Fortnightly Review

Diagnosis and management of migraine

Peter J Goadsby, Jes Olesen

Our understanding of the pathophysiology of migraine and of the pharmacology of the receptor systems involved in its management has improved at many levels in recent years. The classification and diagnostic criteria for headache disorders published by the International Headache Society in 1988[1] permitted a systematic approach to studying the impact of the headache disorders for the first time (table 1). The economic impact of the disease has been clarified[2] as the prevalence of migraine has become more completely characterised.[3] Migraine is common; if it is not diagnosed regularly in general practice it is being missed. To treat migraine adequately it is necessary to make the correct diagnosis and enlist the patient's cooperation by careful explanation of the options available. Treatment should be customised for each patient, based on the patient's needs and on information about the frequency and severity of attacks. Elimination of precipitating factors or triggers may be helpful but is often insufficient. Several drugs and non-pharmacological treatments are available to treat migraine.

Summary points

- Before a primary headache such as migraine is diagnosed, secondary headaches should be considered and eliminated on clinical grounds or by appropriate investigations
- Migraine is primarily diagnosed by eliciting a history of episodic headache with characteristic associated features. The use of diagnostic headache diaries and simple calendars is strongly encouraged
- Optimum treatment of migraine requires explaining the problem to the patient and identifying and avoiding precipitating factors
- Treatment may be non-pharmacological or pharmacological. Drugs may be for treating acute attacks, which is required by nearly all patients, or prophylaxis, which is used by patients with frequent severe attacks
- Treatment for an acute attack should result in mild or no headache by two hours after drug ingestion, while prophylactic treatment should result in a 50% reduction in the frequency of attacks
- Characterisation of the 5-hydroxytryptamine receptor of the 5-HT_1 class has provided better treatments for acute attack and impetus for studying mechanism of migraine

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Diagnosis of migraine

DISTINGUISHING PRIMARY AND SECONDARY HEADACHE

Diagnosing the cause of headache in general practice is a daunting task given the myriad of clinical problems that are seen daily. Indeed, you can never be completely confident or complacent about the clinical process. There are, however, some guiding principles that allow safe, accurate, and rapid diagnosis of headache problems.

The first decision to be reached is whether a headache is primary or secondary. Table 1 lists the common causes of secondary headache, and their diagnosis requires some details of the history of the condition (see box 1). Perhaps the most useful question that can be asked is how long a patient has had headache. A long history requires time to sift through the details, while a short accelerating history demands action. Features such as development of new headache, change in character, substantial increase in frequency or severity, and associated fever or neurological symptoms (including weakness, clumsiness, disturbance of balance, and altered cognitive function) all direct the doctor to seek a cause. This should first be done by careful physical examination for signs such as papilloedema, diplopia, facial weakness, incoordination or weakness of limbs, disturbances of gait, and fever and other signs of systemic illness.

A suspicion of secondary headache must be pursued by appropriate investigations such as blood biochemistry, blood count (including an erythrocyte sedimentation rate in patients aged over 50, in whom the possibility of giant cell arteritis must never be overlooked), and brain imaging by computed tomography. For patients with a clear history of migraine and normal findings from neurological examination, computed tomography has an extremely low yield,

Table 1—*Clinical classification of headache and prevalence of different types in the population (modified from Rassmussen 1995[3])*

Primary headache		Secondary headache	
Type	**Prevalence (%)**	**Type**	**Prevalence (%)**
Migraine	16	Systemic infection	63
Tension-type headache	69	Head injury	4
Cluster headache	0·1	Drug induced headache	3
Idiopathic stabbing headache	2	Subarachnoid headache	<1
Exertional headache	1	Vascular disorders	1
		Brain tumour	0·1

Box 1: Features of patient's history used to define type of headache

- Length of history of headache
- Frequency of attacks
- Length of attacks
- Associated features
  - Nausea
  - Photophobia
  - Phonophobia
  - Fever
  - Altered consciousness
- Exacerbating features
- Relieving features
- Premonitory features
- Prodromal symptoms
- Family history

with about 0·4% of patients having some type of lesion.[4]

MIGRAINE

The biggest obstacle to managing primary headache, and perhaps migraine more than any other, is correct diagnosis. The lack of a classification system and diagnostic tests has hampered doctors for many years. The International Headache Society's classification system for headache published in 1988 listed operational diagnostic criteria for migraine.[1] These were designed primarily for research and teaching. They are not a substitute for a thorough clinical review, but they provide a useful starting point.

