moran F, Bessent RG. Reporting of ventilation perfusion images for pulmonary embolism: accuracy and precision. *Eur J Nucl Med* 1984; **9:** 151–53.
14. Thomas ML, MacDonald LM. Complications of ascending phlebography of the leg. *Br Med J* 1978; ii: 317–18.
15. Kristiansen P, Bergentz SE, Bergqvist D, Nylander G. Thrombosis after elective phlebography as demonstrated with the ^{125}iodine test. *Acta Radiol* 1981; **22:** 577–80.
16. Albrechtsson U, Olsson CG. Thrombosis following phlebography with ionic and non ionic contrast media. *Acta Radiol* 1979; **20:** 46–52.
17. Thomas ML, Briggs GM, Khan BB. Contrast agent-induced thrombophlebitis following leg phlebography: meglumine ioxaglate versus meglumine iothalamate. *Radiology* 1983; **147:** 399–400.
18. Thomas ML, Keeling FP, Piaggio RB, Treweeke PS. Contrast induced thrombophlebitis following leg phlebography: iopamidol versus meglumine iothalamate. *Br J Radiol* 1984; **57:** 205–07.
19. Flanigan DP, Goodreau JJ, Burnham SJ, Bergan JJ, Yao JS. Vascular-laboratory diagnosis of clinically suspected deep-vein thrombosis. *Lancet* 1978; ii: 331–35.
20. Schroeder PJ, Dunn E. Mechanical plethysmography and doppler ultrasound. *Arch Surg* 1982; **117:** 300–03.
21. Hanel HK, Abbott WM, Reidy NC, et al. The role of two non invasive tests in deep venous thrombosis. *Ann Surg* 1981; **194:** 725–30.
22. Dmochowski JR, Adams DF, Couch NP. Impedance measurement in the diagnosis of deep venous thrombosis. *Arch Surg* 1972; **104:** 171–73.
23. Moser KM, Brach BB, Dolan GF. Clinically suspected deep venous thrombosis of the lower extremities: a comparison of venography, impedance plethysmography and radiolabelled fibrinogen. *JAMA* 1977; **237:** 2195–98.
24. Browse NL. The ^{125}I-fibrinogen uptake test. *Arch Surg* 1972; **104:** 160–63.
25. Ennis JT, Elmes RJ. Radionuclide venography in the diagnosis of deep vein thrombosis. *Radiology* 1977; **125:** 441–49.
26. Gomes AS, Webber MM, Buffkin D. Contrast venography versus radionuclide venography: a study of discrepancies and their possible significance. *Radiology* 1982; **142:** 719–28.
27. Beswick W, Chmiel R, Booth R, Vellar I, Gilford E, Chesterman CN. Detection of deep venous thrombosis by scanning of ^{99m}Tc-labelled red cell venous pool. *Br Med J* 1979; i: 82–84.
28. Deacon JM, Ell PJ, Anderson P, Khan O. Technetium 99m plasmin: a new test for the detection of deep vein thrombosis. *Br J Radiol* 1980; **53:** 673–77.
29. Adolfsson L, Nordenfelt I, Olsson H, Torstensson I. Diagnosis of deep vein thrombosis with 99 Tc^{m} plasmin. *Acta Med Scand* 1982; **211:** 365–68.
30. Edenbrandt CM, Nilsson J, Ohlin P. Diagnosis of deep venous thrombosis by phlebography and 99Tc^{m} plasmin. *Acta Med Scand* 1982; **211:** 59–64.
31. Overgaard K. Thromboscintigraphy with 99Tc^{m}-plasmin: a new diagnostic method in deep venous thrombosis of the legs. *Nucl Med Comm* 1984; **5:** 101–07.
32. Husted SE, Nielsen K, Krussell L, et al. Deep vein thrombosis detection by 99mTc-plasmin test and venography. *Br J Surg* 1984; **71:** 65–66.
33. Harwig SSL, Harwig JF, Sherman R, Coleman RE, Welch MJ. Radioiodinated plasminogen: an imaging agent for pre-existing thrombi. *J Nucl Med* 1977; **18:** 42–45.
34. Fenech A, Dendy PP, Hussey JK, Bennett B, Douglas AS. Indium ^{111} labelled platelets in diagnosis of leg vein thrombosis: preliminary findings. *Br Med J* 1980; **280:** 1571–73.
35. Kempi V, Van der Linden W, Von Scheele C. Diagnosis of deep vein thrombosis with 99mTc-Streptokinase: a clinical comparison with phlebography. *Br Med J* 1974; iv: 748–49
36. Jonckheer MH, Abramovici J, Jeghers O, Derume JP, Goldstein M. The interpretation of phlebograms using fibrinogen labelled with 99m Technetium. *Eur J Nucl Med* 1978; **3:** 233–38.

