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The INTERSALT Study: An International Co-operative Study of the Relation of Electrolyte Excretion to Blood Pressure. Design, Methods, Some Results and Implications.

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Abstract

Evidence relating salt and blood pressure is critically reviewed including the problems of bias and confounding in the epidemiological studies. Overviews of controlled trials of sodium reduction and within-population epidemiological studies give similar estimates of effect. In the trials, average blood pressure was lowered by 2.9/1.6 mm Hg systolic/diastolic for daily sodium excretion less by 70-75 mmol, whereas the epidemiological studies gave a regression estimate (corrected for reliability) of 3.7/2.0 mm Hg systolic/diastolic per 100 mmol sodium.

INTERSALT is an international co-operative study of the relation of salt and other factors to blood pressure in 10,079 men and women from 52 centres and 32 countries; field methods, and procedures of the Coordinating Centre are specified. The analysis of multicentre studies is illustrated using INTERSALT data relating systolic pressure to body weight. There was significant heterogeneity of systolic pressure-weight regression coefficients which is explored. Implications for the design and analysis of future studies are discussed.

In INTERSALT, the corrected pooled within-centre regression estimate, adjusted for age and sex, was 3.5/1.5 mm Hg systolic/diastolic per 100 mmol, reducing to 2.2/0.1 with adjustment for confounders. Age and sex specific results suggested a stronger relation at older ages, and for women compared with men. Across the centres, average sodium excretion was positively related to slope of blood pressure with age, such that 100 mmol/day lower sodium was associated with a 9 mm Hg lower rise in systolic pressure from age 25 to age 55. In the three United Kingdom centres, there was relatively high urinary sodium excretion (average 152 mmol/24-hour), sodium/potassium ratio, body mass index and prevalence of heavy alcohol drinking in men. These findings are used to illustrate the potential for non-pharmacological control of blood pressure in the community, and recommendations are made on more desirable levels of sodium intake.

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Author's Statement of Personal Contribution

Offices held: The author was the study coordinator from 1983 until present. He is also a member of the Executive Committee (which has overall responsibility for the study), the Steering Committee (with day-to-day responsibility) and the Editorial Committee (responsible for publications).

Field methods (Chapter 2 and Appendix 1): The author took a lead role in developing the study methods, including the writing of the questionnaire, the design and content of the study forms (including the clinic log book which allocated participant ID numbers), and the production of a field *Manual of Operations* to be used by local centres during the field-work and for training. The *Manual* encompassed all aspects of the field-work: sampling and recruitment, blood pressure measurement (including original methods - developed by the author - for using the random zero device), the urine collection, measurement of height and weight, quality control, organisation of clinic visits, ethical concerns and publications policy.

Equipment and materials: The author was responsible for the choice and specification of the standardised study equipment (blood pressure device, cuffs, stethoscope, urine bottles, aliquot tubes, dipsticks, labels, etc.), for ensuring adequate and timely supply of equipment to the participating centres, and for arranging payment. The author designed a plastic measuring scale and base (to estimate urinary volume) which was constructed at the London School of Hygiene and Tropical Medicine and distributed for use in the local centres.

London Coordinating Centre: The author was responsible for all aspects of the day-to-day management of the study, to include supervision of centres in the field, quality control, overview of procedures at the Central Laboratory, and supervision of the staff and activities of the London Coordinating Centre (i.e., processing of local centre data, processing of data from the Central Laboratory, data handling and data analysis). The author produced a *Manual of Operations for the London Coordinating Centre* (edited version in Appendix 1) summarising the functions and procedures of the Coordinating Centre, and an *Edit and Coding Schedule* for use by Coordinating Centre staff.

Central Laboratory (Leuven, Belgium): The author worked closely with staff at the Central Laboratory to develop quality control systems, to ensure the timely shipment of supplies to the individual centres and of urinary specimens to the Laboratory, and to facilitate the safe and reliable merging of urinary data with data held at the London Coordinating Centre. The author made frequent site visits to the

Laboratory, and continues to oversee the on-going INTERSALT biochemical analyses. The author co-produced a *Manual of Operations for the Central Laboratory* (edited version in Appendix 1).

Training of investigators: The author took a lead role in organising and running the five central training sessions held around the world: London (2), Houston, East Berlin and Singapore. The author produced training materials (slide shows and accompanying text) which were distributed to centres for local training, covering blood pressure measurement, the urine collection, ID numbers and labelling, measurement of height and weight, and organisation of clinic visits. The author trained, tested and certified investigators in blood pressure measurement using live readings (via a double-headed stethoscope) on the random zero sphygmomanometer. The author also supervised local training, testing and certification, and the drawing of random population samples, during a site visit to each of the three centres in the People's Republic of China.

Data analysis: The author had a major role in the direction and supervision of the statistical analysis, and in the presentation and interpretation of results. The author made a particular contribution to developing the method of analysis, which was conducted both at the centre (ecological) level and at the individual level (by pooling centre-by-centre regression results over all centres). The author organised the distribution of "cleaned" data to individual centres (with documentation) together with summary statistics and some exploratory analyses of each centre's data. The author continues to supervise the on-going statistical analyses at the London centre.

Presentation of results, and publications: The author organised a meeting of study investigators and the Executive Committee, where preliminary results of the study and a draft paper were presented. The author made the first public presentation of the main results of the study at the Twelfth Scientific Meeting of the International Society of Hypertension, held in Kyoto, Japan, in May 1988. These results were published in the British Medical Journal in July 1988 in the name of the INTERSALT Cooperative Research Group (see Appendix 4): the author's contribution to the paper was recognised by being named as the author for correspondence. The author wrote a summary of the results (in the name of the Cooperative Research Group) which was published in the Journal of Hypertension. The author was guest editor of a special

INTERSALT issue of the Journal of Human Hypertension (published in October 1989)[1].

Earlier versions of most of the work in this thesis have been published and/or presented at national or international scientific meetings:

Chapter 1. A review of the evidence on salt and blood pressure was presented by the author at the Canadian consensus conference on non-pharmacological approaches to the management of high blood pressure (March 1989) and published.[2] A review of the evidence from across-population epidemiological studies and an overview of within-population studies was presented by the author at a workshop on salt and blood pressure, organised by the National Heart, Lung and Blood Institute (NHLBI), Bethesda, Maryland, U.S.A. (November 1989) and published.[3] The author prepared an overview of randomised controlled studies of sodium reduction and blood pressure for the same meeting, jointly with colleagues from NHLBI. The present author initiated the idea for the overview, and identified papers for inclusion, together with Dr. Jef Cutler, and abstracted the necessary data with Dr. Il Suh (NHLBI). The present author also proposed the method of statistical analysis after discussions with Dr. Michael Hills (London School of Hygiene and Tropical Medicine). This paper is also published.[4]

Chapter 2, and Appendix 1 and 2. The INTERSALT field Manual of Operations and excerpts from the Manual of Operations for the London Coordinating Centre and Central Laboratory are published.[5]

Chapter 3. The author presented an earlier version of this paper at a meeting of the Medical Section of the Royal Statistical Society (March 1988).

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1 INTERSALT Cooperative Research Group, 1989. INTERSALT Special Isssue. Elliott P, ed. J Hum Hypertens 3: 279-408.

2 Elliott P, 1989. The INTERSALT Study: an addition to the evidence on salt and blood pressure, and some implications. J Hum Hypertens 3: 289-298.

3 Elliott P, 1991. Observational studies of salt and blood pressure. Hypertension 17 (suppl. I) I-3 - I-8.

4 Cutler J, Follmann D, Elliott P, Suh I, 1991. An overview of randomized trials of sodium reduction and blood presssure. Hypertension 17 (suppl I): I-27 - I-33.

5 Elliott P, Stamler R, 1988. Manual of operations for "INTERSALT", an international cooperative study of the relation of sodium and potassium to blood pressure. Controlled Clin Trials 9 (suppl.): 1-118S.

Chapter 4. Analyses of INTERSALT data by age and sex[6] and for the three United Kingdom centres[7] are published. The present author initiated and organised the statistical analysis, prepared the statistical tables and wrote the manuscript of both papers.

Chapter 5. Discussion of the age-sex specific results and findings for the United Kingdom centres is published[6,7] as is some of the discussion of public health implications.[2]

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6 Elliott P, Dyer AR, Stamler R, 1989. The INTERSALT Study: results for 24-hour sodium and potassium, by age and sex. J Hum Hypertens 3: 323-330.

7 Elliott P, Rogers S, Scally G, Beevers DG, Lichtenstein M, Keenan G, Hornby R, Evans A, Shipley MJ, Elwood PC, 1990. Sodium, potassium, body mass, alcohol and blood pressure in three United Kingdom centres (the INTERSALT Study). Eur J Clin Nutr 44: 637-645.

Aims and Scope of the Thesis

INTERSALT provides a wealth of data on the relation of electrolyte excretion, body weight, alcohol intake and other factors to blood pressure in the 10,079 individuals in 52 centres worldwide. The thesis could not attempt a comprehensive account of the study, its results and implications; rather, the emphasis is on a critical assessment of the evidence on salt and blood pressure, and on methodological issues.

Thus the laboratory, clinical and epidemiological evidence on salt and blood pressure is reviewed including discussion of confounding and bias in epidemiological studies across and within populations; overviews (meta-analyses) are presented of randomised controlled trials of sodium reduction and of within-population studies (Chapter 1). Detailed INTERSALT field methods and methods of the Coordinating Centre and Central Laboratory are described (Chapter 2 and Appendix 1), and methodological issues arising out of the multicentre study design are explored (Chapter 3).

Results included from INTERSALT are age and sex specific findings relating sodium and potassium excretion to blood pressure, and results for the three United Kingdom centres (Chapter 4). These results are discussed, and some of the public health implications of the study illustrated using data from the United Kingdom centres (Chapter 5).

Chapter 1

Evidence Relating Sodium And Blood Pressure

Evidence relating sodium and blood pressure (BP) has been extensively reviewed elsewhere (Battarbee & Meneely, 1978; Barter, 1982; Brown et al., 1984; Dahl, 1958; Denton, 1982; Elliott & Marmot, 1984; Final Report of the Subcommittee on Nonpharmacological Therapy, 1986; Grimm & Prineas, 1987; Laragh, 1983; MacGregor, 1983, 1985; National Research Council, 1989; Page, 1976; Pickering, 1981; Simpson, 1979, 1984; Swales, 1980; Tobian, 1979). The evidence derives from animal studies, clinical observations, human experimental studies, and epidemiological studies. In this chapter, after a brief review of the animal work, the clinical and epidemiological evidence in man (excluding INTERSALT) is critically assessed and a judgment made as to causality.

This review is timely in the sense that, in addition to INTERSALT, a number of new studies have recently been reported which add importantly to the literature. In particular, the evidence from randomised controlled trials of sodium restriction is re-evaluated in the light of recent data (including an overview analysis of all eligible studies published to date), studies of sodium restriction in populations are discussed, and an overview is presented of published within-population studies relating 24-hour sodium excretion to BP.

1.1 Animal Studies

Experimental hypertension in association with high sodium intake has been induced in several species including the dog (Coleman & Guyton, 1969; Vogel, 1966), the chicken (Lenel, Katz & Rodbard, 1948) and the baboon (Cherchovich et al., 1976). However, most investigation of sodium and BP in animals has been concentrated on the rat; for example, Meneely et al. (1953) were able to induce hypertension in rats by mixing salt with the food and allowing ad libitum consumption of food as well as water.

Several strains of rat have been bred which develop hypertension and stroke when fed high doses of salt. Dahl (1967) fed unselected Sprague-Dawley rats with chow containing 8% sodium chloride. About 75% of the rats developed hypertension within 6 to 9 months, and a few developed severe hypertension with death in one or two months, but the remaining 25% were "resistant" to salt induced hypertension. The rats that had been "sensitive" ("S" strain) or "resistant" ("R" strain) were then selectively in-bred. After 5 to 7 generations of such in-breeding, marked differences

in BP response to a high salt diet were observed (Dahl, 1972). Many of the "S" strain rats died of fulminating hypertension within one to two months, whereas all "R" strain rats remained alive and in good health after 10 to 12 months on the same regimen. When "R" strain rats were crossed with "S" strain, the BP response of the progeny was unpredictable (Dahl, 1972). It is likely that the BP response of "S" strain rats is related to a defect of renal sodium excretion (Tobian, 1979).

A Wistar-derived strain of spontaneously hypertensive rat (SHR) was described by Okamoto and Aoki (1963). Louis, Tabei & Spector (1971) showed that SHR rats developed and maintained hypertension in the virtual absence of salt in the diet, but hypertension was induced earlier and became more severe in animals fed extra sodium. Other studies showed that salt restriction could attenuate the development of severe hypertension in the SHR rat (Yamori, 1982), and also that the adverse effect of a high salt diet could be offset to some extent by adding either 2% (Yamori, 1982) or 4% potassium chloride to the feeds (Louis, Tabei & Spector, 1971). This latter finding is consistent with previous observations of Meneely, Ball and Youmans (1957), who described increased survival in rats fed a high potassium in addition to a high salt diet.

The animal studies suggest a model of sodium-induced hypertension, particularly in genetically susceptible individuals. It is possible that the chloride ion accompanying sodium is also necessary (Kurtz & Morris, 1983; Luft et al., 1988; Whitescarver et al., 1983). Within this model, BP appears to be further influenced by the moderating effects of dietary potassium (Meneely & Battarbee, 1976). To what extent the animal model translates to human essential hypertension remains an open question (Denton, 1982 p.612; Swales, 1980), but at the very least it provides experimental backing for the concept of a sodium-BP relation, and is supportive of and consistent with the evidence from human studies.

1.2 Clinical and Human Experimental Studies

1.2.1 Sodium Reduction

Sodium reduction was advocated in the treatment of hypertension early this century (Allen, 1920; Ambard & Beaujard, 1904) but did not gain favour until the 1940's, when in the absence of effective pharmacological therapy, Kempner (1944) treated severe hypertension (often associated with renal disease) using a low-sodium rice and fruit diet. Although the diet was effective in lowering BP, its low sodium content (approximately 10 mmol daily) and bland and restricted nature proved unpalatable

and unacceptable to many patients (Watkin et al., 1950). The advent of diuretic therapy, which promotes sodium as well as water loss, revolutionised the management of hypertension, and added support to the concept that sodium was important in the development of high BP.

A number of open and uncontrolled studies have suggested that moderate sodium reduction can lower BP both in children (Ellison et al., 1989; Liu et al., 1987) and in adults (Fujita et al., 1980; Gillum et al., 1983; Kawasaki et al., 1978; Miller et al., 1983, 1987; Shibata & Hatano, 1979; Weinberger et al., 1988). Recently, several controlled trials of sodium reduction have been published; these have been reviewed (Cutler et al., 1988; Final Report of the Subcommittee on Nonpharmacological Therapy, 1986; Grimm & Prineas, 1987; Grobbee & Hofman, 1986; Kaplan, 1985). For example, in each of the 13 studies cited by Grobbee and Hofman (1986) a fall in systolic (though not diastolic) BP was recorded during the low-sodium phase. Reductions in systolic pressure were on average 3-4 mm Hg for an 80 mmol reduction in 24-hour urinary sodium excretion, and tended to be greater at older ages, and with higher initial BPs. Most of these trials were small and hence of limited statistical power, and the effects on BP were significant in only three studies.

Four of the sodium restriction trials reported by Grobbee and Hofman (1986) were conducted in double-blind fashion using a randomised cross-over study design (Grobbee et al., 1987; MacGregor et al., 1982; Watt et al., 1983, 1985). This design ensured that nutritional advice was given equally in both arms of the trial (i.e., normal sodium and low sodium) since all participants were required to restrict dietary sodium prior to interventon. The first of these trials was reported by MacGregor et al. in 1982. Nineteen patients with "mild" hypertension were put on a low salt diet and then randomised to receive either placebo or slow-sodium tablets for four week periods whilst on the diet. BPs were then compared between the period on placebo (low salt) and that on salt tablets (control). An average difference in 24-hour urinary sodium excretion of 76 mmol between low salt and control periods was accompanied by statistically significant BP differences of 10 mm Hg systolic and 6 mm Hg diastolic.

Subsequent trials of similar design were less conclusive. Watt et al. (1983) found almost no difference in BP in a trial of 13 patients with mild hypertension who had successfully reduced 24-hour urinary sodium excretion by an average of 79 mmol, although the statistical power of the study was limited and confidence intervals were wide. Further studies in young people with either normal (Watt et al., 1985) or mild

elevations of BP (Grobbee et al., 1987) also found no significant effect on BP of moderate sodium reduction.

A double-blind randomised trial of sodium restriction in newborn infants has also been reported (Hofman, Hazebroek & Valkenburg, 1983). Four hundred and seventy-six newborn infants were randomly assigned to either a low-sodium or a normal-sodium diet during the first six months of life. The average amount of sodium consumed by the low-sodium group over six months was approximately one-third that consumed by the normal-sodium group: 0.89 mole sodium (sd 0.26) vs 2.50 (0.95); and, on comparing the two groups, BP (systolic) at 25 weeks was significantly lower in the low-sodium group by 2.1 mm Hg.

More recently, a number of other well designed randomised controlled studies of sodium reduction have been reported, which were not included in the earlier review of Grobbee and Hofman (1986). Using a modification of the randomised cross-over design, Macgregor et al. (1989) studied the effects on BP of differing degrees of sodium restriction. Patients were randomised to receive various combinations of slow-sodium and placebo tablets, again in double-blind fashion. Twenty patients with primary hypertension were studied on sodium regimens (estimated from urinary excretion) averaging 49 mmol, 108 mmol and 190 mmol per day. Mean BPs in the 3 periods were 147/91 mm Hg (SE 4/2), 155/95 mm Hg (SE 3/2) and 163/100 mm Hg (SE 4/2) respectively, and a significant trend of lower BPs at lower sodium intakes was observed. Of the 19 patients followed up for over a year, 16 had adequate BP control with sodium restriction alone, without resource to anti-hypertensive therapy.

The Australian National Health and Medical Research Council Dietary Salt Study Management Committee (1989) studied 108 people with untreated diastolic pressures between 90 and 100 mm Hg who were randomised into two groups, both of which were advised to reduce sodium intake to below 80 mmol per day. The "normal" sodium group was then given 80 mmol of sodium as slow-release sodium tablets, whereas the "low" sodium group was given matching placebo tablets only. This intervention perod lasted 8 weeks. On comparing the "low" and "normal" sodium groups during intervention, average daily sodium excretion was lower by 71 mmol, and average BPs were lower by 5.5 mm Hg systolic and 2.8 mm Hg diastolic ($p<0.001$, for the difference between the two groups). The study was extended to include a randomised cross-over component (using the slow-sodium/placebo design) which was undertaken by 88 of the participants who had taken part in the parallel group study (Australian National Health and Medical Research Council Dietary Salt Study Management Committee, 1989a). For a mean change in daily sodium

excretion of 67 mmol/day (SE 4), BPs were lower in the low sodium phase by 3.6 mm Hg (SE 0.7) systolic and 2.1 mm Hg (SE 0.4) diastolic, ($p<0.001$).

In a study of type II diabetics with mild hypertension, 34 patients were randomly allocated to either three months of moderate sodium restriction or to usual diabetic diet (Dodson et al., 1989). Compared with the control group, mean daily urinary sodium excretion fell by 60 mmol in the sodium restriction group, and mean supine systolic pressure by 12.9 mm Hg ($p<0.05$). There were no significant differences between the groups in diastolic pressure, although statistical power was limited given the small sample size. In an extension of the study, nine of the sodium restriction group completed a double-blind randomised cross-over study in which 4 weeks' placebo was compared to 4 weeks' supplementation by 80 mmol sodium per day. During the supplementation phase, mean supine systolic pressure was significantly higher than baseline by 11.9 mm Hg; and during the randomised part of the study, comparing sodium supplementation and placebo, BP was significantly lower by 9.7 mm Hg during the placebo (low-sodium) phase.

The studies described above were mostly of short duration and were conducted in subjects with mild to moderate hypertension. A parallel group study lasting three years has recently been reported. It was carried out in normotensive individuals (Hypertension Prevention Trial Research Group, 1990) at two levels of body mass index, and included among the interventions, reduced calorie intake, reduced sodium, and reduced sodium/increased potassium intake. In the lower body mass group at three years, there was only a small difference in 24-hour urinary sodium excretion (16 mmol, estimated from overnight urine collections) between the reduced-sodium and control groups, which was associated with a small non-significant difference in BP (0.1 and 0.2 mm Hg higher systolic and diastolic BPs respectively in the lower sodium group); at six months, however, BPs were non-significantly lower in the reduced-sodium compared to the control group, by 1.7 mm Hg systolic and 0.4 mm Hg diastolic. In the higher body mass group, results of sodium reduction were similar.

A further randomised trial, reported by R. Stamler et al. (1989) tested the use of combined nutritional therapy (reduction in sodium, in overweight and in excess alcohol) in the primary prevention of hypertension. Two hundred young adults with high-normal pressure (diastolic between 80 and 89 mm Hg) were randomised either to nutritional therapy or to a control group. In the nutritional therapy group compared to controls, average 24-hour urinary sodium excretion was lower by 30 mmol, weight

by 2.7 kg and the incidence of hypertension after 5 years was reduced by half (9% in the intervention group compared with 19% in the controls).

The review of Grobbee and Hofman (1986) was not comprehensive. For example, randomised controlled studies of sodium excretion compared with weight loss (Fagerburg et al., 1984) or a low fat diet (Puska et al., 1983) were not included. Furthermore, no attempt was made to differentiate between results from parallel group studies and cross-over studies. Both study designs have advantages and disadvantages. The parallel group study directly tests the effects of sodium restriction versus usual sodium, but valid interpretation depends on sufficient sample size to ensure similar groups at baseline; in addition, statistical power for an equivalent sample size is lower than in cross-over studies. The cross-over design enables two "treatments" to be compared in double-blind fashion: placebo (low sodium) and sodium supplementation (usual sodium), and it is statistically efficient since each participant acts as his or her own control. However, the cross-over study is prone to "period" and "carry-over" effects which may confound the analysis and interpretation, and the effect under study depends on which "treatment" was taken first. For participants randomised first to placebo, the contrast of interest measures the effect of sodium *supplementation* in those on a low-sodium diet; whereas if sodium is taken first (and assuming an adequate lead in period on the low-sodium diet), the contrast is between short term sodium supplementation (tablets) compared with sodium restriction (placebo).

Overview analysis

To overcome the difficulties with previous reviews, and to take account of recent additions to the literature summarised above, the evidence from randomised controlled trials of sodium restriction was re-evaluated in a comprehensive overview (meta-analysis) of all eligible randomised controlled studies of sodium reduction through to January 1990 (Cutler et al., 1991)[8]. Trials were identified by the present author and a co-author (J. Cutler, National Heart, Lung, and Blood Institute) from a previous review (Cutler et al., 1986), reference lists in original articles and reviews, computer searches and information from colleagues. Only published trials were considered eligible for inclusion. Data were analysed separately for trials in hypertensive and those in normotensive subjects and then combined across all trials.

[8] The overview analysis was undertaken by the present author in collaboration with Drs. Jef Cutler and I Soh, and Mr. Dean Follman, National Heart, Lung and Blood Institute (NHLBI), Bethesda, Maryland, USA. The results were presented at a workshop on salt and BP organised by NHLBI, November 1-2, 1989.

If possible, changes in potentially confounding variables were noted, e.g., potassium and alcohol intake.

The main criteria for inclusion were: random allocation of participants to sodium reduction or a control condition; trial design unconfounded by other interventions (mainly anti-hypertensive drugs or potassium supplementation), and reporting of systolic and/or diasatolic BP (in contrast to mean arterial pressure). Trials in infants and young children were excluded, as were two trials which assigned control subjects to a supplemented level of sodium well beyond usual intake (Parfrey et al., 1981; Sagnella et al., 1987); also in the study of Parfrey et al., some of the data were later withdrawn with re-publication in graphical form only (Holly et al., 1981). One further otherwise eligible trial was excluded because data on mean arterial pressure only could be obtained despite communication with the investigator (Tuck et al., 1981). Finally, in the study of Macgregor et al. (1989) discussed above, only data from the high and medium intake arms were used, to make the levels of sodium intake compared most similar to the other studies and to avoid double-counting of the data from the medium intake arm in the pooled analysis.

Information from each paper was abstracted onto a standard form by the present author, and independently by a co-author (I. Suh, National Heart, Lung, and Blood Institute), and any differences were reconciled. Design features noted included parallel group or cross-over study, BP eligibility criteria, extent of blinding of intervention and BP measurement, and duration of intervention. Sample size and outcome data were from the last follow-up visit unless only means of all visits were given. The main outcome measures were changes from baseline (parallel group studies) or differences between treatment phases (cross-over studies) in BP and 24-hour urinary sodium excretion. Means, standard deviations, standard errors, t-values and p-values were recorded for each measure when reported. In a few instances, values had to be estimated from figures. Where possible, information for potentially confounding factors was also recorded, including body weight, urinary potassium excretion and alcohol intake.

For each trial, an attempt was made to estimate the variance of the treatment effect for the outcome measures, i.e., systolic and diastolic BP. Ideally, these values should be obtained from standard deviations of paired differences, between baseline and end of follow up for each group (parallel groups) or between each of the two treatment periods (cross-over design); or, if these statistics are not given, from exact t-values or p-values. If an exact variance of paired differences could not be derived, then one was imputed, either by inverting a boundary p-value (e.g., $p<.05$ became $p=.05$) or

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assuming a correlation of 0.5 between initial and final BP. (These figures are the basis for the standard errors shown in Tables 1 and 2.) Since only nine trials provided adequate data to derive an exact variance for BP changes, and 14 required variance imputation as described, results were pooled weighting simply by sample size (Demets, 1987) thereby assuming that all the trials which were pooled had the same underlying variance for changes in the outcome measures. (The sample size weights are n for cross-over trials, and $n_t n_c / n_t + n_c$ for parallel trials, where n_t and n_c are sample sizes for the treatment and control groups). Pooling was also carried out weighting each trial by the inverse of the variance (Demets, 1987), derived or imputed. The overall variance of BP change, which is required to calculate the standard error of the pooled mean, was estimated by the average of those exact variances of paired differences that could be derived.

Tables 1 and 2 summarise details of individual trials, including whether or not the study was placebo controlled, blinding of BP observers, duration of study, difference in urinary sodium excretion and change in BP between intervention and control, and data on confounding variables. Twenty-three trials met the selection criteria (Australian National Health and Medical Research Council Dietary Salt Study Management Committee, 1989, 1989a; Chalmers et al., 1986; Cooper et al., 1984; Costa et al., 1981; Dodson et al., 1989; Erwteman et al., 1984; Fagerberg et al., 1984; Grobbee et al., 1987; Hypertension Prevention Trial Research Group, 1990; Logan, 1986; MacGregor et al., 1982, 1989; Maxwell et al., 1984; Morgan et al., 1978; Morgan & Myers, 1981; Myers, 1989; Parijs et al., 1973; Puska et al., 1983; Richards et al., 1984; Silman et al., 1983; Skrabal, Aubock & Hortnagl, 1981; Watt et al., 1983, 1985). Five of these trials were reported as two strata or two phases so that there are 28 entries in the tables (Australian National Health and Medical Research Council Dietary Salt Study Management Committee, 1989, 1989a; Dodson et al., 1989; Morgan & Myers, 1981; Puska et al., 1983; Watt et al., 1985). Overall, there were 18 trials in hypertensive and 6 in normotensive individuals, giving data on a total of 1,536 people (one trial, Puska et al., 1983, reported on both hypertensive and normotensive individuals).

Table 1

Randomised trials of sodium reduction in hypertensive individuals

Author year	Sample size[1]	Blinding	Study length (months)	Urinary Na change (mmol/day)	BP change (mm Hg) (SE) SBP	DBP	Reported confounding factors[2]
Crossover studies							
Parijs 1973	15	NR	1	-98	-6.7 (3.76)	+3.2 (3.47)	(Wt)
MacGregor 1982	19	Placebo BP Obs	1	-76	-10 (3.06)	-5 (1.78)	Wt (K)
Watt 1983	18	Placebo	1	-56	-0.5 (1.50)	-0.3 (0.80)	(Wt) (K)
Richards 1984	12	NR	1-1.5	-105	-5.2 (4.10)	-1.8 (3.55)	(Wt) (K)
Grobbee 1987	40	Placebo BP Obs(RZ)	1.5	-72	-0.8 (1.80)	-0.8 (1.55)	(Wt) (K)
MacGregor 1989	20	Placebo BP Obs	1	-82	-8.0 (2.60)	-5.0 (1.62)	(Wt) (K)
Dodson 1989	9	Placebo BP Obs(RZ)	1	-76	-9.7 (4.33)	-5.1 (2.94)	(Wt) (K)
ANHMRC 1989	88	Placebo	2	-67	-3.6 (0.70)	-2.1 (0.40)	(K)
Parallel studies							
Morgan 1978	31/31	BP obs	24	-27	-1.5 (4.60)	-6.9 (2.12)	NR
Costa 1981	20/21	NR	12	NR	-18.3 (4.35)	-5.9 (2.91)	NR
Morgan 1981(male)	6/6	BP obs	2	-98	NR	-6.0 (4.08)	K
Morgan 1981(female)	6/6	BP obs	2	-78	NR	-4.0 (3.30)	K
Silman 1983	10/15	BP obs(RZ)	12	-53	-8.7 (10.23)	-6.3 (4.41)	(Wt) (K)
Puska 1983	15/19	BP obs	1.5	-117	+1.8 (4.14)	+0.5 (2.37)	Wt K Alc (P/S)
Fagerberg 1984	15/15	NR	2.3	-89	-13.3 (5.46)	-6.7 (3.07)	(Wt) (K) (Alc)
Maxwell 1984	18/12	NR	3	-171	-2.0 (4.96)	+2.0 (2.84)	Wt
Erwteman 1984	44/50	BP obs(RZ)	6	-58	-2.7 (2.20)	-3.4 (1.70)	NR
Chalmers 1986	48/52	NR	3	-54	-5.1 (1.42)	-4.2 (0.90)	(K)
Logan 1986	37/38	BP obs	6	-32	-1.1 (2.15)	-0.2 (1.41)	Wt (K)
Dodson 1989	17/17	BP obs	3	-59	-13.0 (5.99)	-1.8 (3.48)	(Wt) (K)
ANHMRC 1989	50/53	Placebo	2	-71	-5.5 (1.48)	-2.8 (0.85)	(Alc)

1. In parallel study"/" denotes treatment group/control group.

2. Parentheses denote controlled factors, and no parentheses denote possible confounders.

Abbreviations: Alc, Alcohol; ANHMRC, Australian National Health and Medical Research Council; NR, Not reported; Obs, observer; P/S, Polyunsaturated fatty acid/saturated fatty acid ratio; RZ, Random-zero sphygmanometer; Wt, Weight.

Table 2

Randomised trials of sodium reduction in normotensive individuals

Author year	Sample size[1]	Blinding	Study length (months)	Urinary Na change (mmol/day)	BP change (mm Hg) (SE) SBP	DBP	Reported confounding factors[2]
Crossover studies							
Skrabal 1981	20	NR	0.5	-170	-2.7 (2.36)	-3.0 (2.03)	Wt (K)
Cooper 1984	113	BP obs	2	-69	-0.6 (0.84)	-1.4 (1.07)	Wt (K)
Watt 1985(HH)	35	Placebo BP obs(RZ)	0.9	-74	-1.4 (0.74)	+1.2 (0.93)	(Wt) K
Watt 1985(LL)	31	Placebo BP obs(RZ)	1	-60	-0.5 (0.82)	+1.4 (0.90)	(Wt) (K)
Myers 1989	172	BP obs	1	-130	-3.5 (1.25)	-1.9 (0.90)	(Wt) (K)
Parallel studies							
Puska 1983	19/19	BP obs	0.5	-117	-1.5 (3.32)	-1.1 (2.03)	Wt K Alc (P/S)
HPTRG 1990	174/177	BP obs	36	-16	+0.1 (1.00)	+0.2 (0.80)	(Wt) K

1. In parallel study"/" denotes treatment group/control group.

2. Parentheses denote controlled factors, and no parentheses denote possible confounders.

Abbreviations: Alc, Alcohol; NR, Not reported; Obs, observer; P/S, Polyunsaturated fatty acid/saturated fatty acid ratio; RZ, Random-zero sphygmomanometer; Wt, Weight; HH, subjects with parents in the top third of their age-specific BP distribution; LL, subjects with parents in the bottom third of their age-specific BP distribution; HPTRG, Hypertension Prevention Trial Research Group.