The criteria identify migraine by its characteristics (see box 2), which is only to say that migraine is a symptom complex or syndrome that manifests as discrete episodes of headache with associated features that may all be characterised broadly as a sensory sensitivity. Migraine is no one thing in the clinical sense—it is headache plus other features—whereas tension-type headache is just headache. Migraine sufferers typically have unilateral headache (but it may be bilateral) and complain of throbbing headache (but equally it may be constant). They usually have some degree of nausea and often have sensitivity to light (photophobia) or sound (phonophobia). They often find normal physical activity that involves movement of the head aggravates the pain. However, human biology knows few rules that do not have exceptions, and many patients will not have all the features of migraine listed in box 2.

Box 2: Diagnostic criteria for migraine without aura

- Migraine without aura
- Attacks lasting 4-72 hours†
- At least two of:
  - Unilateral
  - Pulsating
  - Moderate to severe
  - Aggravated by movement
- At least one of:
  - Nausea
  - Photophobia
  - Phonophobia

†To fulfil criteria of International Headache Society, patient must have had at least five such attacks and have no other medical problem[1]

The system outlined is conservative, so that patients who fall outside the criteria clearly can still have migraine. Thus, the diagnostic criteria are highly specific but rather less sensitive. A safe general rule is that if you are trying to decide between migraine and tension-type headache and the patient has any features suggestive of sensory sensitivity (such as nausea, photophobia, phonophobia, or sensitivity to movement), then little is lost by diagnosing migraine and treating accordingly. It should also be noted that few patients will consult their doctor for episodic tension-type headache that can be controlled with simple analgesics, so that the act of consultation should prompt careful questioning for migrainous features. Another point in this regard is the misdiagnosis of what has been termed stress headache. This is a meaningless term. Stress can trigger any type of headache (fig 1) and must not by itself be used to reach a diagnosis of tension-type headache.[3,5] If the clinical diagnosis is in doubt, quantification and description of the problem by means of a headache diary, which the patient may keep for one to three months, will often help to clarify the clinical syndrome.[6,7] Patients with headache may not fit neatly into a particular clinical syndrome but can almost always be accommodated by a wider diagnostic category if you listen to their whole history.

Non-pharmacological treatment of migraine

Non-pharmacological treatment and the avoidance of any identified trigger factors is the simplest approach, but this is often not possible or feasible. Migraine sufferers have an inherited tendency or predisposition to attacks, which unfortunately may be triggered by many things. These trigger factors have recently been evaluated in a large clinical cohort and are consistent in many populations. They include stress, the menstrual cycle, certain foods, trauma, and caffeine withdrawal. If there is a reproducible trigger than its elimination will reduce the frequency of headaches. Unfortunately, this is often not possible, usually because of the lack of a single reproducible trigger. Patients should be encouraged to consider or record possible trigger factors but should not be rebuked when they are lacking. With regard to finding dietary triggers, management of the diet can be a singularly disappointing exercise that often yields little.

Many non-pharmacological treatments have been suggested for migraine patients, including relaxation exercises, biofeedback, massage, acupuncture, chiropractic, osteopathy, and naturopathy. It is fair to say, however, that methods such as chiropractic, osteopathy, and naturopathy have never been studied in any controlled trials with the exception of feverfew. The distinction must also be made between a treatment, such as reducing the trigger of stress, and a cure, which would in essence mean gene therapy and which is not possible. It is difficult to form a sensible conclusion about the place of many of these treatments, and it remains for their practitioners to submit their methods to rigorous analysis. At present, doctors still often have to turn to drug treatment in order to control individual attacks or to prevent them.

Drug treatment of migraine

PREVENTIVE TREATMENT

There have been small but important improvements in preventive treatment in recent years. The aim of treatment is to reduce the frequency and severity of attacks while keeping side effects to a minimum. Preventive treatment is indicated only for patients who have sufficiently frequent attacks that are not relieved by treatments for acute attacks.