Introduction

THE diagnosis of migraine is based on clinical criteria and should not depend on mechanism or aetiology.[1] Migraine is a multifactorial disease which may be induced through the ingestion of large amounts of chemical mediators in some individuals,[2] or through an allergic reaction to foods in others.[3,4] In the latter group the exact mechanism by which foods cause the migrainous attacks is not clear.

Some food-allergic reactions arise through an immune-complex-mediated mechanism—that is, a form of serum sickness triggered by a type-I hypersensitivity reaction in the gut.[5] In these circumstances the composition of the immune complex or the mediators released govern the damaging capacity.

The aim of this study was to investigate the protective effect of sodium cromoglycate (SCG) given to 9 patients with severe migraine before food-challenge.

Patients and Methods

Patients

9 patients with severe migraine who attended the National Hospital for Nervous Diseases were studied. They had been referred by their general practitioners and local general hospitals for further opinion and were therefore a highly selected group of patients who were refractory to available treatment.

All patients consented to dietary intervention and were asked to record their usual diet and any symptoms arising. The symptoms were scored on a scale of 1 to 4 related to daily activities: 1—mild headache; 2—moderate headache for which simple analgesics were required; 3—severe headache causing disruption of daily activities and requiring more medication; 4—prostrating headache causing patient to seek bedrest and other supportive measures. The scores were entered on a calendar to indicate frequency, duration, and severity.

Dietary Exclusion

Patients were put on a diet avoiding colourings, food additives, sugar, tea, coffee, alcohol, and any known provocants of which they were aware. If no clinical improvement was observed, they were put on diets sequentially avoiding milk and milk products; all grains and cereals including wheat, rye, barley, oats, maize, millet, and rice; and meats, pips, and nuts. After each period of 5 days' exclusion challenges were carried out, and from the diet diary those foods which provoked symptoms were identified. Open challenges were used to confirm the provocation by these foods on at least 3 occasions.

Skin Testing

The patients were skin-tested by means of the prick method and then the intradermal route. The prick tests were usually negative. A small intradermal weal was raised with the injection of 0·05 ml of a 0·1% dilution of suspected allergen in saline. The weal size was measured after injection and then again after 10 min; an increase of more than 2 mm in two directions was classified as a positive response.

Sodium Cromoglycate

Capsules of sodium cromoglycate or placebo were given in a double-blind manner before food-challenge, and the results were recorded. The challenges were of meal-sized quantities of the foods previously identified as provocants and taken in the outpatient department under supervision. Patients were pretreated with doses of 500 mg SCG 2 h and again ½ h before challenge (see table).

Symptoms were charted while the patient was under a 6 h observation in the hospital. Thereafter the patient kept a diary for 24 h. An irrelevant challenge was carried out as a specificity control.

IgE Determination

A modified PRIST assay was used. Paper discs were sensitised with affinity-column-purified anti-human light chain (10 ng/ml), and 50 µl of sera at dilutions of 1:10 and 1:100 were added to the discs in a microtitre tray. The discs were then incubated for 14 h at 4°C on a rocking platform. IgE standards were included in each assay. After washing, 100 µl of iodinated rabbit anti-human IgE was added at a dilution to give 100 000 counts/100 µl well. After further washing and drying the discs were counted in an automatic gamma-counter.

CLINICAL DETAILS OF PATIENTS

Patient	Age/sex (yr)	Challenge	Order of treatment	Symptoms	Choice of treatment
1	60 F	Wheat milk egg	Active 2	Slight headache at 4 h grade 1	Active
			Placebo 1	Headache at 24 h at grade 3	
2	55 F	Milk egg wheat	Active 1	No headache	Active
			Placebo 2	Headache at 24 h grade 4	
3	30 F	Milk	Active 2	No headache	Active
			Placebo 1	Headache grade 4	
4	64 M	Milk wheat	Active 2	No headache, flatulence	
			Placebo 1	No headache, flatulence.	Placebo
5	52 M	Milk wheat	Active 1	Headache grade 1.	Active
			Placebo 2	Headache grade 1, diarrhoea	
6	38 F	Milk wheat	Active 2	Diarrhoea	Active
			Placebo 1	Diarrhoea, nausea, and headache	
7	31 F	Wheat milk	Active 1	No headache	Active
			Placebo 2	Headache at 24 h, grade 2, nausea	
8	45 M	Milk wheat	Active 1	No headache	Active
			Placebo 2	Headache at 48 h grade 1–3 next day	
9	37 F	Milk wheat	Active 2	No headache	Active
			Placebo 1	Abdominal symptoms, nausea, teichopsia, no headache	

Sucrose/Polyethylene-glycol Gradient

A stepped gradient was used to separate immune complexes from the serum.[6] This incorporates a polyethylene-glycol gradient in the lower 3 steps of a sucrose gradient to stabilise and precipitate the complexes, so preventing dissociation of low-affinity complexes. The serum sample was layered on to the top of the gradient, which was spun at 30 000 rpm in an SW50 rotor for 16 h at 20°C.