In hypertensive individuals, eight of the trials were cross-over, entirely or in part, with an aggregate of 221 subjects. Treatment periods were one to two months, with median sodium reduction of 76 mmol (range 56 to 105 mmol). The pooled estimate of BP change in hypertensive individuals from cross-over trials was, for systolic and diastolic BP, -4.33 (SE 0.73)/-1.98 (SE 0.33) mm Hg. Twelve trials reported results for hypertensive subjects from parallel designs. In two of these studies, the parallel group trial preceded a cross-over study included above (Dodson et al., 1989; Australian National Health and Medical Research Council Dietary Salt Study Management Committee, 1989). A total of 652 subjects were studied including these two trials. Median follow-up was 3 months, and median sodium reduction, net of controls, was 65 mmol (range 27 to 171 mmol). One trial did not report urinary data (Costa et al., 1981), but intracellular sodium concentration was lower in the intervention group by 22.8% after 12 months follow-up. The pooled estimate of BP change in hypertensive subjects from parallel group trials was -5.28 (SE 0.89)/-3.36 (SE 0.56) mm Hg, systolic/diastolic BP. When inverse variance weights were used, the BP effects were slightly smaller (Cutler et al., 1991). There were only two parallel group studies in normotensive subjects, so that results by type of study are not given separately.

The pooled results (cross-over and parallel group studies) for both hypertensive and normotensive individuals are summarised in Table 3. In the studies of hypertensive subjects, median sodium reduction of 72 mmol was associated on average with BP lower by 4.9 mm Hg systolic and 2.6 mm Hg diastolic. In the normotensive subjects, sodium reductions ranging from 16 to 170 mmol (median 74 mmol) were associated with BPs lower by 1.7 mm Hg systolic and 1.0 mm Hg diastolic. Over all studies, pooled BP reductions of 2.9 mm Hg systolic and 1.6 mm Hg diastolic were observed. All these BP changes were highly significant. There was also some evidence for a dose response with a tendency for larger falls in BP to be associated with greater reductions in sodium intake (Cutler et al., 1991).

Since this overview was completed, results of a further randomised cross-over study in normotensive individuals have been published (Mascioloi et al., 1991). Forty-eight individuals with average BP 131/84 mm Hg were put on a reduced sodium diet and, after a run-in period of 10 weeks, were randomised to receive either sodium supplementaion of 96 mmol/day or placebo for periods of four weeks each. At the end of the sodium supplementation period, BPs were higher by 3.6 (SE 0.9) mm Hg systolic ($p<.001$) and 2.3 mm Hg (SE 0.8) diastolic ($p=.005$). These results are consistent with the findings from the overview analysis above.

Table 3

An overview of randomised controlled trials of sodium reduction and blood pressure†

	BP Change (SE) (mm Hg)	
	SBP	DBP
Trials in hypertensive subjects (N=18 trials)	-4.92** (0.65)	-2.64** (0.42)
Trials in normotensive subjects (N=6 trials)	-1.70** (0.50)	-0.97* (0.33)
All trials (n=1,536 people)	-2.91** (0.39)	-1.60** (0.25)

† Pooled estimates were obtained by weighting according to sample size.

* $p<0.01$ ** $p<0.001$

In summary, randomised controlled trials have shown that sodium reduction is associated with reductions in BP; this association is likely to be causal as generally issues of bias and confounding were adequately addressed. The size of effect was larger in parallel group than cross-over studies, and in hypertensive than in normotensive individuals.

1.2.2 Sodium Reduction and Drug Therapy

Several investigators have studied the treatment of hypertension by a combination of drug therapy and sodium reduction (Beard et al., 1982; Bulpitt et al, 1984; Dodson, Pacy & Cox, 1985; Kristinsson et al, 1988; Luft & Weinberger, 1988; Macgregor et al, 1987; Weinberger et al., 1988). In general, these studies have shown an additive effect between sodium restriction and drug therapy, although the use of sodium reduction with calcium antagonists may be an exception (Luft & Weinberger, 1988; Cappuccio, et al., 1990) so that lower doses of drugs can be used by some patients whilst still achieving adequate control of BP (Beard et al., 1982; Dodson et al., 1985; Weinberger et al., 1988). For example, in the study of Beard et al. (1982) in which patients on medication for "mild" hypertension were randomly allocated to a reduced sodium or usual diet, about one third of the intervention group were without drug therapy at 12 weeks and a further 50% were managed on a reduced dose of drugs. By contrast, no reduction in therapy was recorded by two thirds of the control group ($p<0.001$, for the difference between the two groups).

Two major controlled trials (both in participants who had been enrolled in the Hypertension Detection and Follow-up Program - HDFP) have reported on the efficacy of nutritional advice in maintaining BP control without drug therapy (Langford et al., 1985; Stamler et al., 1987). In the Dietary Intervention Study in Hypertension (DISH) (Langford et al., 1985) participants who were taking anti-hypertensive medication were randomly allocated either to continue or to stop therapy. Of those randomised to the "no medication" group, participants were further randomised to a control group (no nutritional advice), a sodium reduction group or (for overweight individuals) a weight reduction group. The trial lasted 56 weeks. Overall, 33% lower sodium intake (reduced by about 50 mmol per day) was achieved in the sodium reduction groups. By the end of the trial, 44.9% of overweight individuals who were reducing sodium remained off medication, as did 53.4% of those who were not overweight, compared with 35.3% and 45.0% respectively in the control groups. In multiple logistic regression, compared with controls, sodium reduction was associated with a more than two-fold relative odds of remaining without medication ($p<0.05$).

In the Hypertension Control Program (HCP) (Stamler et al., 1987) participants with mild hypertension which was well controlled on drugs were randomised to one of three groups: discontinued drug therapy and a nutritional programme to reduce overweight, excess salt and alcohol consumption (group 1); discontinued drug therapy, with no nutritional programme (group 2), and continued drug therapy (group 3). 24-hour sodium excretion fell 36% (60 mmol) in group 1, and at four years, 39% remained normotensive without drug therapy compared with 5% in group 2 (controls). The study was designed to test a combination of non-pharmacological approaches and therefore did not give an estimate of the independent effect of sodium restriction on BP: participants in group 1 also experienced an average weight loss of 1.8 kg, and a modest reduction in alcohol intake.

These studies suggest that in hypertensive patients, sodium reduction (either alone or together with weight loss and moderation of alcohol intake) can reduce the amount of medication required to control BP; in some cases, particularly in "mild" hypertension, BP may be controlled by dietary measures alone.

1.2.3 Sodium Reduction in Populations

The results of two controlled studies of sodium reduction in general population samples have recently been published (Staessen et al., 1988; Forte et al., 1989). Staessen et al. (1988) report on a study in two Belgian towns, one randomly selected to intervention, one acting as a control town. Intervention consisted of a media campaign via posters, leaflets, local radio and newspapers, which promoted the avoidance of added salt in cooking and at the table, and the purchase of foods without added salt. In addition, local general practitioners advised individual patients to reduce their sodium intakes. Random samples of households in both intervention and control towns were contacted at baseline in 1979/80, and further samples were recruited five years later, to obtain measurements of BP and self-reported (unsupervised) 24-hour collections of urine (the method of urine collection changing between baseline and follow-up periods). At follow-up, average daily sodium excretion in men had decreased by approximately 12 mmol in both towns, but for women there was a decrease in the intervention town of 17 mmol and an increase in the control town of 8 mmol, the difference being significant at $p<0.01$. Persons aged 50 or more showed larger differences (-24.5 mmol intervention, +17.0 mmol control, $p<0.01$). Although these differences were unrelated to BP, confidence intervals were wide (reflecting both the limited sample size, particularly for the baseline surveys, and the study design which increased variance estimates by using different samples at baseline and follow-up).

Forte et al. (1989) have reported the results of the Portuguese salt intervention trial, which was carried out in two rural communities, one of which acted as control. At the outset, daily average adult salt intake was 21 g (357 mmol), and 30% of people had a diastolic BP of 95 mm Hg or above. Intervention consisted of advice to eat less salt accompanied by a request to the local bakers to reduce sodium in bread. There was a high degree of community involvement, and intervention was strongly supported by village leaders and local medical and nursing staff. Intervention was reinforced by frequent meetings, discussions and small training groups to instruct housewives on cooking with less salt. In the intervention community, average sodium intake fell by 162 mmol and average BPs by 3.6 mm Hg systolic and 5.0 mm Hg diastolic at 1 year, and 5.0 mm Hg and 5.1 mm Hg respectively at 2 years. In the control community, average sodium intake increased by 19 mmol; there was little change in diastolic pressure, but systolic pressure rose during the study, thus increasing the difference between the two groups. This difference in BP trends between the two communities was highly significant ($p<0.001$). In addition, changes in BP in individuals in the intervention community correlated positively and significantly with changes in urinary sodium/creatinine ratio.

A further study of sodium reduction in a school setting has also recently been published (the Exeter-Andover project). In a non-randomised study, Ellison et al. (1989) reduced the sodium content of the food served in one of two boarding schools, with the other school acting as control. After one year, the intervention and control schools were reversed. BP was monitored among 341 subjects during the control years and 309 during the intervention years. The average age of participants was about 15 years. Approximately 28% of sodium intake, as determined from 24-hour food histories, was obtained outside the schools. Students recorded their own BPs using an automatic device. Overall, a 15% to 20% reduction in sodium intake over an intervention period lasting about 24 weeks (i.e., allowing for a run-in period and school holidays) was associated with BPs lower by 1.7 (SE 0.59) mm Hg systolic and 1.5 (SE 0.48) mm Hg diastolic.

The Portuguese salt trial showed that intervention could successfully lower both sodium intake and BP, albeit in a community consuming large amounts of salt. A beneficial effect of intervention was also found in school children in the Exeter-Andover project, where modest changes in sodium intake were associated with changes in BP of between one and two mm Hg. By contrast, the Belgian trial was largely unsuccessful in its intervention, and only relatively small differences in sodium excretion and BP were observed.

1.2.4 Sodium Loading Experiments

Experiments in man have shown that BP may rise following a large salt load, possibly related to a volume effect. McQuarrie, Thompson & Anderson (1936) described observations on four diabetic children in whom excess sodium intake of more than 700 mmol of sodium chloride daily resulted in higher BP. Blood pressure fell when potassium chloride was added to the diet in two patients. Body weight also fell during this period, suggesting that an acute sodium diuresis may have occurred during the potassium supplementation period.

More recently, a series of sodium-loading experiments in both black and white normotensive subjects have been reported (Grim et al., 1977, 1979; Luft, Weinberger & Grim, 1982; Luft et al., 1977, 1979, 1979a). When two-litres of normal saline were given intravenously over four hours to 34 white and 34 black men and women, BP went up, significantly so in black women (Luft et al., 1977). In a subsequent study of similar loading with Normal saline in 270 white and 77 black subjects, BP of the black group was significantly higher than the white group after the sodium load (BP in the white subjects actually fell during hospitalisation) and it remained elevated until after administration of frusemide (Luft et al., 1979); and, in a small study of 14 volunteers, sodium intakes of 600 to 1,500 mmol per day resulted in a rise in BP, especially in black subjects (Luft, et al., 1979a; Luft, Weinberger & Grim, 1982).

In another small study, no significant changes in BP were noted when 8 normotensive white men were fed high sodium diets of either 210 or 410 mmol per day (Kirkendall et al., 1976); and in a study of sodium supplementation of 180 mmol per day following one week's diuretic therapy, BP rose significantly in 33 subjects with borderline hypertension, but not in 12 normotensive subjects (Fujita, Noda & Ando, 1984). However, BP rose when the diets of 10 men from the highlands of Papua New Guinea were supplemented with 128 and 256 mmol of sodium above their usual intake of about 30 mmol per day (Rikimaru et al., 1988).

The effects described here are acute and short-term, and are the result of loading with large amounts of sodium. Only small numbers of people have been studied in this way, and the relevance to the aetiology and pathogenesis of high BP is unclear. Nonetheless, the results are consistent with other evidence in so far as supplementation with (very) large amounts of sodium is associated with higher BP.

1.3 Epidemiological Evidence

Epidemiological evidence relating sodium and BP comes from a variety of studies across and within populations, conducted with differing methodologies and unstandardised measurements of both sodium intake and BP (Elliott & Marmot, 1984; Simpson, 1979). In reviewing the evidence here, the aim is firstly to discuss some of the methodological issues involved so that the results can be put in context, and secondly to summarise the contribution of this large body of work to our understanding of the epidemiology of sodium and BP. Studies in migrants are also reviewed.

1.3.1 Across-Population Studies

A positive across-population association between salt and BP was first described by Dahl (1960) who found, across five population groups, a remarkable straight line relationship between average sodium intake of a population and the prevalence of hypertension. Dahl (1960) noted also that hypertension was uncommon in populations consuming less than 4 or 5 gram of salt per day (i.e., about 70 to 80 mmol), and hypothesised that salt increased the probability of raised BP in a group, though not necessarily in an individual.

Publication of Dahl's straight line graph stimulated others to review the literature for data on mean sodium intake and mean BP of populations (Froment, Milon & Gravier, 1979; Gleibermann, 1973; Macgregor, 1985; McCarron, Henry & Morris, 1982; Simpson, 1984). These studies generally confirmed the Dahl relationship, but, to a greater or lesser extent, suffered from a number of uncertainties and bias. A major concern is that the data were not derived from one standardised source, but from a variety of studies in the published literature in which unstandardised and often unspecified methods were used. Often data on sodium intake and BP for a particular population were derived from different sources, and, in the well-known paper by Gleibermann (1973), the author's own estimates of sodium intake (6 g salt per day) were used for six of the 27 populations studied, whilst in a further ten "a quantitative value for mean salt consumption was reported with or without indications as to how it was calculated" (Gleibermann, 1973). A further problem is that systematic error of measurement in a population (e.g., of BP) may have introduced bias into the across-population comparisons.

Few data on confounding variables were available for consideration in these cross-cultural (ecological) studies. Because of multiple social, geographical and

environmental differences between populations around the world (which may also relate to differences in BP) relationships in ecological studies are particularly susceptible to major and unmeasured confounding (Piantadosi, Byar & Green, 1988). Under these circumstances, there is a danger of making inappropriate inferences concerning relationships in individuals from data on groups. This problem has been termed the "ecological fallacy" and is discussed in more detail in Chapter 3.

One of the most comprehensive ecological studies of sodium and BP was published by Froment, Milon and Gravier (1979), using data in the literature from 28 populations around the world. Results were presented separately by sex, and at approximate ages 20 and 50 years. Data on sodium intake were based on urinary excretion of sodium from 24-hour urine collections (although not necessarily from the same studies as the BP data) except in the Solomon Islands where "spot" (casual) urine collections and questionnaire data were used (Page, Damon & Moellering, 1974), and in St. Kitts, West Indies, where estimates of sodium intake again relied on spot urine collections (Schneckloth et al., 1962). The same value for sodium was included in the regression equations for both men and women, although most surveys have shown lower sodium excretion in women (see, for example, Doyle, Chua & Duffy, 1976; Elliott et al., 1988; Simpson et al., 1978) which may be related in part to differences in body weight (Watson et al., 1980).

Some results using the data published by Froment et al. (1979) are summarised in Table 4. The first two columns give the regression coefficients relating mean BP and mean sodium intake in 50 year old men and women, across all 28 populations described by Froment, Milon and Gravier (1979). The coefficients relating systolic BP and sodium are approximately 10 mm Hg per 100 mmol sodium, and those relating diastolic BP and sodium are between 5 and 6 mm Hg per 100 mmol. However, as shown by Elliott & Marmot (1984) these regression analyses are strongly influenced by the nine populations with low average sodium intakes (less than 2 gram salt per day). Strictly speaking, these nine "low salt" populations are not "independent" of one another, four being included from Papua New Guinea (Maddocks, 1967; Maddocks & Rovin, 1965; Sinnett & Whyte, 1973; Whyte, 1958) and three from the Solomon Islands (Page, Damon & Moellering, 1974). The remaining two populations were the !Kung bushmen of Northern Botswana (Truswell et al., 1972) and the Yanomamo Indians of Brazil (Oliver, Cohen & Neel, 1975). These nine isolated populations were likely to have had the least adequate data for both sodium intake and BP, and to have differed from the remainder in many ways other than sodium intake. When the nine populations are excluded from the analysis,

as shown in the last two columns of Table 4, the regression slopes relating sodium and BP are reduced and, although positive, are no longer significant[9].

The paper by Froment, Milon and Gravier (1979) also allowed an estimate of the relation between sodium and BP slope with age (estimated from data at approximate ages 20 and 50). In the 28 population analysis, the regression coefficients indicated that 100 mmol lower sodium intake was associated in men with a 7.7 mm Hg lower rise in BP over a 30 year period, and an 8.3 mm Hg lower rise in women ($p<.001$ for both analyses). Seven of the 9 "low salt" populations (and 2 others) recorded lower mean BPs with increasing age. Again, the size of association relating sodium and slope of BP with age was reduced when the nine low-sodium populations were excluded.

Positive ecological relations between average sodium intake and average BP have also been found across different communities within individual countries. In Japan, extremely high levels of sodium intake have been recorded, particularly in the Northern prefecture of Akita (Sasaki, 1964) and BPs have also tended to be high in North Japan compared with the South (Hatano, 1975). Komachi and Shimamoto (1980) showed a positive correlation ($r=0.69$) between the prevalence of hypertension at ages 50 to 59 and average daily sodium intake across eight Japanese communities. In China, significant positive correlations ($r=0.62$ in men, $r=0.81$ in women) were found relating average systolic BP and average nine-hour sodium excretion across 12 and ten population samples in men and women respectively (Liu & Lai, 1986); and across the five Chinese centres participating in the CARDIAC Study, there was a positive correlation between urinary excretion of sodium (estimated from 24-hour collections) and both systolic ($r=0.79$) and diastolic BP ($r=0.65$) (Yamori, 1989).

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[9] To some extent, this result may reflect the smaller number of populations and the more limited range of sodium intakes in the analysis which excludes the low-sodium populations. A similar point has been made concerning the truncation of the distribution of centres in INTERSALT, where four low-sodium centres were excluded from some across-population analyses (National Research Council, 1989).

Table 4

Regression coefficients (SE) relating mean blood pressure at age 50 and mean sodium intake across 28 populations, and across 19 populations excreting more than 2 g of salt per day †

	Regression Coefficients (mm Hg/100 mmol sodium)			
	28 Populations		19 Populations	
	Systolic	Diastolic	Systolic	Diastolic
Men	10.0**	6.1**	5.3	2.6
	(2.0)	(1.3)	(3.0)	(1.9)
Women	9.8*	5.5*	3.0	1.1
	(2.9)	(1.6)	(4.2)	(2.4)

† Adapted from Froment, Milon and Gravier (1979)

* $p<0.01$ ** $p<0.001$

In six Solomon Island societies, the community with the highest sodium excretion had the highest BPs (Page, Damon & Moellering, 1974) and in Newfoundland, higher mean sodium intake and higher BPs were found in an island fishing community compared to an inland mining and logging community (Fodor, Abbott & Rusted, 1973). In the United States, higher BPs in Blacks compared to Whites were found both in children (Berenson, Voors & Dalferes, 1979) and in adults (Grim et al., 1980) and were associated in Blacks with lower urinary excretion of potassium, and a higher sodium/potassium ratio (Grim et al., 1980); and in South Africa, where Blacks are known to have a high incidence of hypertension, urinary sodium excretion was higher and potassium lower in a group of black compared to white normotensive adults (Barlow et al., 1982).

Stroke and stomach cancer

Further indirect evidence for an ecological relationship between salt and BP is the observation that mortality from stroke and stomach cancer are highly correlated both across countries and within countries over time (Joossens, 1968, 1980; Joossens et al. 1971). Salt is postulated to be an aetiological factor common to both diseases (Joossens, 1968, 1980). For example, in Belgium, where the mortality from both diseases is declining, Joossens (1979) reports a decline also in 24-hour sodium excretion, from 15.2 g per day (per 1.77 g of creatinine) in 1966 to 8.4 g per day in 1978-79. This contrasts with an estimated sodium intake in 1920 in Belgium of 17 g per day.

Although Joossens' hypothesis is of interest, there are inconsistencies, and a decline in sodium intake has not been observed in all countries studied. For example, in the United States where mortality from stroke has been declining since at least 1920 (Moriyama, Krueger & Stamler, 1971), the amount of salt in the food supply is estimated to have increased by 14% since about 1910 (Friend, Page & Marston, 1979). Whelton and Goldblatt (1982) re-examined the relationship between stomach cancer and stroke mortality and found no significant relationship when percentage changes in mortality from 1958-1970 were compared between different countries. They also found no association between a diagnosis of stroke and stomach cancer of individuals, by analysing multiple cause death certification in England and Wales for 1975 and 1976.

In summary, across-population (ecological) studies of sodium and BP generally support Dahl's finding that the mean sodium intake of a population is positively correlated with mean BP, but they rely on a variety of unstandardised field methods

and are subject to varying degrees of bias and confounding. Regression analyses across populations appear to be particularly influenced by a number of remote and isolated populations with low sodium intakes and low BPs.

1.3.2 Within-Population Studies

A different set of problems befall studies of salt and BP within populations. As pointed out by Watt and Foy (1982), as many as 5700 participants, each collecting a single 24-hour urine specimen, may be required to demonstrate a true regression slope between systolic BP and sodium of 10 mm Hg per 100 mmol sodium, the value of the across-population slope observed by both Gleibermann (1973) and Froment, Milon and Gravier (1979), resulting in a lack of statistical power of all but the largest studies. This is because (at least in most Western populations) true differences in urinary sodium excretion between persons are swamped by the large day-to-day variation within persons, so that individuals are grossly misclassified with respect to their true ("habitual") sodium excretion (Liu et al., 1979). The result is a major bias towards a zero regression relationship between BP and sodium; such bias has been termed "regression-dilution" by MacMahon et al. (1990).

This problem of measurement should be contrasted with the situation for other variables like body weight, where within-person variability is small in comparison to between-person variability, and individuals can be classified appropriately into groups (e.g., based on "high" and "low" values) using a single (casual) measure (Liu et al., 1982). Associations with an outcome variable (e.g., between overweight and high BP) are thus much more readily demonstrated than is the case for sodium and BP.

In addition to regression dilution, another major potential source of bias in within-population studies of sodium and BP is the difficulty in obtaining complete 24-hour urine specimens in general population samples (Pietinen et al., 1976). The effect of undercollection of urine specimens and the importance of regression dilution are illustrated by results of a small methodological study conducted in a random sample from a general practice in North London (Elliott et al., 1988). In this middle aged and elderly population with a large spread of daily sodium excretion, the day-to-day variation in electrolyte excretion of the individual was small in comparison with other studies. Analysis of repeated urine collections in a sub-sample indicated that day-to-day within-individual variation in sodium excretion biased regression slopes by only 14% (based on a single 24-hour urine collection) compared with a downward bias of over 75% in some other studies (Liu et al., 1979). Under these circumstances,

whereby individual sodium excretion was apparently well characterised by a single 24-hour urine collection, the within-population regression estimates relating sodium and systolic BP were similar to those predicted by Gleibermann (1973) and Froment, Milon & Gravier (1979) from the across-population studies; and the results were statistically significant even though the sample size was relatively small.

Results are summarised in Table 5. The regression slope relating systolic BP and sodium was 9.1 mm Hg/100 mmol sodium, after adjustment for age, sex and body mass index. With correction for reliability, which statistically adjusts for the regression-dilution bias introduced by physiological within-person variability in sodium excretion, the systolic BP-sodium regression slope was 10.6 mm Hg/100 mmol sodium. However, because of incompleteness of urine collections, it is probable that this reliability-corrected estimate was still too low. Although all 58 participants reported complete collections, only 28 of the collections were found to be complete by excretion of para-amino-benzoic-acid (PABA), a biological marker given orally (as capsules) during the day of the urine collection. Among the 28 people with complete collections, the regression estimate of the systolic BP-sodium relation, after adjustment for confounding variables, was 14.5 mm Hg/100 mmol sodium. A similar progression in the size of regression slopes was found for sodium and diastolic BP (Table 5).

Further methodological problems of within-population studies include statistical "over-adjustment" of the BP-sodium relationship for covariates (such as body weight) which are much more precisely measured than sodium, giving estimates of the sodium effect which are biased down towards zero in multiple regression analyses (Liu, 1988); and other biases caused by the effects of anti-hypertensive drug treatment on BP, and by hypertensive individuals selectively changing their diets as a consequence of the diagnosis of high BP (Elliott et al., 1987; Hashimoto et al., 1989).

Table 5

Age, sex and body mass index adjusted regression coefficients relating blood pressure and sodium excretion in a North London population§ with consideration of the effects of within-person variability of sodium excretion, and incompleteness of urine collections

	Regression coefficients (SE) (mm Hg/100 mmol sodium)	
	Systolic BP	Diastolic BP
All persons (n=58)	9.1* (3.7)	2.5 (2.0)
All persons, corrected for reliability (point estimate)†	10.6	2.9
"Complete collectors" by PABA‡ excretion (n=28)	14.5* (5.9)	5.9 (3.0)

§ From Elliott et al., 1988

† Correction for reliability based on repeat measures

‡ Para-amino-benzoic-acid

*$p<0.05$

Within-population studies of salt and BP have used a variety of dietary methods to estimate sodium intake, from a salt frequency questionnaire to multiple 24-hour urine collections. Early reports by Dahl and Love (1954) that the frequency of adding salt to food at table was related to prevalence of high BP were supported by the findings of one study (Finn et al., 1981) but could not be confirmed in other studies (Dawber et al., 1967; Miall, 1959). Recent data from the United Kingdom suggest that the proportion of non-discretionary sodium in the diet of Western industrialised populations is as high as 85% of intake, mostly added in the manufacturing process (Sanchez-Castillo et al., 1987; Shepherd & Farleigh, 1987). Given the variability in sodium content of many processed foods (Bender, 1977) methods using diet history are unlikely to give reliable estimates of the sodium intake of individuals. Nonetheless, significantly positive relations of dietary sodium with BP have been described in studies from Belgium (Kesteloot & Joossens, 1988) Northern Kashmir (Mir & Newcombe, 1988; Mir et al., 1986) and Southern California (Khaw & Barrett-Connor, 1988), and significantly negative relations in one study from the Netherlands (Kok et al., 1986). In a study from South Africa (Steyn et al., 1986) and another American study (Swaye, Gifford & Berrettoni, 1972), no significant differences were found in the dietary intakes of sodium in normotensive and hypertensive individuals; and analyses of dietary data from the first US National Health and Nutrition Examination Survey (NHANES) gave conflicting results. In analyses of the same NHANES data set but using different statistical methods, relations of sodium with BP were variously described as positive (Gruchow, Sobocinski & Barboriak, 1985) inverse (McCarron et al.,1984) and also as displaying no relationship (Harlan et al., 1984).

Most studies have measured the urinary excretion of sodium as a proxy for intake. With the marked diurnal cycle in creatinine, electrolyte and water excretion (Ram & Reddy, 1970; Wesson, 1964) and the large variations in sodium excretion which are apparent even hour-to-hour (Stanbury & Thomson, 1951), a minimum collection period of 24 hours is considered necessary to adequately represent sodium intake (Pietinen & Tuomilehto, 1980). However, several studies have reported on the use of a casual or "spot" urine collection which is a far simpler method for epidemiological surveys, although its validity has been questioned (Cummins, Shaper & Walker, 1981). Of the nine population studies using the spot urine method which were identified in the literature, seven reported significantly positive sodium-BP relationships (Costa, 1981; Khaw, 1983; Khaw & Rose, 1982; Kihara et al., 1984; Poulter et al., 1984; Simmons, 1983; Takemori et al., 1989) whereas only two

reported no significant association (Walker et al., 1979; Prior et al., 1968), and none a significantly negative relationship.

Similarly, overnight urine collections are more readily obtained than 24-hour collections, and compliance is likely to be higher in epidemiological surveys (Pietinen et al., 1976). Although correlated with 24-hour urinary excretion of sodium (Liu et al., 1979a; Luft, Fineberg & Sloan, 1982) sodium estimated from overnight collections is also subject to methodological difficulties; for example, there is some evidence that hypertensive individuals excrete a relatively greater proportion of sodium at night than normotensive subjects (Dyer et al., 1987). Six population studies using the overnight urine method have reported significantly positive associations with BP (Faust, 1982; Hsiao et al., 1986; Liu, Tao & Lai, 1984; Liu, Xie & Fang, 1988; Page et al., 1981; Pan et al., 1990) including four studies of Chinese populations (Hsiao et al., 1986; Liu, Tao & Lai, 1984; Liu, Xie & Fang, 1988; Pan et al., 1990). Only one study using overnight sodium excretion has reported a non-significant relationship with BP (Dai, Kuller & Miller, 1984), and, as with spot urines, no significantly *negative* studies were identified in which an overnight urine collection was used to estimate sodium intake. Given the practical and methodological difficulties in conducting these studies, the above results are remarkable, but perhaps indicate a degree of publication bias towards positive results.

Studies of 24-hour urinary sodium excretion and blood pressure: overview analysis

Most within-population studies have used 24-hour urine collections to estimate sodium intake. Both positive and negative correlations with BP have been described, although many studies lack statistical power and are too small to show significant associations. The literature was searched to identify those studies of 24-hour urinary sodium and BP which could be incorporated into an overview analysis. The aim was to include all studies that published a quantitative regression or correlation estimate, either positive or negative, of the relation of sodium to both systolic and diastolic BP in populations. Thus studies which compared sodium excretion in hypertensive and normotensive individuals (i.e., case-control studies) were not eligible, as they do not provide a quantitative estimate of effect; in addition, such studies are difficult to interpret (Watt & Foy, 1982) and are susceptible to bias, both in the selection of individuals (some studies being based in hospital hypertension clinics) and also because hypertensive patients may alter their dietary habits as a consequence of their diagnosis (Elliott et al., 1987; Hashimoto et al., 1989). Excluded from the overview for this reason are two Australian studies (Doyle, Chua & Duffy, 1976; Morgan, Carney & Wilson, 1975), one American (Dahl, 1957) and one Japanese study

(Shibata & Hatano, 1979) which showed a significantly positive association between being hypertensive and sodium excretion; a study from Scotland which showed a significantly negative association (Beevers, Hawthorne & Padfield, 1980), and other studies showing no significant association (Dawber et al., 1967; Bing, Thurston & Swales, 1979; Fodor & Rusted, 1980; Miall, 1959; Phear, 1958; Thulin, Karlberg & Scherstén, 1978; Tuomilehto et al., 1980). Two studies which found no significant difference in sodium excretion on comparing hypertensive and normotensive subjects, also provided regression-correlation estimates at the individual level (Berglund et al., 1976; Ljungman et al., 1981) and are discussed below.

Another group of studies was ineligible for the overview because they reported non-significant BP-sodium associations without giving a quantitative estimate, e.g., results were reported as "not-significant" or showing "no correlation"; this includes studies in the United States (Langford & Watson, 1973), New Zealand (Simpson et al., 1978), Germany (Schlierf et al., 1980), Australia (Armstrong et al., 1979), Malawi (Simmons et al., 1986), South Africa (Sever et al., 1980) and Japan (Komachi and Shimamoto, 1980).

Other studies gave some quantitative estimates, but only when the results were statistically significant. Because nearly all of these significant findings were of a positive association, inclusion of these studies could have introduced a bias towards a positive relation if significantly negative findings were being underreported. Additionally, selective inclusion of significant results (either positive or negative) would tend to enter more extreme values into the overview analysis. Studies excluded from the overview for this reason include those reporting significantly positive BP-sodium associations in China (Kesteloot et al., 1987), Korea (Kesteloot et al., 1980), Belgium (Joossens et al., 1980) and Norway (Omvik, Lund-Johansen & Eide, 1983). Two Swedish studies were also excluded which reported correlations with sodium (for diastoic BP only) separately for hypertensive and normotensive individuals (Berglund et al., 1976; Waern & Aberg, 1979). (The correlations were significantly negative in the hypertensive group and significantly positive in the normotensive group.) Another Swedish study found a significantly positive association between sodium excretion and mean arterial pressure amongst normotensive individuals (but not in the group as a whole) but gave no data on correlations of sodium with systolic and diastolic BP (Ljungman et al., 1981); and a study in the United States found significant correlations between various estimates of 24-hour sodium excretion and mean arterial pressure in simple (but not multiple) regression, but again gave no data for systolic and diastolic BP, although it was

implied that they were significantly correlated with sodium excretion (Grim et al., 1978).

