mountaineering activities would have recovered spontaneously.

How did the treatment lessen pulmonary oedema? In the pseudomonas-induced model of permeability oedema, any increase in pulmonary artery pressure enhances the flux of fluid out of the vascular space and contributes to oedema.[21] Thus exaggerated pulmonary hypertension seems to be an essential pathogenetic factor in HAPO, either as a direct consequence of alveolar hypoxia or indirectly as a result of overreactivity of pulmonary arteries to hypoxia. We conclude that reduction of pulmonary artery pressure was responsible for the therapeutic effects, although we cannot rule out a contribution of other pharmacological actions of nifedipine.

Headache, a known side-effect of calcium channel blockers, persisted in four subjects and required paracetamol medication. It could have been caused partly by the treatment. Otherwise, no adverse drug reactions were observed. The fact that nifedipine did not reduce systemic blood pressure may be explained by the high levels of circulating catecholamines in AMS.[22]

Of the various treatments that have been recommended for HAPO only bed rest (in mild cases) has been tested in a controlled setting.[20] Frusemide was advocated by Singh et al[23] but in other hands it rendered patients susceptible to circulatory troubles, pulmonary embolism, and cerebral oedema.[2,24,25] It has never been proven to enhance oxygenation. Morphine, another inadequately tested remedy, could do more harm than good by depressing the respiratory centres at a time when more respiration is needed. As a non-pharmacological measure positive end-expiratory pressure breathing has been applied briefly[26,27] but its long-term effects may be harmful.[28] Another possible means of short-term improvement is postural drainage.[29]

The therapy of choice in HAPO remains descent to lower altitude. When this is impossible and supplementary oxygen is not available we believe that nifedipine offers the best chance of improvement. This improvement, however, should be exploited to allow descent rather than to allow continued activities at high altitude.

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REFERENCES

1. Houston CS. Acute pulmonary edema of high altitude *N Engl J Med* 1960; **263:** 478–80
2. Schoene RB. Pulmonary edema at high altitude Review of pathophysiology, and update. *Clin Chest Med* 1985; **6:** 491–507.
3. Lobenhoffer HP, Zink RA, Brendel W. High altitude pulmonary edema: analysis of 166 cases. In: Brendel W, Zink RA, eds. High altitude physiology and medicine. New York. Springer, 1982 219–31
4. Schoene RB, Hackett PH, Henderson WR, Sage H, Chow M, Roach RC, Mills WJ, Martin TR. High-altitude pulmonary edema Characteristics of lung lavage fluid. *JAMA* 1986; **256:** 63–69.
5 Hackett PH, Bertman J, Rodriguez G, Tenney J. Pulmonary edema fluid protein in high altitude pulmonary edema. *JAMA* 1986; **256:** 36.
6 Fred HL, Schmid AM, Bates T, Hecht HH. Acute pulmonary edema of altitude clinical and physiologic observations *Circulation* 1962; **25:** 929–37.
7. Hultgren HN, Lopez CE, Lundberg E, Miller H Physiologic studies of pulmonary edema at high altitude *Circulation* 1964, **29:** 393–408

References continued at foot of next column

DOUBLE-BLIND STUDY OF THREE SODIUM INTAKES AND LONG-TERM EFFECTS OF SODIUM RESTRICTION IN ESSENTIAL HYPERTENSION

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Summary 20 patients with mild hypertension (average supine blood pressure without treatment, 164/101 mm Hg) reduced their salt intake to 50 mmol (3 g) per day for a month. They then entered a 3 month double-blind randomised crossover study of three levels of sodium intake: 200, 100, and 50 mmol per day. Blood pressure was significantly reduced on the middle and lowest sodium intakes. The average fall in blood pressure from the highest to the lowest sodium intake was 16/9 mm Hg. Patients continued to restrict their sodium intake for a further year. In 16 of the 20 patients blood pressure remained well controlled with salt restriction alone. Supine blood pressure at 1 year was 142/87 (SE 3/2) mm Hg