Box 3 shows the drugs used in preventive treatment. Since no one drug is clearly superior when its potential side effects are also considered, choosing the most suitable treatment is often a case of selecting from the major drugs on the basis of their side effects. Perhaps the safest effective drugs are pizotifen, propranolol, and valproate. These have been widely used in migraine prophylaxis, and their efficacy and side effects are well known. A reasonable practice is to describe the side

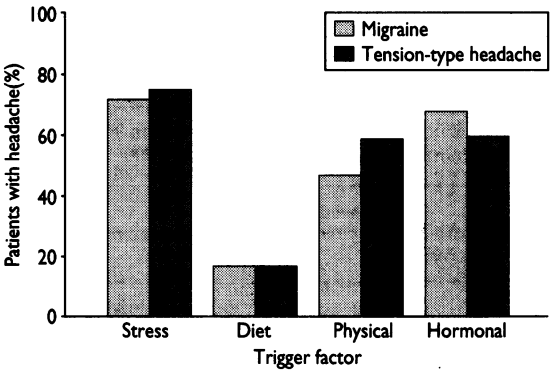

Fig 1—*Relative importance of different trigger factors for migraine and tension-type headache. (Based on data from Scharff et al 1995[5])*

Box 3: Drugs used for prophylactic treatment of migraine

- Pizotifen
- β Blockers such as propranolol
- Valproate
- Tricyclic antidepressants such as amitriptyline or dothiepin
- Methylsergide
- Flunarizine

Note that drug formulations vary by country

effect profile of each drug to patients and to ask which one they would prefer. With the exception of asthmatic patients, who are not offered propranolol but who may tolerate a more cardioselective β blocker such as metoprolol or atenolol, the choice usually comes down to the risk of weight gain and sedation with pizotifen, and similar side effects plus the need for blood tests with valproate, versus impaired exercise tolerance with a β blocker.

Pizotifen is a 5-hydroxytryptamine antagonist, and propranolol, which is a β adrenoceptor antagonist, also has some antagonist properties at some subclasses of 5-HT_2 receptors. Valproate has recently been shown to be of clear benefit in preventing migraine.[8,9] It has several pharmacological actions—enhancing transmission along inhibitory neural pathways that are mediated by γ-aminobutyric acid and actions at some voltage sensitive calcium and sodium channels—and supports the view that migraine may be a disorder of channels involving one of these types of neural pathways. It is an excellent first line choice, so long as women of child bearing age are warned of the risks of teratogenicity. Another popular choice is a tricyclic antidepressant such as dothiepin or amitriptyline, particularly if headaches are frequent. Perhaps the most unfortunate aspect of these drugs is their name: they do not act in preventing headaches by simply affecting a patient's mood, and the view of a migraineur as a sad person in need of simple encouragement alone has no place in modern neurobiologically based management of migraine.

Among the other commonly used prophylactic drugs, methysergide—which acts at a number of 5-hydroxytryptamine receptors—is a highly effective drug that is underused because of the well known side effect of retroperitoneal fibrosis that may occur with persistent use of high doses.

TREATMENT OF ACUTE ATTACKS

The treatment of an acute attack of migraine can be conveniently divided into non-specific and specific treatments. This division suggests that some (specific) antimigraine drugs can arrest the migrainous process without having a direct analgesic action while others (non-specific) cover up the symptoms with an action that includes analgesia. Such a division is somewhat arbitrary but serves to highlight the mechanisms of treatment as they are currently understood. Box 4 shows the suggested categories for the commonly used drugs.