Fourteen studies (of sixteen populations) remained which fulfilled the entry criteria (Bulpitt et al., 1986; Connor et al., 1984; Elliott et al., 1988; Joossens et al., 1971; Karvonen & Punsar, 1977; M'Buyamba-Kabangu et al., 1986; Pietinen, Wong & Altschul, 1979; Prior & Stanhope, 1980; Sinnett & Whyte, 1973; Smith et al., 1988; Staessen et al., 1981, 1983; Strazzullo et al., 1983; Watson et al., 1980). These studies are listed in Table 6, together with their sample sizes, regression coefficients and standard errors. From each population, the regression estimates were either directly obtained (Elliott et al., 1988; Joossens et al., 1971) or algebraically derived from the Pearson-r correlation coefficient and the standard deviations of both sodium and BP (Armitage & Berry, 1987, p.152). One otherwise eligible study of 33 individuals was excluded from the overview, since data on standard deviations were absent (Farleigh, Shepherd & Land, 1985). Data were available only for simple (unadjusted) regression; where data (e.g., standard deviations) were given stratified by some other variable, e.g., age (Prior & Stanhope, 1980) the appropriate unbiased (whole sample) estimate was obtained by analysis of variance (Armitage & Berry, 1987, pp. 186-192). Where possible, regression coefficients were separately obtained for men and for women in each population and then averaged to give an overall estimate of association. Two studies reported data only for men and women combined (Elliott et al., 1988; Pietinen, Wong & Altschul, 1979). Regression slopes were pooled by weighting with the inverse of the variance (Demets, 1987); total sample sizes for the three analyses were 7,099 men, 6,136 women, and 12,503 men and women combined.

The results are shown in Table 7, after correction for reliability using the INTERSALT estimate of 0.46 (INTERSALT Cooperative Research Group, 1988). Statistically highly significant positive relationships were seen in all analyses. As in INTERSALT, regression coefficients were somewhat larger in women than in men (see Chapter 4). Overall, for men and women combined, the regression coefficient corrected for reliability indicated systolic pressure lower by 3.7 and diastolic pressure lower by 2.0 mm Hg for sodium lower by 100 mmol.

Table 6

Overview of studies of 24-hour urinary sodium excretion and blood pressure: Summary of data abstracted

Study	Sex	n	Mean Age	Regression Coefficients (mm Hg/100 mmol sodium) Systolic b(SE)	Diastolic b(SE)
1. Joossens,et al., 1971	M	1314	44.7	3.35***(0.91)	2.29***(0.55)
	W	713	46.6	4.88** (1.82)	1.53 (0.88)
2. Sinnett,et al., 1973	M	138	30-39*	-10.24 (10.29)	-11.63 (7.55)
	W	135	30-39*	-3.45 (7.47)	4.93 (4.84)
3. Karvonen,et al.,1977					
West Finns	M	98	63.7	-4.67 (2.94)	-2.20 (1.48)
East Finns	M	94	62.9	-0.67 (2.32)	1.11 (1.15)
4. Watson,et al., 1980					
Blacks	W	356	†	1.78 (1.29)	0.10 (1.29)
Whites	W	104	†	2.47 (3.08)	-1.76 (4.47)
5. Prior, et al., 1980	M	234	35-44§	3.06 (3.85)	0.45 (2.11)
	W	261	35-44§	2.25 (6.07)	2.18 (3.30)
6. Staessen, et al., 1981	M	233	41.0	-0.95 (1.25)	0.82 (0.90)
	W	202	40.4	2.01 (2.03)	-0.38 (1.34)
7. Staessen, et al., 1983	M	273	41.6	-0.59 (1.19)	1.02 (0.88)
	W	255	39.3	2.07 (1.85)	-0.19 (1.19)
8. Strazzullo, et al., 1983	M	188	40.6	3.99 (2.07)	5.56***(1.45)
9. Connor, et al., 1984	M	170	36	1.79 (1.14)	0.84 (0.92)
	W	182	36	3.77 (1.99)	2.46* (1.13)
10. M'Buyamba-Kabangu et al.,1986	M	144	32	1.85 (3.88)	0.99 (2.77)
	W	169	32	5.27 (3.11)	1.85 (2.04)
11. Bulpitt,et al., 1986	M	459	45	0.29 (1.37)	-0.86 (1.01)
	W	159	46	2.77 (2.76)	2.08 (1.83)
12. Smith, et al. 1989	M	3754	40-59‡	0.61 (0.40)	0.39 (0.25)
	W	3600	40-59‡	1.94** (0.59)	1.04***(0.33)
13. Pietinen, et al. 1979	M&W	50	26.4	7.01** (2.06)	3.75* (1.86)
14. Elliott, et al. 1988	M&W	58	57.9	9.5* (3.6)	4.3* (2.1)

M=Men W=Women §Age group including median age † Young persons (originally screened at high school)
‡ Range
*p<0.05 **p<0.01 ***p<0.001

Table 7

Overview of population-based studies of 24-hour urinary sodium excretion and blood pressure: Pooled regression coefficients b (SE)‡ (mm Hg/100 mmol sodium) by sex, and for men and women combined.

	n†	Systolic BP b(SE)‡	Diastolic BP b(SE)‡
Men	7,099	1.78* (0.66)	1.55** (0.42)
Women	6,136	4.80** (0.98)	2.02** (0.59)
Men & Women Combined	12,503	3.65** (0.62)	1.98** (0.37)

‡ Corrected for reliability using INTERSALT estimate of 0.46 (INTERSALT Cooperative Research Group, 1988)

† Pooled sample size. Two studies gave data for men only (Karvonen & Punsar, 1977; Strazzullo et al., 1983), one for women only (Watson et al., 1980) and two studies gave data for men and women combined only (Elliott et al., 1988; Pietinen, Wong & Altschul, 1979).

*p<0.01 **p<0.001

1.3.3 Longitudinal Studies

The epidemiological studies discussed above, relating sodium excretion and BP in individuals and populations, are cross-sectional with measurements of both variables taken close together in time. The resulting regression-correlation estimates will be too small if the relevant exposure is sodium intake accumulated perhaps over many years, or if sodium intakes are changed as a consequence of high BP. An alternative approach is to follow people up over time to see how well their sodium excretion at baseline predicts future BP levels. Geleijnse, Grobbee & Hofman (1990) report the results of the only one such observational study that has been published (other than a study of migrants discussed below).

A cohort of 596 children aged 5 to 19 years was randomly selected for study between 1975 and 1978, from the population of two districts in the western part of the Netherlands. Geleijnse, Grobbee & Hofman (1990) report on 233 of these children, who were aged up to 17 at entry, and who had at least six yearly examinations. BP was measured using a random zero sphygmomanometer; urine was collected as six timed overnight samples. The estimated change in systolic BP per year was 0.003 mm Hg/mmol sodium which, although not significantly different from zero, was identical to the INTERSALT estimate based on cross-sectional data on differences in BP with age (see Chapter 4, and INTERSALT Cooperative Research Group, 1988). A significantly negative slope of BP with age was found for potassium excretion (-0.045 mm Hg/year/mmol potassium) and a significantly positive slope for the urinary sodium/potassium ratio (0.356 mm Hg/year/unit ratio).

1.3.4 Migrant Studies

Another method of examining the effects of dietary and environmental influences on BP is to study migrants. Most of these studies have compared different cross-sections of people before and after migration. For example, Shaper, Williams & Spencer (1961) investigated the nomadic Samburu tribe of northern Kenya. The staple fare of the men was milk and meat; the diet was high in fat and protein and low in carbohydrate. The men were lean, BPs were low and neither weight nor BP appeared to increase with age. Subsequently, Samburu warriors serving with the army in Kenya were studied and compared to young warriors in their home districts (Shaper et al., 1969). By the second or third years of army service, systolic BP was significantly higher in recruits than in controls, and the difference became more marked after longer army service. Shaper et al. (1969) estimated that salt intake increased on entering the army from about 3.5 g per day (60 mmol) on the traditional

Samburu diet to as much as 16 g per day (270 mmol) on army rations, and suggested that the higher BPs seen in the recruits could have been related to their high salt diets. However, other marked changes in the diet were observed (Shaper, 1972; Shaper et al., 1969) so that which of the various dietary, weight or social changes was causally related to the BP rise, and how much of the BP difference was related to selection effects, remains an open question (Shaper, 1967, 1972). Higher BPs and prevalence of hypertension in migrants from low BP communities have also been observed in other societies (Cruz-Coke, Etcheverry & Nagel, 1964; Prior & Stanhope, 1980; Scotch & Geiger, 1963; Sever et al., 1980).

The effect of migration has recently been reported from a study of the Luo, in which the BP of recent migrants to Nairobi was compared to that of a control population living in the home villages in rural western Kenya (Poulter et al., 1990). Blood pressure was measured with a random zero sphygmomanometer and three 12-hour overnight urine samples were collected on up to five occasions from within 60 days, until up to two years after arrival in Nairobi. Blood pressures of the migrants were higher than those in the rural villages, even at the first examination, approximately one month after migration; mean body weight, pulse rate, urinary sodium excretion and sodium/potassium ratio were all higher in the migrant group, and urinary potassium was lower. Ninety of 163 new male migrants had been examined prior to migration when their BP was similar to that of rural controls, suggesting that the higher BPs in the migrants was not due to selective migration (Poulter, Khaw & Sever, 1988). The authors conclude that environmental factors including an increase in sodium intake, reduction in potassium intake and an increase in the sodium/potassium ratio are important factors in the shift in the BP distribution towards higher values when a low BP community becomes urbanised (Poulter et al., 1990).

1.4 Summary

The evidence relating sodium and BP is largely concordant from animal studies, clinical observations, human experimental studies, and epidemiological studies within and across populations; the balance of evidence favours a causal association. Some of the additional evidence from INTERSALT, again largely consistent, is presented and discussed in Chapters 4 and 5.

The animal studies show importantly the existence of a model for salt-induced hypertension. In humans, the observational data are consistent in showing that higher sodium is associated with higher BP, although as discussed, these studies are subject

to important methodological difficulties and biases which confuse their interpretation. Across-population epidemiological studies are positive, but rely on data drawn from the international literature based on a variety of unstandardised field methods, and are prone to unmeasured (ecological) confounding. Within-population studies, on the other hand, generally lack statistical power, and are subject to major regression-dilution bias (due to large day-to-day variation in sodium excretion) which could conceal true relationships of sodium to BP. Nonetheless, an overview of studies of 24-hour urinary sodium excretion and BP showed positive and highly significant sodium-BP relationships both for men and for women, and for systolic and diastolic BP. An overview of the randomised controlled trials of sodium reduction and BP in individuals showed that lower sodium intake can lower BP; the effect may be more marked at higher BPs and with greater sodium reduction. The estimates of effect from overviews of the within-population epidemiological studies and the randomised controlled trials are quantitatively similar: for daily sodium excretion lower by 100 mmol, systolic BP is lower by 3.7 mm Hg, and diastolic BP lower by 2.0 mm Hg (within-population studies) compared to 2.9 systolic and 1.6 mm Hg diastolic (randomised controlled trials). Estimates obtained from studies across-populations are somewhat larger, and may to some extent reflect ecological confounding (see Chapter 3).

The findings presented here have implications both for individuals, and populations (i.e., for public health). In treated hypertensive patients, clinical observation and trial data suggest that sodium reduction (either alone or in combination with weight loss and moderation of alcohol intake) can reduce the amount of medication required to control BP, and in some cases BP may be controlled by dietary measures alone, particularly in those whose hypertension is "mild" (i.e., uncomplicated and with less marked elevations of pressure). At the population level, the Portuguese Salt Trial showed that intervention can be successful in lowering both sodium intake and BP, although this was not achieved in a community trial in Belgium.

The implications of a policy of sodium reduction, including the issue of possible "sodium sensitivity", are discussed further in Chapter 5.

Chapter 2

The INTERSALT Study: Aims, Design and Field Methods

In this Chapter, the INTERSALT aims, study design and field methods are briefly described; detailed field methods based on the INTERSALT protocol and field Manual of Operations are given in Appendix 1. Procedures of the London Coordinating Centre (at the London School of Hygiene and Tropical Medicine) and Central Laboratory (at St. Raphael University Hospital, Leuven, Belgium) are also described in Appendix 1 in an edited version of the Manual of Operations for these centres. A brief description of the rationale for the study, its aims, design and field methods has been published and is included in Appendix 4 (INTERSALT Cooperative Research Group, 1986).

2.1 Origin and Aims of INTERSALT

INTERSALT arose out of a project given to fellows at the First Advanced 10-day Teaching Seminar of the Council on Epidemiology of the International Society and Federation of Cardiology (ISFC), held in Tuohilampi, Finland, in 1982. The fellows were asked to re-evaluate the across-population evidence on salt and BP and design a study to test Dahl's salt hypothesis (Dahl, 1960). The study soon grew to become a major international cooperative study, conducted in 52 centres and 32 countries worldwide. It was recognised early on that the key to its success was the collection of highly standardised data, with great emphasis put on detailed specification of methods, centralised training and a high degree of quality control.

The main aims of INTERSALT were firstly, to investigate relationships across populations between BP (and high BP) and the urinary excretion of sodium, potassium and the sodium/potassium ratio, and secondly, to investigate these same relationships in individuals. Major confounding variables were age, sex, body weight and alcohol intake. Various subsidiary hypotheses were also identified (for example, the relation of calcium and magnesium excretion to BP).

2.2 Design, Sample Size and Power

INTERSALT was a multicentre cross-sectional epidemiological study. Selection of centres was done according to presumed sodium intake, to achieve as large a variation as possible across-centres in the main independent (x) variable under study. Thus centres were chosen in presumed low-sodium populations such as the Yanomamo and Xingu Indians of Brazil, and presumed high-sodium centres in Japan,

Portugal and China. In the event, although four low-sodium centres were included, there was none with a truly high intake (INTERSALT Cooperative Research Group, 1988).

The sample size was calculated so as to achieve high statistical power (>90%) to detect across-population regression slopes of BP-sodium, significant at the 5% level, equal to regression slopes predicted by Froment, Milon & Gravier (1979) at young (around 20 years) and older ages (around 50 years). The across-centre standard deviation in sodium used in the power calculations was taken to be 5.83 g salt/day based on the recruitment of 45 centres into the study and a presumed distribution of sodium excretion as follows: 6 with 2.0 g salt/day; 11 with 7.0; 11 with 10.0; 11 with 14.0, and 6 with 22.0 g salt/day. Estimates of variance of BP across populations were taken from the regression analyses given by Froment, Milon and Gravier (1979) and an estimate of within-population variance of BP was obtained from the Whitehall Study.

With more than 45 centres, each with 50 people in each age-sex group (males/females; young/old), the statistical power was more than 95% for the across-centre analyses. Increasing the number of participants per centre had little effect on the across-centre power calculations. For the within-centre (individual) relationships, the statistical power of the study was dependent on the total sample size recruited into the study, and was little influenced by the number of centres; in analyses of 10,000 people, the study had power to detect correlations between variables of the order of r=0.02, significant at the 5% level.

It was recognised in advance that the statistical power for the across-centre analysis would be much reduced if the spread of sodium excretion across centres was limited either by failure to recruit low- or high-sodium centres, or by excluding them in the analysis.

2.3 Field Methods

In this section the INTERSALT field methods are briefly summarised. Methods are specified in detail in an edited version of the INTERSALT Field Manual of Operations which is given in Appendix 1. The Manual was used as the basis for training of investigators from the 52 centres of the study, and was used by the centres during field collection. The data forms which were used in the study and which accompany the Manual can be found in Appendix 2. A more complete account of the

INTERSALT methods is published, including those for the London Coordinating Centre and the Central Laboratory (Elliott and Stamler, 1988).

Briefly, each centre was asked to recruit 200 men and women aged 20-59 years, stratified by age and sex into eight 10-year groups (i.e., men 20-29, men 30-39, etc.). Whenever possible the samples were selected at random from population lists (e.g., electoral or general practice registers, lists of factory employees) or by chunk sampling of defined populations (e.g., whole island or village communities). A brief description of the 52 centres (in 32 countries) included in the study is given in Appendix 3.

Whenever an unacceptable report - for example, incomplete urine collection - was identified during data collection, the centre was asked to recruit an extra (supplementary) participant from the same age and sex group in strict order of random allocation. This was to facilitate the goal of 200 analysable reports per centre; occasionally, fewer than 200 were available. Thus data were received on 10,648 eligible participants, of whom 569 (5.3%) were excluded, 568 because of problems with the urine collection and one because of an incomplete BP measurement. Data on the remaining 10,079 people - 5,045 men and 5,039 women - were the basis of the INTERSALT reports.

Blood pressure (sitting) was measured twice on a single occasion by a trained observer using a random zero sphygmomanometer (0-20 mm variation in the random zero) and the bell of a Littmann stethoscope, after participants had emptied their bladders and sat quietly for 5 minutes. A range of cuff sizes was used to allow for differing arm circumferences. Diastolic pressure was recorded when sounds disappeared (phase 5).

Each participant provided both a casual ("spot") urine specimen and a 24-hour urine collection, the start and end of which were supervised by clinic staff. Urine collections were rejected if found to be incomplete on interview, or if urinary volume was less than 250 ml in 24 hours. The height of urine in each jar was measured on a standard platform and scale devised at the London School of Hygiene and Tropical Medicine (Figure 9) and later converted into volume by computer in London. A random 8% of participants completed a second urine collection for the estimation of within-individual variability in electrolyte excretion, enabling a correction to be made for reliability. Urine aliquots were kept at -20^0 C and sent frozen to the Central Laboratory in Leuven, Belgium, for the measurement of electrolyte concentration.

Height and weight were measured in standard fashion, using a stadiometer and beam balance where possible. Seven day alcohol intake was assessed by questionnaire, using local data to convert consumption into ml absolute alcohol per week. The questionnaire also included history of hypertension, current medicines (including anti-hypertensive agents), education, social state and changes in diet (including salt intake). When necessary data forms and the questionnaire were translated into the local language and checked by back-translation into English. Indoor and outdoor ambient temperatures were recorded.

Data forms were sent to London for review, edit, coding, data entry and analysis. They were checked on receipt for completeness and consistency, and queries were referred back to the local centres for clarification. The London Centre also reviewed each centre's recruiting documents and urine collection registers as a further check on sampling procedures and data completeness and accuracy. All data were entered twice into the computer; a random 5% of forms were double-coded.

Sodium and potassium were analysed by emission flame photometry (American Association of Clinical Chemists, 1961). Reference samples were created at the start of the study and included in each day's analysis to monitor laboratory variation. Quality control was monitored in London by comparing results on anonymous duplicate (split) samples sent blind to the Central Laboratory for the estimation of technical error. Percent technical error was 1.4% (sodium) and 1.9% (potassium).

Chapter 3

Design Issues in Multicentre Epidemiological Studies: An Example from INTERSALT

3.1 Introduction

In this Chapter, some of the theoretical and practical issues that arise in the design and analysis of multicentre epidemiological studies are discussed. An approach to the analysis is illustrated using INTERSALT data relating systolic BP to body weight both across-and within-centres, and possible heterogeneity of the within-centre relationships is explored. Implications for the design of future studies are addressed.

Many studies "..are not large enough to answer the questions we want to answer as reliably as we would want to answer them" (Peto, 1987). Although Peto was referring above to the sometimes huge sample sizes demanded of modern clinical trials, equally his remarks could apply to many epidemiological studies. Often achieving the sample size desired of a study is beyond the resources of a single institution or centre. One possibility for enhancing sample size is to extend the investigation to several centres, in a so-called multicentre study. When such data are collected, i.e., at the group (population) level as well as in individuals, they are said to have a *hierarchical structure* (Goldstein, 1987).

The hierarchical or multi-level structure of many data sets and its importance in statistical modelling has been recognised in both the sociological literature (Firebaugh, 1978; Goodman, 1953, 1959; Robinson, 1950; Valkonen, 1969) and in studies of educational effectiveness (Aitken & Longford, 1986; Goldstein, 1987). In educational research, the inherent hierarchical structure of the data is readily apparent, with effects on individual pupil performance depending on peer grouping within classes, classes within schools and higher level aggregates, for example schools within local education authorities (Aitken & Longford, 1986). However in the epidemiological literature, relatively little attention has been paid to the implications of this data structure, either in the design of studies or in the statistical analysis.

In one of the few epidemiological papers to address this issue, Feinleib and Leaverton (1984) took as an example the first U.S. National Health and Nutrition Survey (NHANES I), in which data were collected across the United States in 100 examination centres from a national probability sample of U.S. residents (National Center for Health Statistics, 1977). The data were originally presented without regard

to the centre structure (see for example, National Center for Health Statistics, 1983) effectively treating them as if from one large population sample. To examine relationships both within and across the centres, Feinleib and Leaverton (1984) reanalysed some of these data, but with retention of the hierarchical structure. Some striking differences emerged between the within- and across-centre findings, for example in the relations of body weight to serum cholesterol. Piantadosi, Byar and Green (1988) carried out a similar analysis using data from the Second Health and Nutrition Survey, and again found important differences in the within- and across-centre results. As discussed further below, the across-centre findings in these analyses were relatively unstable, since nearly all of the variation in the explanatory variables was within centres and there was relatively little variation across centres (Piantadosi, Byar & Green, 1988).

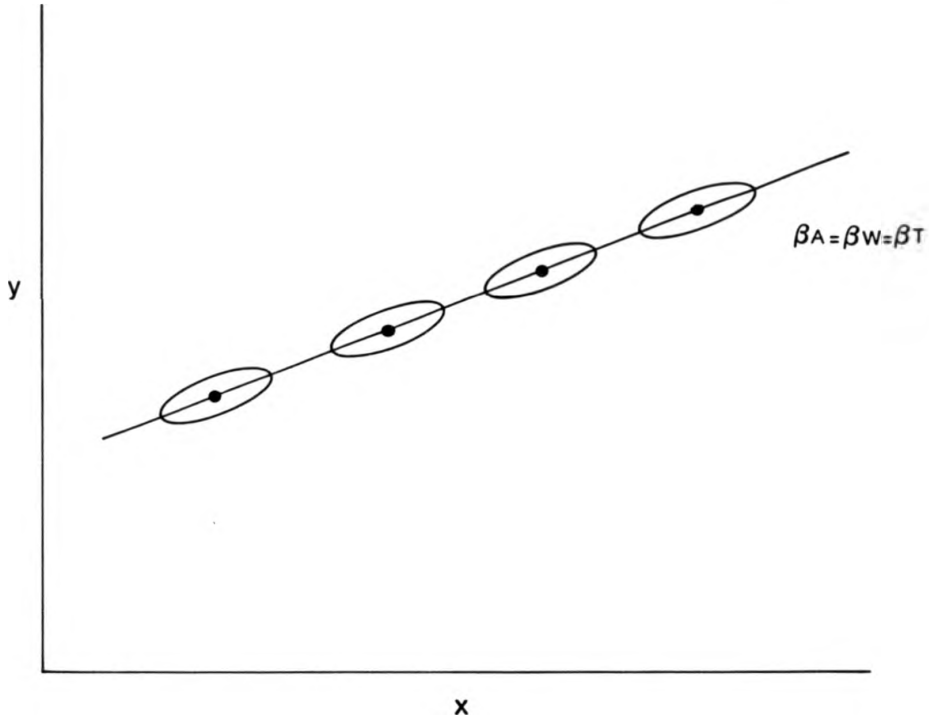
Feinleib and Leaverton (1984) further analysed the NHANES I data to see whether any of the within-centre associations differed when examined across the centres; they found for example, significant heterogeneity of the within-centre correlations relating individual body weight and systolic BP. They discuss the difficulties of generalising findings even from within the same "level" of analysis, e.g., between geographical areas within a country, or from one time-frame to another, and conclude that pooling of data without regard to the inherent structure may lead to a biased estimate of effect.

The danger of extrapolating from findings across centres to relations at the level of individuals is well-known, and has been called the "ecological fallacy" (Piantadosi, Byer & Green, 1988; Robinson, 1950). Nevertheless, Blackburn and Jacobs (1984) argue that in epidemiological studies both across- and within-population relationships are important and judgments as to causality should depend on both sets of data. They cite as an example the relationship between saturated fat intake and serum cholesterol which is strongly positive across populations (consistent with the experimental evidence) and weak or absent within populations.

3.2 The Multicentre Design: Theoretical Considerations

Let us consider a hypothetical case where data are collected on individuals in a number of population *centres*. Figure 1 illustrates a hypothetical "true" relationship between an outcome variable y and an "explanatory" variable x measured in the different centres. The dots give average x and y of the centres and the ellipses represent the cloud of observations on individuals in each centre.

Figure 1



Representation of "true" relationship between response variable y and independent variable x in different centres, with fitted regression lines

Key: β_A = across-population slope; β_W = within-population slope;
β_T = regression slope in individuals, ignoring centre

Potentially, three different regressions can be specified: an ecological (*across*-centre) regression of mean y on mean x, with true regresson slope β_A; a *within*-centre regression of individual values of y on individual values of x, with true regression slope β_W; and a regression of individual y on individual x *ignoring centre*, with true regression slope β_T. For the purposes of the arguments set out here, we shall assume that all three regression slopes coincide, i.e., the "true" regression slope of y on x, shown in the figure by the solid regression line, is $\beta=\beta_A=\beta_W=\beta_T$.

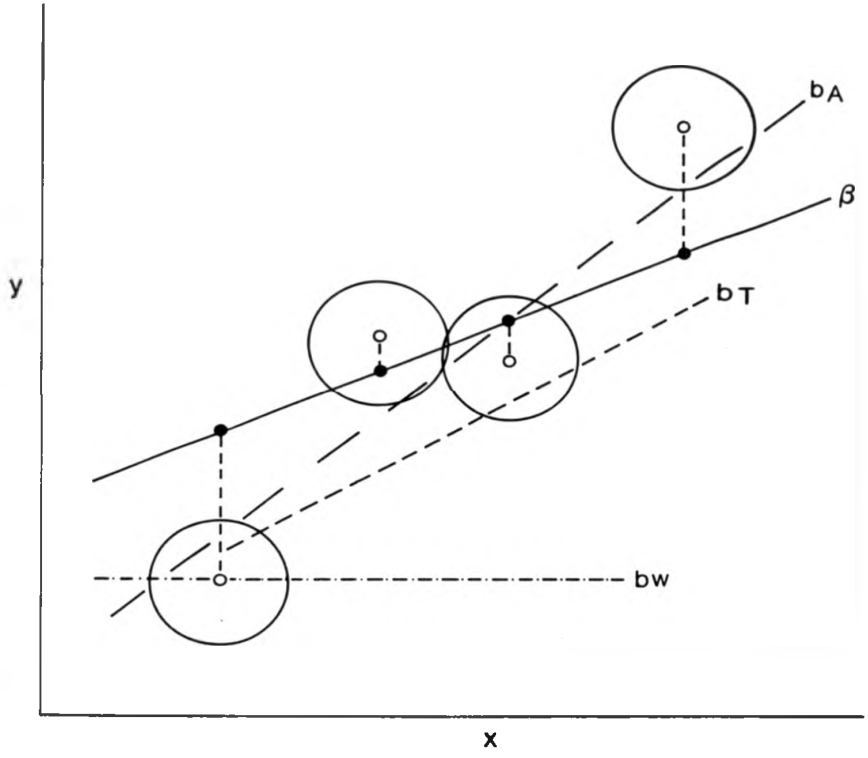
Now consider what might happen when the "true" data illustrated in Figure 1 are observed (measured) in practice, as shown in Figure 2. Here the filled dots represent the "true" across-centre relationship between y and x (as Figure 1) and the open dots the observed relationship (the difference being due to across-centre confounding by variables other than y and x). The observed within-centre relationship of y on x is shown as circles around the open dots, again representing the cloud of individual observations within the centre, but now in this example the relationship is weak because it has been diluted by within-centre confounding, and also by "measurement errors", i.e., so-called "regression dilution" (see Chapter 1 and Section 3.4, Discussion, below). The observed across-centre regression of mean y on mean x is b_A, and the average observed within-centre regression slope is b_W. Whereas β_A, β_W and β_T coincide (Figure 1) the observed regression slopes b_A and b_W are very different, the regression being strongly positive across centres and essentially zero within centres. This situation is commonly observed in epidemiology, as discussed by Blackburn & Jacobs (1984) in reference to the relation of dietary fat to serum cholesterol (noted above) or as seen in Chapter 1 with reference to salt and BP.

The observed regression slope b_T (obtained by disregarding the hierarchical structure of the data) lies between b_W and b_A; in general (in simple regression) it is the *weighted average* of b_W and b_A, where b is given weight = R_{XX} and b_W weight ($1-R_{XX}$), and where R_{XX} is the proportion of the total sum of squares of x that is across-centres (Aitken & Longford, 1986; Piantadosi, Byar & Green, 1988);

i.e., $$b_T = R_{XX}\, b_A + (1 - R_{XX})\, b_W.$$

Being a combination of b_A and b_W, b_T is not in itself of interest, yet in most multicentre studies, the data are combined and reported in this way without regard to the inherent hierarchical structure; this has been called "lumping" or "collapsing" of the data (Demets, 1987).

Figure 2



Representation of "observed" relationship between response variable y and independent variable x in different centres.

The data in Figure 1 have been subjected to positive ecological confounding across centres, and "regression-dilution" bias within centres.

Key: ß = "true" regression slope (as Figure 1); b_A = observed across-population slope; b_W = observed within-population slope; b_T = observed slope in individuals, ignoring centre

3.2.1 The Hierarchical Model

In this section, the hierarchical model is briefly discussed; further details can be found elsewhere (Aitken & Longford, 1988; Goldstein, 1987). Let us again consider the simple regression model shown in Figures 1 and 2 relating a y-variable to a single x-variable, where the data have been collected in a number of centres giving a simple hierarchical structure. (The method can readily be extended to encompass more complex models with a number of explanatory variables). An estimate of the regression coefficient relating average change in y to unit change in x is required; potentially *two* regression estimates are of interest: b_A (from the *across*-centre or ecological regression of average y on average x) and b_W (from the regressions relating individual y to individual x *within*-centres). As can be seen below, these two estimates are statistically independent (Aitken & Longford, 1988; Blackburn & Jacobs, 1984; Goldstein, 1987).

For convenience, in the following discussion, the regression equations are centred around the mean and not around the origin. Suppose that we observe centre differences in y are observed that can not be explained by the regression of y on x within centres, then:

$$\text{(i) } y_{ij} = \alpha_i + \beta_i(x_{ij} - \bar{x}_i) + e_{ij} \text{ (Within-centre model)}$$

where y_{ij} and x_{ij} are the y- and x-values of the jth individual in the ith centre; α_i ($= \bar{y}_i$) is the mean "centre effect" for the ith centre; β_i is the within-centre regression coefficient for the ith centre; $\bar{x}_i$ is mean x in the ith centre and e_{ij} is a Normally distributed within-centre error term with mean zero. This is known as a "fixed effects" model, since no attempt has been made to model the variation in either the α_i or β_i , rather a separate regression model with slope β_i has been fitted in *each* centre.

Let us now assume that the centres are *randomly* selected (i.e., without reference to the y values) from a population of centres. True random sampling of centres is unlikely in practice but this should not be critical providing that selection is *haphazard* (i.e. non-systematic) with respect to the y-values. We can now relate the variation in the mean centre effects α_i ($= \bar{y}_i$) to $\bar{x}_i$ as follows:

$$\text{(ii) } \alpha_i = \alpha + \beta_A(\bar{x}_i - \bar{x}) + f_i \text{ (Across-centre model)}$$

where α is the regression constant; $\bar{x}$ is the mean x across centres; β_A is the across-centre regression slope, and f_i is a cross-centre error term, again Normally distributed with mean zero.