O OELZ AND OTHERS: REFERENCES—*continued*

8. Roy SB, Guleria JS, Khanna PK, Manchanda SC, Pande JN, Subba PS Haemodynamic studies in high altitude pulmonary oedema. *Br Heart J* 1969, **31:** 52–58.
9 Penaloza D, Sime F. Circulatory dynamics during high altitude pulmonary edema. *Am J Cardiol* 1969, **23:** 369
10. Hackett PH, Creagh CE, Grover RF, et al High-altitude pulmonary edema in persons without the right pulmonary artery. *N Engl J Med* 1980; **302:** 1070–73.
11. Kobayashi T, Koyama S, Kubo K, Fukushima M, Kusama S. Clinical features of patients with high-altitude pulmonary edema in Japan *Chest* 1987, **92:** 814–21
12. Stanbrook HS, Morris KG, McMurtry IF Prevention and reversal of hypoxic pulmonary hypertension by calcium antagonists *Am Rev Respir Dis* 1984; **130:** 81–85
13. Oelz O A case of high-altitude pulmonary edema treated with nifedipine *JAMA* 1987; **257:** 780
14 Oelz O, Maggiorini M, Ritter M, et al. Behandlung des Hohenlungenodems mit Nifedipin *Schweiz Med Wschr* 1989, **119** suppl 28: 47 (abstr)
15. Ferrazzini G, Maggiorini M, Kriemler S, Bartsch P, Oelz O Successful treatment of acute mountain sickness with dexamethasone *Br Med J* 1987, **294:** 1380–82
16. Bommer W, Weinert L, Neumann A, Neef J, Mason DT, DeMaria A. Determination of right atrial and right ventricular size by two-dimensional echocardiography. *Circulation* 1979; **60:** 91–100
17. Yock PG, Popp RL Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984, **70:** 657–62.
18. Hatle L Non-invasive methods of measuring pulmonary artery pressure and flow velocity. Cardiology, an international perspective New York. Plenum, 1984 783–90
19 Vock P, Fretz C, Franciolli M, Bartsch P. High-altitude pulmonary edema: findings at high-altitude chest radiography and physical examination. *Radiology* 1989, **170:** 661–66
20 Marticorena E, Hultgren HN Evaluation of therapeutic methods in high altitude pulmonary edema. *Am J Cardiol* 1979; **43:** 307–12.
21. Brigham KL, Woolverton WC, Blake LH, Staub NC. Increased sheep lung vascular permeability caused by pseudomonas bacteria *J Clin Invest* 1974, **54:** 792–804
22. Bartsch P, Shaw S, Franciolli M, Gnadinger MP, Weidmann P Elevated atrial natriuretic peptide in acute mountain sickness. *J Appl Physiol* 1988, **65:** 1929–37
23. Singh I, Khanna PK, Srivastava MC, Lai M, Roy SB, Subramanyam CSV Acute mountain sickness. *N Engl J Med* 1969; **280:** 175–84
24. Hultgren HN. Furosemide for high altitude pulmonary edema. *JAMA* 1975, **234:** 589–90
25. Gray GW, Bryan AC, Frayser R, Houston CS, Rennie IDB Control of acute mountain sickness. *Aerospace Med* 1971; **42:** 81–84
26. Larson EB Positive airway pressure for high-altitude pulmonary oedema. *Lancet* 1985; i. 371–73.
27 Schoene RB, Roach RC, Hackett PH, Harrison G, Mills WJ Jr. High altitude pulmonary edema and exercise at 4400 meters on Mount McKinley. Effect of expiratory positive airway pressure *Chest* 1985, **87:** 330–33
28. Oelz O. High altitude cerebral oedema after positive airway pressure breathing at high altitude. *Lancet* 1983; ii: 1148.
29. Hultgren HN. Emergency maneuver in high altitude pulmonary edema. *JAMA* 1986, **255:** 3245–46.

with a 24 h urinary sodium excretion of 54 (7) mmol. These results show a progressive blood pressure fall as salt intake is reduced and that, in many patients with mild essential hypertension, blood pressure can be controlled without the need for drug therapy.

