

Intersalt data

We received many letters commenting on the cluster of papers on salt that we published in May last year. We had several problems with the letters but have now resolved these and are publishing the letters now. These 10 letters and three others are available on the BMJ's website (www.bmj.com).

Cross cultural studies such as Intersalt study cannot be used to infer causality

EDITOR—The practical issue of whether moderate dietary salt restriction can lower blood pressure was resolved in the classic Glynccorwg community study in south Wales, which found it to be ineffective.¹ Clearly then the claims of the Intersalt investigators that their findings support “the reduction of salt intake to control adverse blood pressure levels” must be wrong—and the reasons are not hard to find.²

Firstly, cross cultural studies such as the Intersalt study cannot be used to infer causality as they are based on the false assumption that the populations of diverse societies—irrespective of their genetic and cultural composition—have the same susceptibility to environmental factors. Indeed, it is this very difference in susceptibility that explains why it is not possible to show a cross cultural correlation between smoking and lung cancer. For both the countries of northern Europe and of the Mediterranean there is a clear dose-response relation (confirming causality), but the adverse effects of smoking are much more pronounced in the countries of northern Europe.³

The multiplicity of confounding variables in cross cultural studies makes it almost inevitable that these studies will fail to reflect genuine cause and effect relations (such as smoking and lung cancer), while the associations they do identify are likely to be spurious. Hence the only epidemiological method for determining whether salt intake is implicated in raised blood pressure is to use within population studies, in which the problem of differing susceptibilities does not arise. Here the results of the Intersalt study are both trivial and contradictory: a fall of 1 mm Hg in diastolic pressure for every extra 100 mmol sodium excretion in 24 hours for men and women between the ages of 20 and 39, and a change of similar magnitude but in the reverse direction for those between the ages of 40 and 59.

This leaves only the clinical studies of the effects of salt reduction on blood pressure to be considered. Malcolm Law's assertion, in his commentary, that these studies show that “dietary salt intake is a serious health hazard” is based on a

reference to his own meta-analysis,⁴ whose methods, he fails to point out, have been subjected to critical scrutiny and conclusions rejected.⁵

The important question that emerges from these papers is why the combined intellects of so many distinguished epidemiologists should maintain that the evidence incriminating salt in hypertension is so convincing when clearly it adds up to very little. Readers of the *BMJ* may rightly wonder how many of the other epidemiological discoveries of recent years linking diet with disease are similarly insecure.

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- 2 Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, et al for the Intersalt Cooperative Research Group. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ* 1996;312:1249-53.
- 3 Keys A. *Seven countries: a multivariate analysis of death and coronary heart disease*. Cambridge, MA: Harvard University Press, 1980.
- 4 Hanneman RL. Intersalt: hypertension rise with age revisited. [With commentaries by M Law and J Stamler et al.] *BMJ* 1996;312:1283-7.
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Data linking sodium intake to subsequent morbid and fatal outcomes must be studied

EDITOR—Papers and editorials in the issue of 18 May 1996 addressed the relation of dietary sodium intake and blood pressure. The heart of the matter is whether a low sodium diet reduces blood pressure in populations. The *BMJ* printed a more and *JAMA* a less enthusiastic view of the magnitude of this relation.¹ Several commentators in the *BMJ* then made the unjustified leap of converting what is a scientific controversy about a physiological mechanism into a public health issue.

Public health recommendations must be based on proof of safety and benefit. Even if a low sodium diet could lower the blood pressure of most people (probably not true) and both the diet and the change in blood pressure could be sustained (not established), this alone would not justify a recommendation to reduce sodium intake.

For such advice to be responsibly given there must be evidence that the change will improve and not impair health. While the advantage of a lower blood pressure, at any level, is well established,² it is not true that every method to lower blood pressure would necessarily improve health. Some techniques to lower blood pressure, like giving short acting calcium antagonists,³ may not be safe.

All interventions aimed at enhancing or extending life by manipulating a single mechanism inevitably produce a variety of effects, some of which may not be advantageous. Extrapolation from mechanistic thinking demands evidence that the sum total of all the effects of the intervention—and not just one, such as lowering blood pressure—will help and not harm; and particularly here since the target is the whole population.

A low sodium intake produces many effects, not all of which are salutary.⁴ The integrated impact of these effects remains to be established. The scanty evidence directly linking sodium intake to morbidity and mortality is not encouraging.⁵

Unfortunately, we simply do not know whether a universal change in sodium consumption will cause benefit or harm. Insufficient evidence—for good or ill—is not

Advice to authors

We receive more letters than we can publish: we can currently accept only about one third. We prefer short letters that relate to articles published within the past four weeks. We also publish some “out of the blue” letters, which usually relate to matters of public policy.

When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the *BMJ* article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters, whether typed or sent by email, should give each author's current appointment and full address. Letters sent by email should give a telephone and fax number when possible. We encourage you to declare any conflict of interest. Please send a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

We may post some letters submitted to us on the world wide web before we decide on publication in the paper version. We will assume that correspondents consent to this unless they specifically say no.

Letters will be edited and may be shortened.

a sturdy basis for making health policy. Gratuitous exhortation, reflecting the hopes of even the most well meaning authorities, is no substitute for data. Toward this end, a good start would be to collect and analyse further observational data linking sodium intake to subsequent morbid and fatal outcomes.