Non-specific treatment

This consists of analgesic and anti-inflammatory drugs. Anti-inflammatory drugs may have a particularly important role in treating migraine if sterile perivascular inflammatory responses do play a part in acute attacks of migraine, although clinical evidence for this theory is lacking and the drugs certainly have analgesic properties. Drugs such as aspirin or paracetamol—long used with metoclopramide to aid absorption and reduce nausea—still have a place in treating in relatively mild migraine attacks.[10] They have the virtue of being simple, safe, and well tried. The key to success is to use them as early as possible in an attack at an effective dose (such as 900 mg of aspirin) and to add an antiemetic such as domperidone or metoclopramide if any symptoms of nausea arise. Another useful anti-inflammatory drug is naproxen, which should be taken at the start of headache with or without metoclopramide. Naproxen has the advantage of being available in suppository form, bypassing the gastric route if there is nausea and vomiting and greatly increasing efficacy. However, a substantial number of patients given this form of naproxen report a burning sensation in the rectum, which limits this route of administration. Unfortunately, a proportion of migraineurs also suffer altered bowel habit, particularly diarrhoea, during and just before a headache, which also lessens the usefulness of suppositories.

Narcotics such as codeine, pethidine, and morphine are probably the worst choice of analgesic, particularly if headaches are frequent. They are short acting and so may lose effect during an attack, allowing the headache to return and requiring the patient to take a second dose. It is now widely recognised that analgesics, especially though not exclusively those with codeine, can promote headache, and the resulting analgesic overuse headache can be extremely difficult to manage.[11] The use of stronger centrally acting opiates such as pethidine (meperidine) and morphine carries risk and is relatively contraindicated.[12] Any patient with particularly frequent headaches should have a careful history of analgesic intake and should keep a record of use so that any escalation can be detected early. The problem is readily recognised when a patient escalates from over the counter drugs to prescription only analgesics. This should alert the patient's general practitioner to the need for prompt consideration of alternative management strategies, particularly specialist referral.

Specific antimigraine treatment

These compounds are used specifically to stop an acute attack of migraine but have no analgesic properties themselves. There are broadly two classes—ergotamine, and its related compounds, and agonists of 5-HT_{1B} and 5-HT_{1D} receptors, of which sumatriptan

Box 4: Drugs used for treatment of acute attacks of migraine

Drug type	Route of administration
*Non-specific drugs**	
• Analgesic drugs	
Paracetamol	Oral
Codeine phosphate	Oral, intramuscular
Pethidine	Intramuscular
• Anti-inflammatory drugs	
Aspirin	Oral, intravenous
Ibuprofen	Oral
Diclofenac	Oral, intramuscular
Naproxen	Oral, rectal
Ketorolac	Intramuscular
• Mixed	
Chlorpromazine	Intramuscular
Specific drugs	
• Ergotamine	Oral, rectal, aerosol inhaler
• Dihydroergotamine	Intramuscular, nasal spray
• Sumatriptan	Oral, subcutaneous, nasal spray

*With or without metoclopramide or domperidone
Note that drug formulations vary by country

is the only currently registered compound. The use of sumatriptan in treating migraine and cluster headache has provoked enormous pharmacological interest, and several other compounds are in development, including alniditan, eletriptan (UK 116044), zolmitriptan (311C90), rizatriptan (MK462), and avitriptan (BMS 180048).

Sumatriptan quickly and reliably relieves acute attacks of migraine in a half to two thirds of patients when it is given orally. Subcutaneous administration of 6 mg sumatriptan improves 88% of migraine attacks.[13] It is effective in migraine with or without aura, and its effect seems unrelated to the time of administration. It is remarkably quick acting, usually within minutes for parenteral administration. Orally administered sumatriptan performed much better than placebo in a double blind, placebo controlled crossover study[14] and in large studies conducted in parallel groups.[15] Doses of 50 mg and 100 mg are available in Britain, while 25 mg tablets are available in some other countries such as the United States. Since available data do not show significant differences in the effect of different doses patients should receive the lowest possible oral dose, with higher oral doses and the subcutaneous formulation being reserved for resistant cases. In responders the headache settles in 30 minutes or so, with only a small proportion of sufferers requiring an additional tablet early on in the attack. In about a third to a half of patients the headache will return within 24 hours but is almost always responsive to a second tablet.

Mechanism of action

While there is little doubt that agonists of 5-HT_1 receptors are useful in treating acute attacks of migraine, there is considerable controversy about the mechanism of that action.[16] For many years the vascular hypothesis held that migraine was primarily a disease of the cranial blood vessels or in some way due to abnormal opening of arteriovenous shunts in the cranial circulation. Emerging information on the trigeminal innervation of the cranial circulation and the observation of a spreading oligaemia in the aura phase of migraine[17] have led to a complete re-evaluation and the development of a neural hypothesis for migraine.