Suppose also that there is a within-centre regression coefficient β_W common to all centres, then substituting β_W and equation (ii) into (i), we have:

$$\text{(iii)}\ y_{ij} = \alpha + \beta_A(\bar{x}_i - \bar{\bar{x}}) + \beta_W(x_{ij} - \bar{x}_i) + f_i + e_{ij}$$

and if $\beta_A = \beta_W$ (= common slope β):

$$\text{(iv)}\ y_{ij} = \alpha + \beta(x_{ij} - \bar{\bar{x}}) + f_i + e_{ij}\ \text{(Hierarchical model)}$$

This is called a "hierarchical" model since the error term contains both across- and within-centre components, which are statistically independent, i.e., $\text{cov}(e_{ij}, f_i)$ is zero. However, observations on two individuals y_{ij} and $y_{ij'}$ in the same centre are *not* independent having covariance equal to $\text{var}(f_i)$; the intraclass correlation, $\text{var}(f_i)/[\text{var}(f_i) + \text{var}(e_{ij})]$, is a measure of the *homogeneity* of individuals in the same centre relative to other centres.

3.2.2 An Approach to the Statistical Analysis

Because observations on individuals within centres are not independent of one another, standard regression techniques are no longer appropriate since they will under-estimate residual variance and give spuriously low standard errors for the regression coefficients.

Although computer algorithms are being developed to analyse hierarchical data and to produce a single regression coefficient based on both within-centre (individual) and across-centre (group) components, an empirical approach is adopted here whereby estimates of β_A and β_W are obtained directly, allowing them to be compared. Interpretation then depends on epidemiological as well as statistical considerations.

1. Regress $\bar{y}_i$ on $\bar{x}_i$ to obtain b_A

2. Using the separate within-centre regression coefficients b_i, *pool* over all centres using $\text{var}(b_i)^{-1}$ as weights to obtain b_W.

The procedure in 2. above minimises the variance of the pooled estimate b_W and gives the most powerful test of the null hypothesis that β_W (*and* all β_i) = 0. This is equivalent to a pooling (overview) analysis of clinical trials (Demets, 1987), except that in the case of a well conducted multicentre epidemiological study all data are obtained in a *single* study using common protocol, standardised field methods, etc., and there is no publication bias or missing data.

If the null hypothesis is rejected, we have good evidence for a *qualitative* relationship between y and x in individuals within-centres. But what is the best *quantitative* estimate of that relationship? Are all the separate within-centre regression coefficients b_i measuring the same quantity, or is there evidence for *heterogeneity* of the b_i, and if so what is the underlying distribution of the b_i?

Consider now a more complex ("random effects") model in which the β_i, the "true" within-centre regression coefficients, are considered to be randomly distributed about some overall mean β, so that:

$$(v)\ \beta_i = \beta + g_i \quad \text{(Random effects model for within-centre coefficients)}$$

where g_i is a Normally distributed across-centre "error" term for the β_i with mean zero and variance $\sigma^2_{\beta A}$.

Substitution into (i) gives:

$$(vi)\ y_{ij} = \alpha_i + (\beta + g_i)(x_{ij} - \bar{x}_i) + e_{ij}$$

But b_i, the estimate of β_i, has the form:

$$(vii)\ b_i = \beta_i + h_i = (\beta + g_i) + h_i$$

where h_i is a Normally distributed within-centre error term with mean zero and variance $\sigma^2_{\beta i}$.

A simple test of *heterogeneity* of the separate within-centre estimated regression coefficients b_i is available (DerSimonian & Laird, 1986).

Since g_i and h_i are independent (being respectively an across-centre and a within-centre error term), $\text{var}(b_i) = \sigma^2_{\beta A} + \sigma^2_{\beta i}$. Pooling b_i with weights $\text{var}(b_i)^{-1}$ to get an estimate of b_W therefore implies *equal* weights if $\sigma^2_{\beta A} \gg \sigma^2_{\beta i}$ and weighting by *precision* if $\sigma^2_{\beta A} \ll \sigma^2_{\beta i}$ (Berlin et al., 1989).

Thus if there is no evidence of heterogeneity, the most appropriate estimate of the within-centre relationship is given by the weighted average of b_i together with its standard error, using $\text{var}(b_i)^{-1}$ as weights. But if significant heterogeneity exists, it has been argued (Berlin et al., 1989; DerSimonian & Laird, 1986) that the best summary of the within-centre coefficients b_i is one that allows for an estimate of the across-centre variance $\sigma^2_{\beta A}$; this will give a more conservative test of significance than weighting by precision. Not all authors would agree, however, preferring

instead to use inverse variance weights in all situations, i.e., the fixed effects approach (Peto, 1987).

When there is evidence of heterogeneity of the b_i, the model is further complicated if centre-level variables can be found which help "explain" the heterogeneity in b_i (e.g., b_i increases with increasing $\bar{x}_i$). In this case the underlying model is of the form:

$$\text{(viii)}\quad \beta_i = \beta_0 + \beta_1(\bar{x}_i - \bar{x}) + k_i \qquad \text{(Systematic heterogeneity in the } \beta_i\text{)}$$

where β_0 and β_1 are respectively the regression constant and across-centre regression coefficient relating the within-centre coefficient β_i and $\bar{x}_i$, and k_i is the (residual) Normally distributed error term for the β_i, with mean zero.

The multicentre design affords the opportunity to explore this across-centre heterogeneity in the within-centre regression slopes; this could give useful insights as to aetiology, and provide direction for further investigation.

3.3 A Worked Example: The INTERSALT Study

In this section, the methods outlined above are illustrated with reference to the relations of body weight to systolic BP in the 5,045 men of the INTERSALT Study. Body weight was chosen as an index of body size and fatness in preference to body mass index, since it has been shown previously that the size of BP-body mass index regression coefficients is sensitive to differences in height (Dyer, Elliott & Shipley, 1990).

The INTERSALT study design and methods are described in Chapter 2, and detailed statistical methods are given in Chapter 4. Briefly, the stratified nature of the sampling ensured approximately 100 men in each of the 52 centres. The centres were selected to give a large spread of mean sodium (x) values. Mean systolic BP and mean weight were calculated for each centre, unadjusted for age and age-stratified (adjusted). The unadjusted total sums of squares of weight were calculated and partitioned into across- and within-centres sums of squares. Systolic BP-weight regression coefficients were estimated across the centres (b_A) and within-centres (b_i) unadjusted, adjusted for age, age and height, and "fully adjusted", i.e., adjusted for age, height, sodium and potassium excretion, and alcohol intake. In the across-centre analysis, the means of the above variables were entered into the regression models except for alcohol which was entered as two variables: percent drinkers and median alcohol intake of drinkers. In the within-centre analyses, the individual values of the

explanatory variables were entered into the analysis, except for alcohol which was entered as two (0,1) variables, i.e., no alcohol vs. 1-299 ml/week and no alcohol vs. 300+ ml/week. Three different summary estimates of the within-centre regression coefficient (b_W) and its standard error were calculated: the unweighted mean, $b_{W(U)}$; the "fixed effects" mean, weighted by the inverse of the variance of the individual centre coefficients, $b_{W(F)}$ and the "random effects" mean $b_{W(R)}$ weighted by adding an across-centre component of variance to the within-centre variance, according to the method of DerSimonian and Laird (1986). The regression coefficient ignoring centre (b_T) was also estimated.

3.3.1 Results

When the variation in the x-values (body weight) was partitioned into across- and within-centre sums of squares, 38% of the variation was found to be across-centres and 62% within-centres (i.e., $R_{XX} = 0.38$).

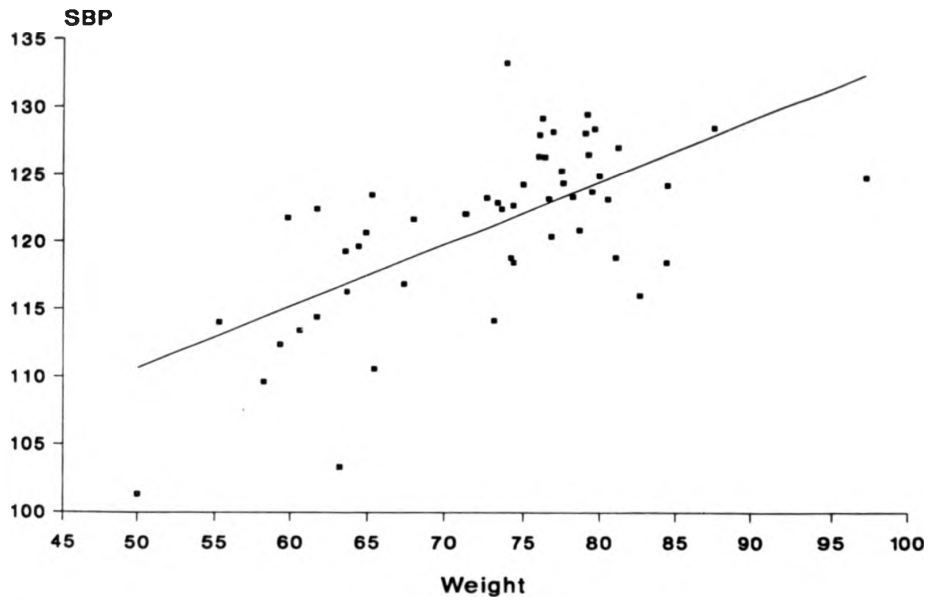
The age-standardised across-centre plot relating mean systolic BP and mean weight is shown in Figure 3, together with the fitted regression line (b_A). The relationship is strongly positive ($p<.00001$), with systolic BP higher by an estimated 4.6 mm Hg (SE 0.76) per 10 kg average body weight.

In the first of the within-centre analyses, the number of positive within-centre regression coefficients, the number negative, and the number nominally significant at $p<.05$ were calculated for each of the regresion models as shown in Table 8. Depending on which regression model is chosen, between 48 and 51 of the coefficients are positive, and up to 30 of these are statistically significant at $p<.05$. The weak non-parametric sign test rejects the null hypothesis that the regression slopes are equal to zero, i.e., half of them positive and half negative, $p<.00001$ (Table 8).

The size of the regression coefficients (adjusted for age) and their 95% confidence limits are shown ranked from negative to positive in Figure 4, with the overall "fixed effects" estimate ($b_{W(F)}$) and its 95% confidence interval shown in heavy ink at the bottom of the figure. In accordance with Table 8, there are only 3 negative coefficients, and the 95% confidence limits of 30 of the positive coefficients exclude zero.

The frequency distribution of these coefficients is shown in Figure 5, ranked in class sizes each 0.1 mm Hg/kg wide. As can be seen, the modal value is 0.25 mm Hg/kg, and there is slight skewing to the right indicating possible overdispersion.

Figure 3



Scatter plot of age-standardised mean systolic blood pressure (mm Hg) against mean body weight (kg), and fitted regression line, men, 52 centres

Table 8

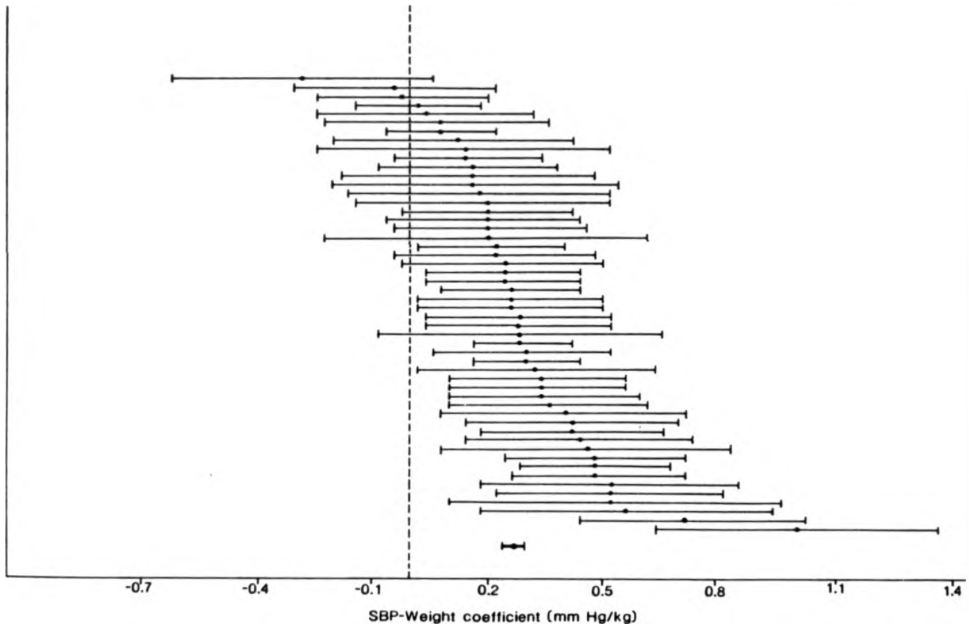
Summary of within-centre regressions relating systolic BP and weight in the 5,045 men in INTERSALT, unadjusted, adjusted for age, age and height, and fully adjusted†: number of coefficients positive, number negative and sign test

	Unadj.	Adj. age	Adj. age,ht	Fully adj.†
No. of positive coeffecients	48	49	51	51
No. significant ($p<0.05$)	30	30	28	25
No. of negative coefficients	4	3	1	1
No. significant ($p<0.05$)	0	0	0	0
Sign test z-score	6.10	6.38	6.93	6.93

All z-scores, $p<0.00001$

† Adjusted for age, height, sodium, potassium, alcohol

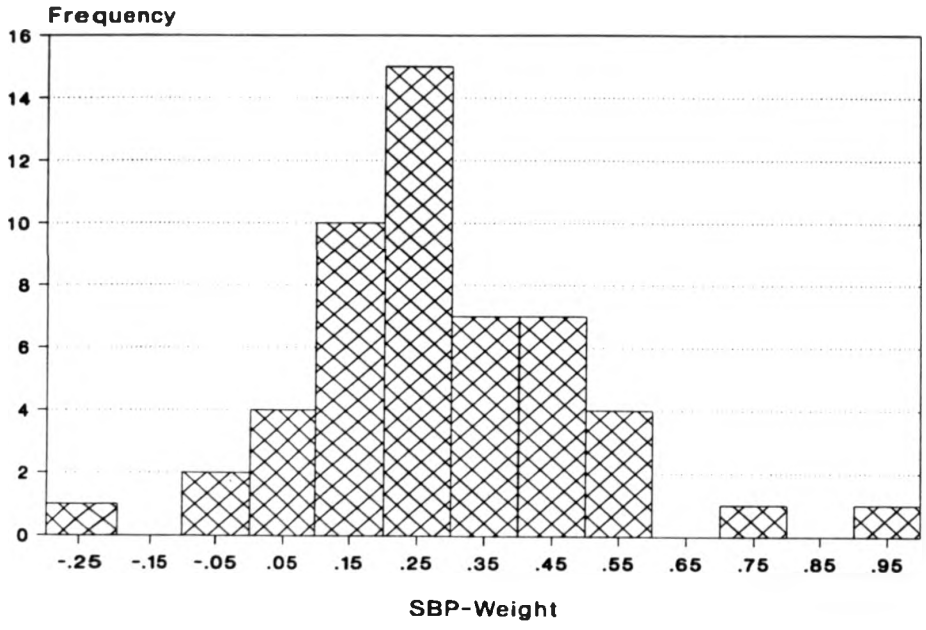
Figure 4



Diagramatic representation of the age-adjusted regression coefficients and 95% confidence intervals relating systolic blood pressure (mm Hg) and body weight (kg) in men, in the 52 centres of INTERSALT.

The heavy point and line at the bottom of the figure give the pooled regression coefficient, and its 95% confidence interval.

Figure 5



Frequency distribution of the age-adjusted regression coefficients relating systolic blood pressure (mm Hg) and body weight (kg) in men in the 52 centres of INTERSALT

Table 9 summarises the results of across- and within-centre regressions of systolic BP-weight, and also those done ignoring centre (b_T). As can be seen, the across-centre coefficient b_A is heavily influenced by the addition of across-centre confounding variables to the regression models, ranging from 4.6 (unadjusted and age adjusted) to 2.6 mm Hg/10 kg (fully adjusted). It is also much less precisely estimated than the regressions in individuals (b_W and b_T) since it is based on 51 degrees of freedom rather than 4,500-5,000 in the individual analyses.

The within-centre coefficients b_W are confounded (in opposite directions) by age and height, but with both these variables in the model, the addition of other variables makes little difference to the size of the regression coefficients. The least stable is $b_{W(U)}$ which is to be expected as it is more susceptible to outliers in the tails of the distribution (Figure 5). The estimates $b_{W(F)}$ and $b_{W(R)}$ are similar, although the latter has a higher standard error due to the addition of an across-centre component into the variance estimate. All these coefficients are highly statistically significant ($p<.00001$). In the unadjusted model, and the model adjusted for age, within-centre regression coefficients are (significantly) smaller than the across-centre coefficient b_A by 30% or more, whereas in the other two models, within-centre coefficients are some 10% to 25% larger.

As expected, in the unadjusted analysis, b_T lies between b_A and b_W, although this is not necessarily the case when potentially confounding variables are added to the model. b_T is largely unaffected by the addition of individual-level confounding variables to the regression models. The χ^2 test of heterogeneity is highly significant in all the regression models, although as more within-centre variables are added its value decreases. This suggests that some of the heterogeneity of slopes may be explained by within-centre confounding, although it may partly reflect the size of the within-centre variance estimates, which tend to increase as more variables are added to the model.

In an attempt to "explain" some of this heterogeneity, the systolic BP-weight regression slope from each centre was correlated with mean centre values of a number of explanatory variables, as shown in Table 10. As can be seen, in two of the models, the regression coefficient is positively and significantly correlated with mean sodium/potassium ratio, and in all 3 models, negatively and significantly correlated with mean weight and height of the centres. The scatter plot illustrating this relationship for weight is shown in Figure 6, i.e., the higher the mean body weight of a centre, the smaller the regression slope relating systolic BP and weight within that centre.

Table 9

Summary of across- and within-centre regression coefficients (SE) relating systolic BP and weight in the 5,045 men in INTERSALT, unadjusted, adjusted for age, age and height, and fully adjusted†

Coefficient (mm Hg/10 kg)	Unadj.	Adj. age	Adj.age, ht	Fully adj†
b_A	4.58 (0.76)	4.59 (0.76)	2.93 (1.29)	2.62 (1.08)
$b_{W(U)}$	3.20 (0.32)	2.84 (0.28)	3.51 (0.32)	3.40 (0.30)
$b_{W(F)}$	2.82 (0.16)	2.59 (0.17)	3.13 (0.19)	3.13 (0.20)
$b_{W(R)}$	3.04 (0.27)	2.72 (0.25)	3.33 (0.28)	3.26 (0.28)
b_T	3.57 (0.15)	3.44 (0.14)	3.58 (0.18)	3.38 (0.18)
$\chi^2_{(51)}$	128.9	105.2	102.9	89.7

All coefficients are significant, $p<0.00001$, except b_A (adj. age, ht and fully adj.), $p<0.05$

Legend:

b_A Across-centre coefficient

$b_{W(U)}$ Summary within-centre coefficient - Unweighted mean

$b_{W(F)}$ Summary within-centre coefficient - Fixed effects mean

$b_{W(R)}$ Summary within-centre coefficient - Random effects mean

b_T Coefficient in individuals, ignoring centre

$\chi^2_{(51)}$ χ^2 test of heterogeneity of within-centre coefficients on 51 d.f.

† Adjusted for age, height, sodium, potassium, alcohol

Table 10

Simple pearson-r correlation coefficients relating systolic BP-weight regression coefficients and mean values of various centre-level variables, INTERSALT, 52 centres, men

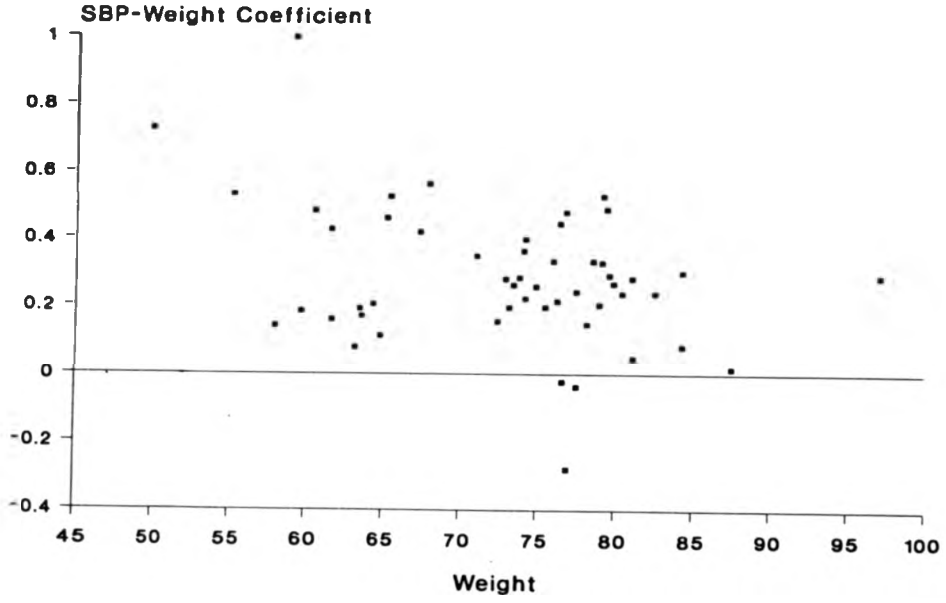
SBP-wt coeff:	Wt	Ht	Na	K	Na/K	Alc 1	Alc 2
Adj age	-.35*	-.37**	.07	-.33	.36**	-.04	-.04
Adj, age, ht	-.42**	-.38**	.17	-.35*	.51***	-.12	.05
Fully adj†	-.41**	-.44**	.01	-.26	.26	-.14	.04

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

† Adjusted for age, height, sodium, potassium, alcohol

Abbreviations: Wt, weight; Ht, height; Na, sodium; K, potassium; Na/K, sodium/potassium ratio; Alc 1, prevalence of alcohol drinking; Alc 2, alcohol intake of drinkers.

Figure 6



Scatter plot of age-adjusted systolic blood pressure-weight regression coefficients (mm Hg/kg) vs mean weight (kg), 52 centres, men

Finally, Table 11 shows the multiple R^2 of the multiple regression models relating the systolic BP-weight regression coefficient to the other explanatory across-centre variables. Between 14 and 28% of the variance of the systolic BP-weight coefficients could be "explained" by the across-centre variables studied. These regression models are statistically significant ($p<.01$ to $p<.05$), but none of the variables shown remained individually significant in the multiple regression models.

3.4 Discussion

The analysis outlined above illustrates some important issues:

1. Because of the INTERSALT study design in which centres were deliberately selected (on sodium values) to be very different, some 38% of the variation in x (weight) was across-centres. This compares with the analyses of NHANES data mentioned above, in which nearly all of the variation was within centres (Piantadosi, Byar, and Green, 1988), so that the regression estimate ignoring centre (b_T) was virtually identical to the within-centre regression slope b_W. By contrast, in INTERSALT, b_T is difficult to interpret, being a combination of both across- and within-centre effects.

2. The analysis across centres was much less stable than that within centres, and gave regression estimates ranging from some 30% higher to some 10% lower than the within-centre coefficients. The across-centre findings were far more susceptible to confounding.

3. The analysis not only gave an efficient and precise estimate of within-centre effect (based on a pooling of results in more than 5,000 individuals) but also allowed the effect within the centres to be examined for heterogeneity across centres. This is a unique feature of the multicentre design.

4. When (significant) heterogeneity was found, some of that heterogeneity could be explored by examining the relations of the within-centre regression coefficients to measured across-centre variables.

In general, once estimates of the across-centre regression coefficient β_A and the within-centre coefficient β_W have been obtained, difficulties in interpretation arise. If b_A and b_W are similar they can readily be reconciled to give an overall estimate of the relationship of y to x based on both across- and within-centre data. But what should be done if b_A and b_W are very different?

Table 11

Multiple R^2 for regression models of systolic BP - weight regression coefficients against various centre-level variables, INTERSALT, 52 centres, men

	Regression Model	
SBP-wt coeff:	Wt, ht	Wt, ht, Na, K, Alc 1, Alc 2
Adj age	.14*	.26*
Adj age, ht	.20**	.28*
Fully adj†	.20**	.26*

* $p<0.05$ ** $p<0.01$

† Adjusted for age, height, sodium, potassium, alcohol

Abbreviations: Wt, weight; ht, height; Na, sodium; K, potassium; Alc 1, prevalence of alcohol drinking; Alc 2, alcohol intake of drinkers

The approach suggested here is to present both b_A and b_W separately, since both are liable to error: interpretation then depends on the relative weight one places on ecological or individual relationships. As with the INTERSALT analysis, the estimated across-centre regression coefficient b_A is particularly liable to ecological confounding, much of which may be unmeasured and which may introduce serious bias. The across-centre slope b_A is also sensitive to systematic differences between centres in the techniques or circumstances of measurement (e.g., systematic undercollection of urine in one or more centres biasing estimates of 24-hour sodium excretion), and it is estimated with less precision than b_W unless there are large across-centre differences in mean x. On the other hand, b_A is much less sensitive than b_W to (random) "measurement error" in the explanatory variable x, provided sample sizes within centres are adequate.

Here the term "measurement error" is taken in its widest sense to mean all the circumstances leading to "random" variation in measurement (including biological or physiological variation) and hence to mis-classification of individuals on the measured variable. This is unlikely to have been an important source of error in the analysis presented here of BP and body weight, since body weight is measured with reliability close to one (Liu et al., 1982; Marks, Habicht & Mueller, 1989). However, it would be a major problem in analyses of BP and sodium excretion (as discussed in Chapter 1) or dietary fat and serum cholesterol (Jacobs, Anderson & Blackburn, 1979). As mentioned previously, the situation showing positive ecological confounding and within-centre measurement error is shown graphically in Figure 2, leading to biased estimates of effect both across-centres (postive bias) and within-centres (negative bias).

In summary, "measurement error" in the x variable will tend to bias the within-centre regression coefficient b_W towards zero; but whereas for b_W the bias can be estimated and corrected using repeat measures (Liu et al., 1979), for b_A, bias due to unmeasured ecological confounding may be unsuspected and can not be corrected.

3.5 Implications for Future Studies

Given the choice of conducting a large epidemiological study in one place, or investigating the same number of people in many different centres, which would be the optimal design? The answer to this question is not straightforward, but a number of issues should be considered:

1. By adopting the multicentre design, there is little loss of power for examining relationships at the level of individuals (b_W). Furthermore, the opportunity to explore relationships across the centres (b_A) is gained, provided enough centres are included in the study (empirically, about 30+).

2. In the multicentre study, the individual (within-centre) results can be examined for heterogeneity. If heterogeneity exists, it can be further explored; if it does not, then the study gives some evidence *internally* for generalisability. This could be a major gain.

3. On the other hand, the statistical analysis is complicated by the need to stratify by centre, and some analyses (for example, dose response relationships) may be difficult to carry out within a multicentre framework.

4. There may be gains in organisation, cost-sharing and staff recruitment in the multicentre study since each centre is responsible for a smaller amount of data collection than if the study were conducted in one place. On the other hand, there is loss of control from the organisational centre, and large added costs in terms of centralised training and coordination.

In conclusion, recent advances in techniques of meta-analysis and the understanding of hierarchical models make multicentre studies an attractive design under certain circumstances. Without loss of statistical power for individual-level relations, the ability to look for across-centre relations and heterogeneity of effect is gained, and lack of heterogeneity gives some generalisability to the results. In addition, costs can be shared. This has to be offset against the organisational difficulties of conducting studies in many centres. As with matching in case-control studies, the statistical analysis needs to take account of the inherent structure of the data introduced by the study design.

Chapter 4

INTERSALT: Age and Sex Specific Results for 24-Hour Sodium and Potassium, and Findings for the Three United Kingdom Centres.

Overall findings for 24-hour sodium and potassium in the 10,079 men and women of the study are published (INTERSALT Cooperative Research Group, 1988; see Appendix 4). Briefly, in individuals, urinary sodium excretion and the sodium/potassium ratio were positively and significantly related to BP, and, after adjustment for confounding variables, potassium excretion was negatively and significantly related to BP. In addition, across the centres, average sodium excretion was positively and significantly related to the average change (slope) of BP with age.

In this Chapter, results of two further analyses are presented: age- and sex-specific results for sodium and potassium, and results for the three United Kingdom (U.K.) centres. The results are discussed in Chapter 5.

4.1 Methods

Field methods are summarised briefly in Chapter 2, and a detailed account of the methods is given in Appendix 1.

4.1.1 Statistical Methods

Age-sex analysis: all centres

Values of sodium and potassium excretion were the product of urinary concentration and volume corrected to 24 hours. Body mass index was the ratio of weight (kg) to $(\text{height})^2$ (m^2). Analyses are reported for the 5,045 men and 5,034 women with complete data. Both within- and across-centre analyses were carried out (see Chapter 3).

In the within-centre analyses, the relations of BP to urinary sodium, potassium, and sodium/potassium ratio, were explored by multiple linear regression in each of the 52 centres of the study. Centre-specific regression coefficients were then combined (pooled), weighting by the inverse of the variance, to give overall study estimates of the relation of BP to each of the independent variables. Separate analyses were run for men aged 20-39, men 40-59, women 20-39, women 40-59, and for men and women combined at ages 20-29, 30-39, 40-49 and 50-59. Because of the balanced

nature of the sampling procedure, the sample size for each of these analyses was approximately one quarter of the total (i.e., about 2,500 people). Adjustments were made for age and sex as appropriate. Further adjustments were made for body mass index, alcohol intake, and (for the sodium model) potassium excretion, or (for the potassium model) sodium excretion. Alcohol intake was entered as two (0,1) variables, i.e. zero vs 1-299 ml (0,1) and zero vs 300+ ml (0,1). Analyses for all ages combined were also run for men, for women, and for men and women combined, adjusted appropriately for age, sex and the other confounders.

For each analysis, a test of significance (two-sided) was obtained by comparing the combined regression coefficient to its combined (pooled) standard error, giving a z-score. The significance of association between BP and the independent variable is given by the size of the z-score, enabling regression models to be compared at different ages, or between the sexes.

Regression estimates obtained from these models in individuals are seriously biased towards zero because of within-individual variability of electrolyte excretion (see Chapter 1). Study-wide estimates (ignoring age and sex) of the degree of "regression-dilution" were obtained by correlating (within each centre) the first and second measure of electrolyte excretion in the 8% of particpants with repeated measurements. These centre-specific Pearson-r correlation coefficients were then combined (pooled) over all centres by using the z-transform and weighting by the inverse of the variance. The weighted z was re-transformed to r, giving an estimate of reliability for each variable. Finally, regression coefficients were "corrected" for reliability of measurement, by dividing the combined regression coefficient by the combined coefficient of reliability (INTERSALT Cooperative Research Group, 1988).

In the analysis across centres, median sodium excretion, potassium excretion and sodium/potassium ratio were related to a number of BP variables. These were slope of BP with age (estimated separately for each sex by linear regression of BP on age within each centre), median BP and prevalence of high BP (defined as systolic pressure of 140+ mm Hg, or diastolic pressure of 90+ mm Hg, or on anti-hypertensive medicaton). For median BP and prevalence of high BP, analyses were done for men and for women standardised for age (20-39 years and 40-59 years) and for men aged 20-39, men 40-59, women 20-39, and women 40-59. Aross-centre analyses were also carried out after adjustment for median body mass index and alcohol intake (entered into these analyses as two variables: prevalence of drinkers and median alcohol intake in drinkers).

Four centres with low sodium excretion (less than 50 mmol per day), low BP and little or no rise of BP with age were found to strongly influence across-centre associations. The across-centre analyses were therefore carried out with and without these four centres (INTERSALT Cooperative Research Group, 1988).

United Kingdom centres

Three U.K. centres were included in INTERSALT, and age-sex stratified random samples were drawn in each centre, from the general practice master patient index (Belfast), from the roll of employees at an electrical components factory (Birmingham) and from a general practice age-sex register (South Wales) (Appendix 3). To facilitate the goal of 200 age-sex eligible participants per centre, the populations were over-sampled, and replacements were found - in strict order of random allocation - whenever an unacceptable record was obtained (i.e., incomplete urine collection as determined by interview, or pregnancy). Data collection took place between June 1985 and April 1986 (Belfast), April and November 1985 (Birmingham) and March and April 1985 (South Wales). Investigators from each centre attended a central training meeting in London in December 1984.