Introduction

MODERATE salt restriction to an intake around 80–100 mmol sodium per day (about 5–6 g NaCl) lowers blood pressure in many but not all patients with sustained mild essential hypertension.[1,2] However, whether blood pressure might fall further as salt intake is reduced below these levels is unknown. There is also little evidence about whether salt restriction alone effectively lowers blood pressure over a long period.[3] We therefore studied the effect of three different levels of sodium intake for a month each in a double-blind randomised crossover study in patients with sustained mild essential hypertension who were on no other treatment. The patients then continued to restrict sodium intake and were followed up for a year.

Patients and Methods

Patients were referred by local general practitioners and were included in the study if, after 2 months of observation on no treatment, their supine diastolic blood pressure was between 90 and 110 mm Hg and no underlying cause had been found for their high blood pressure. Patients with renal failure, ischaemic heart disease, or cerebrovascular disease were excluded from the study as were patients taking an oral contraceptive or any other drug. Each patient gave informed consent. Of the 20 patients who entered, all completed the double-blind study. There were 11 men, 9 women; 15 whites and 5 blacks. The mean age was 57 years (range 42–72). Mean 24 h urinary sodium excretion when first seen was 162 (SE 16) mmol (range 58–296). 5 patients had a urinary sodium excretion above 200 mmol per 24 h.

All patients were instructed to reduce their daily sodium intake to around 30 to 50 mmol by not adding any salt at table or in cooking and by avoiding all food containing large amounts of salt. Salt-free bread, margarine, and some other foods were provided. Written instructions and recipes were also given to all patients. All patients were seen by a dietitian and, where appropriate, the spouse or whoever cooked in the household was also seen. At each visit, nurses reinforced the dietitian's instructions. After 2 weeks of sodium restriction, two 24 h urine collections were made to check compliance with the diet and after 4 weeks on the diet all measurements were repeated.

Patients then entered a randomised double-blind three-way crossover study. The three phases lasted a month each while the patients continued to restrict dietary sodium intake. The phases were 16 'Slow Sodium' placebo tablets (Ciba-Geigy) per day, giving a total sodium intake of about 50 mmol; 7 slow sodium tablets (10 mmol NaCl each) plus 9 placebo tablets per day, giving an approximate total sodium intake of 100 mmol; and 16 slow sodium tablets per day, giving an approximate sodium intake of 200 mmol.

During the crossover study blood pressure, weight, and pulse were measured at the end of each month and two 24 h urines were collected for measurement of sodium, potassium, and creatinine. Blood was also taken at the end of each month's treatment for measurement of urea, creatinine, electrolytes, plasma renin activity,[4] aldosterone,[5] and, in 12 patients, noradrenaline.[6] All bloods were taken without stasis after patients had been sitting upright for 5–10 min between 0900 and 1200. Patients were seen on the same day of the week at the same time of day by the same nurse in the same room, and blood pressure was measured in the same arm by nurses using semi-automatic ultrasound sphygmomanometers ('Arteriosonde') with attached recorders.[7] The measurements were therefore free from observer bias. Supine and standing blood pressures were the mean of five readings taken with 1–2 min intervals. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. Patients were carefully instructed orally and by printed instructions on how to collect 24 h urines, and the mean of two consecutive 24 h urines was taken as the sodium excretion at that time.

After completion of the crossover study patients continued with sodium restriction and were seen every 1–2 months. Every 3 months patients collected two 24 h urines.

Analysis of variance (ANOVA) with repeated measures and t tests were used where appropriate. Underlying trends in the changes in dietary sodium intake during the crossover study were tested with polynomial contrasts for linear and quadratic models. Results are means (SE).