The pain sensitive innervation of intracranial structures arises from the first division of the trigeminal nerve, the ophthalmic branch. The neurones of the trigeminal ganglion are bipolar and transmit nociceptive signals to the trigeminal nucleus in its most caudal extent in the caudal medulla and its extension into the C1 and C2 spinal cord in the dorsal horn. From this synapse the quintothalamic tract transmits impulses to the thalamus into the ventroposteromedial nucleus, which are then relayed to cortex.[18] It is clear that stimulation of the trigeminal ganglion in humans, cats, and rats can release the powerful vasodilator neuropeptide calcitonin gene related peptide. This peptide is located in the trigeminal neurones that innervate the cranial circulation, and its concentration in the cranial circulation is elevated during acute attacks of headache in humans. Furthermore, release of calcitonin gene related peptide can be blocked both in animal models and in migraine sufferers by administration of sumatriptan.[19] Since sumatriptan does not seem to inhibit neurones in the trigeminal nucleus unless the blood-brain barrier is disrupted, it is most likely that its primary action is as a presynaptic blocker of the trigeminal nerve ending.

Moskowitz has suggested that the pain of migraine is due to a sterile inflammation in the aura mater mediated by the release of calcitonin gene related peptide described above.[20] Both sumatriptan and dihydroergotamine block this neurogenic extravasation of plasma but do not affect extravasation of plasma

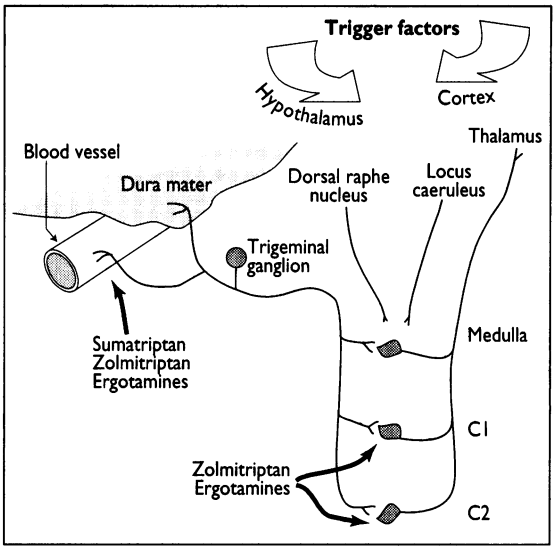

Fig 2—*Schematic drawing of neurobiology of migraine. Migraine is probably triggered through hypothalamic or cortical mechanisms. Trigeminal innervation of pain sensitive intracranial structures, aura mater, and blood vessels provides pain input through trigeminal ganglion to trigeminal nucleus. The nucleus extends from medulla to C2 (accounting for commonly reported neck pain with migraine) and sends fibres to thalamus. 5-Hydroxytryptamine receptors on blood vessel (5-HT_{1B}) and neurone (5-HT_{1D}) mediate vasoconstriction and presynaptic inhibition, thus antagonising vasodilator effects of calcitonin gene related peptide. Peripheral transmission is blocked by sumatriptan and ergotamine, while central transmission is also blocked by zolmitriptan*

mediated by substance P or neurokinin A, suggesting that the vascular action of sumatriptan as a selective carotid vasoconstrictor is not necessary for its anti-inflammatory effect.[20] However, there is no clear clinical evidence to support the theory of a sterile inflammation in migraine. Notwithstanding the presence or absence of sterile inflammation, the bulk of evidence seems to indicate that the pivotal role of sumatriptan in ameliorating acute attacks of migraine is its inhibition of trigeminal neuronal firing through activation of a 5-HT_{1D} presynaptic autoreceptor (fig 2). Recent molecular biological studies suggest that the vascular 5-HT_{1B} receptor is different to the neuronal presynaptic receptor, leading to the possibility that drugs may become available that can differentially affect these mechanisms and thus determine if one or both are needed to stop a migraine attack. Moreover, since the trigeminal system has bipolar neurones, the terminals in the trigeminal nucleus are possible targets for treatment and their activity can be inhibited by dihydroergotamine and zolmitriptan (311C90).