For the U.K. centres, means (and standard deviations) were calculated separately by centre in men and women aged 20-39 and 40-59 years, and then averaged over those centre and age-sex specific groups. Comparison between groups was by unpaired t-tests or χ^2 as appropriate; multiple comparison across groups was done by the Student-Newman-Keuls method after first testing for heterogeneity by analysis of variance.

Multiple regressions of BP-sodium are presented separately for the U.K. centres, according to the methods outlined above in the age-sex analysis. Although regression coefficients in the U.K. centres can usefully be compared with the rest, it should be recognised that any differences from the overall results may reflect chance variation among centres rather than real differences.

Each individual in the three U.K. centres was assigned a "risk score" (for high BP) depending on level of urinary sodium and potassium excretion and body mass index relative to the appropriate age and sex adjusted medians in that individual's centre, and whether or not the individual drank at least 300 ml alcohol per week. For each of the above variables, 0 was defined as "lower risk" (for high BP) and 1 as "higher risk" (i.e., for sodium excretion and body mass index, 0 = below adjusted median, 1 = above adjusted median; for potassium excretion, 0 = above adjusted median, 1 =

below adjusted median, and for alcohol consumption, 0 = <300 ml/week, 1 = ≥300 ml/week). The sum of these (0,1) values gave the "risk score" for each individual. Sex-specific mean BPs (age-adjusted) were then calculated for "lower risk" individuals (i.e., "risk score" zero) and for "higher risk" individuals (i.e., those with "risk scores" of one, two, or three or more, and also those with scores of one or more).

4.2 Results

4.2.1 Age and Sex Specific Results: All Centres

Median values (men and women combined) for urinary sodium ranged from 0.2 mmol/24 hour (Yanomamo Indians of Brazil) to 242.1 mmol/24 hour (Tianjin, North China); for urinary potassium from 23.4 to 81.1 mmol/24 hour, and for sodium/potassium ratio from <0.01 to 7.27. Median systolic pressure ranged from 95.4 to 132.4 mm Hg, and diastolic pressure from 61.4 to 82.1 mm Hg. Amongst the 48 centres (excluding the four low sodium centres) median values of sodium and potassium excretion were on average higher for men than for women (174.7 vs 142.6 mmol/24 hour, $p<0.001$, and 57.3 vs 47.4 mmol/24 hour, $p<0.01$, respectively), as were median systolic BP (120.9 vs 115.5 mm Hg, $p<0.001$) and diastolic pressure (75.6 vs 71.4 mm Hg, $p<0.001$). In addition, men had on average higher creatinine excretion (13.2 vs 8.8 mmol/24 hour, $p<0.001$) and greater urinary volume (1.37 vs 1.24 l/24 hour, $p<0.05$). Sodium/potassium ratio and body mass index were similar in the two sexes.

Results in individuals of the relations of urinary sodium, potassium and sodium/potassium ratio to BP are summarised in Tables 12-14. These give regression coefficients by sex and age, combined over all 52 centres, together with their corresponding standard errors and z-scores. The coefficients are uncorrected for within-person variability in electrolyte excretion (reliability) and hence underestimate the size of true relationships with BP; however, inspection of the z-scores allows the relative strengths of the relationships by age and sex to be examined.

With adjustment for age, sodium was positively and significantly associated with systolic and diastolic pressure of individuals, both for men and for women (Table 12). These positive and significant relationships were also found in seven of the eight age-sex specific analyses (the exception being diastolic pressure in men aged 20-39 where the relationship was negative but non-significantly different from zero). For all but one of these analyses, the z-scores suggested stronger associations in women than in

men; the size of regression coefficients in women was as much as twice that of the corresponding coefficients in men. Adjustment also for potassium excretion, body mass index and alcohol intake, reduced these associations between sodium excretion and BP except for diastolic pressure in men aged 20-39, which became more negative and significant (Table 12).

In the age-specific analyses (men and women combined) with adjustment for age and sex, sodium was positively related to BP, significantly so for systolic pressure at all ages and for diastolic pressure at ages 50-59 (bottom of Table 12). With adjustment also for the other confounders, only the relationship between sodium and systolic pressure at ages 50-59 remained significant. Regression coefficients were generally larger at older ages, reflecting to some extent stronger relationships between sodium and BP (as evidenced by the size of the z-scores) but also an increasing spread in the dependent variable (BP) with advancing age.

Findings after correction for reliability do not appear in the Tables, but are reported here. The analysis of repeat measurements indicated a reliability coefficient for sodium of 0.46, and hence a correction factor for sodium-BP coefficients of 1/(reliability), or 2.17 (INTERSALT Cooperative Research Group, 1988). Recent work suggests that this study-wide estimate (i.e., ignoring age and sex) is likely to be too low (A. Dyer, personal communication). Nonetheless, the regression analysis in women, adjusted for age and corrected for reliability using the study-wide estimate, indicated systolic pressure lower by 4.7 mm Hg per 100 mmol sodium (i.e., 0.215 x 10 x 2.17) and diastolic pressure lower by 1.8 mm Hg per 100 mmol sodium. Adjustment also for potassium excretion, body mass index and alcohol intake, reduced these estimates to 2.8 mm Hg systolic and 0.2 mm Hg diastolic. Age-specific estimates for men and women combined were also correspondingly larger when corrected for reliability; for example, at ages 50-59 after adjustment for age, sex, potassium excretion, body mass index and alcohol intake, the regression coefficient indicated systolic pressure lower by 3.6 mm Hg per 100 mmol sodium (i.e., 0.165 x 10 x 2.17).

Table 12

Summary of combined within centre regression coefficients (b), standard errors (SE) and z-scores (Z) relating 24-hour urinary sodium excretion and blood pressure in individuals. Results by sex and age, uncorrected for reliability of measurement.

	Systolic Blood Pressure				Diastolic Blood Pressure			
	Adjusted age (& sex)+		Adjusted age (sex) & other confounders#		Adjusted age (& sex)+		Adjusted age (sex) & other confounders#	
	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z
Men								
20-39	0.105(0.034)	3.14**	0.008(0.039)	0.20	-0.020(0.030)	-0.67	-0.087(0.035)	-2.53*
40-59	0.115(0.046)	2.50*	0.110(0.056)	1.99	0.102(0.031)	3.30***	0.043(0.036)	1.19
All ages	0.120(0.029)	4.09***	0.056(0.034)	1.67	0.057(0.022)	2.54*	-0.006(0.025)	-0.24
Women								
20-39	0.186(0.040)	4.69***	0.083(0.046)	1.83	0.082(0.033)	2.48*	0.027(0.038)	0.69
40-59	0.226(0.059)	3.82***	0.155(0.068)	2.28*	0.075(0.036)	2.06*	-0.012(0.042)	-0.29
All ages	0.213(0.037)	5.86***	0.131(0.042)	3.13**	0.085(0.025)	3.40***	0.009(0.028)	0.34
Men & Women								
20-29	0.165(0.035)	4.74***	0.079(0.041)	1.90	0.008(0.032)	0.25	-0.037(0.038)	-0.97
30-39	0.141(0.039)	3.64***	0.069(0.044)	1.56	0.043(0.032)	1.35	-0.023(0.036)	-0.64
40-49	0.119(0.047)	2.52*	0.102(0.056)	1.81	0.063(0.033)	1.90	0.025(0.040)	0.64
50-59	0.224(0.059)	3.80***	0.165(0.069)	2.39*	0.086(0.035)	2.46*	0.019(0.041)	0.47
All ages	0.163(0.023)	6.97***	0.100(0.026)	3.79***	0.068(0.017)	4.08***	0.003(0.019)	0.16

\+ Adjusted for age in men, and in women, and age and sex in men and women combined

\# Adjusted for age, (sex), body mass index, alcohol intake and potassium excretion

† mm Hg/ 10 mmol sodium

* p<0.05 ** p<0.01 *** p< 0.001

Relationships between potassium excretion and the BP of individuals are summarised in Table 13. The relationships to pressure were similar in the two sexes, and were mostly negative and stronger at older ages, and in the fully adjusted analysis. Thus, with adjustment for age (sex) sodium excretion, body mass index and alcohol intake, significantly negative associations between potassium excretion and systolic pressure were observed for men and for women at ages 40-59, and for men and women combined at ages 40-49 and 50-59. For diastolic pressure, associations in the fully adjusted analysis were significantly negative for men (all ages) and for men and women combined at ages 40-49.

The study-wide reliability coefficient for potassium was 0.57, giving a correction factor for regression coefficients of 1.75. Thus the regression coefficient relating potassium excretion and systolic pressure for men and women combined at ages 50-59, adjusted for confounders and corrected for reliability, indicated BP lower by 0.7 mm Hg for potassium higher by 10 mmol (i.e., -0.395 x 1.75).

The relations of sodium/potassium ratio and BP in individuals are summarised in Table 14. In general, results were similar to those for sodium, although more consistent, being stronger and more positive for women and - at least for systolic BP - at older ages. Thus, with adjustment for age (and sex) positive and significant associations between sodium/potassium ratio and BP, systolic and diastolic, were seen in all analyses except for men aged 20-39 and men and women combined at ages 20-29. With adjustment also for body mass index and alcohol intake, relationships with systolic pressure remained significant in all analyses except men aged 20-39, women aged 20-39 and men and women combined at ages 20-29. For diastolic pressure, only the relationships for men and women combined at ages 30-39, and at all ages were significant.

The study-wide estimate of reliability for sodium/potassium ratio was 0.39, giving a correction factor of 2.59. Thus, with full adjustment and correction for reliability at ages 50-59 for men and women combined, the regression coefficient indicated systolic pressure lower by 2.6 mm Hg per unit decrease in the sodium/potassium ratio.

Table 13

Summary of combined within centre regression coefficients (b), standard errors (SE) and z-scores (Z) relating 24-hour urinary potassium excretion and blood pressure in individuals. Results by sex and age, uncorrected for reliability of measurement.

	Systolic Blood Pressure				Diastolic Blood Pressure			
	Adjusted age (& sex)+		Adjusted age (sex) & other confounders#		Adjusted age (& sex)+		Adjusted age (sex) & other confounders#	
	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z
Men								
20-39	0.181(0.101)	1.79	-0.022(0.109)	-0.20	-0.092(0.091)	-1.01	-0.151(0.100)	-1.51
40-59	-0.110(0.128)	-0.86	-0.386(0.138)	-2.80**	-0.025(0.088)	-0.29	-0.177(0.094)	-1.88
All ages	0.032(0.084)	0.38	-0.214(0.090)	-2.39*	-0.051(0.065)	-0.79	-0.193(0.069)	-2.79**
Women								
20-39	0.180(0.110)	1.64	0.016(0.121)	0.13	0.028(0.094)	0.30	-0.052(0.105)	-0.50
40-59	-0.283(0.162)	-1.75	-0.561(0.175)	-3.20**	-0.063(0.110)	-0.58	-0.226(0.120)	-1.89
All ages	-0.034(0.099)	-0.34	-0.266(0.106)	-2.50*	-0.013(0.073)	-0.17	-0.150(0.079)	-1.91
Men & Women								
20-29	0.262(0.099)	2.64**	-0.004(0.113)	-0.04	-0.035(0.092)	-0.38	-0.141(0.105)	-1.34
30-39	0.142(0.116)	1.22	-0.046(0.125)	-0.36	0.002(0.098)	0.02	-0.070(0.106)	-0.66
40-49	-0.371(0.131)	-2.84**	-0.583(0.139)	-4.19***	-0.169(0.096)	-1.77	-0.336(0.105)	-3.20**
50-59	-0.058(0.162)	-0.35	-0.395(0.178)	-2.22*	0.044(0.102)	0.43	-0.101(0.112)	-0.90
All ages	0.012(0.065)	0.19	-0.254(0.070)	-3.63***	-0.020(0.048)	-0.41	-0.165(0.052)	-3.18**

\+ Adjusted for age in men, and in women, and age and sex in men and women combined

\# Adjusted for age, (sex), body mass index, alcohol intake and sodium excretion

† mm Hg/ 10 mmol potassium

* p<0.05 ** p<0.01 *** p< 0.001

Table 14

Summary of combined within centre regression coefficients (b), standard errors (SE) and z-scores (Z) relating 24-hour urinary sodium/potassium ratio and blood pressure in individuals. Results by sex and age, uncorrected for reliability of measurement.

	Systolic Blood Pressure				Diastolic Blood Pressure			
	Adjusted age (& sex)+		Adjusted age (sex) & other confounders#		Adjusted age (& sex)+		Adjusted age (sex) & other confounders#	
	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z	b(SE)†	Z
Men								
20-39	0.297(0.156)	1.91	0.131(0.154)	0.85	0.095(0.139)	0.68	-0.049(0.138)	-0.35
40-59	0.993(0.249)	3.99***	0.948(0.252)	3.76***	0.410(0.170)	2.42*	0.222(0.168)	1.32
All ages	0.658(0.147)	4.48***	0.508(0.146)	3.49***	0.295(0.111)	2.66**	0.126(0.109)	1.15
Women								
20-39	0.468(0.157)	2.98**	0.241(0.154)	1.56	0.266(0.129)	2.05*	0.147(0.127)	1.16
40-59	1.326(0.245)	5.41***	0.963(0.247)	3.90***	0.450(0.148)	3.05**	0.285(0.150)	1.90
All ages	0.936(0.151)	6.19***	0.636(0.149)	4.25***	0.354(0.101)	3.51***	0.198(0.100)	1.98
Men & Women								
20-29	0.230(0.148)	1.56	0.152(0.151)	1.00	-0.206(0.137)	-1.50	-0.246(0.140)	-1.75
30-39	0.651(0.170)	3.82***	0.482(0.167)	2.88**	0.527(0.137)	3.86***	0.371(0.135)	2.74**
40-49	1.093(0.234)	4.68***	0.877(0.231)	3.79***	0.457(0.160)	2.86**	0.304(0.158)	1.92
50-59	1.183(0.261)	4.54***	1.023(0.268)	3.82***	0.349(0.160)	2.18*	0.260(0.163)	1.60
All ages	0.810(0.106)	7.62***	0.621(0.105)	5.94***	0.319(0.075)	4.24***	0.166(0.074)	2.26*

\+ Adjusted for age in men, and in women, and age and sex in men and women combined

\# Adjusted for age, (sex), body mass index and alcohol intake

† mm Hg/ unit

* p<0.05 ** p<0.01 *** p< 0.001

In the across-centre analyses, median sodium excretion was positively and significantly related to the slope of systolic and diastolic BP with age in men, in both the 52 and 48 centre analyses, and with and without adjustment for confounding variables. For women, relationships with slope of BP with age were positive in all analyses, but were significant only in the analyses across 52 centres. These results are summarised in Table 15; in the 52 centre analyses, regression coefficients were larger in women than men, although the reverse was true in the 48 centre analyses, such that with full adjustment across 48 centres, coefficients in men were some 50% or more higher than the corresponding coefficients in women.

In the fully adjusted analysis in men and women combined, and across the 48 centres (excluding the four low-sodium centres), the regression coefficient indicated that the increase in systolic BP over a 30 year period (e.g., from age 25 to age 55) would be less by 9 mm Hg for sodium excretion lower by 100 mmol per day (i.e., 0.03 x 30 x 10 = 9 mm Hg). In the equivalent analysis for diastolic BP, the regression coefficient indicated BP less by 4.5 mm Hg per 100 mmol over 30 years.

When median sodium excretion was related across centres to median BPs and prevalence of hypertension, results were less consistent. Across 52 centres in the age-standardised analysis, sodium was positively and significantly related to median systolic BP and diastolic BP, in both men and women; however, after adjustment for body mass index and alcohol intake and exclusion of the four low-sodium centres, relationships were both positive (systolic BP) and negative (diastolic BP) but no longer significant. Relations of both potassium and sodium/potassium ratio to these BP variables were inconsistent, being both positive and negative (results not shown).

Table 15

Summary of across-centre regression coefficients (SE) relating sodium and systolic and diastolic blood pressure slope with age in men and women, 52 and 48 centres, age standardised and multiple adjusted†

	Regression coefficients (mm Hg/year/10 mmol sodium)			
	Age stand.		Mult adj.†	
No. of centres:	52	48	52	48
Systolic BP slope with age				
Men	0.021***	0.021*	0.028***	0.026*
	(0.006)	(0.010)	(0.007)	(0.010)
Women	0.037***	0.007	0.033***	0.015
	(0.008)	(0.013)	(0.008)	(0.014)
Men and Women	0.030***	0.019	0.034***	0.030**
	(0.006)	(0.010)	(0.006)	(0.011)
Diastolic BP slope with age				
Men	0.018***	0.014*	0.019***	0.015*
	(0.003)	(0.006)	(0.004)	(0.006)
Women	0.022***	0.009	0.020***	0.010
	(0.004)	(0.006)	(0.004)	(0.007)
Men and Women	0.021***	0.014**	0.021***	0.015**
	(0.003)	(0.005)	(0.003)	(0.006)

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

† Standardised for age, and adjusted for body mass index and alcohol intake

4.2.2 United Kingdom Centres

Six hundred and forty-one eligible participants (including replacements) attended the three centres, of whom 43 (6.7%) were excluded, 41 for an incomplete urine collection and 2 who were pregnant. Data on the remaining 598 people (299 men and 299 women) are included in this report, 199 in Belfast, 200 in Birmingham and 199 in South Wales. Response rates (given by the ratio of clinic attenders to eligible persons selected for study) were 55%, 83% and 83% respectively in the three centres.

Means and ranges of selected variables by centre are given in Table 16. Mean systolic pressure was higher in South Wales (124.3 mm Hg) than Belfast (120.3 mm Hg, $p<0.05$) and Birmingham (119.6 mm Hg); diastolic pressure was significantly ($p<0.05$) higher in Belfast (73.8 mm Hg) than in the other two centres (71.2 mm Hg and 71.3 mm Hg). Mean body mass index ranged from 24.8 kg/m^2 (Belfast) to 25.7 (South Wales) and mean sodium excretion from 150.8 mmol/24-hour (Belfast) to 153.1 (Birmingham): these differences were not significant. Mean potassium excretion was significantly ($p<0.001$) lower in Belfast than in the other two centres (56.9 mmol/24-hour vs 63.0 and 63.1 mmol/24-hour); and the prevalence of heavy drinking (defined as ≥300 ml/week) was higher in Belfast (20.2%) than in Birmingham (11.5%, $p<0.05$) and South Wales (14.0%). A wide range of individual values was recorded; for example, systolic BP ranged from 89 to 210 mm Hg, diastolic pressure from 35 to 122 mm Hg and sodium excretion from 31.7 to 393.2 mmol/24-hour.

Mean values in men were significantly ($p<0.001$) higher than in women for BP, weight, height, urinary volume, and urinary excretion of sodium, potassium, chloride, calcium, magnesium and creatinine (Table 17). The prevalence of heavy drinking as defined was also significantly higher in men (27.5% vs 3.0%, $p<0.001$).

Pulse rate was significantly ($p<0.001$) higher in women, but body mass index and urinary sodium/potassium ratio were similar in the two sexes (Table 17). Overall in the three centres, mean BP was 121.4/72.1 mm Hg, body mass index 25.2 kg/m^2, sodium excretion 152.1 mmol/24-hour, potassium excretion 61.0 mmol/24-hour and sodium/potassium ratio 2.64 (Table 17). The relations of urinary sodium, sodium/potassium ratio, and potassium to BP in the three U.K. centres and in all INTERSALT centres, are summarised in Table 18. Overall, INTERSALT found significant positive relations in individuals between BP and urinary sodium excretion, sodium/potassium ratio, and, with adjustment for confounding variables, significant negative associations between potassium excretion and BP. In addition, the average

sodium intake of centres was positively and significantly related to the slope of BP with age (Table 15). In the U.K. centres, relationships were mostly positive between systolic pressure and both sodium and sodium/potassium ratio, and were both positive and negative in the other analyses. Confidence intervals were wide (reflecting the relatively small sample size in each centre) such that the U.K. results were consistent with the overall INTERSALT findings.

Pooled regression coefficients of BP with body mass index and heavy alcohol intake (≥300 ml/week) are shown in Table 19. Overall in INTERSALT, body mass index and heavy alcohol intake were positively and significantly related to the BP of individuals. In each of the three U.K. centres, positive coefficients were found in all analyses relating both body mass index and heavy alcohol drinking to BP.

To illustrate the potential benefit of a multifactorial approach to control of BP in the population, a cross-stratification analysis was carried out for all 598 individuals in the three U.K. centres as described in the Methods above. Individuals within each centre were ranked according to risk score and mean BPs were calculated as shown in Table 20. Twenty men and 27 women were identified as at "lower risk" for high BP (i.e., risk score zero): mean systolic pressure for men, and both systolic and diastolic pressure for women, were lowest in this group. By contrast, higher average BPs were found in those with scores of two or more: tests for heterogeneity were significant for both systolic and diastolic pressure in men ($p<0.001$) and for systolic pressure in women ($p<0.05$) (Table 20). The difference in BP (systolic/diastolic) between those with lowest and highest risk scores was approximately 12/7 mm Hg for men and 7/5 mm Hg for women.

Comparison of those with risk score zero and the remainder (risk score of one or more) is not shown in the Tables but is given here. For men with score zero, age-adjusted mean systolic pressure was 114.6 mm Hg (SE 3.4) compared with 125.5 (0.9) (score one or more) ($p<0.01$) and for women, 113.2 mm Hg (SE 2.6) vs 118.5 (0.8), ($p=0.06$). Corresponding figures for diastolic pressure were for men 71.2 mm Hg (SE 2.5) vs 74.8 (0.7), ($p=0.19$) and for women 65.7 mm Hg (SE 1.7) vs 70.1 (0.5), ($p<0.05$).

These results and some implications for U.K. food and health policy are discussed in Chapter 5.

Table 16

Three U.K. centres: Age and sex standardised means (sd) and ranges of selected variables by centre

	Belfast (N=199)				Birmingham (N=200)				S. Wales (N=199)			
	Mean	(sd)	Min	Max	Mean	(sd)	Min	Max	Mean	(sd)	Min	Max
SBP (mm Hg)	120.3	(13.7)	95	174	119.6	(14.8)	89	182	124.3	(16.7)*	89	210
DBP (mm Hg)	73.8	(10.8)^{o}	35	112	71.2	(10.0)	44	109	71.3	(10.7)*	42	122
Wt (kg)	69.0	(11.2)	42.8	105.6	69.2	(10.9)††	47.0	107.5	72.5	(14.1)**	39.7	139.7
Ht (m)	1.67	(0.07)	1.44	1.90	1.66	(0.06)††	1.42	1.89	1.68	(0.06)	1.41	1.90
BMI (kg/m^2)	24.8	(4.0)	17.6	42.5	25.2	(3.8)	18.2	48.8	25.7	(4.8)	17.0	54.6
Pulse (bt/min)	72.6	(12.0)	43	117	73.9	(10.1)	49	99	76.3	(11.7)**	42	120
Alcohol (≥300 ml/wk)	20.2%^{o}				11.5%				14.0%			
24-hour urinary excretion:												
Na (mmol/24hr)	150.8	(56.4)	31.7	342.8	153.1	(46.4)	53.3	313.6	152.3	(54.9)	52.9	393.2
Na/K(mmol/mmol)	2.79	(1.04)	0.90	7.78	2.59	(0.97)	0.68	8.92	2.54	(0.86)*	0.97	5.96
K (mmol/24hr)	56.9	(18.5)^{oo}	15.9	143.0	63.0	(18.9)	23.5	167.0	63.1	(22.0)**	20.3	160.6
Cl (mmol/24hr)	151.7	(58.3)	12.8	345.3	156.1	(47.5)†	54.8	364.5	151.7	(57.7)	39.5	444.9
Ca (mmol/24hr)	4.83	(2.23)	0.56	13.13	4.93	(2.06)††	0.34	13.43	4.43	(1.97)	0.95	12.89
Mg (mmol/24hr)	4.14	(1.32)	1.32	8.81	3.93	(1.18)	0.91	6.95	4.38	(1.43)	1.22	9.70
Creat (mmol/24hr)	10.9	(2.3)	3.6	18.8	11.0	(2.3)	4.8	22.9	11.3	(2.7)	3.7	25.0
Vol (l/24hr)	1.53	(0.81)^{o}	0.51	8.09	1.74	(0.65)†	0.62	4.11	1.55	(0.70)	0.39	4.29

Multiple comparison was done by the Student-Newman-Keuls method.

South Wales significantly different from Belfast: * p<0.05, ** p<0.01

Birmingham significantly different from South Wales:† p<0.05, †† p<0.01

Belfast significantly different from Birmingham: ^{o} p<0.05, ^{oo} p<0.01

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; Wt, weight; Ht, height; BMI, body mass index; Na, sodium; K, potassium; Na/K, sodium/potassium ratio; Cl, chloride; Ca, calcium; Mg, magnesium; Creat, creatinine; Vol, volume.

Table 17

Three U.K. centres combined: age and centre standardised means (sd) of selected variables by sex, and for men and women combined

	Men (N=299)	Women (N=299)	Men & Women (N=598)
Systolic BP (mm Hg)	124.8 (16.0)	118.0* (14.2)	121.4 (15.1)
Diastolic BP (mm Hg)	74.5 (11.7)	69.7* (9.1)	72.1 (10.5)
Weight (kg)	75.6 (11.6)	64.8* (12.6)	70.2 (12.1)
Height (m)	1.73 (0.07)	1.60* (0.06)	1.67 (0.06)
BMI (kg/m^2)	25.2 (3.3)	25.2 (4.9)	25.2 (4.2)
Pulse (beats/min)	72.4 (11.9)	76.1* (10.6)	74.3 (11.3)
Prevalence of heavy drinking (≥300 ml/wk)	27.5%	3.0%*	15.2%
24-hour urinary excretion:			
Sodium (mmol/24hr)	168.5 (59.1)	135.6*(45.5)	152.1 (52.7)
Sodium/potassium ratio (mmol/mmol)	2.63 (0.93)	2.66 (0.98)	2.64 (0.96)
Potassium (mmol/24hr)	68.3 (23.1)	53.7*(16.0)	61.0 (19.8)
Chloride (mmol/24hr)	172.0 (62.5)	134.4*(45.8)	153.2 (54.8)
Calcium (mmol/24hr)	5.35 (2.31)	4.11*(1.85)	4.73 (2.09)
Magnesium (mmol/24hr)	4.47 (1.47)	3.83*(1.14)	4.15 (1.31)
Creatinine (mmol/24hr)	13.1 (2.9)	9.0* (1.8)	11.1 (2.4)
Volume (l/24hr)	1.75 (0.85)	1.47*(0.56)	1.61 (0.72)

Key: BMI, body mass index

* Women significantly different from men, $p<0.001$

Table 18

Regression coefficients (SE) relating blood pressure (BP) and 24-hour urinary sodium (Na) excretion (mm Hg/10 mmol Na) urinary sodium/potassium (Na/K) ratio (mm Hg/molar ratio) and urinary potassium (K) excretion (mm Hg/10 mmol K), for the 3 U.K. centres and all INTERSALT centres. Adjusted for centre and for age and sex, and age, sex and other confounders†

	Systolic BP				Diastolic BP			
Regression:	Adjusted for age and sex		Adjusted for age, sex and other confounders†		Adjusted for age and sex		Adjusted for age, sex and other confounders†	
BP-Na								
UK Centres:								
- Belfast	0.374*	(0.172)	0.224	(0.201)	0.119	(0.138)	-0.038	(0.156)
- Birmingham	0.020	(0.299)	-0.056	(0.242)	-0.058	(0.157)	-0.163	(0.160)
- South Wales	0.461*	(0.218)	0.494*	(0.249)	-0.133	(0.143)	0.021	(0.164)
All INTERSALT Centres	0.163***	(0.023)	0.100***	(0.026)	0.068***	(0.017)	0.003	(0.019)
- corrected for reliability+	0.354		0.217		0.148		0.006	
BP-Na/K								
UK Centres:								
- Belfast	0.443	(0.960)	0.044	(0.975)	0.355	(0.761)	-0.276	(0.749)
- Birmingham	0.105	(1.089)	0.092	(1.063)	-0.462	(0.745)	-0.454	(0.705)
- South Wales	1.750	(1.328)	2.177	(1.347)	-0.324	(0.868)	-0.279	(0.885)
All INTERSALT Centres	0.810***	(0.106)	0.621***	(0.104)	0.319***	(0.075)	0.166*	(0.074)
- corrected for reliability+	2.098		1.608		0.826		0.431	
BP-K								
UK Centres:								
- Belfast	0.819	(0.532)	0.520	(0.529)	0.173	(0.424)	-0.118	(0.407)
- Birmingham	-0.562	(0.553)	-0.056	(0.242)	0.076	(0.379)	-0.163	(0.160)
- South Wales	0.188	(0.560)	-0.810	(0.630)	-0.358	(0.362)	-0.608	(0.411)
All INTERSALT Centres	0.012	(0.065)	-0.254***	(0.070)	-0.020	(0.048)	-0.165**	(0.052)
- corrected for reliability+	0.021		-0.446		-0.035		-0.289	

† BP-Na adjusted for age, sex, body mass index, potassium, alcohol; BP-Na/K adjusted for age, sex, body mass index, alcohol; BP-K adjusted for age, sex, body mass index, sodium, alcohol .

+ Reliability coefficient estimated from data on repeat urine measurements

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Table 19

Regression coefficients† (SE) relating blood pressure (BP) to Body Mass Index (BMI) and heavy alcohol intake (≥300ml/week) for the 3 U.K. centres, and for all INTERSALT centres. Adjusted for age, sex and other confounders+

	Systolic BP		Diastolic BP	
BP-BMI				
UK Centres:				
Belfast	0.73*	(0.25)	0.96**	(0.19)
Birmingham	0.94*	(0.28)	0.88**	(0.18)
South Wales	1.07**	(0.24)	0.70**	(0.16)
All INTERSALT Centres	0.775**	(0.036)	0.597**	(0.026)
BP-Alcohol				
UK Centres:				
Belfast	2.83	(2.92)	2.28	(2.26)
Birmingham	2.69	(4.04)	1.43	(2.67)
South Wales	4.57	(3.98)	3.04	(2.61)
All INTERSALT Centres	3.34**	(0.57)	1.98**	(0.41)

† Coefficients estimate the difference in BP (mm Hg) per unit BMI, or, for alcohol, for drinkers of ≥300ml/week compared to non-drinkers

+ BP-BMI adjusted for age, sex, sodium, potassium, alcohol; BP-Alcohol adjusted for age, sex, sodium, potassium, BMI

** $p<0.01$ *** $p<0.001$

Table 20

Three U.K. centres combined: mean (SE) blood pressure (mm Hg) by sex and by "risk score"†, estimated from individual values of sodium and potassium excretion, body mass index and alcohol intake. Adjusted for centre, and for age.

	Men			Women		
	N	Systolic	Diastolic	N	Systolic	Diastolic
"Risk score"†:						
0	20	114.6 (3.4)	71.2 (2.5)	27	113.2 (2.6)	65.7 (1.7)
1	91	119.9 (1.6)	70.2 (1.2)	121	116.1 (1.2)	69.8 (0.8)
2	125	129.0 (1.4)	76.5 (1.0)	117	120.5 (1.3)	70.3 (0.8)
3+	63	126.7 (1.9)	77.9 (1.4)	34	120.1 (2.3)	70.7 (1.6)

F - test for hetrogeneity (df = 3 & 290):

Males, systolic = 9.48, diastolic = 8.34 ($p < 0.001$)

Females, systolic = 3.46 ($p < 0.05$), diastolic = 2.01 ($p = 0.1$)

† For each invidual, the "risk score" is calculated by summing (0,1) values for that individual relative to the appropriate age, sex and centre adjusted values, where 0 = "lower-risk" and 1 = "higher risk" (i.e., for sodium and body mass index: 0 = below adjusted median, 1 = above adjusted median; for potassium: 0 = above adjusted median, 1 = below adjusted median, and for alcohol consumption 0 = less than 300 ml/week, 1 = at least 300 ml/week).

Chapter 5

Discussion, Conclusions and Recommendations

In this Chapter, the results of the age and sex specific anlyses and the findings for the three U.K. centres presented in Chapter 4 are briefly discussed; and the results of INTERSALT relating sodium and BP are put into the context of the other evidence presented in Chapter 1. Some of the implications of the study are also addressed and recommendations made with regard to sodium intake of both individuals and populations.