The supernatant was removed and the precipitate washed and resuspended in buffer. Almost all the complexes of 25S or more, 80% of the 19S, 22% of the 11S, and only 8% of the 8S were recovered in the precipitate.

Isokinetic Sucrose Ultracentrifugation Gradient

An isokinetic sucrose ultracentrifugation gradient was set up as previously described.[7] Approximately 35 fractions are obtained from each gradient, allowing sensitive discrimination between monomeric and complexed IgE. Each of the fractions from both gradients was tested for IgE.

Results

Skin Tests

Prick tests with a wide range of food allergens were negative in all patients. With intradermal testing positive responses were shown to a variety of foods but mainly to milk, wheat, and eggs (see table). Other foods were tested but were not used for challenge studies.

Food-challenge and Effect of SCG

SCG or placebo was given in a double-blind manner and in random order, the code being held by Dr H. Eveleigh (Fisons plc) until the trial was complete. Of the 9 patients challenged, 8 showed a preference for SCG: 5 were completely protected from symptoms and 3 were partially protected when compared with placebo, this being a statistically significant difference ($p = 0 \cdot 025$, sign test of pairs).

Immune Complexes after Food-challenge and Effect of SCG

In the 3 food-allergic patients in whom immune complexes were measured before treatment with SCG, IgE was detectable in a complexed form in 2 patients within 2 h and in all 3 patients within 4 h of food-challenge. When the patients were pretreated with SCG, IgE was not seen in the precipitate of the sucrose/polyethylene-glycol gradient (fig 1). To confirm the precipitable IgE, the isokinetic sucrose gradient was used. This showed similar results.

When an irrelevant food allergen was used for challenge, IgE-containing immune complexes were not seen (fig 2).

Discussion

We[4] and others[3] have shown that migraine in some patients can be relieved by dietary exclusion. We show here that formal food-challenge can also provoke migraine and that pretreatment with oral SCG exerts a protective effect. This

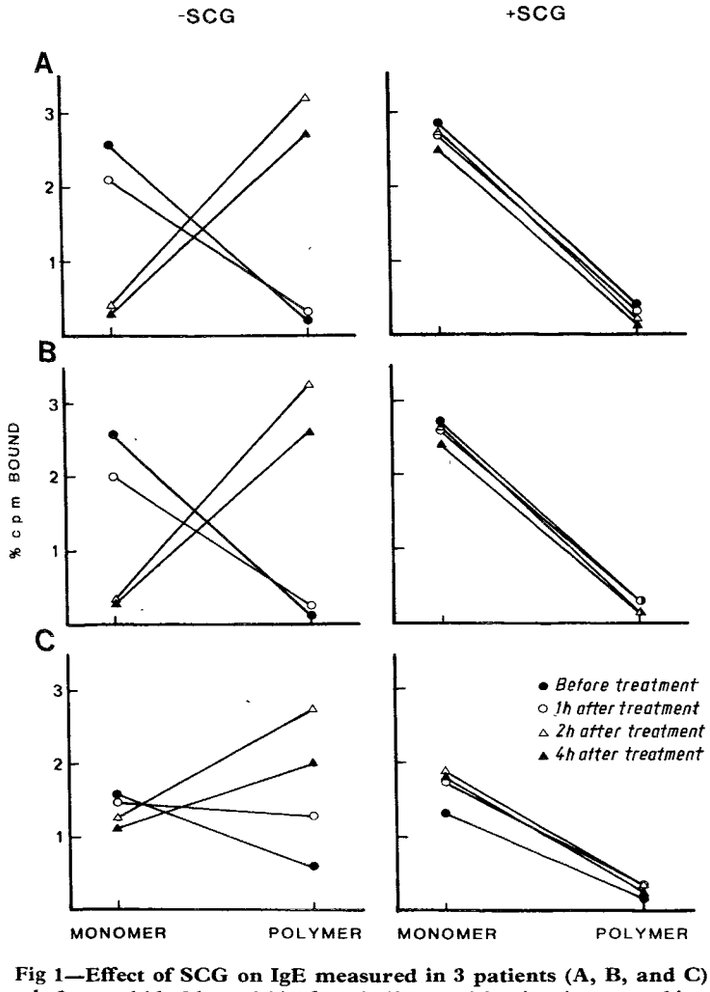

Fig 1—Effect of SCG on IgE measured in 3 patients (A, B, and C) before and 1 h, 2 h, and 4 h after challenge with migraine-provoking food.

