- The utility of neuroimaging in the evaluation of headache patients with normal neurologic examinations. *Neurology* 1994;44:1353-4.
- 5 Scharf 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.

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; $R^2=0.474$, $P<0.05$

Salt Institute, 700 North Fairfax Street, Alexandria, VA 22314-2040, USA
Richard L Hanneman, president

BMJ 1996;312:1283-7

among the lowest initial systolic blood pressures, while the low salt centres had much higher values.

Figure 2 shows the significant inverse relation between initial systolic blood pressure (the intercept) and urinary sodium excretion. Our analysis of the data suggests that the higher a society's initial urinary sodium excretion, the lower its mean systolic blood pressure. These important data were not provided in the original Intersalt paper.

If the slope of the relation of blood pressure to urinary sodium excretion is properly adjusted for the intercept, we believe the data show no significant relation between urinary sodium excretion and the rate of increase in blood pressure with age. Our analysis of these data is reflected in figure 3. When the 48 acculturated centres are considered, the relation is flat;

Fig 2—Relation of urinary sodium and initial systolic blood pressure, excluding four low salt centres (Kenya, Papua New Guinea, and Brazil (Xingu and Yanomamo)); $R^2=0.117$, $P<0.05$

Fig 3—Relation of urinary sodium and intercept adjusted slope of systolic blood pressure with increasing age. Dotted line indicates fit for all centres; solid line indicates fit without labelled centres

Fig 4—Relation of slope of systolic blood pressure with increasing age and R^2 value; $R^2=0.856$, $P<0.05$

when all 52 centres are included, the regression slopes non-significantly upward.

We have also calculated the R^2 value for each of the 52 centres. Figure 4 illustrates the relation between the R^2 value and the slope for increasing systolic blood pressure with age. This highly significant direct relation shows that three of the four low salt centres had R^2 values of zero with slopes below the zero line. This finding implies a threshold for slope, below which R^2 is independent of slope. For the low salt centres, the relation between blood pressure and age breaks down, but these are the centres that are the most influential in determining the relation between slope and urinary sodium excretion. As the Intersalt investigators appreciated, these four centres appear as a subset that deserves special and separate consideration from the rest of the centres.

We realised the importance of what was uncovered once we had access to these "new" data. Their interpretation is critical to both high blood pressure research and public policy. Our analysis of these data also suggests that both public policy and scientific judgments based on the original Intersalt report must be reassessed. Furthermore, our experience underscores the fact that the entire Intersalt database, including the data provided to us, must be made available in its entirety to independent third parties for a thorough re-evaluation. We believe the scientific community, including the governments which supported Intersalt and relied on its findings to set public policy and law, should accept nothing less.

- 1 Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium. *BMJ* 1988;297:319-28.
- 2 Swales JD. Salt saga continued. *BMJ* 1989;297:307-8.

(Accepted 12 February 1996)

Commentary: Evidence on salt is consistent

Malcolm Law

A rise in blood pressure is not an inevitable consequence of aging. In some societies blood pressure remains at about 110/70 mm Hg throughout life.^{1,2} Dietary salt, low dietary potassium, alcohol, and body weight contribute to the increase in blood pressure with age in Western countries. The Intersalt study quantifies the effect of each of these factors while allowing for the others.¹

The new Intersalt paper is a valuable addition to the evidence on salt and blood pressure.³ In the original Intersalt paper the different analyses on sodium and blood pressure varied, some suggesting a strong association, others a weaker one.¹ Now the position has been

clarified; all the Intersalt analyses confirm salt as an important determinant of blood pressure. The average increase in blood pressure with age (from 25 to 55 years) was greater in centres with higher sodium intake, by 10 mm Hg systolic for a 100 mmol/day higher sodium.^{1,3} More directly, median blood pressure increased with median sodium intake across the 52 centres.^{1,3} Because these two analyses could have been disproportionately affected by the four centres with very low sodium intake, subset analyses omitting the four were done. This made virtually no difference to the result of the first analysis; the second was consistent with the original result, although not