5.1 Age and Sex Specific Results

Summarising the results in Chapter 4, the study found positive and significant relationships in individuals between urinary sodium excretion and BP in both men and women. These positive and significant relationships were also found in seven of eight age-sex specific analyses. In most analyses, z-scores suggested closer associations in women than in men: the size of regression coefficients in women was as much as twice that of the corresponding coefficients in men. In age-specific analyses for men and women combined, sodium excretion was positively related to BP, significantly so for systolic pressure at all ages and for diastolic pressure at ages 50-59; these regression coefficients were generally larger at older compared to younger ages. Results for sodium/potassium ratio in individuals were similar to those for sodium, being stronger in women than in men, and (at least for systolic pressure) at older compared to younger ages. With adjustment for confounding variables, potassium excretion was negatively and significantly related to the BP of individuals; again these relationships were more marked at older ages. Across the centres, median sodium excretion was positively and significantly related to the slope of systolic and diastolic blood pressure with age in men, in both the 52 and 48 centre analyses, and with and without adjustment for confounding variables. For women, relationships with slope of blood pressure with age were positive in all analyses, but were significant only in the analyses across 52 centres. Other across-centre relationships were less consistent.

These results confirm the importance of sodium and potassium in relation to the BP of individuals, despite the well-known problems of within-individual variability which seriously bias these relationships (Liu et al., 1979); and they extend the findings of the main INTERSALT report (INTERSALT Cooperative Research Group, 1988) to age- and sex-specific sub-groups. The power of the sub-group

analyses to detect significant associations between BP and electrolytes is lower than in the study as a whole, and the power to detect significant interactions is limited (e.g., different sized relationships in men and women, or at different ages) since the study was designed to test out hypotheses in all 10,000+ participants. Nevertheless, there was some indication of stronger relationships in women than in men of sodium (and sodium/potassium ratio) with BP, consistent with the findings in the other epidemiological studies discussed in Chapter 1 (Table 7). There was also indication of stronger relationships at older compared to younger ages, as has been predicted (Simpson, 1988).

The reasons for the differences by sex and age are not clear, and may to some extent indicate different reliability of measurement for men and women, and at different ages. Alternatively, the stronger relationships in women compared to men might reflect a reduced ability in women to handle an equivalent sodium load given their smaller frame and hence kidney size (Simpson et al., 1982). The difference with age may also reflect reduced ability to handle a sodium load with advancing age and hence decreasing renal function, or possibly the effect of greater cumulative exposure to sodium which is apparent at older ages. The results with age are consistent with the findings of Grobbee and Hofman (1986) with respect to their review of the trials of sodium reduction discussed in Chapter 1 (i.e., an apparent greater effect at older ages) and warrant further investigation in laboratory as well as epidemiological studies.

Recent work suggests that the estimates of reliability which were published previously (INTERSALT Cooperative Research Group, 1988) are probably too high, so that correction factors (which are the inverse of reliability) are too low (A. Dyer, personal communication). Taken together with the larger effects at older ages, these results suggest that previous INTERSALT estimates of the relations between sodium, potassium and BP are conservative. Even with correction for reliability as indicated previously (INTERSALT Cooperative Research Group, 1988), the analysis at ages 50-59 suggests that 100 mmol lower sodium excretion is associated with average BP lower by 4.9 mm Hg systolic and 1.9 mm Hg diastolic (after adjustment for age and sex), or 3.6 mm Hg systolic and 0.4 mm Hg diastolic (with adjustment also for potassium excretion, body mass index and alcohol intake). As previously reported (INTERSALT Cooperative Research Group, 1988) equivalent figures for the analysis of men and women combined at all ages are respectively 3.5 mm Hg systolic, 1.5 mm Hg diastolic, 2.2 mm Hg systolic and 0.1 mm Hg diastolic.

Across the 52 centres, the positive, significant and independent association between average sodium excretion and slope of BP with age was present in men and women for both systolic and diastolic pressures with and without adjustment for confounding variables. Across 48 centres (excluding the four low-sodium centres) it remained significant in men, and positive but non-significant in women. For men and women combined, this across-centre association gave the estimate that the rise in systolic BP over a 30 year period (e.g., from age 25 to age 55) would be less by 9 mm Hg for a 100 mmol lower average sodium excretion.

Average sodium excretion was also positively and significantly related to average BPs and prevalence of hypertension across all 52 centres. This is the analysis most comparable to the famous straight line graphs of Dahl (1960), Froment, Milon and Gravier (1979) and Gleibermann (1973), who included populations with very low and very high levels of sodium intake: as shown in Chapter 1 (Table 4), the size of the coefficients is reduced when populations at the extremes of sodium intake are excluded from the analyses. The same phenomenon can be seen in INTERSALT when the four low-sodium centres are excluded, since in these analyses, the power to detect significant associations is low given the limited range of average sodium excretion amongst the 48 centres (Chapter 2). Relationships in INTERSALT are further confounded by average body weight, since some populations (particularly those in the Far East) tend to have relatively high sodium excretion, but low body weight which is itself related to BP (Dyer & Elliott, 1989). Thus there is important ecological confounding in INTERSALT which, as discussed in Chapter 3, makes interpretation of the across-centre findings hazardous; taken together with the relatively low statistical power in these across-centre analyses compared with the high power within-centres, this suggests that far more weight in INTERSALT should be given to the within- rather than the across-centre findings.

5.2 Findings for the United Kingdom Centres

The study gives standardised data on BP levels, electrolyte excretion and other factors in representative samples of defined populations in three U.K. centres. In common with other European centres in INTERSALT, the U.K. centres had relatively high average BPs, body mass index, sodium excretion and sodium/potassium ratio; prevalence of heavy alcohol drinking (≥300 ml/week) in men was also high (27.5%). Only the relatively high mean potassium excretion in the U.K. (61 mmol/24 hr) could be considered favourable, but even so, it was exceeded in 17 of the 52 centres (INTERSALT Cooperative Research Group, 1988).

Mean sodium excretion was 152 mmol/24-hour (equivalent to 8.9 g salt per day). Few other data on sodium intake in the U.K. are available; James, Ralph & Sanchez-Castillo (1987) reviewed studies of salt consumption in Britain published between 1959 and 1984, in which salt intake was assessed by the urinary excretion of sodium or chloride. Estimates in men ranged from 9.7 g salt/day in South Wales (Watt, Foy & Tudor Hart, 1983) to 15.7 g in Plymouth (Dauncey & Widdowson, 1972) compared with 9.8 g (169 mmol sodium) in the INTERSALT U.K. centres; in women, previous estimates ranged from 6.5 g salt/day in South Wales (Watt, Foy & Tudor Hart, 1983) to 10.1 g in Renfrew, Scotland (Beevers, Hawthorne & Padfield, 1980), compared with the 7.9 g (136 mmol sodium) reported here.

Estimates of salt intake were derived from 24-hour urine collections in random general population samples in two of the studies (both in Cambridgeshire) reviewed by James, Ralph & Sanchez-Castillo (1987), giving values of salt excretion of 10.6 g/day (Sanchez-Castillo et al., 1987) and 10.1 (Williams & Bingham, 1986) in men, and 7.4 g/day (Sanchez-Castillio et al., 1987) and 7.5 (Williams & Bingham, 1986) in women. Only four other studies could be identified by the present author in which estimates of sodium excretion were based on 24-hour urine collections from random population samples in Britain (Bulpitt et al., 1986; Elliott et al., 1988; Gregory et al., 1990; Smith et al., 1988). In a small study in a North London general practice, mean sodium excretion was 193 mmol/24-hour (11.3 g salt/day) in men and 142 mmol/24-hour (8.3 g salt/day) in women (Elliott et al., 1988); in London civil servants, it was 171 mmol/24-hour (10 g salt/day) in men and 136 mmol/24-hour (7.9 g salt/day) in women (Bulpitt, et al., 1986); in a large population survey in Scotland, mean values were 193 mmol/24-hour (11.3 g salt/day) in men and 143 mmol/24-hour (8.4 g salt/day) in women (Smith et al., 1988); and in a recently published population survey of the dietary habits of British men and women (Gregory at al., 1990), mean sodium excretion was 174 mmol/24-hour in men (10.2 g salt/day) and 141 mmol in women (8.3 g salt/day).

Thus the somewhat limited data available suggest a relatively high average salt consumption across the U.K. which has probably varied little in recent years. This contrasts with the experience of other countries, e.g., Belgium (Joossens & Geboers, 1985) and Japan (Hashimoto et al., 1989) where sodium consumption appears to have declined. The apparent constancy of sodium intake in the U.K., however, conceals marked individual variability: in the present study, values of sodium excretion of up to 393 mmol/24-hour (23 g salt/day) were recorded.

Significant ($p<0.05$) positive relations were observed between sodium and systolic pressure in two centres (Belfast and South Wales). These findings are consistent with some of the other studies in the U.K. which found positive and significant relationships between sodium and BP (Elliott et al., 1988; Smith et al., 1988; Khaw, 1983). Within the context of INTERSALT, however, they may to some extent represent chance variation amongst the 52 centres; results were similarly positive and significant in 13 other centres (INTERSALT Cooperative Research Group, 1988). Some implications of the INTERSALT findings for U.K. food and health policy are discussed in section 5.4.2 below.

5.3 Findings of the INTERSALT Study in the Context of Other Evidence on Salt and Blood Pressure

The evidence reviewed in this thesis from controlled trials of sodium reduction, epidemiological studies except INTERSALT, and the INTERSALT study itself, is consistent in showing that lower urinary sodium excretion is associated with lower BP. Furthermore, these different types of study give quantitatively similar estimates of effect. To some extent this finding might be fortuitous, in so far as the epidemiological studies are prone to bias and confounding as discussed in Chapter 1, while the trials may underestimate the sodium-BP relation due to carry-over effects, and incomplete reversibility.

Thus the overview of randomised controlled trials presented in Chapter 1 gave the estimate that a reduction in sodium excretion averaging 70 to 75 mmol per day lowered BP in hypertensive subjects by 4.9 mm Hg systolic and 2.6 mm Hg diastolic, and by 1.7 mm Hg and 1.0 mm Hg respectively in normotensive subjects (Table 3). The overview of within-population epidemiological studies, again presented in Chapter 1, gave a pooled (simple) regression estimate that 100 mmol lower sodium was associated with BP lower by 3.7 mm Hg systolic and 2.0 mm Hg diastolic in men and women combined, after correction for intra-individual variability in sodium excretion (Table 7); and the corrected pooled within-centre regression estimate from INTERSALT in men and women combined was that, with adjustment for age and sex, 100 mmol lower sodium was associated with BP lower by 3.5 mm Hg systolic and 1.5 mm Hg diastolic, reducing to 2.2 mm Hg and 0.1 mm Hg respectively after adjustment for other confounders (INTERSALT Cooperative Research Group, 1988; and Table 18). Across the centres in INTERSALT, average sodium excretion was positively and significantly related to slope of BP with age, such that 100 mmol lower sodium was associated with a 9 mm Hg lower rise in systolic BP from age 25 to age 55 (Table 15).

A number of considerations relevant to the interpretation of the INTERSALT results should be noted. As discussed in Chapter 3, the design allowed relationships to be studied both in individuals and across centres, although the across-centre analyses are particularly prone to bias from unmeasured (ecological) confounding. Thus the study is perhaps best regarded as a pooling of 52 separate epidemiological studies in individuals, with standardised methods, equipment and protocol in all centres, and with central coordination of quality control, data collection, and of the data and biochemical analyses.

Under these circumstances, the study gave a powerful *qualitative* test of the sodium-BP relationship. However, it is likely that a combination of factors led to an underestimate of the *size* of that relationship: firstly, the study was cross-sectional, relating *current* sodium excretion (as a proxy for current intake) to *current* BP. If sodium is implicated in higher BP, it is likely that exposure since childhood, even from birth, is important (Hofman, Hazebroek & Valkenburg, 1983). Secondly, as discussed, a single 24-hour urine collection is a relatively weak method for quantifying the "true" (habitual) electrolyte excretion of the individual, due to large within-individual variability. Even though there was an attempt to correct for this error using study-wide estimates of reliability, the adjustment that was made probably underestimated the bias, as noted above. Thirdly, although the protocol required that the start and end of the 24-hour collection be supervised by clinic staff, and each person was queried about completeness of collection, nevertheless it is likely that varying degrees of incompleteness of urine collection took place in some (or all) of the centres, which would again tend to lead to underestimates of true associations (Elliott et al., 1988).

Fourthly, many populations in the study (e.g., those in Japan and the United States) have been subjected to public health campaigns against a high salt intake. This could bias true associations downwards, or even convert positive relations to negative, if, as was in fact seen in the study, hypertensive individuals in the population were selectively reducing sodium intake (Hashimoto et al., 1989). Fifthly, a number of individuals in the study were on anti-hypertensive medication (indeed, the majority at older ages in some centres) and hence BPs as measured were artificially low. Again the effect would be in the direction of reducing observed relationships between sodium and BP; and sixthly, adjustment for body mass index and other confounders, which are positively correlated with sodium excretion but are more accurately measured, may have led to an underestimate of the independent effect of sodium in the multiple regression analyses (Liu, 1988).

Despite this likely underestimation of effect, the sum of evidence relating sodium to BP from animal studies, clinical observations, clinical trials and epidemiological studies is persuasive, and consistent with a judgment as to causality. In the remainder of this Chapter, some of the public health implications of these findings are briefly considered.

5.4 Some Public Health Implications

In this section, some of the issues are reviewed concerning a possible public health recommendation for improved lifestyles to lower BP and in particular, a policy of sodium reduction to lower BP in the community. After a brief discussion of the nature of the BP problem in populations, the issue of salt sensitivity is discussed, as is whether a recommendation to lower sodium intake in the community would be appropriate, and likely to be safe and of benefit.

First, the risk associated with raised BPs in the community is considered. This is discussed in detail elsewhere, as is the potential for non-pharmacological approaches to BP control in the community (Elliott, in press; Marmot & Elliott, 1989; J. Stamler et al., 1989). The following points are relevant:

BP associated risk is not confined to the minority with established hypertension, but is a problem for the population as a whole. This is best illustrated using data on the 360,000 men aged 35 to 57 years at entry, who attended the first screen of the Multiple Risk Factor Intervention Trial (MRFIT), and whose mortality experience has now been reported after 6 years of follow-up. There was a graded and continuous increase in coronary heart disease mortality with increasing BP above "baseline" (i.e., BPs higher than 76 mm Hg diastolic or 118 mm Hg systolic), so that some 80% or more of the cohort were at increased risk (Stamler, Neaton & Wentworth, 1989). Men with the highest BPs (e.g., systolic BP 160+ mm Hg) had the highest individual risk of death and contributed as a group about 30% of the deaths attributed to raised BP in the MRFIT screened cohort; however, over 60% of those attributable deaths occurred in the far larger group with entry systolic BPs of 130 to 160 mm Hg, i.e., within the so-called "normal" to "mild hypertension" range (Elliott, in press). Thus for a measure like sodium reduction to be effective in reducing the community burden of BP-related disease, intervention needs to be directed at the population as a whole, not just at those with the highest pressures.

Small changes in the average BP of a population could have a large effect both on the prevalence of hypertension (due to the continuous nature of the BP distribution)

and on mortality from cardiovascular disease. For example, using multiple logistic regression coefficients from the Whitehall study (M. Shipley, personal communication) it can be predicted that average systolic BPs lower by 2, 3 or 5 mm Hg are associated with annual mortality from cardiovascular disease lower by 3.2%, 4.8% and 7.8% respectively in middle-aged men. These figures can be regarded as the potential gain to the community from lifelong changes in environment or lifestyle factors, resulting in a slower rise of BP through young adulthood and middle-age (Marmot & Elliott, 1989).

5.4.1 Salt Sensitivity?

By analogy with experience in rats, it has been argued (Luft, Weinberger & Grim, 1982) that only a proportion of the population, about 20% according to Tobian (1979), is sensitive to the pressor effects of sodium, so that sodium restriction should be directed at this sub-group and not at the population as a whole (Luft et al., 1988). If this were true, one might expect that positive relationships in individuals between salt and BP would be "generated" by the minority who were "sodium sensitive" (and who would therefore attain the highest pressures): for the remainder of the population, associations between sodium and BP should be absent or much reduced. This hypothesis can be tested directly using INTERSALT data. Regression analyses relating sodium and BP were run excluding those with hypertension (BPs at or above 140 mm Hg systolic or 90 mm Hg diastolic, or on anti-hypertensive medication). Sodium remained positively and significantly related to BP in these analyses, with regression coefficients only marginally lower than those obtained in the study population as a whole (Stamler, 1991).

These results suggest that the positive association of sodium and BP in individuals is observed across the BP range, and is not restricted to a minority with BPs at the high end of the distribution; they further imply that a policy of sodium reduction would be better directed at the population as a whole, than at a sub-group of "sodium sensitive" individuals. Since "sodium sensitivity" (i.e., a positive individual BP response to sodium) appears to be continuously and Normally distributed in the population, and not a discrete entity (Weinberger et al., 1986), studies labelling individuals as "sodium sensitive" or "sodium insensitive" have perhaps reflected random variation as much as true biological variability (Grobbee, 1991).

The concept of "sodium sensitivity" has not been convincingly demonstrated in man (except perhaps for a greater effect of sodium on BP at older ages) and as yet there is no reliable marker of "sodium sensitivity" (Grobbee, 1991). This implies that an

approach to intervention based on "sodium sensitive" individuals is not appropriate. By contrast, at the level of populations, it is likely that lower average sodium intake would result in lower average BP, despite known variability in the individual response to sodium.

5.4.2 What Changes in Lifestyle Factors are Required to Produce Worthwhile Changes in Average Blood Pressure?

Despite likely underestimation of the INTERSALT regression estimates (see above), they provide a useful basis for making judgements concerning the likely reductions in BP to be gained from appropriate lifestyle changes. Consider for example, results from the three U.K. centres. The relatively small sample size in any one centre and large within-person variability in electrolyte excretion restrain the use of the individual U.K. centre regression coefficients for estimation purposes; but implications for the U.K. can appropriately be based on pooled results of all 52 centre regression coefficients in INTERSALT, corrected for reliability, and applied to the distributions observed in the U.K.

Thus reduction in average sodium excretion by one-third, i.e., by 50 mmol per day (from 150 mmol to 100 mmol) accompanied by an increase in average potassium excretion by one-third, i.e., by 20 mmol per day (from 60 mmol to 80 mmol) would also change sodium/potassium ratio by about 1.25 units (from about 2.5 to 1.25). The above changes are within the observed distributions of these electrolytes within the U.K., being in each case (at least on the day of study) about one standard deviation about the mean, and represent realistic medium-term goals for population values of these variables.

By applying the regression coefficients from the fully adjusted models relating electrolytes and BP (Chapter 4, Tables 12-14) it can be estimated that these changes would be associated with differences of about 2-3 mm Hg in average population systolic pressure. Further, the across-centre findings indicate that a 50 mmol reduction in sodium intake might reduce the rise in systolic pressure over 30 years by 4 to 5 mm Hg (Chapter 4). As discussed above, differences in average BP of this magnitude have been shown in follow-up studies to be associated with large differences in mortality (J. Stamler et al., 1989; Stamler, 1991). Additional benefits might be expected from favourable changes in average body mass index or (for heavy drinkers) in alcohol intake, both of which were positively and significantly related in INTERSALT to the BP of individuals, independent of the effects of sodium and potassium (Table 19).

The cross-stratification analysis in the U.K. centres allowed direct comparison of BPs to be made at different levels of the lifestyle factors identified above, despite likely mis-classification of individuals due to within-individual variability and other biases which would tend to reduce BP differences. For the group of men and women at "lower risk" of high BP (i.e."risk score" zero) based on simple stratification about the relevant age, sex and centre-adjusted medians, and including only those who were not heavy drinkers, BPs were (significantly) lower than the remainder by up to 11 mm Hg systolic (men) and 4.5 mm Hg diastolic (women).

In summary, the three U.K. populations included in INTERSALT were characterised by relatively high BPs, sodium excretion, sodium/potassium ratio, body mass index and (in men) a high prevalence of heavy alcohol drinking. Applying overall findings from INTERSALT to the U.K. data suggests that more favourable levels of these variables, together with a modest increase in potassium consumption, could result in a shift downwards in the population BP distribution and a reduction in the prevalence of hypertension. These non-pharmacological approaches to BP control could be expected to reduce mortality from stroke and coronary heart disease.

5.4.3 Is Sodium Reduction Safe?

This question was reviewed by Dahl (1958) who concluded that the sodium intake of Western societies was many times physiological need, and that there was little evidence to suggest harmful effects of even severe sodium restriction (to below one gram of salt a day). Four populations in INTERSALT were found to excrete on average less than 50 mmol sodium per day. Median excretion of the Yanomamo Indians of Brazil was only 0.2 mmol per day; they were engaged in a high level of physical activity, and did not have evident malnutrition or protein deficiency (Carvalho et al., 1989; Mancilha-Carvalho, De Oliveira & Esposito, 1989).

As with other public health measures, there will be a few individuals for whom a recommendation to reduce salt intake would not be appropriate (Brown et al., 1984a), e.g., patients with salt-losing nephritis. However reduction in average population salt intake by one-half would still imply a level considerably in excess of usual physiological need. In half of the 48 INTERSALT populations (excluding the four low-sodium centres) at least 15% of participants had sodium output less than 100 mmol on the day of study, and in three of these centres, at least 15% had sodium output below 70 mmol.

Restriction of sodium to around 50 mmol in individual patients, or to an average of 70-100 mmol in whole populations, appears to be a safe procedure. Variation in 24-hour sodium excretion within the INTERSALT populations was surprisingly large, even after correction for intra-individual variability (which increases estimates of variance based on a single 24-hour urine collection); thus it is apparent that many individuals, even in Western populations, already consume diets relatively low in sodium.

5.4.4 Is Sodium Reduction Achievable?

The short- to medium-term trials reviewed in Chapter 1 show that reduction in sodium intake to below 80 mmol, or even 50 mmol, per day is acceptable and achievable in well-motivated patients with mild to moderate hypertension. Findings of the Hypertension Prevention Trial Research Group (1990) in its three year trial, and of the community trial in Belgium (Staessen et al., 1988) were less encouraging, although observational studies suggest that sodium intake in Belgium is in fact on the decline (Joossens & Geboers, 1985). As noted in Chapter 1, recent data from the U.K. suggest that discretionary use of sodium (added in cooking and at the table) may account for only 15% of sodium intake (Sanchez-Castillo et al., 1987) so that attempts to lower sodium consumption need to address the issue of salt added by the manufacturer in processed foods, and in particular bread, meats and cereal products (Bull & Buss, 1980). This would most likely require cooperation of government as well as the food industry to ensure adequate food labelling and to provide a wide variety of low-sodium and sodium-free foods.

5.5 Conclusions and Recommendations

In summary, recent controlled clinical trials of sodium reduction, and epidemiological studies including INTERSALT, are remarkably consistent in their estimates of the size of the sodium-BP relationship. Potentially, a reduction in sodium intake is of benefit both to individuals with higher levels of BP, through improved BP control, and to the community at large through a reduction in average BP. Of the non-pharmacological approaches to BP management considered here (reduction in sodium intake, reduction in the prevalence of obesity and of heavy alcohol drinking, and an increase in potassium intake), it may be that sodium reduction is the most amenable to change: since most sodium consumed is non-discretionary, being added in food processing, it potentially can be lowered through population-based rather than individual action, e.g., government legislation, clear food labelling and greater access to low-sodium and sodium-free foods.

A reduction in sodium intake is a safe and valuable measure in the management of patients with mild to moderate hypertension. Individual responses to sodium restriction vary, and adequate BP control can only sometimes be achieved by moderate sodium restriction alone. Nevertheless, improved BP control can be achieved by many patients who reduce their sodium intakes, so that they can be maintained on a reduced dose of anti-hypertensive drugs. At the population level, a general lowering of sodium intake is both desirable and feasible, but would necessitate a major national and community effort.

Recommendation 1: In persons with mild to moderate hypertension, a trial of reduced sodium intake can safely be recommended either alone or in combination with other dietary measures, including weight loss (for overweight individuals) and moderation of alcohol intake. Reduced sodium intake is also a useful adjunct to pharmacological therapy. To be effective, sodium intake should be reduced to less than 80 mmol per day, and in some cases to 50 mmol per day: special dietary counselling and the provision of low-sodium or salt-free foods may be required.

Recommendation 2: At the population level, average sodium intake should be reduced by at least one third (e.g. from 150 mmol to 100 mmol per day in the U.K.). This is a realistic medium-term goal. Other population measures should include a reduction in the prevalence of obesity, a moderation of alcohol drinking and an increase in dietary potassium intake. It can be expected that over time these population-wide measures would reduce the community burden of mortality from coronary heart disease and stroke.

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Appendix 1: Field Methods

This appendix gives edited versions of the INTERSALT Field Manual of Operations, and the Manual of Operations for the London Coordinating Centre and the Central Laboratory. A fuller account is available (Elliott & Stamler, 1988).

1. Field Manual of Operations

The detailed field methods which were used in the study and as the basis for training of investigators from the 52 centres were described in a *Manual of Operations*. The Manual was made available to each centre for local training and for use in the field. An edited version is given here. The data forms which accompany this Manual are in Appendix 2.

1.1 Sampling and Recruitment

The goal for each centre is the recruitment of 200 persons with complete urinary and BP measurements, 25 in each of 8 age-sex strata. The aim is to have this sample of 200 as representative as possible of the base population.

First, a description of the population is forwarded to London giving available information on characteristics like urban/rural status; main type of economic activity; economic level; weather; usual diet pattern, including information on salt use; general level of health, ethnic composition and, if known, population size and age-sex distribution.

A sample of the base population is drawn, and age-eligible persons are invited into the study. To assess how closely those taking part in the study resemble the population from which they came, a detailed recruiting record is kept.

Taking the sample

There are three possible sampling situations:

1. Ideally, there is a list of those in the defined population, aged 20-59, with known information on the age, sex, and address of each person.

2. There is a list of names and locations (e.g., voters' list) without knowing age or sex.

3. There are no names but a defined geographical location from which to sample (e.g., a neighbourhood, a village, etc.).

In the first situation, a random sample of 400 is drawn with 50 names of each sex in each 10-year age group. Allowing for refusals, this should permit recruitment of 25 in each subgroup.

If your list has names and locations but does not specify age and sex, then a random sample of 600 is drawn to help account both for refusals and for any unevenness in age-sex distribution. As an individual is approached for recruiting, age and sex are determined, so as to invite 25 from each age-sex group.

If there is no list of names, then as each household is contacted, persons aged 20-59 are identified before proceeding as above.

Recruitment

To maximise recruiting, Investigators should make more than one effort to contact persons in the sample. For example, if the telephone is used to recruit participants, several efforts should be made to make contact before moving on to the next individual or household. These attempts should cover the various times of the day and days of the week.

The general purposes of the study should be explained (e.g., a study of life style and BP), but no specific mention should be made of salt, since this could lead to change in usual salt intake at the time of examination.

The Recruiting Record

This record serves three purposes:

1. It indicates the order in which people are to be invited into the study.

2. It helps keep count of the numbers recruited in each age-sex stratum.

3. By keeping count of contact results, it helps assess response rate and the representativeness of the participants.

Sequence

Investigators should attempt to recruit persons for participation in unbiased order. For local centres which randomly draw an age- and sex-stratified sample of 400 this means that investigators should attempt to recruit participants in each age-sex stratum in the order in which they have been randomly selected, so that the first 25 in each age-sex stratum are invited before the 26th. However, ensure an even spread of clinic appointments across the age-sex strata.

For centres who sample from a base population without knowing age and sex, this means starting with the first name of the 600 persons sampled and working one's way down, until the goal of 25 in each age-sex stratum is reached.

For those sampling from households, without a prior list of names, the recruiting should be in a predetermined and systematic manner (e.g., listing all the addresses in a street and going to each house in order).

Where there are prior lists, names should be entered, in order, into the recruiting record before recruitment starts.

Where there are no lists of names, wherever feasible, household identification (address, etc.) should be entered, in order, into the recruiting record before recruitment starts.

For those centres working from a list of known names (whether or not age and sex are indicated), the first part of the Recruiting Record will look like this:

RECRUITING RECORD

(For centres with list of known names)

PART I.

Name of Person Randomly Selected	Sex	Age	Not Age Eligible	Contact Results: Unable to Contact 1st time	Unable to Contact 2nd time	Contacted: Agreed	Contacted: Refused
1.							
2.							
3.							
'							
'							
400 (End list here when age-sex is known)							
'							
'							
600 (End list here when age-sex is unknown)							

(The above will take many pages)

For centres sampling either from lists of names or from households, the second part of the Recruiting Record will help keep track of how many have agreed to appointments in each age-sex stratum. It needs to be updated as recruiting proceeds. Recruitment ends when the goal of 25 in each age-sex stratum has been reached.

PART II: (A separate form serves as Part II of the Recruiting Record)

RECRUITING RECORD

Summary of recruiting, by age-sex strata
Number with appointments

	Men: Age				Women: Age			
Date	20-29	30-39	40-49	50-59	20-29	30-39	40-49	50-59

Special Note on Recruitment

While the aim is to recruit 25 in each age-sex group, there may be need for additional persons in the event (hopefully rare!) that one of the 25 either fails to attend the clinic appointment or fails to complete the 24-hour urine collection. Where there is a prior sample list, this means going back to that list for the 26th person in the appropriate age-sex group, and inviting that person to attend.

When there was no list at the start, you will want to return to those in the right age-sex group, whom you identified but did not invite in the first round, or you may need to return to identify other eligible people. Response to these additional invitations should also be entered on the Recruiting Record.

Supplementary ID Numbers

Supplementary ID numbers have been assigned to each centre to identify extra participants. An extra participant is to be recruited if, for a given participant attending the clinic appointment, at least one of the following occurs:

1. Neither of the required BP readings (Measurement I and Measurement II, including the random zero) is adequately recorded.

2. The 24-hour urine collection is judged to be incomplete, that is on the Completeness Questionnaire, Form U (Appendix), the participant indicates either that urine was not always voided into one of the urine collection jars (Part A - "No") or that one or more jars containing urine were not returned (Part B - "No") or that urine was missing for some other reason (Part C - "Yes") and more than a few drops were lost (Part D - Box 2).

3. (For women only) The participant indicates in question 41 of the Questionnaire (Form Q) that she is pregnant. (Women known in advance to be pregnant should not be recruited into the sample).

Four ID numbers have already been set aside for extra participants, at the end of each age-sex stratum in the Log Book. Some centres may require additional supplementary ID numbers. Extra Log Book pages (with additional supplementary ID numbers) have therefore been drawn up:

** 301 - 320 Men age 20-29
** 351 - 370 Men age 30-39
** 401 - 420 Men age 40-49
** 451 - 470 Men age 50-59
** 501 - 520 Women age 20-29
** 551 - 520 Women age 30-39
** 601 - 620 Women age 40-49
** 651 - 670 Women age 50-59
** Centre Code

It is important that procedures for recruiting supplementary (extra) participants should be the same as for the main sample, e.g., repeated attempts should be made to contact them to ensure a high response rate.

The London Coordinating Centre should be immediately informed when an extra participant is to be recruited, and the reason should be given. In addition, local centres will be contacted immediately if review of forms in London indicates that an extra participant should be recruited.

In all cases, when an extra participant has been recruited, all the data (forms, urine aliquots) for the replaced participant should be processed and shipped in the usual way.

1.2 Blood Pressure Measurement

Preparation

1. Before BP is measured, the participant should be asked if he or she has refrained from eating, drinking anything other than water, smoking or taking strenuous exercise in the past half-hour. Include travelling to the clinic in the assessment of 'strenuous exercise'. For example, if participants have to climb a hill, this should be taken into account, and participants given adequate time to rest prior to BP measurement. The participant should not have been asked to fast in preparation for this visit. (Check off these items on Form G.)

2. The participant should have removed outer garments, jackets, etc. Sleeves of shirts, blouses, etc. should be rolled up so that the upper right arm is bare for the BP cuff. (If the right arm is missing, injured, or deformed, expose the left arm.) The shirt should not constrict, and the BP cuff should not be over the garment. Garments must be removed if obstructing, and a loose fitting gown provided.