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- 1 Midagley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure. *JAMA* 1996;275:1590-7.
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Conclusions drawn in paper "revisiting" Intersalt data are of questionable validity

EDITOR—Despite editorial assertions to the contrary,¹ the conclusions drawn in the paper by Paul Elliott and colleagues "revisiting" the data from the Intersalt study are of questionable validity.² The original report showed that 24 hour urinary sodium excretion was not significantly related to the prevalence of hypertension.³ This second reanalysis depends on two statistical manoeuvres to draw the opposite conclusion. The first manoeuvre is to correct for regression dilution bias. The authors have assumed that the differences between true mean blood pressures and the measured blood pressures were greater than those allowed for in the first analysis. Since they have no means of knowing what the true blood pressures were at the time of the Intersalt measurements, there is no valid basis for their assumption.

Secondly, the effect of body mass index is removed from the multiple regression analysis. This was not an allowance for an assumed error but the withholding of an accurately measured variable which in the original report showed a strong and significant independent relation with blood pressure. The reason given for this startling decision is a supposed correlation between body weight and sodium excretion. There surely is no logical basis for believing that fat people eat more salt than thin people, and the exclusion of body mass index from the multiple regression analysis is without justification. Without all this statistical prestidigitation, the third visit to the Intersalt study still does not stand up.

As an ad hoc adviser to several food manufacturing interests, including some that add salt to their products, I take exception to the suggestion that my views are necessarily

more "commercial" than those of the academics. Surely the science speaks for itself.

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Epidemiological studies should be designed to reduce correction needed for measurement error to a minimum

EDITOR—George Davey Smith and Andrew N Phillips's critique¹ of the most recent Intersalt paper,² and the response of the Intersalt investigators in their commentary,¹ raises an important issue. Measurement error can bias estimates of effect in epidemiology, and some correction is needed to remove the bias. The correction made, however, needs careful justification. The main problem relates to the error structure of the two variables one is attempting to associate and the degree of correlation between these measurement errors. The critical issue is the quantitative effect due to correlation between measurement errors.

In the Intersalt study the outcome, blood pressure, is measured at the same time as urinary sodium excretion. Both measures are taken to represent the long term average value for that individual. Both will be measured with considerable error. Correlation between the two errors may not be negligible, due, for example, to parallel seasonal effects. For the interpopulation association, no problem should arise. For the intrapopulation association, however, the correction for measurement error will depend on the between error correlation.

The Intersalt authors assume the correlation to be zero, and because urinary sodium has a large measurement error the correction they make is large. For systolic blood pressure, 1.6 mm Hg/100 μ mol sodium intake/day is "corrected" to 4.3 mm Hg/100 μ mol/day. This value is considered to be consistent with the between population regression coefficient of 7.1. (These values refer to the estimates adjusted for age and sex, over all age groups. Similar consideration would apply to the multivariate estimate.) If the two errors are correlated, however, the correction is overdone. Approximately, for values of the correlation of 0.1, 0.3, and 0.5 the proper corrected values should be 4.0, 3.5, and 2.9 respectively. If one considers a correlation of 0.5—for example, with parallel seasonal effects—to be credible then the agreement claimed by the Intersalt investigators between regression coefficients based on within and between population comparisons is substantially overstated. If one believes a value of 0.1 to be the largest likely to occur

then the Intersalt conclusion is approximately correct. Given the dearth of information on what the correct value is likely to be, the large correction made in the Intersalt study seems to be inadequately justified. More generally,

- corrections for measurement error are not free of assumption
- when the correction is large the assumptions must be clearly stated and evidence presented in their support, perhaps with a sensitivity analysis
- large corrections presented without such supporting evidence are unsound.

Statistical complexity should not be used to conceal inadequacies of the data. Generating accurate quantitative data on the variance-covariance structure of measurement error is difficult. The clear message is that epidemiological studies should be designed to reduce to a minimum the correction needed for measurement error. This can be achieved by improving the measurement instruments, taking repeat measures, and choosing study populations to maximise the between individual variance. None of these are achieved by simply increasing the study size.

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- 1 Davey Smith G, Phillips AN. Inflation in epidemiology: "The proof and measurement of association between two things" revisited. [With commentary by A R Dyer et al.] *BMJ* 1996;312:1659-64.
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Correction for regression dilution bias in Intersalt study was misleading

EDITOR—We were surprised by the response of Alan R Dyer and colleagues in their commentary on our article on correction for regression dilution bias in the Intersalt study.¹ They fail to address the substantive points adequately while restating evidence on the association between dietary salt and blood pressure, which was not the concern of our article.

A random 8% of participants in the Intersalt study had repeat 24 hour urine collections and blood pressure measurements taken on average three weeks after the initial measurement. The repeat 24 hour urine collections were used to estimate the degree to which single 24 hour collections were inadequate indicators of usual sodium excretion. The reliability coefficient calculated from these repeat measures was used to greatly inflate the estimated strength of association between sodium excretion and blood pressure. However, if changes in urinary sodium excretion and blood pressure between the first and the repeat measurements tend to coincide then the association between sodium excretion and blood pressure would not have been underestimated to the degree to which the correction method assumes. We cited papers that show that changes in sodium excretion and blood pressure do indeed coincide, for

measurements taken one to two months apart. As N E Day shows [letter above], if the correlations between changes in sodium excretion and changes in blood pressure are even of moderate strength then the correction method used by the Intersalt team is highly misleading.