Results

Supine blood pressure in 20 patients after the 2 month observation period on no treatment was 164/101 (4/2) mm Hg. After 4 weeks of 16 slow sodium tablets per day supine blood pressure was 163/100 (4/2) mm Hg (24 h urinary sodium 190 [11] mmol). After 1 month of 7 slow sodium tablets and 9 placebo tablets per day supine blood pressure was significantly lower at 155/95 (3/2) mm Hg ($p < 0.01$) (24 h urinary sodium 108 [10] mmol). After a month on 16 placebo tablets (24 h urinary sodium 49 [8] mmol) supine blood pressure was 147/91 (4/2) mm Hg, which was significantly lower compared with the highest ($p < 0.001$) and the middle ($p < 0.01$) sodium period. Changes in standing blood pressure during the study were similar to those found for supine blood pressure (table). The

BLOOD PRESSURE AND LABORATORY DATA AFTER 4 WEEKS ON DIFFERENT SODIUM INTAKES (CROSSOVER STUDY)

—	Approximate sodium intake (mmol per day)		
	50	100	200
Supine blood pressure (mm Hg)			
Systolic*	147 (4, 139–154)	155 (3, 148–163)	163 (4, 155–169)
Diastolic*	91 (2, 87–95)	95 (2, 90–100)	100 (2, 95–105)
Standing blood pressure (mm Hg)			
Systolic*	144 (4, 136–152)	154 (4, 146–162)	162 (4, 155–169)
Diastolic*	98 (2, 94–103)	104 (3, 98–109)	107 (3, 102–113)
Bodyweight (kg)	73·1 (2·3, 68·3–77·8)	73 4 (2 3, 68·5–78·3)	73 6 (2 4, 68 6–78·6)
Plasma			
Renin activity (ng/ml per h)†	2·3 (0·4, 1 5–3·2)	1·6 (0 3, 0·8–2·3)	1 4 (0·3, 0·8–1·9)
Aldosterone (pmol/l)*	541 (56, 423–658)	371 (42, 283–459)	298 (32, 232–364)
Noradrenaline (pg/ml) (n = 12)	576 (120, 313–839)	683 (118, 424–945)	586 (118,327–846)
Urine			
Sodium (mmol per 24 h)*	49 (8, 34–65)	108 (10, 88–129)	190 (11, 168–212)
Potassium (mmol per 24 h)	68 (5, 59–77)	75 (6, 63–88)	76 (6, 64–88)

Mean (n = 20) (SE, 95% confidence interval).
Significant treatment effect by ANOVA: *$p < 0.0001$ and †$p < 0.01$.

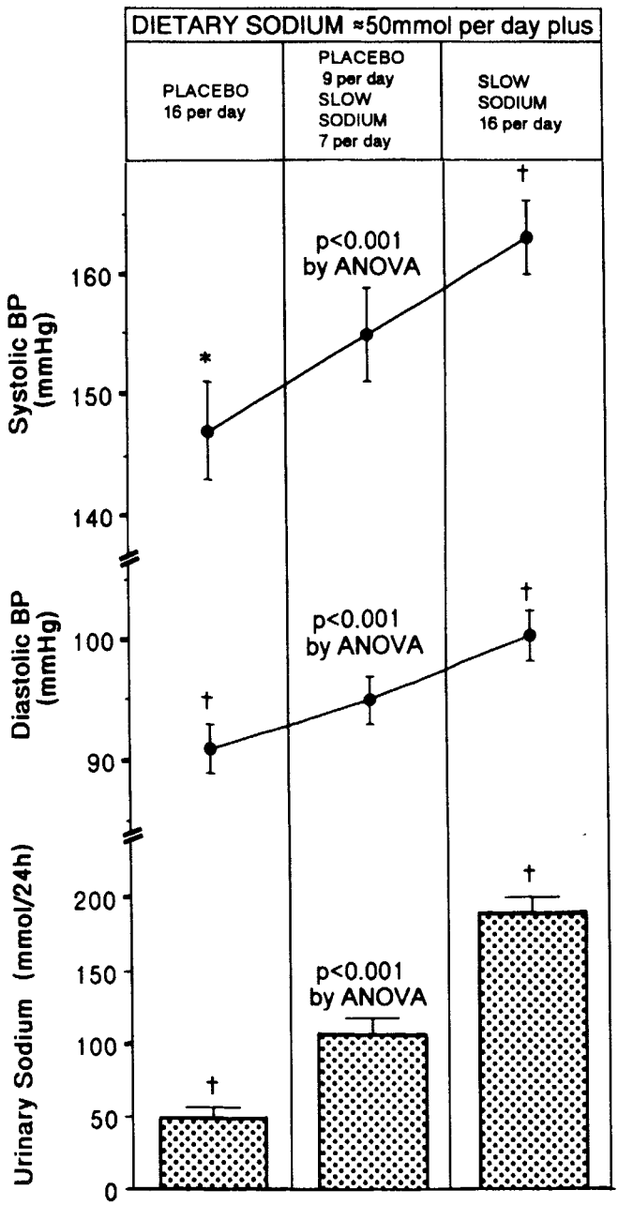

Fig 1—Blood pressure and urinary sodium excretion after 4 weeks during each phase of crossover study (n = 20).

