they travel to obtain transplants, are just beginning to address their responsibilities to protect their people from exploitation and to develop national self-sufficiency in organ donation. The medical leaders who played major roles in the promulgation of laws and regulations within the past 2 years in China, Pakistan and Philippines were participants in the Istanbul Summit meeting. The Declaration describes universal approaches to providing care for the living donor and also emphasizes the need for effective practices that support deceased organ donation.

The implications of the Istanbul Declaration definitions, principles and recommendations are profound. They call for a legal and professional framework in each country to govern organ donation and transplantation activities. They call for a transparent regulatory oversight system that ensures donor and recipient safety and enforces the prohibitions of unethical practices. Governments should ensure that the provision of care and follow-up of living donors be no less than the care and attention provided for transplant recipients. Professional societies should not continue to enable membership status for those individuals that violate the principles of the Declaration. Pharmaceutical companies and public and private funding agencies must affirm the Declaration in their consideration of clinical research support.

The Istanbul Declaration preserves the goodness of the act of organ donation without victimizing the poor of the world to be the targeted source of organs for the rich.

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Editorial comment with reply:
The continuing salt war: the final battle?

Salt intake and cardiovascular disease

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McCarron, in his review on salt [1], makes some serious and misleading mistakes. For example, he claimed that, in two of our own randomized double-blind crossover trials of modest salt restriction [2,3], we restricted potassium intake. This is incorrect and can be ascertained from a superficial reading of both papers. The average potassium intake on the individuals’ usual diet, as measured by 24-h urinary potassium excretion, was the same as that for the UK population. Secondly, there was no significant change in 24-h urinary potassium with a reduction in salt intake during the run-in period while individuals were on a reduced salt diet. Thirdly, not like McCarron implied, participants did not change their diet during the randomized crossover phase of the studies. Instead they took slow sodium and placebo tablets in a randomized double-blind crossover manner to achieve a difference in salt intake. There was no significant change in 24-h urinary potassium excretion throughout the studies. These results can be clearly seen in the table on page 353 of the first paper [2] and the table on page 1245 of the second paper [3]. Our studies, therefore, contrary to McCarron’s claims, clearly document that a modest reduction in salt intake lowers blood pressure in hypertensive individuals without any change in potassium intake.

Our results are strongly supported by the Dietary Approaches to Stop Hypertension (DASH)-Sodium study that is a similar well-controlled, but open, feeding trial where a reduced salt intake has a significant effect on blood pressure, not only on the usual American diet with no change in potassium intake but also on the DASH diet that is rich in fruits, vegetables and low-fat dairy products [4]. Our results are also supported by the Cochrane review of all of the longer term modest salt reduction trials, which demonstrates significant reductions in blood pressure both in hypertensive and normotensive individuals. Additionally, there is a clear dose–response relationship. A reduction of 6 g/day of salt intake would lower blood pressure...
by 7/4 and 4/2 mmHg in hypertensives and normotensives, respectively [5].

Another example is when McCarron discusses the INTERSALT study [6] and claims that the results are negative. He fails to point out that, following an analysis of the data by the Salt Institute, the INTERSALT authors reanalysed all their data and they consistently demonstrated, once again, that salt intake is significantly related to blood pressure and the rise in blood pressure with age worldwide [6–8].

McCarron claims that Alderman’s studies support his suggestion that salt reduction might increase the risk of myocardial infarction and total mortality [9–12]. (Note that Alderman is also one of the consultants to the Salt Institute [13].) Both McCarron and Alderman can be seen on the Salt Institute website commenting with Dr Suzanne Oparil and Dr Alexander G. Logan on various aspects of salt and blood pressure [14].) McCarron, again, has either not read or has chosen to ignore the detailed criticisms that followed Alderman’s studies in which there were severe methodological problems [15–20]. For instance, in Alderman’s study on salt and myocardial infarction [9], 24-h urinary sodium was measured after all individuals had restricted their salt intake for 5 days in order to stimulate the renin–angiotensin system. No measurement of salt intake was made on the subjects’ usual diet, so, in no way, can this 24-h urine reflect their usual intake. Furthermore, no other collections were done throughout the study. In addition, the single 24-h urines that were collected on a low salt diet showed that, in the lowest quartile of salt intake, there was a much lower 24-h urinary creatinine excretion indicating that there had been an incomplete collection of the 24-h urines [19], a fact that Alderman failed to include in the original paper.