Dyer and colleagues state that "to the best of our knowledge, there are no data showing physiological day to day parallel fluctuations of sodium or blood pressure." They miss the point that fluctuations in sodium excretion and blood pressure do not need to coincide on a day to day basis to invalidate their method. If the fluctuations correspond over a three week period, which was the interval in their validation study, then this will render their correction method fallacious. What is most odd about their response is that the Intersalt investigators do indeed have the data that can test this point, as they measured both blood pressure and sodium excretion in their validation study. How can they then state that no such data exist? We ask that they report the correlations between the changes in sodium excretion and the changes in blood pressure over the three week period to allow other investigators to evaluate whether one of the central assumptions of their correction method is met.

The Intersalt investigators seem not to appreciate the difficulties of correcting for measurement imprecision in the presence of confounders. Body mass index is only a proxy for the various aspects of body composition that confound the association between sodium excretion and blood pressure. The mathematical construct of weight divided by the square of height is clearly not a perfect measure of these. The appropriate reliability coefficient is that between body mass index and the relevant aspects of body composition, not between body mass index measured on two occasions. The importance of measurement error in confounders is, fortunately, well recognised by other investigators.²

All of the conclusions of our paper remain unchallenged by the response by Dyer and colleagues; indeed, they are strengthened by the demonstration that a research team that uses these methods to essentially triple the magnitude of their association between sodium excretion and blood pressure does so without a clear appreciation of the implications of these correction methods. The use of epidemiology to inform public health policy would be furthered better by improving study design³ than by using obfuscating and potentially erroneous statistical "corrections," the assumptions of which have not been adequately tested.

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- 1 Davey Smith G, Phillips AN. Inflation in epidemiology: "The proof and measurement of association between two things" revisited. [With commentary by A R Dyer et al] *BMJ* 1996;312:1659-64.
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Slow decremental change in dietary sodium load in whole populations is needed

EDITOR—As authors of papers whose conclusions could be misused by the commercial salt interests,^{1,4} we support the professional consensus in favour of a decremental reduction in dietary sodium load in whole populations everywhere. In our experience, individuals who endured abrupt reductions in sodium load from about 150 mmol to about 60 mmol found their new diet almost intolerable. Our research team and their families shared the experience of our subjects for the first week and agreed with them entirely. An important, though unfortunately unmeasured, consequence was that all subjects added more fat to their food in an attempt to make it taste of something, so that an abrupt reduction in sodium intake can in these circumstances increase rather than reduce overall cardiovascular risk. Doctors who rely on instructing their patients to abjure salt forthwith are careful never to verify compliance by measuring sodium outputs.

Graham A MacGregor and Peter S Sever emphasise the delay of about one month before taste adapts to a new dietary sodium intake, a period that probably varies between individuals.⁵ Given time for this adaptation to take place, large reductions in dietary sodium may not be difficult; without it, a huge range of foods—all soups, breads, and most cheeses, as well as obvious items like Marmite, bacon, and kippers—disappear from one's diet. And when people have adapted and they can no longer stand the taste of what remains "normal" for everyone else, they can no longer find a reasonable choice of prepared foods, eat out in a restaurant, or dine with their friends.

We need a slow, decremental, across the board approach, strictly regulated so that competing food manufacturers don't cheat; successive targets should be based on evidence from continuing market research on how, or even whether, changes are perceived by consumers (nobody seems to have noticed the 20% reduction in sodium in bread). Without regulation, sodium load will continue to rise, as food manufacturers move toward North American levels of taste deception.

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- 1 Watt GCM, Edwards C, Hart JT, Hart M, Walton P, Foy CJW. Dietary sodium restriction for mild hypertension in general practice. *BMJ* 1983;286:432-6.

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Science demands data sharing

EDITOR—Research indicating the influence of dietary salt on blood pressure is convincing.¹ However, the size and scientific methodology of the Intersalt study give particular weight to its conclusions.² That the Salt Institute should put a counter case is not surprising³ since the scientific debate takes place in a market economy.

Accepted scientific practice demands that results should be reproducible by independent scientists. Financial considerations mean that it is not realistic to reproduce data comparable to those of the Intersalt study, but the conflict between the Intersalt Cooperative Research Group and the Salt Institute focuses on the reproducibility and validity of the statistical analysis of the Intersalt data.

While it is reasonable for medical researchers to retain their data until they have published their primary analysis, the Intersalt Steering and Editorial Committee⁴ claims the data as "the confidential property of local investigators" and so forces dissenters into a limited framework of scientific discussion.

Though I would not wish to support the analyses of Richard L Hanneman,⁵ I find I have as many doubts about the statistical analysis of the Intersalt group and the commentaries on Hanneman's analysis.³ Some of my qualms are:

- the criss crossing of population trends mentioned by Hanneman, and described by Malcolm Law in his commentary as "bizarre" and "implausible," is seen to occur if the trend lines are plotted
- the claim by J Stamler and colleagues that the use of the intercept is statistically invalid⁵ is incorrect, and the biological argument used is spurious
- the expected effect of a difference of 100 mmol in 24 hour sodium excretion (for example, 70 v 170 mmol) over an age range of 30 years (for example, 25 v 55) is problematic, since the magnitude of the standard error of this measure depends critically on the end values of the intervals that are chosen
- has the Intersalt group taken into account the possible inhomogeneity of the variances about the regressions? Has the prediction theory been correctly based on the errors in regressor variables model?

For the medical-scientific community to achieve a shared understanding it is necessary that confirmatory secondary analyses be carried out by other researchers. For these reasons, and the powerful ethical

arguments made in Tony Delamothe's editorial,⁴ the sharing of medical research data is long overdue. A good model is provided by the Economic and Social Research Council's data archive, which ensures use only by bona fide researchers and that the primary researchers are appropriately acknowledged.