3. BP should be measured in a quiet location.

4. The participant should be seated. When seated, the participant's right (left) arm should be allowed to rest, palm up, with elbow on the desk or table so that the antecubital fossa is level with the heart. To achieve this, either the position of the participant in the chair should be adjusted, or the arm may be raised or lowered on a comfortable support. Incorrect positioning of the participant's arm could introduce systematic error into the measurement.

   The participant should not be placed in an uncomfortable position.

5. The participant's legs should not be crossed.

6. Three standard cuff sizes are available: adult, large adult, and child. The correct size of cuff is essential for accurate BP measurement. Cuffs are marked with two "Range Lines" on the inner surface of the cuff, and an "Index Line" at the end of the cuff, to indicate to the user whether the cuff is the correct size for a particular limb.

7. The cuff should first be used like a tape measure, to be certain that the cuff is the correct size for the limb: hold the end of the cuff containing the rubber bladder over the upper arm, and pull the other end towards the participant

under the arm. The Index Line should lie within the Range Lines for the cuff size. If the Index Line either falls directly on a Range Line or outside the range, select the next smaller or larger cuff.

8. The centre of the pocket holding the inflation bag is marked 'Φ'. Once the correct cuff size has been chosen, palpate for the brachial artery (just above the cubital fossa, towards the inner side of the arm), and apply the cuff so that the 'Φ' lies over the brachial artery. The cuff should be applied firmly enough to prevent slipping. The lower edge of the cuff should be 2-3 cm above the cubital fossa, to allow sufficient room for the bell of the stethoscope. The top edge of the cuff should not be restricted by clothing.

9. Before taking pulse and BP, the participant should be resting in the sitting position, with the cuff applied, and with no change of position for five minutes. Conversation should be limited. However, a brief explanation of the procedure can be repeated at this time if necessary.

10. When these preparations have been completed, be sure that Form M is filled out, describing these preparations. Include time of day when measuring began. Record time using the 24-hour clock, e.g., 1 hour after noon = 13.00.

Measurement

1. The Hawksley random zero sphygmomanometer, with random zero 0-20 mm is used (Figures 7 and 8).

2. It is essential, for standardised measurement, that a strict order of taking pulse and BP measurements is kept as a fixed routine.

3. The observer should be in a comfortable position in relation to the examination table. The sphygmomanometer's mercury column should be in a perfectly upright position, the centre of it at the eye level of the examiner. The mercury column should face the observer and not be in the participant's view.

4. Measure resting pulse. Locate the radial pulse (at the wrist) with fingers of your left hand, and count the number of beats for 30 seconds, using a stopwatch. Write this value on Form M.

5. The cuff should now be connected to the sphygmomanometer.

6. For the random zero device: turn the diaphragm tap on the front of the device to 'open' and allow the mercury column to settle, then turn the diaphragm tap to 'close'.

7. Establish the Pulse Obliteration Pressure as follows: feel the participant's radial pulse with the fingers of your left hand. Inflate the cuff slowly and note the level (to the nearest 2 mm Hg) of the top of the meniscus of the mercury column at the point at which the radial pulse disappears. Then immediately deflate the cuff by disconnecting the cuff and the sphygmomanometer. Write down this value on Form M.

8. Add 10 to the Pulse Obliteration Pressure. Calculate the Peak Inflation Pressure as follows: either Pulse Obliteration Pressure + 10 mm or 180 mm, whichever is the greater. Write down the value. The cuff should be inflated to this new value for each BP measurement. (Occasionally the Peak Inflation Pressure will need to be increased. See Technical Notes below for details.)

9. Re-connect the cuff and the sphygmomanometer.

10. Again, locate the radial pulse with the fingers of your left hand, and count the number of beats for 30 seconds (using the stopwatch). Write down this value.

11. For the random zero device: turn the diaphragm tap to 'open' and leave it at 'open', and allow the mercury column to settle. Before inflating the cuff, turn the thumbwheel at the right side of the device (Figure 8) by gently spinning it three times with the forefinger of the right hand.

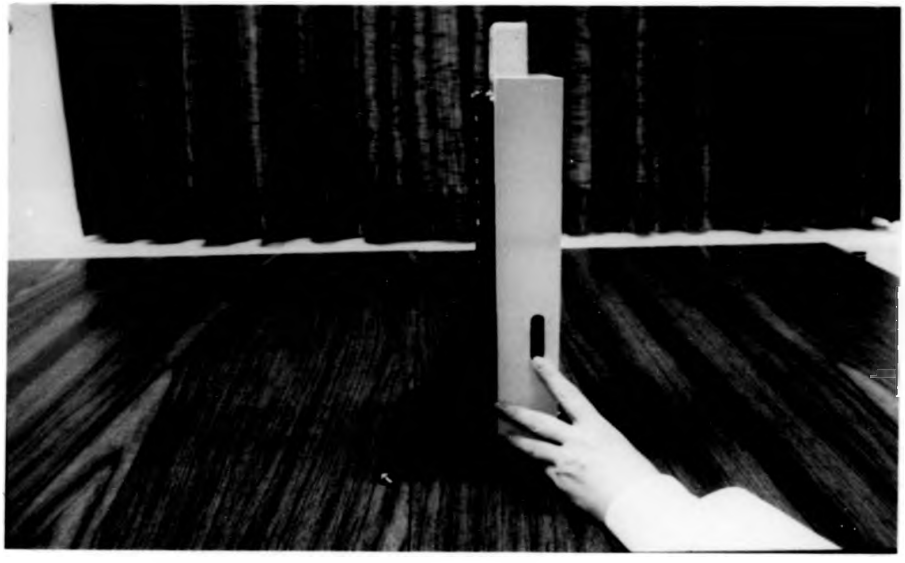
12. Place the stethoscope in the ears with the earpieces pointing forward. Ensure that the valve on the stethoscope head is turned to the bell position, or the sound will not be transmitted.

13. Using the fingers of the left hand, locate the brachial pulse at the point of maximal pulsation immediately below the cuff. The bell of the stethoscope should be placed here. If it is not possible to feel the brachial pulse, the bell of the stethoscope should be placed over the area of the upper arm immediately inside the biceps muscle tendon. The bell should not touch the cuff, rubber, or clothing.

Figure 7

The Hawksley random zero sphygmomanometer, front view, showing diaphragm tap on the left

Figure 8



The Hawksley random zero sphygmomanometer, side view, showing thumb wheel

14. Looking at the manometer with the centre of the scale at eye level and the column perfectly upright, inflate the cuff rapidly to a pressure equal to the Peak Inflation Pressure.

15. Holding the pressure constant with the hand bulb, wait five seconds to allow time for the diaphragm chamber of the random zero device to fill properly. (Count five slowly.) Turn the diaphragm tap to the left, to the position marked 'close'.

16. Control the pressure fall with the valve on the hand bulb to allow the column of mercury to fall at a rate of 2 mm per second. Listen for the Korotkoff sounds with the stethoscope.

17. Record the systolic and 5th phase diastolic BP readings to the nearest 2 mm Hg, uncorrected for the zero. The systolic is recorded at the appearance of the first sound in a series of at least two sounds. The diastolic pressure Phase 5 is recorded at the mercury level one beat below the last sound heard. (It is not at the level of the last sound.) If BP sounds can be heard down to zero, record diastolic pressure as zero.

18. After observing and recording systolic and diastolic BP, release the remaining pressure by opening the bulb valve, disconnect the tube, and after allowing the system to come into equilibrium, note and record the 'zero' reading. Do not subtract the zero from systolic and diastolic BP readings on Form M as this will be done by computer. However, for local feedback to the participant, the true systolic and diastolic BP should be calculated. These may be written down in the left margin of the form.

19. Turn the diaphragm tap to 'open'.

20. Repeat 30 second pulse and a second BP measurement as described in 10. to 18. above. Record on Form M, as Measurement II.

Technical Notes

1. If for any reason the observer is unable to determine (or forgets) any phase, write a dash in the space on the form. This is the correct way to indicate missed information. If an entire reading is missed, completely deflate the cuff and start again with a replacement reading. Always wait at least 30 seconds between readings.

2. Record on Form M any difficulties in obtaining BP measurements (e.g., irregular pulse). If participant is in atrial fibrillation, record the pressure in the usual way and note "atrial fibrillation" on the form. Any problems so noted in measuring BP will receive special coding when the data are entered into the computer.

3 In reading the manometer, record at the line reached by the rounded top of the mercury column (the meniscus). If the top of the meniscus is exactly between lines, the reading is made at the line immediately above. If the mercury column bounces, take the reading at the lowest part of the bounce.

4. Procedure for increasing the Peak Inflation Pressure: Occasionally the Korotkoff sounds may be heard as soon as one places the stethoscope over the brachial artery and begins to listen. If this happens, the observer should immediately deflate the cuff by disconnecting the cuff and sphygmomanometer, and recalculate Peak Inflation Pressure as follows:

Draw a line through the previously recorded Peak Inflation Pressure, increase the number by 10 and write the new number beside the original one. The new number includes an increase of 10 as illustrated below:

PULSE OBLITERATION PRESSURE	200	
PEAK INFLATION PRESSURE = PULSE OBLITERATION PRESSURE + 10 mm OR 180 mm WHICHEVER IS GREATER	~~210~~	220

Wait 30 seconds and then proceed with the BP measurement. Repeat the procedure if necessary.

5. The random zero sphygmomanometer has all the parts of the standard mercury manometer. In addition, it has a mechanism built into the box-shaped back that changes the level of mercury in the calibrated glass tube. The mechanism includes a second mercury reservoir the size of which can be changed to hold a larger or smaller amount of mercury in the reservoir, and therefore allow different amounts of mercury to remain in the calibrated glass tube and the outside reservoir. The size of the second reservoir is changed by spinning the thumb wheel on the right side of the device (Figure 8). The second reservoir is opened and closed with a dial on the face of the manometer, called the diaphragm tap (Figure 7).

1.3 Urine Collection

Spot (casual) urine

1. A spot urine is to be collected immediately before the start of the 24-hour collection. Affix the participant's receptacle label, marked SPOT RECEPTACLE, onto one of the large receptacles. Use spot receptacle with a lid, to avoid spillage. Write the participant's name on the label. Ask the participant to void directly into the receptacle, emptying the bladder completely.

2. When done, take the labelled receptacle to the laboratory area and:

   Record name, ID, and split sample ID if assigned, onto the Urine Collection Register.

   Enter the date and time as the start of the 24-hour collection and also check the box marked "Spot" indicating it has been received.

   The time should also be entered on Form G and other relevant questions checked off.

3. Place one of the dipsticks provided (N-LABSTIX) into the freshly voided urine, completely immersing all reagent areas in the urine. Then immediately remove the dipstick.

   Tap the edge of the stick against the side of the spot urine container to remove excess urine.

   Hold the stick in a horizontal position to prevent possible mixing of chemicals from adjacent reagent areas.

   Compare test areas with the corresponding colour chart on the side of the N-LABSTIX bottle, reading at the times specified for each area (Note: accurate timing is essential for reliable quantitative results), i.e., Nitrite 40 secs; Blood 40 secs; Ketones 15 secs; Glucose 30 secs; Protein, pH time not critical. Hold the dipstick close to the colour chart, and match up colours carefully.

   Record the results by marking an 'X' in the appropriate boxes on the LABSTIX form Form L.

4. After the dipstick procedure is completed, add a teaspoon of boric acid to the urine in the receptacle and stir gently. Place labelled receptacle with the spot urine in the refrigerator. Aliquots from this specimen will be taken the next day.

24-hour collection - Start

The timing of the 24-hour urine collection starts immediately after voiding the 'spot' urine: 'spot' urines are not to be included in the 24-hour urine collection.

1. Obtain a set of four or five 24-hour urine collection jars already prepared with preservative. Write the number of jars given in the space marked "Jars Given", on the Urine Collection Register. Obtain a funnel and carrying case.

2. Write the participant's name and ID on jar labels and affix one on each jar. Number the jars (e.g., from 1 to 4) as they are given to participant, writing the number on the jar label.

3. For 24-hour urine specimens to be used in the evaluation of daily electrolyte intake, it is essential to ensure as far as possible that collections are complete for an accurately described time period, and therefore careful instruction of study participants is required.

4. Instruct the participant in the use of the funnel and jars. While use of the funnel is essential for women, it can be optional for men. Indicate that the jar should always be held during voiding.

5. All urine voided from that moment, including the remaining time spent at the clinic, should be collected until the same time the following day.

6. Many people when having a bowel movement involuntarily also urinate. To avoid loss of this urine, explain to participants that when they feel the urge to have a bowel movement, they should first pass urine into the collection jar, emptying the bladder completely.

7. Tell participant that when any jar is about $^2/_3$ full, a new jar should be started with the next voiding. This is to prevent overflow.

8. The participant should be given jars, funnel, carrier, and Form I, Instructions and asked to return to the clinic the same time the following day for completion of the 24-hour collection. Ensure that time of return is noted in

the clinic's reception diary. In exceptional circumstances the final specimen could be passed at home 24 hours after the start of the collection provided a staff member is present in the home to record the time. The London Coordinating Centre must be informed of any such exception, by completing the question in Form U at the end of the collection.

Notes

1. If a participant is unable to void for the 'spot' urine, wait half an hour and ask the participant to try again. If the participant is still unable to void, pulse and BP should be measured, and then the participant given several glasses of water. Proceed with the remainder of the clinic visit until the participant indicates that he or she is able to void. Then take the 'spot' urine and start the 24-hour collection in the usual way.

2. One-litre reusable plastic jars, with lids that screw on tightly to prevent leakage and which can be washed well between users, are provided by the Coordinating Centre. While 24-hour volume varies among individuals, each participant is to be provided with the likely maximum, equivalent to a capacity of 4 or 5 litres. If experience in the individual populations, which may differ in output based on climate, usual intake, etc., shows that this number is too small or too large, adjustment is to be made.

3. The carrier appropriate for each population, and even within a population, can be expected to vary. Attache cases, camera bags, shopping bags can be used. Local customs are to help determine the type of carrier to be used. A key point is that the carrier is to help prevent the jars from tipping, with loss of some of the specimen, and with inconvenience to the participant. If possible, carriers should have a foam rubber lining.

Completing the 24-hour collection

1. To ensure that the end of the 24-hour urine collection is appropriately completed, the participant returns to the clinic shortly before the 24 hours are over, and the final urine specimen is collected at that time. Ask the participant to empty his/her bladder completely.

2. Do not be concerned if the collection time varies slightly from 24 hours since this can be accounted for in the data analysis, as long as the actual time of completion is recorded by the staff member.

3. Remember that the final sample of urine voided is to be included in the 24-hour collection. Be sure to ask the Completeness Questions on Form U and the special question on menstruation for women. Check that all equipment has been returned (urine collection jars, funnel and carrier) and that the collection jars are correctly labelled.

4. Enter the end time, and day of the week, as a check, on Form U. In addition, the end date and time, the number of urine collection jars returned, and the number of jars used in the 24-hour urine collection should be recorded in the Urine Collection Register.

5. If the Completeness questions indicate that a jar containing urine was not returned, and efforts to retrieve the urine specimen were not successful, or urine was voided other than into the jar, or more than a few drops were missing, e.g., through spillage, then this will be considered an incomplete collection for data analysis. Nonetheless, the aliquots from this urine should be sent in the usual way. They can still supply some data relevant to our study, even if not part of the 24-hour data. As noted earlier, centres should recruit an extra participant in the same age-sex group to ensure that the centre supplies 200 complete 24-hour collections. See the sampling instructions for how this person is to be selected for recruitment. Use the supplementary ID codes for this new person.

Repeat 24-hour urine collection

1. To assess how much individuals in different populations vary from themselves in electrolyte excretion, (intra-individual variability) about 12% of the participants in each centre are to be invited to return to the clinic within 1 to 3 weeks for a repeat collection of urine and a repeat BP measurement. Allowing for unwillingness or inability to return of some of those selected for repeats, inviting 12% should result in a repeat rate of 8-10%.

2. Those invited for the repeat visit will be the same individuals from whom split samples were obtained in the first visit. (Note: these individuals are identified in the Log Book by split sample ID codes.)

3. If a person is invited to return, the invitation must be extended when the participant is being seen at the end of the initial 24-hour urine collection. Otherwise, timely re-contact will have to be made, to ensure that the repeat visit is 1 to 3 weeks after the first visit.

4. In requesting the participant to return, explain that 1 out of 8 participants is being asked to return to check on how much people vary over time on those things we have measured.

5. The repeat appointment will include pulse and BP measurement, and a further 24-hour urine collection. Give the participant the Repeat Visit instruction sheet, for attending the clinic at the appointed time. Remind the participant that at the repeat visit, collection of urine is again to be started at the clinic and completed at the clinic 24 hours later.

6. All persons who participate in the repeat examination are to have a full set of aliquots taken and labelled with the participant's own ID, as well as a full set of split sample aliquots labelled with the split sample ID.

The Urine Collection Register

1. The local centre laboratory is to keep a record of all specimens received, the number of jars distributed, the number returned, and the number of jars used in 24-hour urine collections to help check on completeness. In addition, dates of refrigeration, freezing, and shipment of aliquots from the clinic are recorded. All this information is kept on the Urine Collection Register.

2. The procedure is as follows:

   a. When the receptacle containing the 'spot' urine is received in the laboratory area, the participant's name, ID, and split sample ID, if assigned, should be entered into the Urine Collection Register.

   b. Indicate that the 'spot' urine was received, and enter the start date and time of the 24-hour urine collection. This information should be both on Form G and the Register.

   c. Write down the number of jars that were given for the 24-hour urine collection. This will generally be 4 or 5.

   Twenty-four hours later, at the completion of the urine collection:

   d. Record the end date and time of the urine collection. This information should be both on Form U and on the Urine Collection Register. Also, enter the number of jars returned and the number of jars used during the 24-hour collection. If any jars are missing, ascertain whether these jars contained any of the urine passed during the last 24 hours. If a jar or jars were used but not returned, make every effort to retrieve the

missing urine that day (for example, if it was left at home but is still intact). If this is not possible, make a note on Form U. (In any case, try to retrieve the missing jars since otherwise there will not be enough jars to meet your requirements for the study.)

e. The remainder of the Urine Collection Register is filled out as the specimens are prepared in the laboratory. The items to be entered include:
- checking the 'split' column if blinded split samples are being sent
- date of refrigeration, freezing, shipping.

f. The Urine Collection Register is a working form for the centre and will stay there until all collections have been completed. At that time, a copy of the Register is sent to the London Coordinating Centre without the names, which should be cut off the copy before sending it.

Measuring urine volume

The 3 values that are needed to assess 24-hour electrolyte output are:

concentration (reported, for example, as millimole per litre), determined by the Central Laboratory

volume (number of millilitres)

time (number of hours and minutes)

We have discussed the importance of accurate timing. The next critical step is correct measurement of the volume.

1. Since we are all using standard collection jars supplied centrally (1-litre capacity and 19 cm in height), it will be possible to measure the height of urine in the jars (in centimetres), which can later be converted into volume (ml) by the computer. This will eliminate the need to measure by pouring.

2. The height of the urine in each jar is determined using the special platform with vertical scale attached, developed by the London School of Hygiene and Tropical Medicine (Figure 9). Record the value onto Form U, in centimetres to the nearest 0.1 cm. Each jar is to be read and recorded separately. The total height of the urine for the entire specimen and hence the volume will be calculated by the computer. Note that each line on the measuring scale represents 0.1 cm.

Each jar is numbered on the jar label when it is given out to the participant. Record the height of urine in each jar in the appropriate (numbered) space on Form U. This is to reduce the risk of measuring the same jar twice, or missing out a jar. For added security, write down on Form U the number of jars containing urine (the same number will be recorded in the "Jars Used" column of the Urine Collection Register).

There is room on Form U to record height of urine in each of six 1-litre jars, although in most cases the number of jars used will be less than 6. Put a dash in the space provided, for jars not used.

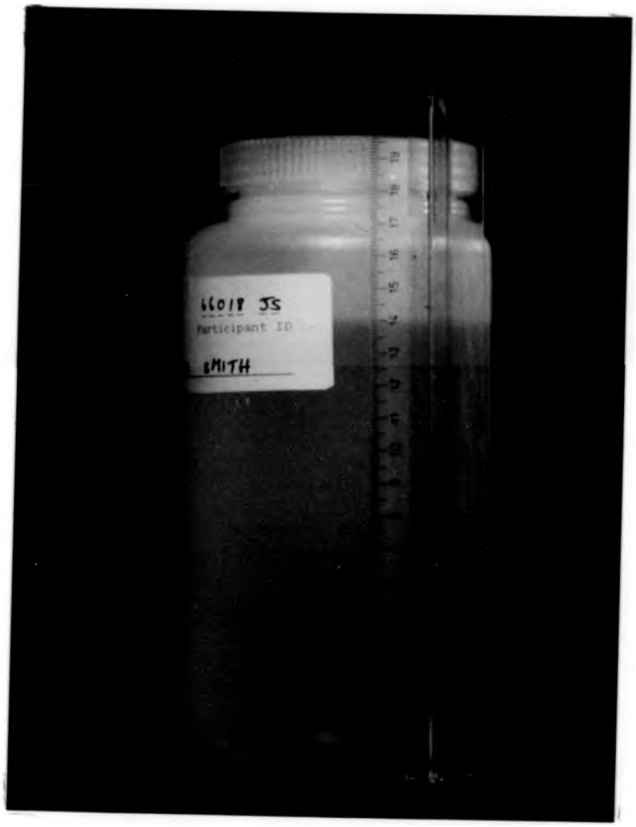
3. In reading the line on the scale nearest the top of the urine, the collection jar should be at eye level. This means either that the observer should be seated at a table sufficiently high to permit this, or that there should be an eye-level shelf on which the measuring platform could be placed. Jars should be perfectly upright when read. If the top of urine falls halfway between two 0.1 cm lines, record the higher value.

4. The next step after carefully recording the height of urine in the collection jars is preparing the sample for aliquots.

Preparing to take aliquots

1. Remember to take aliquots from the spot and 24-hour urine collection of one participant at a time, to avoid confusing collections from different participants.

Figure 9



Measuring scale for urine heights, and 24-hour urine collection jar

2. Retrieve the spot urine receptacle from the refrigerator and place together with the 24-hour collection for that participant. Aliquots are first taken from the spot receptacle. Gently stir the urine in the receptacle, and take two aliquots. Use of a small beaker with a pouring spout, or a pipette, is suggested. Complete all the work on the spot urine before preparing the 24-hour specimens.

3. Next prepare to take aliquots from the 24-hour collection. Thoroughly mix all the urine from the 24-hour collection of the individual participant into a large bucket. Since electrolyte output may differ at different times of the day, this mixing is very important. The mixing should not be done too rapidly or vigorously, in order to avoid frothing.

4. When mixed, remove the necessary number of aliquots for the 24-hour collection and pour into the tubes supplied centrally. Use a pourer or pipette. The number of tubes and their proper labelling is described below.

Before describing further how the aliquot tubes are to be filled, etc., it is necessary to describe the labelling procedure.

Labelling

The Central Laboratory will supply each centre with the necessary number of sticky labels.

1. We have already mentioned the labels for the collection jars given to the participant. They have space for entering the participant's ID code, and say "JAR LABEL" on them

2. You will also receive a FILE LABEL, with space for entering the participant's ID code and split sample ID, if assigned.

3. All other labels for the first visit will have the ID number already printed on them, and also indicate how they are to be used.[10] The participant's initials will need to be added to make up the ID code.

4. Each label has, as the last digit, a number indicating its purpose.

---

[10] IDs will not be printed in advance on labels for the repeat visit, since these participants are also those with split samples.

Label 1 = Spot urine aliquot for the Central Laboratory

Label 2 = Spot urine aliquot to freeze and store locally (this is a backup against possible loss in transit)

Label 3 = 24-hour aliquot - Central Laboratory

Label 4 = 24-hour aliquot - Central Laboratory

Label 5 = 24-hour aliquot - Central Laboratory

Label 6 = 24-hour aliquot - Central Laboratory

(3, 4, and 5 are for present analyses; 6 is for future analyses and will be stored centrally)

Label 7 = 24-hour aliquot to freeze and store locally, as backup against possible loss.

Two other labels are:

Label 8 = Spot urine receptacle

Label 9 = Label for the urine data form, Form U.

5. The identifying information on the labels is laid out in the following way:

Type of specimen or for Form	Participant ID or Split-Sample ID	1st visit or repeat	Label number

As an example: for a spot urine aliquot going to the Central Laboratory, on a first visit, the label will be:

SPOT	66073	1	1

You will need to fill in the initials that are part of that participant's code.

A 24-hour aliquot label for local storage for this visit of this participant will look like this:

FULL	66073	1	7

Again, fill in the initials (first initial of first name and of last name).

6. If this participant has been assigned a split sample ID, then another complete set of labels with that ID will have been prepared by the Central Laboratory, which is printing the labels. (Of course, the Laboratory will not know these are split sample IDs.)

   As an example, suppose the participant used in the earlier example (66073 DK) also has a split sample ID code. Then, the label for the split sample of the 24-hour aliquot for local storage for this visit will look just like the above label, but will substitute the split sample ID code for the original one:

FULL	66092	1	7

(Fill in the artificial split sample initials as printed in the Log Book to complete the split sample ID code.)

7. The three possible entries (in letters) on the left side of the label are:

   SPOT (for labels 1, 2, 8 - spot urine aliquots and receptacle)

   FULL (24-hour aliquot, for labels 3, 4, 5, 6, 7)

   FORM (to place on the urine form - Form U - label 9)

8. The centre of the label is for the participant ID or the split sample ID, with numbers either printed in advance, or - for repeats - to be filled in locally. (Initials are always added locally.) The first two digits of this ID number are always the code for your centre.

9. The right side of the label is for indicating two other items:

Visit Number	Label Number
1 (original visit)	1 to 9 (to identify type of specimen and whether to ship or store; see above)
or 2 (repeat visit)	

10. The Central Laboratory will provide extra blank labels, for spoiled labels.

11. The Central Laboratory will also provide special labels for the 'Dry Run' (pilot field study) marked with the centre number = 99.

12. When writing on labels, use the indelible waterproof marking pen provided centrally.

Taking aliquots

1. Prepare one set of urine aliquots at a time to avoid confusing urine collections from different participants.

2. First prepare the aliquots from the spot urine receptacle before going on to the bucket with the mixed 24-hour sample, again in order not to confuse the two different types of specimens. DO NOT prepare the 24-hour labels until spot urine aliquots are completed.

Spot urines:

3. Prepare the correct labels for the spot urine, completing the ID code.

4. Apply the labels to the tubes and secure them with transparent tape wrapped all the way around the tube.

5. Fill the two aliquot tubes for spot urine. Use a pourer or pipette.

6. If this participant also has a split sample ID, fill four aliquot tubes.

7. Each centre will receive aliquot tubes with push tops. Their capacity is 9 millilitres (approximately 7 cm in height), but do not fill them to the top, since they will break on freezing. Leave a gap of about 2 cm at the top of each tube. Make sure tops are pushed firmly down into the tubes (i.e., until you hear a click).

24-hour urine collections:

8. Complete the correct labels (those marked "FULL", meaning the full 24 hours, in contrast to only a spot sample). Apply them to the tubes and cover the label with transparent tape wrapped around the tube.

9. Next, prepare 5 aliquot tubes from the bucket containing mixed 24-hour specimens. Again, be sure that all jars of the collection have been measured, and then mixed together. (If there is a split sample ID, then 10 tubes are required.) Fill tubes as above, leaving 2 cm. unfilled and snap the tops in securely (until you hear a click).

10. The final step prior to storage is to place the remaining label - marked FORM - in the space provided on page 3 of Form U, the urine data form. There is also space for the split sample FORM U label, if appropriate.

Storing the urine aliquots

1. Although the use of preservative to some extent protects the urine specimen against bacterial growth, there is nevertheless a deterioration in creatinine which becomes apparent within 24-48 hours at a storage temperature of -20° C. All aliquots must therefore be refrigerated at 4°C within 24 hours and frozen at -20°C within seven days.

2. On-site refrigerators (or freezers) need some back-up electrical supply, e.g., car batteries, to take over in case of breakdown.

3. If there is no freezing facility at the local clinic, urine aliquots will require local transportation for freezing. They must be transported in refrigeration boxes. Cooling elements (supplied from the Central Laboratory) which are to be placed in the refrigeration boxes should first be frozen at -20°C for at least 12 hours. Six hours each way maximum can then be allowed for transport between the local storage (with freezer) and the clinic. It is essential that local centres are able to comply with the above requirements - if more than twelve hours total elapses, the cooling elements will thaw and the temperature in the refrigeration boxes will rise above +4°C.

4. Refrigeration and freezing dates are to be entered in the URINE COLLECTION REGISTER.

Shipping urine aliquots

1. The Central Laboratory for all chemical analyses is at the St. Rafael University Hospital, Capucijnenvoer 33, B-3000 Leuven, Belgium. Shipment of urine aliquots is to be by air freight for most centres. For some European centres, transport by special courier services may be more appropriate. Railway transportation should not be used.

2. Urine aliquots must be shipped frozen (-20°C) in refrigeration boxes which will be provided.

3. Shipment of aliquots should be as follows:

The first shipment is to be after two weeks of data collection, or after 25 urine collections have been made, whichever is the sooner; the remaining aliquots and their split samples from first clinic appointments should be sent together, in two refrigeration boxes. The final batch of specimens should be sent at the end of all data collection, to comprise all urine aliquots from repeat appointments and all the corresponding split samples. This final batch should not be sent until advised by the London Centre, to ensure that all the local centre's first visit aliquots will already have been analysed.

Procedure for shipping urine aliquots

1. Make contact with the air freight handling department of the international airport nearest to the local storage site, and book the specimens on a flight to Brussels.

2. Notify the air freight department that samples should be kept at -20°C, both in the airport of departure while awaiting transfer to the aircraft and in the aircraft itself.

3. Arrangements should be made at least two weeks before the date of shipment. It is recommended that local Investigators first make contact with the airport freight handling department before data collection begins, to determine local regulations and flight procedures.

4. Two weeks before shipment, send a telex[11] to the Central Laboratory and similarly to the London Coordinating Centre, to alert them to the coming shipment. The telexes should contain the following information:

INTERSALT CENTRAL LABORATORY

C/O ST. RAFAEL UNIVERSITY HOSPITAL - LEUVEN - BELGIUM

ATTN: .....

CENTRE: .....

AIRPORT OF DEPARTURE: .....

DATE OF SHIPMENT: .....

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[11] A fax would now be more appropriate.

LOCAL HOUR OF SHIPMENT: .....

NUMBER OF PACKAGES: .....

AIR FREIGHT NUMBER: .....

FLIGHT NO(S): .....

DATE OF ARRIVAL IN BRUSSELS: .....

LOCAL INVESTIGATOR: .....

For the London Coordinating Centre the first three lines have to be replaced by:
INTERSALT COORDINATING CENTRE
C/O LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

5. If no telex machine is available locally, it is critically important that the above information be received before shipment, so that the shipment can be picked up. In these circumstances, two weeks before shipment, an international telegram should be sent or a call made to London, and London will advise the Laboratory. In addition, the telexes should be sent from the airport on the day of shipment.

6. Enter shipping date from the clinic in the centre's URINE COLLECTION REGISTER.

Packing the refrigeration boxes (Figure 10)

1. Ensure cooling elements have been kept frozen at -20°C for at least 12 hours prior to packing.

2. Before loading the box and shipping to Leuven, fill out the SHIPPING FORM, listing each participant ID code and number of tubes per participant, in the shipment. One copy of the form should go in the box, to Belgium, and a photocopy should go to London. The one in the box should be in a waterproof jacket.

3. Place four cooling elements flat at the bottom of the polystyrene refrigeration box. Next place four cooling elements on their sides, so that two lie up against each wall of the box along its length (Figure 10).

4. For each participant take the five aliquot tubes to be sent to the Central Laboratory (labels 1, 3, 4, 5, 6) and bind them together in a line with Scotch tape.

5. Place each set of five tubes upright in the box, parallel to the cooling elements along the side walls. Four sets of five tubes can be placed along the length of the box, and twelve sets of five tubes along its width. This will yield a total of 240 tubes on each layer (Figure 10).

6. Place four cooling elements flat on top of the tubes below, and repeat the procedure above until all tubes are packed. Fill the rest of the box with wrapped newspaper to ensure that the tubes remain in place during transit.

7. Close the box, and wrap packing tape around the junction between the box and the lid, so that the lid of the box is firmly secured.