Alderman’s other studies on salt and mortality [10–12], in our view, are also flawed. Firstly, the method of one single 24-h dietary recall as used in these studies is known to be extremely inaccurate in assessing salt intake. Furthermore, there was no account taken of discretionary salt intake. As pointed out in correspondence in the Lancet subsequently, many women in the lowest quartile of salt intake, who had a calorie intake of near starvation level, had survived for 20 years and they actually weighed 4 kg more than those in the highest quartile of salt intake [16–18]. A well-conducted prospective study in a random sample of the Finnish adult population where 24-h urinary sodium excretion was measured on their usual diet [21] and the recently published randomized trial evidence on cardiovascular outcome in the USA [22] have demonstrated that a lower salt intake was associated with a reduction in cardiovascular disease. Indeed, a 25–30% reduction in salt intake from ~10 g/day caused a 25% decrease in cardiovascular events [22].

There is overwhelming evidence that blood pressure throughout its range seen in developed countries is a major cause of cardiovascular disease [23]. A meta-analysis of all blood pressure treatment trials have demonstrated that the reduction in cardiovascular disease mortality was related to the extent of the fall in blood pressure irrespective of the type of drugs given [24]. McCarron, again, ignores such evidence and continues to claim that ‘... how blood pressure is lowered matters in terms of reducing cardiovascular disease and all-cause mortality’. In support of this, he misrepresents some of the findings in the ALLHAT study, stating that, ‘... one of the antihypertensive medications that effectively lowered BP (blood pressure) was associated with an increased risk of CVD (cardiovascular disease) and death’. In the paper McCarron referred to, the ALLHAT investigators were comparing the effect of two blood-pressure-lowering drugs, i.e. doxazosin and chlorthalidone [25]. The authors correctly concluded that chlorthalidone was more effective than doxazosin in reducing the risk of combined cardiovascular disease events, particularly congestive heart failure. However, chlorthalidone was more effective in lowering blood pressure by 2–3 mmHg, a point that McCarron failed to acknowledge. In other words, both drugs were thought to lower cardiovascular mortality, but chlorthalidone was more effective due to the bigger blood pressure fall.

Ironically, McCarron enthusiastically endorses other dietary and lifestyle measures to control blood pressure, e.g. weight control, moderate alcohol intake, increased fruit and vegetable consumption and smoking cessation (despite the fact that there is no evidence that smoking cessation causes any change in blood pressure per se). Whilst we agree with McCarron that all of these changes should be implemented to prevent cardiovascular disease, McCarron needs to ask himself why he excludes salt reduction from such multiple risk factor modifications in spite of the fact that the evidence for a reduction in salt intake is much stronger than that for other dietary and lifestyle changes. Indeed, the evidence for salt that comes from many different sources [26], e.g. epidemiology, migration, animal, human genetics, treatment trials, population-based intervention and randomized trials on cardiovascular outcomes, is as strong as that linking cigarette smoking with arterial disease. McCarron also fails to point out the important fact that a modest reduction in salt intake is by far the easiest of all lifestyle changes because, unlike other changes, a reduction in salt intake does not necessarily involve a change in the eating habits of individuals, but requires the food industry to reduce the very large and unnecessary amounts of salt they add to foods. In most developed countries, 75–80% of salt intake now comes courtesy of the food industry [27]. Several countries, including the UK, have now adopted the strategy of small (10–20%) but repeated reductions in the amount of salt being added by the food industry. These differences cannot be detected by the human salt taste receptors [28] and cause no problems in food technology. Such a strategy is being implemented in the UK right now and the food industry, many of which are international, is cooperating and is playing a major role in this. A recent survey demonstrates that, since the start of the salt reduction programme, 24-h urinary sodium in a random sample of the UK adult population has fallen by 10% from 9.5 to 8.6 g of salt per day (P < 0.001), i.e. just under 1 g/day [29]. Other countries have also successfully implemented such salt reduction programmes, e.g. Finland where salt intake, since the 1970s, has been reduced by one-third [30,31]. With the reduction in salt intake in Finland, there was an accompanying fall of >10 mmHg in both systolic and diastolic blood pressure and a decrease of 75–80% in both stroke and coronary heart disease mortality, as well as an increase of 5–6 years in life expectancy [30]. The reduction in salt intake is a
major contributory factor for these results, particularly the fall in blood pressure as both body mass index and alcohol consumption were increased during that period. An increase in potassium intake via the use of reduced-sodium, potassium- and magnesium-enriched salt and an increased consumption of fruit and vegetables, and a reduction in fat intake, also played a part in the fall in cardiovascular disease.