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- 1 MacGregor GA, Sever PS. Salt—overwhelming evidence but still no action: can a consensus be reached with the food industry? *BMJ* 1996;312:1287-9.
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- 4 Delamothe T. Whose data are they? *BMJ* 1996;312:1541-2.

Reply for Intersalt Steering and Editorial Committee

EDITOR—James Le Fanu selects one trial on salt and blood pressure, ignoring others.¹ He also cites only two (among 36) published Intersalt coefficients for individuals, whereas all 18 coefficients for sodium and systolic pressure and nine for sodium and diastolic pressure are significant.²

Michael Alderman cites a 1996 overview of trials but fails to note (a) its report of significant falls in the systolic pressure of non-hypertensive and hypertensive individuals with reduced sodium intake, (b) several criticisms of this overview, and (c) findings of larger reductions in blood pressure in other overviews.¹ Contrary to what Alderman says, recommendations for moderate salt reduction in populations are studied judgments by expert groups, including two reports that he co-signed. When discussing safety, Alderman cites his two papers but fails to note critiques of them and inability to replicate his findings.^{3,4}

Contrary to Alexander Macnair's comments, the 1988 analysis across 52 Intersalt population samples (prior hypothesis) showed that median urinary sodium excretion was significantly related to hypertension ($P < 0.01$).

N E Day, George Davey Smith and Andrew N Phillips, and we agree that uncorrected coefficients underestimate the size of the association of sodium with blood pressure in individuals. We agree with Day that "corrections for measurement error are not free of assumptions"; hence we presented uncorrected and multivariate corrected estimates with and without body mass index² and gave detailed methods and extensive sensitivity analyses.⁵

Davey Smith and Phillips call for the Intersalt correlations between change in sodium excretion and change in blood pressure for the 8% of people in whom repeat measurements were made. They were 0.15 for systolic pressure and approximately zero for diastolic pressure. These correlations are insufficient to make the corrections Davey Smith and Phillips discuss; estimates of within-person covariance and covariance

reliability between sodium and blood pressure are needed. In the Intersalt study, obtaining such estimates validly was not possible due to 52 small population samples (200 men and women in eight age-sex groups); some extreme differences between first and repeat blood pressures; and a fall in mean blood pressure of 3.3/1.6 mm Hg over the three weeks between measurements,⁵ invalidating the usual assumption of a constant mean.

Other studies tell us whether correlated fluctuations exist over a period of around three weeks. Recent analyses from the trials of hypertension prevention found—as Intersalt assumed—little or no short term covariation of sodium and blood pressure (N Cook, fourth international conference on preventive cardiology, Montreal, 2 July 1997). Such data, casting further doubt on assertions from Davey Smith and Phillips, indicate that the Intersalt corrected estimates—a sodium intake of 100 mmol less/day influences systolic pressure of individuals by -3 to -6 mm Hg and diastolic pressure by 0 to -3 mm Hg—are scientifically sound, although likely still to be underestimates.

In the context of extensive concordant data from all research disciplines supporting the conclusion that high dietary salt intake has an important role in causing population-wide adverse blood pressure levels, the Intersalt data—both cross population and within population—have profound meaning for public policy, as has been widely recognised by unbiased expert groups.

We agree with Graham Watt and Julian Tudor Hart that food manufacturers should gradually reduce salt in their products, with clear food labelling.

A response to Keith Rennolls's letter and an extended version of this letter are available on the *BMJ* website.

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risk factor intervention trial (MRFIT) [abstract]. *Can J Cardiol* 1997;13(suppl B):272B.

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Collaborative efforts must be made to reduce sodium in diet

EDITOR—The article by Richard L Hanneman was entertaining in its demonstration of the lengths to which the food industry, specifically the Salt Institute, will go to obfuscate and confuse the question of salt's relation to blood pressure.¹ The criticisms in the article related to the Intersalt study² have been extensively covered, and it would be redundant to review these again. However, the important and extensive area of evidence from clinical trials has largely been ignored by Hanneman and the Salt Institute.

The Shapiro Center for Evidence-Based Medicine has been working in clinical trials of sodium reduction and blood pressure for 20 years. Earlier trials on sodium reduction combined with other lifestyle changes (weight loss, alcohol reduction) showed the usefulness of sodium reduction in removing and minimising the need for blood pressure drugs in hypertensive patients who had previously been treated for years with such drugs.³ More recently, the centre has conducted double blind crossover trials of sodium supplementation in white and black normotensive subjects, which showed that reducing sodium intake and giving back sodium in levels similar to average daily sodium intake will significantly influence blood pressure.⁴ Other studies have confirmed these results.⁵ Dietary sodium intake is clearly a major determinant of blood pressure based on epidemiological data (that is, data from the Intersalt study) confirmed by prospective, randomised, placebo controlled trials.

Let's stop debating what for some time has been ridiculously obvious; let's move on to working collaboratively to reduce the sodium in the diet (which is ingested largely in the form of processed foods and fast foods) so that the population at large will benefit.