*p < 0·01 and †p < 0·005 compared with phase of 7 slow sodium tablets per day.

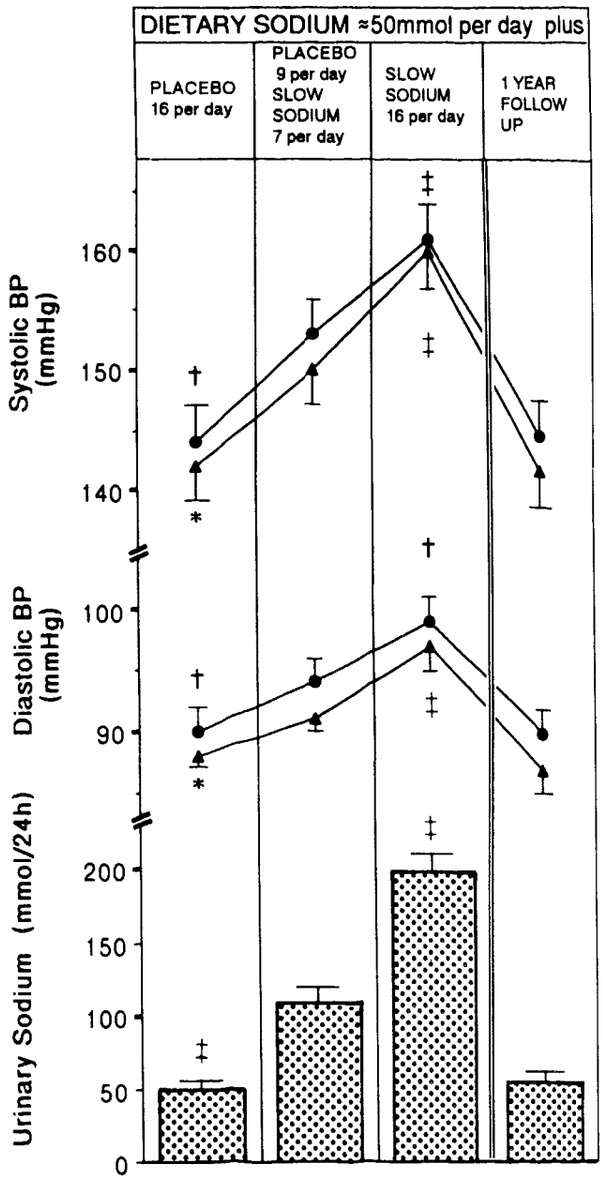

Fig 2—Follow-up.

●——●, n = 19; ▲——▲, n = 16 (see text for details).

*p < 0·05; †p < 0·01; and ‡p < 0 001 compared with phase of 7 slow sodium tablets per day.

percentage increase in mean blood pressure going from the 50 mmol to the 100 mmol sodium per day intake was 5·0%, and 10·3% going from the 50 mmol to the 200 mmol intake. Differences in blood pressure found between the three periods of sodium intake were not affected by the order in which sodium intake was altered. During the crossover study, as daily sodium intake in the group as a whole was increased from 50 to 200 mmol, there was a corresponding increase in blood pressure (fig 1), which was consistent with a statistically significant linear trend (linear F ratio = 41·2, $p < 0·0001$; quadratic F ratio = 2·2, $p < 0·05$). This result indicates that in the group as a whole there was a linear dose response for the changes in sodium intake.