Clearly, the salt industry has a big commercial interest in keeping salt intake high as 40% of sales currently come from sales of salt to the processed food industry. There are also commercial reasons for putting salt into food. However, it is clear from the UK food industry that these commercial interests are far outweighed by the fact that they would prefer their customers not to develop premature cardiovascular disease. If the amount of salt added to food is decreased, there will be an increase in life expectancy and, importantly for the food industry, an increase in the number of customers to whom they can sell their food. The recent results from the UK also demonstrate that it is surprisingly easy to reduce salt intake, and other countries should follow the examples of the UK and start taking action now. A modest reduction in population salt intake worldwide would result in a major improvement in public health at a low cost, as or more than the savings from reduced potassium- and magnesium-enriched salt and an increased consumption of fruit and vegetables, and a reduction in fat intake, also played a part in the fall in cardiovascular disease.

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Reply

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I hesitate to subject the readers of NDT to the continued banter between Dr MacGregor [1] and I, which dates back over 20 years with a debate at the 1984 Annual Meeting of the American Society of Nephrology [2]. The letter by He and MacGregor continues the immutable argument they have imposed on this legitimate area of scientific research. As I characterized the behaviour of the strong advocates of sodium restriction in my commentary, MacGregor and He have again 'stacked the odds by repeatedly citing compromised reports . . . to build their argument that salt is the odds-on favorite' as the nutritional cause of CVD [3].

To spare NDT's readership, I will dispense with responding to the diversionary tactic of addressing minor issues by these authors. I would note, however, that they do not address the fact that a substantive body of data proving that lower salt intake will reduce all-cause mortality, that humans will live longer, healthier lives does not exist [3]. As concluded in my commentary, it is time 'to answer the lower sodium/higher life expectancy question'.

The century-long sodium-blood pressure debate must be settled with science, not opinion. I propose that we commit to an international supervised, independent trial that prospectively assesses the relationship between free living sodium intake, as measured by multiple 24-h urinary sodium excretions, and accepted measures of morbidity and mortality in an adequately powered study design of sufficient duration to definitely answer the question of whether or not lower sodium intake is associated with longer, healthier lives.

Should the outcome of that trial prove what, to date, the majority of retrospective studies of databases indicate—that there is a greater likelihood of no benefit or actual harm from reduced sodium diets—then the efforts and resources of both the proponents and opponents of universal sodium restriction can be appropriately focused on those lifestyle factors that we know, and that I emphasized at the conclusion of my commentary, will improve human health and life expectancy.

As a concluding note, Dr MacGregor's feigned surprise at my endorsement of these lifestyle measures is itself surprising and somewhat disingenuous as he is well aware of the fact that we have supported these for more than 20 years. In our initial debate, MacGregor attacked our 1984 Science [4] paper, which was based on US government data. That paper was the original description of what has become known as the DASH diet. The data and conclusion in that paper strongly endorsed that dietary pattern, now also the basis of the US Food Guide Pyramid. As in my recent commentary, we did not recommend in the 1984 Science paper a reduced sodium diet because the database, the National Health and Nutrition Examination Survey (NHANES I), did not indicate that Americans who consumed lower sodium diets had lower blood pressures [4].

As I maintain in my NDT commentary, we must move beyond the salt–blood pressure debate, which obviously can be both defended and attacked with the currently available data, and address the paramount question: does sodium intake play a role in overall human health. As scientists and purported experts in this field, it is incumbent upon us to unite our resources towards resolving this question. As scientists, we are reminded with almost daily headlines—e.g. Vioxx, hormone replacement therapy, Vytorin—of our responsibility to predicate public health policy and treatment guidelines not on presumptions, surrogate endpoints and, thus, incomplete assessment but on hard outcomes, that is morbidity and mortality evidence. I look forward to Dr MacGregor publicly acknowledging, as I have repeatedly, support for such an international study.

Conflict of interest statement. None declared.

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