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- 1 Hanneman RL. Intersalt: hypertension rise with age revisited. [With commentaries by M Law and J Stamler et al.] *BMJ* 1996;312:1283-7.
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Sodium contents of restaurant foods in United States are high

EDITOR—The many articles on salt and hypertension in the *BMJ* of 18 May 1996—including Fiona Godlee’s insightful commentary on the salt industry¹—were excellent. In the United States the salt and food industries continue to undermine advice by health authorities to reduce salt intake. For example, on 21 May 1996 *JAMA* issued a press release with the headline “Reducing salt in diet has little effect on blood pressure.” The release neglected to mention that the meta-analysis, funded by the Campbell Soup Company’s Institute for Research and Technology, found a significant drop in systolic blood pressure before the authors excluded the trials in which subjects were fed diets controlled by institutions.²

The snowballing effect of such reports is insidious. Two weeks after *JAMA*’s press release the *New York Times* ran an article declaring that, “contrary to previous advice, recent studies indicate that salt is not the villain it was once said to be.”³ The article later stated: “doctors still caution people who suffer from hypertension—estimated to be 10 percent of the population—to cut way back on salt.” In fact, 25% of American adults (50-60% of adults aged 60 or older) have hypertension. The only “authority” quoted in the article was Richard Hanneman, president of the Salt Institute.

The United States has made some progress in reducing sodium levels in packaged foods. Our surveys indicate that these levels seem to be dropping at a rate of just over 1% a year.⁴ However, Americans now spend nearly half of their food dollars on—and obtain a third of their energy from—foods eaten out of the home. There, sodium levels remain undisclosed and disturbingly high. The table shows the sodium contents that our nutritional analyses of restaurant foods (composites of nine to 12 samples purchased at mid-priced restaurants in at least three cities) have yielded for various selected entrees and meals.

Sodium content of various foods sold at restaurants in United States

Item	Sodium (mg)
Tuna salad sandwich	1320
Lasagne	2055
Ham sandwich	2200
Spaghetti with sausage	2435
House fried rice	2680
General Tso’s Chicken	3150
House Lo Mein	3460
Beef burrito platter	3920
Fried seafood platter	4405

These findings indicate that many Americans are exceeding, in a single meal, the 2400 mg of sodium recommended for an entire day. Only with the continued efforts of health authorities will the sodium

content of restaurant foods and processed foods fall to safer levels.

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Women’s autonomy in childbirth

Courts should also take evidence from obstetric anaesthetists

EDITOR—In the debate on consent for caesarean section where is the voice of the anaesthetist forced to give a general anaesthetic to the unwilling mother?¹ Or perhaps the anaesthetists were willing accomplices? So far I have met no obstetric anaesthetist who would participate in this scenario. Were the risks of general anaesthesia presented to the courts that sanctioned the operation?

The consultant obstetric anaesthetist is part of a team of midwives, obstetricians, and neonatologists who provide maternal care and seek to reduce the risks of pregnancy.^{2,3} The partners in the forced caesarean section seem to be obstetricians and psychiatrists. This is inadequate for any court to make decisions about maternal welfare—or fetal welfare, as was the case. Informed consent implies consultation with both a surgeon—that is, the obstetrician—and the anaesthetist who is going to give the anaesthetic.⁴ The risks of surgery and anaesthesia may be quite different. If a court requires an operation to be performed, let the court also take evidence from a specialist obstetric anaesthetist.

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- 1 Dolan B, Parker C. Caesarean section: a treatment for mental disorder? Tameside and Glossop Acute Services Unit v CH (a patient) [1996] 1 FLR 762. [With commentaries by S Bewley, A Whitfield, H Bastian, and C Conroy.] *BMJ* 1997;314:1183-7. (19 April.)
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An absurd law that needs changing

EDITOR—The recent debate about caesarean sections ordered by the courts without the mother’s consent failed to take issue with the central absurdity.^{1,2} Why does a viable term fetus have no legal recognition or rights? Are we really content to consider such a fetus expendable “for any rational or irrational reason or for no reason at all?”¹

Taking on a pregnancy confers rights but also brings responsibilities, which in the later stages are akin to those attached to looking after a young child. Absolute autonomy is eclipsed by the presence of a dependent offspring. The law, as it stands, seems to be clear cut and we must abide by it. It is also ludicrous, and we should campaign to have it changed.

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General anaesthesia does not usually affect the fetus

EDITOR—I am surprised at Wendy Savage’s assertion that “in Britain virtually all surgical terminations of pregnancy take place under general anaesthesia, which will affect the fetus.”¹ As every obstetrician and anaesthetist knows, general anaesthesia causes unconsciousness in the mother but not necessarily in the fetus. The anaesthetic agents are delivered via the maternal circulation to the mother’s brain; maternal blood does not directly perfuse the fetal brain. Anaesthesia is induced in the fetus only if anaesthesia is prolonged. I am sure that Savage has seen many infants scream lustily immediately after delivery by caesarean section under general anaesthesia. Whether the fetus can or cannot feel pain is open to debate, but in either case maternal anaesthesia does not render the fetus unconscious.

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- 1 Savage W. Do fetuses feel pain? *BMJ* 1997;314:1201. (19 April.)

Prophylactic and empirical antifungal treatment in cancer complicated by neutropenia

Combining different antifungal strategies in same systematic review is inappropriate

EDITOR—Peter C Gøtzsche and Helle Krogh Johansen have concluded that antifungal agents should be restricted to neutropenic patients with proved fungal infections.¹ Their meta-analysis, however, combined incompatible studies and was not systematic, omitting several randomised placebo controlled trials of antifungal prophylaxis (for example, that by Schaffner and Schaffner²) and including incomplete studies.³ We are concerned that this study has now been placed in the Cochrane database, where it will be seen to be the last word on

the use of antifungal agents in neutropenic patients.