During the crossover study there was an increase in plasma renin activity and aldosterone as sodium intake was reduced. These increases were significant except for the increase in plasma renin activity on changing from the 200 to the 100 mmol sodium intake. There were no significant changes in plasma noradrenaline, sodium, potassium, or creatinine and urinary potassium or creatinine excretion. There was a gain in weight as sodium intake was increased but the changes were not significant (table).

Long-term Response

Of the 20 patients who completed the crossover study 19 have now been followed up for over a year. 1 patient moved and was lost to long-term follow-up. During follow-up, 3 of the 19 patients required the addition of drug therapy to control their blood pressure. In the remaining 16 patients blood pressure was considered adequately controlled with sodium restriction alone (systolic pressure below 155 mm Hg and diastolic below 95 mm Hg). In these patients blood pressure before entry to the study after 2 months of observation was 160/100 (2/3) mm Hg. During the crossover study with the 50 mmol sodium intake, blood pressure was 142/88 (3/1) mm Hg; during the 100 mmol intake, 150/91 (3/1) mm Hg; and during the 200 mmol sodium intake, 160/97 (3/2) mm Hg. After a year of sodium

restriction blood pressure was 142/87 (3/2) mm Hg with urinary sodium excretion of 54 (7) mmol per 24 h (fig 2). Thus blood pressure after a year of sodium restriction was similar to that during the crossover study on the 50 mmol sodium intake, when 24 h urinary sodium excretion in these 16 patients was 49 (7) mmol.

If all 19 patients who entered the long-term follow-up study are included the results were similar. Blood pressure (mm Hg) and 24 h urinary sodium (mmol) were: 144/90 (3/2) and 49 (8); 153/94 (3/2) and 111 (10); 161/99 (3/2) and 191 (11); and 145/90 (2/2) and 51 (6) on the low, middle, and high sodium intakes and during the 1 year follow-up, respectively (fig 2). For the 3 patients whose blood pressure was not controlled with salt restriction alone, the blood pressure and 24 h urinary sodium excretion on long-term follow-up was the measurement before withdrawal.

Discussion

Our double-blind randomised crossover study demonstrated that in a group of patients with mild sustained essential hypertension there was a progressive fall in blood pressure as sodium intake was reduced. The fall in blood pressure from a daily intake of 200 mmol to 50 mmol of 16/9 mm Hg is the same or greater than that seen with single drug therapy in controlled double-blind studies. This fall in blood pressure with sodium restriction was sufficient to control blood pressure in the longer term without the need for drug therapy in 16 of our 20 patients. Indeed, after a year of follow-up, blood pressure was similar to that found in the crossover study for an equivalent urinary sodium excretion (ie, around 50 mmol per day), which shows that the effect was long term. If all 19 patients who entered long-term follow-up are considered the changes in blood pressure with sodium restriction alone were similar, although the absolute levels were slightly higher. In other words, the 3 patients whose blood pressure was not controlled in the longer term with salt restriction had more severe hypertension throughout the study but responded similarly to salt restriction.

The study also showed an apparently linear dose response to sodium restriction in this group of patients. This graded response suggests that at least over the range of sodium intakes studied, there is no threshold value below which sodium intake needs to be reduced. Therefore, to obtain the maximum effect, sodium intake should be reduced as far as is practicable. The 100 and 200 mmol salt intake in our study spans that seen in the Intersalt study,[8] where the average sodium consumption as judged by urinary sodium excretion was around 160 mmol per 24 h with a range of about 100 to 240 mmol per 24 h in different communities, excluding the four communities with a urinary sodium excretion of less than 50 mmol per day. Urinary sodium excretion in the 20 patients we studied was similar to this finding with one quarter of the patients having a urinary sodium excretion above 200 mmol per 24 h before entry to the study. The mechanism whereby sodium restriction lowers blood pressure is not clear, but one of the compensatory effects that may reduce its effect in lowering blood pressure is increased release of renin and thus angiotensin II.[9] A blunted renin response and therefore a greater fall in blood pressure is more likely to occur in patients with established hypertension, in older patients, and in black patients. The differing renin response to sodium restriction probably explains at least in part why some patients respond better to sodium restriction than others.[10,11] In patients who are not controlled by sodium restriction alone, the addition of a beta-blocker[12] or a converting enzyme inhibitor[13] has an additive effect.