Conclusion

The development of new compounds active in neurological disorders provides clues to both the pathophysiology of the clinical problems and more satisfying practice. Several new compounds targeting 5-hydroxytryptamine, neuropeptide, and other receptors are under examination. The changes in treating acute attacks of migraine have produced better understanding and classification of the pharmacology of 5-hydroxytryptamine and provide impetus for improving the classification of headache.

1 Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8(suppl 7):1-96.
2 Cull RE, Wells NEJ, Miocevich ML. The economic cost of migraine. *British Journal of Medical Economics* 1992;2:103-15.
3 Rassmussen BK. Epidemiology of headache. *Cephalalgia* 1995;15:45-68.
4 Quality Standards Subcommittee of the American Academy of Neurology.

The utility of neuroimaging in the evaluation of headache patients with normal neurologic examinations. *Neurology* 1994;44:1353-4.
5 Scharff L, Turk DC, Marcus DA. Triggers of headache episodes and coping responses of headache diagnostic groups. *Headache* 1995;35:397-403.
6 Russell MB, Rassmussen BK, Brennum J, Iversen HK, Jensen RA, Olesen J. Presentation of a new instrument: the diagnostic headache diary. *Cephalalgia* 1992;12:369-74.
7 Russell MB, Iversen HK, Olesen J. Improved description of the migraine aura by a diagnostic aura diary. *Cephalalgia* 1994;14:107-17.
8 Hering R, Keritsky A. Sodium valproate in the prophylactic treatment of migraine: a double blind study versus placebo. *Cephalalgia* 1992;12:81-4.
9 Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple blind, placebo-controlled crossover study. *Neurology* 1994;44:647-51.
10 Tfelt-Hansen P, Henry P, Mulder LJ, Scheldewaert RG, Schoenen J, Chazot G. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared to oral sumatriptan for migraine. *Lancet* 1995; 346:923-6.
11 Olesen J. Analgesic headache. A common, treatable condition that deserves more attention. *BMJ* 1995;310:479-80.
12 Langemark M, Olesen J. Drug abuse in migraine patients. *Pain* 1984;19:81-6.
13 Ferrari MD. Treatment of migraine attacks with sumatriptan. *N Engl J Med* 1991;325:316-21.
14 Goadsby PJ, Zagami AS, Donnan GA, Symington G, Anthony M, Bladin PF, *et al.* A double blind placebo controlled crossover study of sumatriptan in the treatment of acute migraine attacks. *Lancet* 1991;ii:782-3.
15 Oral Sumatriptan Dose-Defining Study Group. Sumatriptan—an oral dose-defining study. *Eur Neurol* 1991;31:300-5.
16 Humphrey PPA, Goadsby PJ. Controversies in headache. The mode of action of sumatriptan is vascular? A debate. *Cephalalgia* 1994;14:401-10.
17 Olesen J. Cerebral and extracranial circulatory disturbances in migraine: athophysiological implications. *Cerebrovasc Brain Metab Rev* 1991;3:1-28.
18 Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. *Headache* 1991;31:365-71.
19 Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterising cerebrovascular and neuropeptide changes seen in man and cat. *Ann Neurol* 1993;33:48-56.
20 Moskowitz MA, Cutrer FM. Sumatriptan: a receptor-targeted treatment for migraine. *Annu Rev Med* 1993;44:145-54.

Intersalt: hypertension rise with age revisited

Richard L Hanneman

This article comes from the Salt Institute, the trade organisation of salt producers. It is a reanalysis of some of the data of the Intersalt study published in the BMJ in 1988. A much larger reanalysis of the study by the original authors is published on p 1249. We have published this paper from the Salt Institute because it is an interesting example of how special interest groups use data to advance their position. The paper is followed by highly critical commentaries from Malcolm Law, an epidemiologist who was not part of the Intersalt team, and by the authors of the Intersalt study. An editorial by Thelle reviews the current evidence on salt and health, while Godlee looks at the politics of the food industry and health promotion and Delamothe examines who owns data produced from large trials.