The authors have examined the impact of prophylaxis and treatment in the same analysis. In fact, they have combined four different strategies—prophylaxis, early empirical treatment (at the onset of fever), delayed empirical treatment (after three to four days of unresponsive fever), and later empirical treatment (after seven days of persistent fever)—to draw an overall conclusion about individual agents. In addition, the authors include a study from 1980 (when the mortality in this population, as shown in table 3, was much greater than currently). This study used oral, non-absorbable amphotericin as prophylaxis, and its inclusion is certain to dilute out the effects of treatment with intravenous amphotericin.

Nevertheless, the analysis shows that amphotericin does have a significant effect on mortality, but the authors fail to include this as one of their key messages. Intravenous amphotericin is also used to prevent recurrence of previous life threatening invasive aspergillosis during subsequent neutropenia. Efficacy was shown in a non-randomised study,⁴ but it would be unethical to repeat this in a prospective randomised trial because half of patients undergoing bone marrow transplantation will suffer a recurrence if not given prophylaxis.

The authors have ignored the fact that prophylaxis also prevents mucosal candidiasis, by specifically excluding these data from their analysis. In some trials prophylactic fluconazole has reduced the incidence of mucosal candidiasis from more than 30% (in patients treated with placebo) to less than 10%.

Antifungal prophylaxis and treatment in this population is a complex issue. For example, the use of prophylaxis almost certainly affects patients' subsequent response to empirical treatment.⁵ The main problem that this paper has highlighted is that there is a dearth of trials. Perhaps the most useful conclusions that can be drawn are that intravenous amphotericin (which has mostly been used as empirical treatment) reduces mortality and that fluconazole used as prophylaxis (although significantly reducing superficial and invasive fungal infections) does not.

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Authors' reply

EDITOR—As we described in our paper, we did a careful systematic search for studies. Christopher C Kibbler and colleagues claim that we omitted several studies, but they give only one example, which we did not miss, since our data search was done in 1995 and the study did not appear on Medline before 1996. Our review will be updated in the Cochrane Library,¹ but the addition of the study by Schaffner and Schaffner will not change our conclusions. We are not aware of any missed studies but invite readers to help so that the information can be as comprehensive as possible. The fact that we included a study published so far only as an interim analysis does not change our conclusions either (but we wonder why researchers should publish interim analyses if the data should not be allowed to be used). Cochrane reviews are definitely not “the last word”—quite the contrary, since we invite comments and criticism and the reviews get updated when new trials appear.

The authors mistakenly believe that inclusion of a study from 1980 dilutes the results on the effects of amphotericin. If this study is excluded, the odds ratio for death with amphotericin becomes 0.55 (95% confidence interval 0.32 to 0.95) instead of 0.58 (0.37 to 0.93), which is very similar. We argued in our paper on our meta-analysis why we did not find a convincing effect of amphotericin on mortality.

We have chosen to present the totality of the evidence in a table which allows readers to do their own subgroup analyses should they so wish. Readers should be aware, however, of the risk of biased conclusions when post hoc analyses are performed that were not specified in the meta-analysis protocol.^{2,3} We have already done several subgroup analyses and are not convinced that the analysis that the authors suggest is more important than the ones we did: if prophylaxis is effective one would expect it to be effective in all four subgroups suggested. Furthermore, the numbers of trials and outcomes are clearly too small for the suggested analyses.

We did not ignore the fact that prophylaxis prevents mucosal candidiasis, since colonisation was one of our outcomes. We believe, however, that this condition can be treated when it occurs and does not justify prophylactic or empirical treatment.

We agree that there is a dearth of studies, but this is an argument for doing more studies and not for using routine antifungal prophylaxis.

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1 Gøtzsche PC, Johansen HK. Antifungal prophylactic or empiric therapy vs placebo or no treatment in cancer patients with neutropenia. In: Garner P, Gelband H, Olliaro P, Salinas R, Volmink J, Wilkinson D, eds. *Infectious diseases module of the Cochrane database of systematic reviews*. Issue 3. Oxford: Update Software, 1997. [Updated 3 June 1997 and quarterly; available in the Cochrane Library (database on disk and CD ROM).]

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Cooperation between pharmacists and general practitioners benefits patients

EDITOR—David Kernick suggests that community pharmacies should be abolished with dispensing being left to doctors and the sale of non-prescription drugs left to supermarkets.¹ Thankfully, most general practitioners disagree and recognise the value of pharmacists.

Pharmacists have an important role in primary care, and this complements the roles of other healthcare professionals. During their four year education (soon to be extended to five years) pharmacists develop an understanding of all aspects of drug treatment; they know more about this subject than any other healthcare professional.

The pharmacist's dispensing role has never been more important. Although the mechanical aspects of dispensing have been reduced because drugs are now dispensed in the manufacturer's original packaging, modern drugs are much more potent and complex and so the knowledge required to dispense them is greater—doses need checking, drug interactions must be looked at, and patients advised on how to take the drugs for maximum therapeutic benefit with the minimum of risk. According to two papers published 10 years apart in the *Journal of the Royal College of General Practitioners*, the rate of error in prescribing—over 3%—has not changed despite computerisation.² It must be in the patient's best interest that two professionals look at each prescription.

I am amazed at the suggestion that the sale of non-prescription drugs should be left to supermarkets. Do we really want to see “Buy one, get one free” promotions for paracetamol? This situation would be contrary to the joint statement of the BMA, the Royal College of Nursing, and the Royal Pharmaceutical Society of Great Britain.³ Many non-prescription drugs are unsuitable for people with certain conditions or interact with other drugs.