The major problem with salt restriction is whether patients are able or want to comply with the diet for long periods. The experience of Simpson,[14] the recent Australian trial,[2] and our data show that moderate salt restriction (to 80 mmol sodium, 5 g NaCl, per day) is quite easy in patients who eat at home and can be achieved by not adding salt to food either at the table or in cooking and avoiding foods that are known to have a large amount of salt added. Compliance with moderate salt intake is helped by the adjustment of the salt taste receptors, which become more sensitive to sodium. After 3–4 weeks of the diet, high salt foods taste unpleasant and for many patients become unpalatable. The further reduction of sodium intake, as we did in this study, to around 50 mmol a day does require the provision of some salt-free products that are not generally available, especially salt-free bread. Our experience is that if salt-free bread is available then patients can easily adhere to an intake of around 50 mmol per day provided they do not eat out regularly. The greater availability of salt-free bread and the ability to obtain processed, canteen, restaurant, and "fast" food without large amounts of salt already having been added would help in enabling patients with high blood pressure to maintain a low sodium intake. Our results show that in many patients with mild hypertension who are prepared to reduce salt intake to this amount blood pressure can be controlled without the need for additional therapy.

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REFERENCES

1. MacGregor GA, Markandu ND, Best FE, et al. Double blind-randomised crossover trial of moderate sodium restriction in essential hypertension. *Lancet* 1982; i: 351–55.
2. Australian National Health and Medical Research Council Dietary Salt Study Management Committee. Fall in blood pressure with modest reduction in dietary salt intake in mild hypertension. *Lancet* 1989; i: 399–402.
3. Stamler R, Stamler J, Grimm R, et al. Nutritional therapy for high blood pressure: final report of a four-year randomized controlled trial. The hypertension control program. *JAMA* 1987; **257:** 1484–91.
4. Roulston JE, MacGregor GA. Measurement of plasma renin activity by radioimmunoassay after prolonged cold storage. *Clin Chim Acta* 1978; **88:** 45–48.
5. James VHT, Wilson CA. Determination of aldosterone in biological fluids. In: Reid E, ed. Assay of drugs and other trace compounds in biological fluids: methodological developments in biochemistry, vol 5. Amsterdam: Elsevier, 1976: 149–58.
6. Henry DP, Starman BJ, Johnson DG, Williams RH. A sensitive radioenzymatic assay for norepinephrine in tissues and plasma. *Life Sci* 1975; **16:** 375–84.
7. George CF, Lewis TJ, Petrie A. Clinical experience with use of ultrasound sphygmomanometer. *Br Heart J* 1975; **37:** 804–07.
8. Elliott P, ed. The Intersalt study. *J Hum Hypertens* 1989; **3:** 279–407.
9. Cappuccio FP, Markandu ND, Sagnella GA, MacGregor GA. Sodium restriction lowers high blood pressure through a decreased response of the renin system-direct evidence using saralasin. *J Hypertension* 1985; **3:** 243–47.
10. MacGregor GA, Markandu ND, Sagnella GA. Dietary sodium restriction in normotensive subjects and patients with essential hypertension. *Clin Sci* 1982; **63** (suppl): 399S–402S
11. Longworth DL, Drayer JIM, Licher MA, Larach JH. Divergent blood pressure responses during short-term sodium restriction in hypertension. *Clin Pharmacol Ther* 1980; **27:** 544–46.
12. Erwteman TM, Nagelkerke N, Lubsen J, Koster M, Dunning AJ. B-blockade, diuretics, and salt restriction for the management of mild hypertension. a randomised double blind trial. *Br Med J* 1984; **289:** 406–09.
13. MacGregor GA, Markandu ND, Singer DRJ, Cappuccio FP, Shore AC, Sagnella GA. Moderate sodium restriction with angiotensin converting enzyme inhibitor in essential hypertension a double blind study. *Br Med J* 1987; **204:** 531–34.
14. Simpson FO. Salt and hypertension: current data, attitudes and policies. *J Cardiovasc Pharmacol* 1984, **6:** S4–S9.