In all 3 patients there was a fall in monomeric and an increase in complexed IgE after challenge. Pretreatment with SCG prevented the changes.

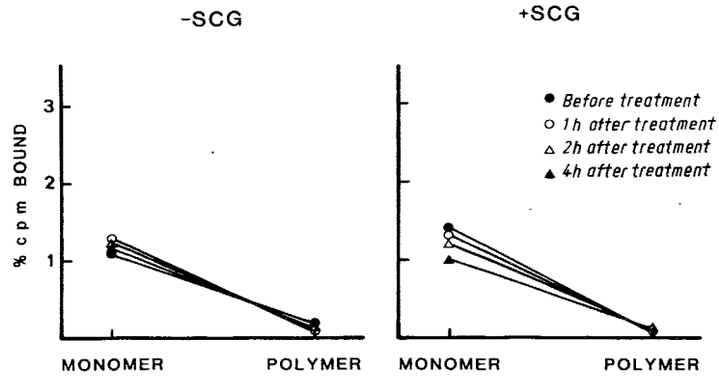

Fig 2—Effect of SCG on IgE measured before and 1 h, 2 h, and 4 h after challenge with irrelevant food.

There was no reduction in monomeric peak and no increase in complexed IgE.

suggests that a food-allergic mechanism gives rise to symptoms in these patients. Their sensitivities to various foods were demonstrated by means of elimination, challenge, and positive intradermal testing.

Challenging with the relevant food also led to the appearance of immune complexes containing IgE. These were absent when the patient was pretreated with SCG but were present when placebo was given. The fact that SCG is poorly absorbed from the gastrointestinal tract suggests that it acts locally on the gut mucosa to block an immunological "trigger" for the absorption of antigen,[9] immune complexes,[8] and possibly mediators.[10]

The platelet is now known to have Fc receptors for IgE.[11] Patients with migraine show platelet hyperaggregability,[12] which may result from the presence of immune complexes containing IgE and IgG. There are several ways in which immune complexes containing IgE could produce migraine. The complexes may aggregate platelets, producing small microthrombi, or allow the release of platelet mediators.[10] They may also react with mast cells in the cerebral vasculature.

The observation that these patients are protected by oral SCG does suggest that an allergic gatekeeper mechanism in the gut triggers the production of symptoms, with immune complexes acting as a messenger.[5] Further research to identify the specificity of the mixed immune complexes in these patients is in progress.

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REFERENCES

1. Blau JN. Towards a definition of migraine headache *Lancet* 1984; i: 444–45.
2. Hannington E. Migraine. *Trans Med Soc* 1971; **87:** 32.
3. Egger J, Carter CM, Wilson J, Turner MW, Soothill JF. Is migraine food allergy? A double blind trial of oligoantigenic diet treatment. *Lancet* 1983; ii: 865.
4. Monro J, Brostoff J, Carini C, Zilkha K. Food allergy in migraine: A study of dietary exclusion and RAST. *Lancet* 1980; ii: 1–4.
5. Brostoff J, Carini C, Wraith DG. Food allergy: An IgE immune complex disorder. Theoretical and chemical aspects of allergic diseases. Stockholm: Alnqvist and Wiksell International, 1983.
6. Male D, Roitt IM. Analysis of the components of immune complexes. *Mol Immunol* 1979; **16:** 197.
7. Brostoff J, Johns P, Stanworth DR. Complexed IgE in atopy. *Lancet* 1977; ii: 741–42.
8. Brostoff J, Carini C, Wraith DG, Johns P. Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium cromoglycate *Lancet* 1979; i: 1268–70.
9. Paganelli R, Levinsky RJ, Brostoff J, Carini C, Wraith DG. Immune complexes containing food proteins in normal and atopic subjects. *Lancet* 1979; i: 1270–72.
10. Little CH, Stewart AG, Fennessy M. Platelet serotonin release in rheumatoid arthritis: A study of food-intolerant patients. *Lancet* 1983; ii: 297–99.
11. Joseph M, Auriault C, Capron A, Voring H, Viens P. A new function for platelets: IgE dependent killing of schistosomes. *Nature* 1983; **303:** 810.
12. Couch JR, Hassenein RS. Platelet aggregability in migraine. *Neurology* 1977; **27:** 643.