Making non-prescription drugs available only through pharmacies ensures that people get expert advice about choosing and using their medicines to treat common ailments and, more importantly, advice to see the doctor when this is the right course. Why should Kernick want to deny this service to the public?

Each part of the healthcare profession has much to offer the new primary care led NHS. Many doctors and pharmacists

already have excellent relationships at the local level. Pharmacists want cooperation with the medical profession, not confrontation. To suggest that pharmacies should be abolished and that the role of pharmacists should be taken on by general practitioners is as ludicrous as suggesting that general practitioners should disappear and pharmacists should refer people straight to consultants.

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Cycling offers important health benefits and should be encouraged

EDITOR—Barry Pless and Ron Davis state that most cyclists' head injuries are not caused in accidents involving cars.¹ This may be true when head injuries of all severities are considered together, but surely the focus should be on the severe ones. My analysis of five years of road casualty figures for Great Britain showed that 58% of cyclists who died did so after being hit by a car and a further 36% did so after being hit by other vehicles—mainly lorries—and that in only 6% of fatalities was no motorised vehicle involved.²

The authors' assertion that it is unproved that wearing a helmet gives cyclists a false sense of security flies in the face of a large body of evidence on risk compensation³; it seems extraordinary that a change in behaviour after the reduction in perceived risk would be invalid only in this instance.

The authors acknowledge that the law on the mandatory wearing of helmets in Australia has led to less cycling but seem unconcerned because "the public health issue is to reduce head injuries." They challenge the statement that the health benefits of cycling outweigh the dangers posed to cyclists in current road conditions on the grounds that the sources cited for the statement are "not established." In fact, the BMA's report *Cycling: Towards Health and Safety* used actuarial data to determine the life years lost by cyclists killed in road crashes, which were then compared with the life years gained by people engaging in exercise programmes such as cycling several times a week.⁴ Cyclists who cover at least 40 kilometres each week halve their risk of heart disease when compared with those who do not cycle.⁵

Pless and Davis also claim that "those who abandon cycling may substitute better modes of aerobic activity." In practice, few people are in a position to do so—for instance, they may drive to a health club to exercise on static equipment. Bicycles enable

most of the population however, not only to meet their daily travel needs but also to keep fit in a routine way, particularly where local authorities have the foresight to invest relatively small amounts of public funds to make the road environment for cycling much safer.

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Changes in population distribution of sense of coherence do not explain changes in overall mortality

EDITOR—Trends in health and mortality are complex,¹ and the desire for shortcuts to an understanding of the underlying determinants is easy to comprehend. As we suggested in our commentary on John P Bunker and colleagues' article, however, by failing to appreciate the complexity of the processes, many of the current theories mislead rather than inform and become barriers rather than aids both to understanding health and to developing activities to improve it.² Frada Eskin complains that, as we did not discuss Eskin's favourite theory in our commentary, we are missing the chance to "unravel the mysteries of disease and ill health."³ The "excellent sociologically based" sense of coherence model proposed by Antonovsky—in which making sense of what happens in our lives, why it happens, and what we can do to change it is seen as key—could, Eskin suggests, provide the answer we are looking for. Unfortunately, this is not the case. The empirical data offer limited support for a causal role of sense of coherence either in any general sense or with respect to the risk of disease or death from particular causes. As even sympathetic commentators observed, the sense of coherence scale is an undersocialised measure,⁴ and in many studies it is used as something closer to a personality type than a mediator between social forces and health.

In Britain over the past one and a half centuries overall mortality has fallen for both sexes and in all age groups, but at very different rates in the specific groups.¹ Accelerations, decelerations, and reversals in the fall in mortality have occurred. For some causes of death—for example, stroke, tuberculosis and stomach cancer—falls have been continuous; for others—for example, coronary heart disease—there have been rises then falls in mortality; for others—for example, brain and prostate cancer—rises in mortality have been seen. Trends in morbid-

ity (though data are limited) are similarly diverse.

In attempts to explain such patterns, changes in the population distribution of sense of coherence are clearly not a promising candidate. What is required is the combination of a sense of historical and social change with anthropological, biological, and medical understanding. The tentative steps to such an analysis in particular situations are beginning to appear.⁵ This, however, requires hard work rather than the propagation of slogans. By appearing to consider that the "mysteries of disease and ill health" can be solved by a 29 item personality scale Eskin is (unwittingly) providing a good example of the simplistic overgeneralisation that our commentary discussed.

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- 1 Charlton J, Murphy M. *The health of adult Britain 1841-1994*. London: Stationery Office, 1997.
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Treating hypothyroidism

Biochemical tests are important in diagnosis

EDITOR—Like Gordon R B Skinner and colleagues, we recognise that the clinical diagnosis of hypothyroidism is a challenge for general practitioners¹; recent reviews of the published literature make it clear that the non-specific nature of the signs and symptoms of hypothyroidism means that biochemical tests of thyroid function (specifically serum thyroid stimulating hormone) are an essential component of the diagnosis.²⁻⁵

There were several shortcomings in the letter from Skinner and colleagues. The clinical criteria of hypothyroidism used are neither stated nor referenced. The method of selecting patients is not stated; as a result the letter wrongly implies that for every four to five patients with biochemical evidence of hypothyroidism there are 75 who are clinically hypothyroid but biochemically euthyroid. No recognition is given to the natural history of primary hypothyroidism which requires an increase in thyroid stimulating hormone to maintain thyroid hormone production in a failing gland. Consequently, the authors wrongly place equal weight on the measurement of thyroid stimulating hormone and free thyroxine as diagnostic tests of hypothyroidism especially at the early (subclinical) stage.