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The 30 July 1988 issue of the *BMJ* contained the primary publication of the Intersalt study, as well as an editorial by Professor John Swales that provided important notes of caution about the interpretation of the findings in terms of salt's role in the aetiology of high blood pressure.[1,2] Intersalt was an important epidemiological investigation of the relation of sodium intake, as reflected by urinary sodium excretion and blood pressure. As stated in the article's abstract, Intersalt could not identify an association between urinary sodium excretion and either mean blood pressure or the prevalence of hypertension. These two conclusions were strong evidence that, in contrast to widely held earlier beliefs, salt consumption was not predictive of increased blood pressure world wide.

The Intersalt investigators went on to conclude that urinary sodium excretion was predictive of the rate of rise in blood pressure with increasing age. This conclusion was based on 52 individual regression analyses determining the slope of the relation between the increase in blood pressure per year and urinary sodium excretion. The authors calculated that 100 mmol/day higher sodium intake would account for a 9 mm Hg increase in blood pressure within the age range of the study. As the primary Intersalt hypotheses were largely negative, such a strong relation between salt intake and the increase of blood pressure with advancing age seems surprising.

Intersalt was a cross sectional study and not a longitudinal, prospective assessment of this issue. Only the latter approach would have properly addressed this third conclusion. Nevertheless, this third conclusion has been widely popularised as compelling evidence that a restriction in dietary sodium chloride intake is justified. Government agencies and panels in the United Kingdom, the United States, and other countries have cited this Intersalt conclusion as paramount evidence for the argument that, were a society to lower its salt intake, blood pressure and hypertensive heart disease would decrease. In the United States, this conclusion has been cited repeatedly as the scientific cornerstone for the new food labels and health claims covered by the Nutrition Labeling and Education Act.

Critics have expressed concerns about the presentation of the Intersalt data, as to whether all the information necessary to properly interpret the findings was disclosed. One such concern, which was evident at the time of publication, was whether the slopes of blood pressure with age had been adjusted for the blood pressure intercepts in each of the 52 individual regression equations. If centres with a high salt intake had lower blood pressures than centres with lower salt intakes at age 20 years, the steepness of slope would be primarily a function of the initial blood pressure rather than a function of salt intake. If the regression equations are arbitrarily constructed with an intercept of zero, such an effect would be masked. It would be important to disclose such a finding to readers.

The original Intersalt publication did not report the intercept and the R^2 value (as a measure of goodness of fit) for the individual centres' regression equations relating the change in blood pressure with age. Both of these factors are essential to answering the question posed above—whether slope depends primarily on initial blood pressure rather than salt intake—and in deciding whether these 52 slopes should be pooled together and treated as equally significant, but the Intersalt investigators were not willing to disclose these values.

Through a lengthy process involving negotiations between lawyers for the Salt Institute and legal counsel representing the Intersalt colleagues, we obtained sufficient additional data from Intersalt to assess whether the postulate outlined above was true. Our analysis of the data (fig 1) shows the significant inverse relation between the initial systolic blood pressure (as predicted from the regressions) and the slope for increasing systolic blood pressure with age. High salt consumers from Portugal and China, for example, had among the highest slopes, while the Yanomamos from Brazil and Papuans from New Guinea had the lowest slope values. However, the high salt centres also had

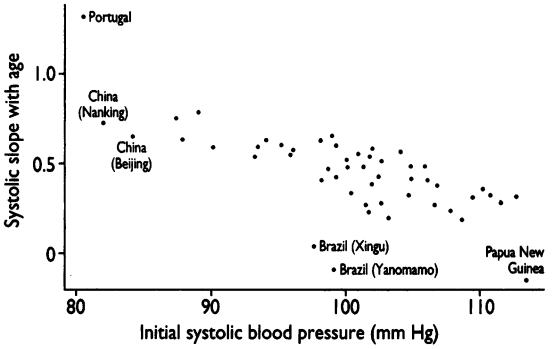

Fig 1—*Relation of initial systolic blood pressure (estimated from regression) and slope of increasing systolic blood pressure with age; $R^2=0.474$, $P<0.05$*