New objective scientific evidence is always a useful addition to current knowl-

edge and understanding. Therefore, there may be merit in a short term incremental trial of thyroxine in a cohort of patients who are clinically hypothyroid but biochemically euthyroid, provided that objective criteria are used for patient definition and assessment during treatment; the trial is blind and placebo controlled with crossover; appropriate biochemical measurements are made before and during the trial; and it is recognised that no evidence will be obtained about the likely success of continued treatment or of any long term side effects of such treatment.

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- 1 Skinner GRB, Thomas R, Taylor M, Sellarajah M, Bolt S, Kett S et al. Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients. *BMJ* 1997;314:1764. (14 June.)
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Threshold of thyroid stimulating hormone should be higher before treatment is started

EDITOR—A P Weetman summarised the available data on hypothyroidism. I am, however, concerned about the suggestion that all patients with thyroid antibodies and with a normal thyroxine concentration but raised thyroid stimulating hormone concentration (whatever its value) should be treated with thyroxine.¹ The Whickham survey reported that only 55% of such patients developed hypothyroidism after 20 years of follow up.² The recommendation to treat patients with a thyroid stimulating hormone just above the upper limit of normal assumes that the patient's hypothalamic-pituitary axis would not secrete more thyroid stimulating hormone despite sensing the body's need for more thyroxine. It also assumes that the doctor (in most cases the general practitioner) would know the particular concentration of thyroid stimulating hormone to aim for in a particular patient. This is debatable³; patients are frequently referred to my clinic for assessment of the correct dose of thyroxine.

I would suggest a threshold of thyroid stimulating hormone of, for example, 10 mU/l or a compelling clinical indication before starting thyroxine treatment in this group. Patients not given thyroxine treatment should be followed up every six to 12 months indefinitely.

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Test sales do not have impact on prevalence of smoking by children

EDITOR—The office of trading standards in Liverpool suggests that it is possible to reduce cigarette sales to minors from 100% to 3% on the basis of test sales in which a child is recruited to attempt to purchase cigarettes while being observed covertly by a trading standards officer (R Croft, fourth WHO seminar for a tobacco-free Europe, Skovde, Sweden, June 1994). If the child is successful, the shop is prosecuted. The drop in observed sales has been interpreted as a genuine reduction in the availability of cigarettes to children. Legislation has now made test sales standard practice. But does this approach work successfully in other districts, and can it be shown to affect the availability of cigarettes to children and thus affect the prevalence of smoking?

A cross sectional survey of two schools in Gateshead was carried out in May 1995 and May 1996. The trading standards office carried out test sales in shops around one school, school A, between these dates. The aim of the survey was to assess whether the test sales had an impact on smoking behaviour. All year 10 students (ages 14-15 years) were surveyed in the two schools (224 in 1995 and 163 in 1996). Availability, source and ease of purchase of cigarettes, and prevalence of smoking were ascertained using questions derived from a questionnaire of the Office of Population Censuses and Surveys to enable comparisons to be made with national data.¹ Focus groups were also carried out to explore the availability of cigarettes in more detail.

In 1995 in school A 23/59 (39%) girls and 15/58 (26%) boys smoked. This prevalence was much higher than that in school B, where 12/51 (24%) girls and 8/56 (14%) boys smoked. These prevalences did not fall greatly by 1996. Altogether 55/58 (95%) children who were regular smokers bought cigarettes from shops at least weekly. Only 3/121 (2.5%) in 1995 and 5/85 (6%) in 1996 reported ever having had someone refuse to sell them cigarettes. This is a similar figure to the one from the national survey by the Office of Population Censuses and Surveys.¹ This is not surprising since the test sales resulted in no purchases and therefore no prosecutions, despite the fact that the students were still able to buy cigarettes with ease from nearby shops.

Thus this study suggests that test sales may not be a useful measure of the availability of cigarettes to children. A problem with this type of enforcement work is that a proxy

outcome is being measured. Our work suggests that the number of successful test sales does not have an impact on access to cigarettes by young people or on the prevalence of smoking. Until such evidence is available it is hard to justify continuing with test sales.

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- 1 Office of Population Censuses and Surveys. *Smoking among secondary school children in 1994*. London: OPCS, 1995.

Internet is useful for information on rare conditions

EDITOR—The recent letters about the medical uses of the internet do not mention its usefulness in providing information that is time sensitive in patients' care.¹ We were asked to anaesthetise a child with Costello syndrome (of which around 20 cases have been recorded) for an emergency laparotomy at night. On that night the child's father offered all references (but not texts) on the syndrome from the page he maintained on the world wide web.

The child's chief signs were vomiting from obstruction, dehydration, and cardiac arrhythmias, all of which are important to an anaesthetist. The anaesthesia was marked by a difficult intubation under emergency conditions, and, with the parents' permission, a case report was prepared.²

The text of the case report was also posted on the page that the father maintained on the web (<http://sargon.mmu.ac.uk/helaina.htm>). It has been accessed by another hospital in Britain treating a child with the same condition, and by an oncologist who was faced with the very specialised problem of a new tumour in a child with the syndrome. It has also been used by another member of our staff, who reanaesthetised the child.

Newsgroups discuss problems within their remit when questions can be posted and answered within a few hours. The internet also allows medical minority interest groups to access information of critical interest to them (<http://sargon.mmu.ac.uk/rindex.htm>) so that morbidity in these rare conditions can be lessened.

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