8. Place the polystyrene refrigeration box in the cardboard packing box provided and securely seal the latter with packing tape. Label this box as described below.

9. Ensure that the air freight department is aware that specimens are to be shipped at -20°C.

10. The following labels are to be affixed to the outside of the box:

    A large label with the preprinted address of the Central Laboratory;

    A return label with the address of the local Investigator;

    Some special labels indicating the nature of the content of the refrigeration box:

    HANDLE WITH CARE

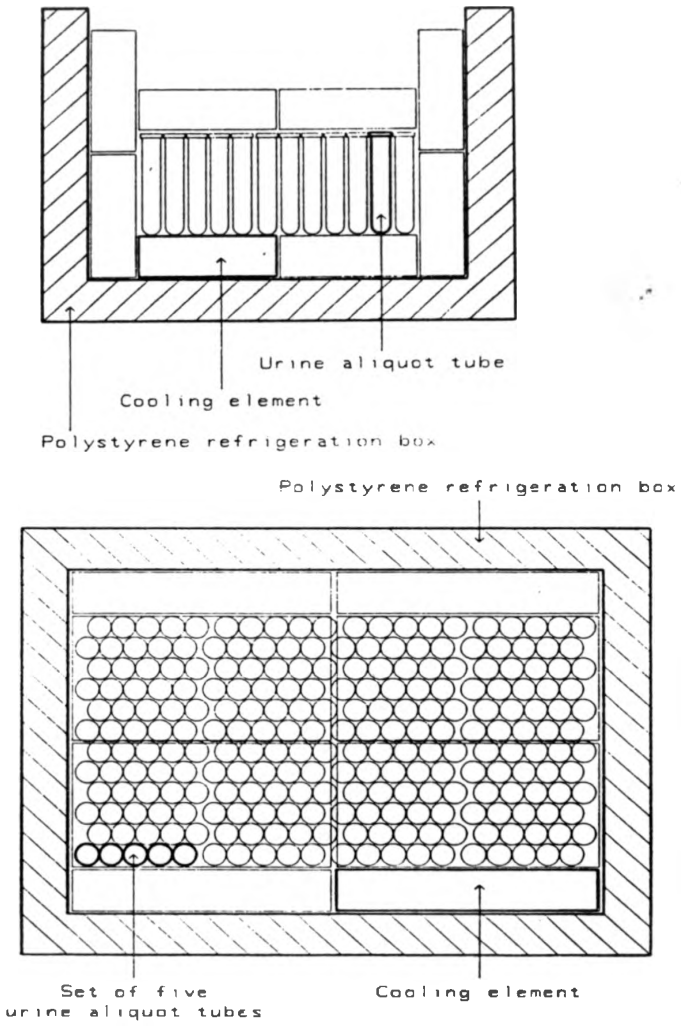
    DEGRADABLE GOODS TO BE KEPT AT -20°C

    NO DRY ICE, WET ICE ONLY

    NO COMMERCIAL VALUE

    All these labels will be provided centrally.

Figure 10



Packing the refrigeration box:
Upper - cross-sectional view, Lower - top view

Notes

1. Back-up urine aliquots should be kept locally at -20°C until clearance has been received from the London Coordinating Centre.

2. Do not send repeat specimens (or their split samples), until word has been received from the London Coordinating Centre.

3. If dry ice is used, this needs to be cleared with the airline, and the labels adjusted accordingly.

Communication Procedure

On receipt of the urine aliquots in Leuven, the Central Laboratory will inform the London Coordinating Centre by telex of the number of aliquots received, the condition in which they were received, and of any discrepancy noted. For example, if one of the five requested urine aliquots (aliquot numbers 1, 3, 4, 5, and 6) is missing for a particular participant, or if the ID code is incomplete, or if samples are thawed, this will be reported immediately to London, so that the London Coordinating Centre can rapidly inform the local centre of any problems and of actions to be taken.

1.4 Possible Confounding Variables

These include items recorded on the questionnaire, height and weight

Questionnaire (Form Q)

The main purpose of the Questionnaire is to obtain information on variables that could act as confounders of the true relationship between BP and sodium-potassium. The Questionnaire is discussed here. (See Appendix 2.)

Administration

1. The Questionnaire is given only at the first visit.

2. It is designed to be self-administered. However, assistance should be given if difficulty arises in interpretation. In some instances the questionnaire will be completely interviewer-administered. Training on interview techniques will be included in regional training sessions.

3. Questionnaires have been prepared in English, but should be translated into local language and resubmitted to the London Coordinating Centre for back-translation and verification before they can be used.

4. In addition, local Investigators are to develop a four point 'social scale' (1 = lowest, 4 = highest) to characterise participants relative to socioeconomic status within their particular population. (See Appendix 3.) This may require additional questions, for example, on housing, water supply, etc., which should be inserted after question 38, the question on years of schooling. These additional questions should be written in the local language and sent to the London Coordinating Centre for back-translation and approval. Based on answers to these questions and/or the common INTERSALT questions, the participant's social scale (code 1 - 4) should be designated and recorded on Form C - Checklist for the Questionnaire. If occupation is used to derive social scale, code married women by their own occupation if working, otherwise by husband's occupation.

5. The interviewer should review all questionnaires for completeness and legibility. Unless specified, the answers to the questions are mutually exclusive (for example, Yes/No). If any queries or inconsistencies arise (for example, marking an 'X' in more than one box), these should be brought to the attention of the participant, and appropriate amendments or changes made.

6. Questionnaires will also be reviewed by the London Coordinating Centre for completeness, consistency, and legibility. Queries arising will be referred back to the local centres for urgent clarification.

Guidelines for individual items

1. Date of birth and age (Questions 1 - 2)

   Give best estimate of date of birth/age if not known. Write 'ESTIMATED' on the form if exact information is not available.

2. Marital Status (Question 4)

   For polygamous marriages, answer 'Now married'. Co-habitants are considered as 'Now married' (box 1) irrespective of legal marital status.

3. Medication (Questions 12 - 13)

It is essential that a full list of drugs be obtained. These may be identified either by the generic names or the proprietary names. If the participant is taking medicines but cannot recall the names, these should be brought to the clinic the following day (when the participant returns to complete the 24-hour urine collection). While they should be listed here, they should also be listed and coded on Form C when the staff member is reviewing the Questionnaire.

4. Diet (Questions 19 - 22)

Because of the potential confounding effects on the relationship between sodium excretion and BP, it is essential to determine whether participants have changed their diets because of high BP or concern over the development of high BP. Both change in amount eaten and specific avoidance of sodium could have an important effect.

Question 22, "If you have made changes in your diet ... ", refers to answers in Questions 19, 20, and 21.

5. Alcohol (Questions 23 - 27)

   a. Participants are asked to give information on the amount of alcohol consumed over the past 7 days, that is, the 7 days immediately prior to the day of the clinic appointment. To aid in recollection, information has been requested by days of the week.

   b. Since the usual unit for drinks will differ in different countries, the question has been asked in the general form of 'how much?' Locally, the staff member should be sure the unit is indicated. If the answer is 'a glass', try to ascertain the size of the glass. (If participant doesn't drink, enter 'NONE').

   c. Obviously the size, nature, and alcohol content of different drinks will vary in different populations. Investigators in each local centre should submit to the London Coordinating Centre a list of locally available alcoholic drinks, with indication of 'standard' volume and alcohol content. The alcohol content of each drink should be expressed as the equivalent in millilitres of pure ethyl alcohol.

      You must be sure London can translate the drinks listed into ml of absolute alcohol.

6. Employment (Questions 28 - 35)

Usual work refers to the job in which the participant has been employed for most of his or her working life.

Present work refers to the job in which the participant is currently employed.

For example, a toolmaker who loses his job after 40 years and becomes a gardener, should reply that his usual job is "toolmaker" and present job is "gardener".

Questions 29 and 31, "Service worker" (box 6) refers to someone employed in service of the public, for example "waitress" or "train driver". In these questions, the participant is asked to mark 'X' in one appropriate box for his/her employment, and that of his/her spouse. If the interviewer believes, after referring to questions 28 and 30, that the wrong box has been marked, the interviewer should place an 'X' in red ink alongside the correct box.

Housewives in part-time paid work should be coded according to their job (not housework).

Semi-skilled workers should be coded as "manual labour" (box 5).

Students should be coded as "other" (box 10) and write "student" next to box.

7. Years of Schooling (Question 38)

The aim is to determine the level of school completed. If a person took 6 years to complete 4th grade (and this was his total schooling), the answer to the question is 4 years of schooling, not 6.

8. Birth Control Pills (Question 40, 40A)

Women using a depot preparation of progestogen for birth control should leave Yes/No boxes blank. However, write down in the margin that depot preparation is being used. This will be specially coded in the London Coordinating Centre.

The correct place to code the pill is Question 40, not Form C.

9. Menses (Question 42)

Since potassium level in the urine could be affected by the presence of blood, this question is important. It is asked both on the questionnaire and, using Form U, at the end of the 24-hour collection.

10. General

    a. If any response is written in a language other than English, please translate back to English. This could apply to Questions 14, 21, 24, 25, 28, 30, and 33B.

    b. Form C is to be filled out by a staff member after the Questionnaire has been completed and reviewed. The staff member should then enter staff number on Form C.

Height and weight

These are measured only at the first visit, not at any repeat visit. Height is to be measured first, followed by weight. Height and weight should be measured twice, resetting the height measure or beam balance between each of the two measurements. If the two measures differ by 2 cm or more for height, or 1 kg (or 2 lb) or more for weight, then a third measurement should be taken and written down alongside the second measurement. (In this case, the coders at the London Coordinating Centre will average the two closest readings for height or weight.) Standard procedures for the measurement of height and weight were adopted, based on the WHO-MONICA protocol.

Time of day

Since BPs vary during the day, time of measurement of BP should be recorded on the measurement form (FORM M), using the 24-hour clock.

Temperature

1. Ambient temperature also may influence BP and should be recorded during the day (FORM G).

2. There should be a reliable thermometer at the clinic site, to record indoor temperature.

3 If possible, there should also be an outdoor thermometer. An alternative is to record the official temperature as given by the local weather bureau, via telephone.

4. Since the temperatures may vary markedly during the day, they should be checked every few hours and the appropriate values entered for the individual participants.

1.5 Quality Control

A key reason for undertaking this study is to provide a rigorous scientific test of observations made earlier where there were not standardised measurements across a number of populations.

For INTERSALT, critical to the success of our joint undertaking is strict adherence to a detailed standardised set of procedures, with a high level of care and accuracy in all aspects of the work. The following steps aim at controlling and assessing the quality of the work.

All staff members taking part in INTERSALT must be trained, either directly at Regional Training meetings, or by persons who themselves have been trained at the Regional meetings.

Blood pressure measurement

In order to take BP measurements in INTERSALT, the observer must not only have been trained by INTERSALT methods, but must also pass two tests certifying proficiency in standardised measurement.

1. The first test is a 'test tape' prepared by the London School of Hygiene and Tropical Medicine, testing accuracy in hearing and recognition of the Korotkoff sounds.

2. The second test is evaluation of performance used in actual measurement (placement of cuff, operation of the random zero device, etc.). In addition, performance of the staff member taking systolic and diastolic pressure of a volunteer will be monitored by a trained and certified BP observer (e.g., the local Investigator, if certified), using a double-headed stethoscope.

   Only staff members certified as passing both tests may take BP measurements in INTERSALT.

3. When a staff member passes these tests, the local Investigator should complete and sign the BP Certification form and forward this to London, prior to involving this staff member in field work.

4. It is strongly recommended that not more than 2 staff members be given the task of BP measurement. The larger the number doing the measurements, the more difficult it is to obtain good quality control.

5. Each local centre needs to forward to the London Coordinating Centre the names of all staff trained (and certified), and London will assign a staff number. This applies to those doing BP measurement and any other study tasks (laboratory, interview, etc.).

6. This number should be entered on all forms, as required, by the staff member completing that form.

Notes

1. Testing and certifying at Regional Training meetings is the first (but only the first) and necessary step towards proficient BP measurement. For BP observers to become fully familiar with the INTERSALT procedures, in particular the use of random zero device, it is essential that further training and practice sessions be arranged by local Investigators in their own centres.

2. The minimum requirement for passing the random zero test is two consecutive approved measurements on an individual. If one or both of the two required measurements is not acceptable, the entire procedure should be repeated on another individual.

Dry Run

While centre staff may be familiar, in general, with many of the procedures to be followed in INTERSALT, there is still the necessity to practice, in detail, the specific procedures filling out forms, the smooth running of the clinic visit in the prescribed order, and handling of laboratory specimens.

This test run should be organized at the end of local training and should rehearse each step, starting with recruiting procedures, selecting the sample, completing the RECRUITING RECORD, LOG BOOK. A typical visit should be simulated, including preparation of forms and urine jars, taking all measurements, administering

of the Questionnaire, instructing the participant, receiving the returned 24-hour specimen, evaluating completeness, measuring, obtaining and labelling aliquots, keeping appropriate records (URINE COLLECTION REGISTER, Form U, etc.) and preparing for shipment.

The 'Dry Run' should last at least two days, to permit a full test of the procedure of ending the 24-hour collection, etc. Persons volunteering to be 'participants' may be other staff members, but should go through all steps, including the 24-hour collection. If more time is needed for the test run, it should be taken.

The progress of the 'Dry Run' should be reviewed with the London Coordinating Centre using the telephone if at all possible, to save time.

Completed forms marked 'Dry Run', should be sent immediately to London for review.

Note

Special 'Dry Run' mock LOG BOOK pages, and corresponding labels, will be provided, but with 'centre code' of 99 as the first two digits of each 'Dry Run' ID number.

Blind split samples

Since the main independent variables in INTERSALT are sodium and potassium it is crucial that they be measured accurately. The quality of the Central Laboratory's functioning is critical, and the main purpose of blinded split samples is to help assess this. To a more limited degree, using this procedure also helps check on quality of local processing of specimens.

The method of handling split samples has been discussed in detail in Section 1.3.

a. As noted, specimens from participants with split sample IDs as well as their own ID, are to be divided and a complete double set of aliquots is to be taken. This set is to be labelled with split sample ID labels, while the original set is to have the participant's ID code.

b. It is very important that nothing should be done to 'unblind' the Central Laboratory as to which split sample IDs represent which participants. When sending the Shipping Form, the numbers should be in consecutive order, so that there is no indication as to which are the split sample IDs.

Checking accuracy of ID code

1. Each centre needs to develop its own system for checking that the right code has been put on each form and each tube.

2. ID codes are to be put on each page of forms, in case they become separated.

3. The participant's ID code should be entered in advance on all data forms assembled in the participant's file.

4. Another point where IDs need the most careful check is in the clinic laboratory, to ensure that the correct 24-hour specimens and correct spot urines are identified, as well as correct selection and labelling for split samples. One means of reducing error, is to process only one specimen at a time.

   Checking by a second staff member could be useful, including checking of entries into the URINE COLLECTION REGISTER.

5. A final place to check ID codes is on the SHIPPING FORM, where the listing and quantity need to be double-checked, preferably by a second staff member.

Quality of the data forms

1. Forms should be edited in a systematic way at the end of each day. Any missing information could then be obtained when the participant is seen at the end of the 24-hour collection.

2. Local Investigators should review the forms before they are shipped to London, to help ensure their quality.

3. Forms should be copied before sending the originals to London.

4. Forms should be shipped by air, first class, every week until the field work is completed. If there is some means of sending them registered (as well as air mail first class), this would add some assurance for their delivery.

5. Data forms are heavy and bulky. They should be packed securely for postage to London. Ordinary brown paper envelopes are not sufficient for more than a few forms.

Coordinating Centres and Central Laboratory

1. Both the London Coordinating Centre and the Central Laboratory have developed procedures for monitoring quality of field work and of the central procedures (see Parts 2 and 3 below).

2. In the case of the Central Laboratory, in addition to the external control via blind split samples to help calculate laboratory technical error, a careful system of internal controls will be carried out, with results of both sent to the London Coordinating Centre.

3. There will be close and frequent contact between London, Chicago (the two Coordinating Centres), and Leuven (Central Laboratory) to monitor progress and to identify any problems needing attention.

4. Frequent progress reports will be prepared by London-Chicago to keep the Executive Committee informed of the status of the work.

5. London will ensure that its data entry and retrieval systems function rapidly to permit early identification of problems. This then will be followed by timely and direct communication with the local Investigators, to permit appropriate corrective actions.

6. It is essential that every effort be made to respond promptly to these requests in order to ensure the integrity of the data.

1.6 Organisation of the Clinic Visit

Preparing for the visit: Identifying participants

1. As noted earlier, the RECRUITING RECORD should contain the names of those to be invited for a clinic appointment.

2. Once an appointment is made, the name, date, and time are entered in the clinic's appointment diary. (To help with the next step, it would be useful to put age and sex next to the name.)

3. When the participant appears for the appointment, his or her name is entered into the LOG BOOK, on the correct age-sex page, using the next available ID number. The participant's initials (first letter of first and last name) are added to the ID number, now forming a complete ID code.

Preparing the Participant File

1. To make the clinic visit run more smoothly and to reduce error in ID codes, sets of participant files should be prepared in advance, with ID numbers placed on all data forms and on the file label. (Initials, to complete the ID, are placed on all forms and on the file only after the participant appears for the clinic visit, when age, eligibility, and attendance are ascertained.)

2. The ID numbers for each centre come from the LOG BOOK pages supplied from London.

3. The assembled files should be kept in numerical order, and when the participant appears and his/her name is entered on the appropriate LOG BOOK page, the file with his/her number is retrieved, initials are then entered on the file label, LOG BOOK, and all data forms. The file then follows the participant through the rest of the clinic visit.

4. The visit file is to contain the following material (listed here in order of use during the visit):

   Form F (File Frontpage, for name, address, ID)

   Form G (General information about preparation of the participant for the measurements)

   Form I (Instructions to participant on collecting urine)

   Form L (Labstix form, for results of dipstick on spot urine)

   Form M (Measurement of BP, pulse, height, weight)

   Form Q (Questionnaire)

   Form C (Checklist, about completeness of Questionnaire, social scale, etc.)

   Form U (Urine collection data form)

5. The labels for this ID number should also be placed in the file in advance. They include:

   Urine receptacle label
   Aliquot labels
   Form U label (for 24-hour collection).

There is also a file label, which should have the ID number entered when the file is prepared. (The initials are to be entered when this number is assigned as a person appears at the clinic).

6. If the participant also has a split sample ID, the split sample labels and repeat visit labels should be clipped together and placed at the back of the file. The split sample ID code is also to be entered onto the file label.

7. Since these participants with split sample IDs are also to have a repeat visit, additional forms need to be numbered and entered into the file:

   Form R (Repeat reminder)
   Form G (General information about preparation for measurement)
   Form I (Instructions to participant on 24-hour urine collection)
   Form L (Labstix form, for results of dipstick on spot urine)
   Form M (Measurement of pulse and BP - height and weight are not measured again)
   Form U (Urine collection form)
   (Since the Questionnaire is not repeated at the repeat visit, there is no need for Forms Q or C).

8. These prepared files should be stored in numerical order and be easily accessible in the reception area. (After the visit, they may be stored in alphabetic order.)

Preparing urine collection jars for the 24-hour collection

1. An ample supply of urine collection jars needs to be prepared in advance, with a sufficient number for expected daily clinic attendance. Each clinic will have received 96 standard jars (sufficient for about 20 participants, estimating 5 collection jars per participant). Since this supply is not enough for 200 participants and 20-25 repeats, the jars must be re-used, after proper cleansing.

2. To prepare jars, place a heaped tablespoon of boric acid (10-15 g) into the jar and put the lid on.

3. Affix a jar label on each jar. No information is entered on this label in advance. Participant ID and name should be entered on each label, when the

jars are given to the participant. (An indelible marking pen for this purpose is supplied centrally.)

4. Between collections, jars should be washed with mild detergent and rinsed well with warm water. If jars or lids begin to retain urine odor, they should be discarded.

Facilities needed for the clinic visit

It is recommended that facilities for each clinic include:

1. A reception area for registering participants attending the clinic appointment or returning to complete 24-hour urine collections.

2. A toilet facility for passing 'spot' urine specimens and for completing 24-hour urine collections.

3. A quiet examination area where BP, height, and weight can be measured. There should be adequate space for two chairs and a table for BP measurement. There should be a hard, flat floor surface for measurement of height and weight, and room for a height rule and beam balance or other scale.

4. An area for completion of Questionnaire, and for receiving instructions for 24-hour urine collections.

5. A 'laboratory' area for washing out and preparing urine collection jars, for measuring volume of 24-hour urine collections, for preparing aliquots, and for storing specimens on-site in a refrigerator (4°C) or freezer (-20°C).

6. Storage space for materials and equipment, and for record forms.

7. Access to a freezer (-20°C).

8. Access to a photocopying machine.

Scheduling appointments

1. When participants are contacted, they should be informed of the general nature of the study, that BP, height, and weight will be measured, that they will be required to answer a questionnaire, and that a 24-hour urine collection will be made to help give a picture of people's diets. To ensure accuracy of timing of 24-hour urine collections, it is necessary that collections be both

started and completed at the clinic. Participants should therefore be told that they will be required to attend the clinic for their given appointment, and again 24 hours later to complete the urine collection.

2. Since BPs may be higher at the end of the day than at other times, every effort should be made to schedule appointments during usual working hours. If possible, appointments should be spread equally over the day, and over the usual five day working week. No appointments should be scheduled for the sixth day or seventh (rest) day, although the clinic needs to be open on the sixth day, with a member of staff available, to complete 24-hour urine collections begun on the fifth day.

3. Because we want, as much as possible, standard conditions for measuring BP, we need to control for certain activities that can influence pressure.

   Participants should be instructed to avoid the following activities for at least a half-hour before the clinic appointment: strenuous exercise, eating, drinking anything other than water, and smoking.

   These instructions are contained in the form 'Attending the Clinic Appointment'. If necessary, this should be translated into the local language.

4. While the participant is not to eat for $^1/_2$ hour before the visit, he or she should not be fasting. If there is any ancillary study involving INTERSALT participants that may require fasting, then this must be done on a separate occasion, not together with the INTERSALT clinic visit.

5. Since pregnancy may affect both BP and dietary habits, women known to be pregnant at the time of recruitment should not be invited to participate in the study. If however a woman is subsequently found to be pregnant (question 41 of the Questionnaire), she should be included in the sample. In addition, an extra woman, in the same age group, should be recruited, and assigned a supplementary ID number.

6. A participant may fall acutely ill (for example, acute diarrhoea) at a time when a clinic appointment has been scheduled. Since this may affect both BP and urinary excretion, a new appointment should be scheduled after recovery from the illness.

The Log Book[12]

1. When the participant arrives at the clinic, the receptionist greets him or her, enters the name in the LOG BOOK and adds participant's initials to complete the ID code.

2. The LOG BOOK is made up of pages prepared in advance centrally and supplied to each local centre.

3. There are approximately 250 ID numbers assigned to each centre. These include:

   200 numbers, for the 25 participants in each of 8 age-sex groups
   25 numbers (approximate) for split sample IDs
   30 numbers, as supplementary, for extra participants

4. The LOG BOOK lists these numbers in numerical order, with 2 pages assigned to an age-sex group (e.g., men age 20-29).

5. When a participant enters, the receptionist should check his or her age and turn to the proper age-sex page in the LOG BOOK. Occasionally, because of a recent birthday, or incorrect census information, the participant's age will differ from that given in the RECRUITING RECORD. The participant should be allocated to the appropriate age group as of the day of the clinic appointment. This may necessitate adjustment of the age-sex lists derived from the RECRUITING RECORD.

6. The participant is then given the next ID on the LOG BOOK page, and the plastic file with that number is drawn, with all its forms.

7. The receptionist aids in filling out FORM F, the first form in the file, providing space for name, ID code, split sample code if assigned, and Social Security number (or other identification appropriate to the country).

Conducting the first clinic visit

Procedure for data collection and recording is as follows and should be performed in the order noted:

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[12] A more detailed description of the Log Book is available (Elliott P & Stamler R, 1988)

1. Register participant, obtaining name and age.

2. Enter name into LOG BOOK on appropriate age-sex page, obtaining ID number and completing code by adding 2 initials.

3. Obtain file of forms with that ID number. Add initials to all pages.

4. Aid in filling out FORM F, with basic identification.

5. Complete FORM G, on preparation of participant for BP measurement.

6. Obtain 'spot' urine sample: affix participant ID label onto urine receptacle, adding initials to ID code.

7. Record participant's name, ID, etc., and time 24-hour collection begins in URINE COLLECTION REGISTER. Also record time on FORM G.

8. Place dipstick provided ('N-LABSTIX') into freshly voided spot urine and record results on Form L-Labstix.

9. Add teaspoon of boric acid crystals to the spot urine and place filled urine receptacle in refrigerator.

10. Instruct participant in 24-hour collection, giving FORM I.

11. Give participant 24-hour urine collection jars, filling out jar label. Give out funnel (for women) and carrier.

12. Make appointment for completion of 24-hour urine collection. Enter time into clinic appointment diary. (It should preferably be a few minutes short of 24 hours).

13. Take measurements: complete FORM M

14. Measure pulse and BP

15. Measure height

16. Measure weight

17. Administer Questionnaire - FORM Q (Self-administered or, if needed, with staff assistance).

18. Review completion of Questionnaire and fill out FORM C (Checklist).

19. Remind the participant of his/her return the next day for the end of the 24-hour collection.

End of the 24-hour collection

1. Receive the carrier, all jars, and the funnel.

2. Ask the participant to take one of the returned jars and use it to collect final specimen. Ask participant to empty bladder completely.

3. Record time of completion (FORM U).

4. Ask questions on completeness of sample size (Form U), and, for women, on menstruation.

5. If any jars are missing, make effort to retrieve that day.

6. If participant is not to have a repeat visit, this ends the clinic visit.

7. Bring jars to laboratory area; enter data in Urine Collection Register next to participant's number, on date and time 24-hour collection ended, the number of jars used, and the number of jars returned.

8. For those participants with split sample ID, a request to return for Repeat Visit needs to be made at the time 24-hour collection is completed.

Repeat visit

One difference between procedures for the Repeat visit and the first clinic visit is that there is no measurement of height and weight, nor is the Questionnaire repeated at the Repeat visit. A second difference is that all persons attending the Repeat visit are to have blinded split urine aliquots.

The procedures for the Repeat visit are:

1. Receive participant, note return in LOG BOOK, draw his/her file.

2. Fill out FORM G, on preparation for measurement.

3. Take 'spot' urine, use dipstick and record on FORM L-Labstix. Add boric acid and refrigerate the specimen.

4. Record in URINE COLLECTION REGISTER the ID code, split sample ID code, number of 1-litre jars given for 24-hour collection, and start time. Circle the participant's name in red ink. This will readily identify entries in the Urine Collection Register for Repeat visits (and avoid re-invitation after the Repeat visit).

5. Record 24-hour collection start time also on FORM G.

6. Give instructions for 24-hour collection (FORM I).

7. Obtain labelled 1-litre jars, fill out labels, and give to participant, together with funnel and carrier.

8. Make appointment for completion of 24-hour collection; enter time in appointment diary.

9. Take measurement of pulse and BP (FORM M: do not repeat height and weight).

10. Remind participant to return in 24 hours.

11. End of 24-hour urine collection:

    a. Procedures are the same as for the first visit.

    b. Receive participant, check completeness of collection, using FORM U.

    c. Receive all jars. If any are missing, try to retrieve.

    d. Give participant one of his/her jars and ask to void final specimen of the collection into that jar.

    e. Record time of completion on FORM U.

    f. Bring all the jars to the laboratory area and complete entry in URINE COLLECTION REGISTER, remembering to include split sample ID information.

Remember that specimens must be refrigerated within 1 day and frozen (-20°C) within 7 days.

Notes

1. If a participant does not appear within $^1/_2$ hour of the appointment for ending the 24-hour collection, on either first or repeat visits, every effort should be

made to contact him/her for completion of the collection. Even if the end is then 1 or 2 hours after the 24-hour point, the computer can take this into account as long as actual time of the collection is recorded.

2. Local criteria for responding to elevated BP or abnormal urine findings need to be determined in advance, and the appropriate place in the clinic schedule for any action should be decided.

1.7 Forms

Three types of forms are to be used in a standard way: data collection, instructions to participants, records and administration.

1. All forms have been drafted jointly by the London and Chicago Coordinating Centres. Each local centre will receive a master copy of each form, for local reproduction.

2. The exception is the LOG BOOK, whose pages have been produced centrally, containing all ID numbers assigned to each individual centre. This simply needs to be placed in a binder and used as is.

3. Certain forms may need translation into the local language. All translated forms need to be sent to the London Coordinating Centre for back-translation into English, to assure that meaning is identical. This must be done prior to use in the field.

4. If forms are produced in a language other than English and therefore are retyped locally:

   a. Please make sure that layout and coding are like the original form, to facilitate entry into the computer. This is especially true for the Questionnaire, where questions need to be lined up properly for coding in the right-hand column.

   b. Where responses appear in a language other than English, be sure English translation is written (in capital letters) next to the other language.

5. Be sure participant ID appears on each page of each form, in case pages become separated.

6. There is only one form to be sent to London on which the split sample ID is identified as such, and that is the 24-hour urine collection form (FORM U).

   It also appears on the Frontpage file form, identifying the participant, name, address, etc., but that form is not sent to London. It is for local use only.

   The split sample ID appears on the Shipping Form but is not identified there as a split sample ID, otherwise the Laboratory will be unblinded as to split samples.

7. Be sure the forms indicate whether the visit is a first appointment or a repeat visit.

8. Be sure the number of the staff member completing the form is on each form. Only data collected by a staff member certified to collect those data will be included in the study.

9. All forms should be edited prior to shipment and every effort made to correct errors or obtain missing information. The local Investigator should keep close and timely surveillance on how well forms are being completed.

10. Completed forms should be photocopied and the original sent to London.

11. Completed forms should be shipped to London once a week.

12. Send all forms from a participant's visit together. If there is no Repeat visit, the forms may be forwarded in his/her plastic file after the first visit. List in numerical order on the sheet provided all the participant IDs included in the shipment of forms to London. Include this list together with the shipment of forms and send a photocopy to London under separate cover. A copy of the list should also be kept locally.

13. If a Repeat visit is scheduled, the forms from the first visit should be stapled together and sent to London. After the Repeat visit, the remainder of the forms should be sent together in the participant's plastic file.

14. Forms received in London will be reviewed rapidly, and any errors will be brought to the attention of the local centre as soon as possible.

Note: When entering numbers, be sure all dashes are filled, using leading 0s where necessary, e.g., 0 0 1.

1.8 Ethical Concerns

Abnormal blood pressure

In the course of measuring BP, you are likely to come across individuals with pressures above normal. A persistent diastolic pressure of 95 mm Hg or higher has been designated 'abnormal' by the World Health Organization, and a persistent pressure 90-94 mm Hg is considered above normal in many countries.

If BP is above normal, local Investigators should be guided both by local practice and by the following suggestions:

1. If the diastolic pressure is 90-104 mm Hg, the pressure could be re-measured when the participant reports next day for completion of the 24 hour urine collection, or at the Repeat visit for participants with such visits.

2. If the pressure remains in this range, it is suggested that the participant should be referred to the usual source of medical care, and, with the participant's permission, the BP data should be forwarded.

3. If diastolic pressure is 105 mm Hg or higher, more vigorous steps to pursue referral should be taken.

Urinary screen (dipstick)

Urine dipsticks ('N-LABSTIX') will be provided centrally. Each dipstick records 6 measures - nitrite, blood, ketones, glucose, protein, and pH. The following findings are noteworthy and merit attention: a positive reading for nitrite (which may be indicative of urinary tract infection); more than trace positive for blood in men or non-menstruating women; more than trace positive for glucose or protein; and positive for ketones, in the presence of glycosuria.

If any of the results mentioned above are recorded, it is suggested that the participant be referred to the normal source of medical care, and, with the participant's permission, the urinary dipstick data should be forwarded.

Confidentiality

Neither the London Coordinating Centre nor the Central Laboratory should receive the names of study participants. Only the ID code should be forwarded.

The London Coordinating Centre will at a later date review the URINE COLLECTION REGISTER, RECRUITING RECORD, and LOG BOOK. Names should be removed from the copies forwarded to London.

In all respects, confidentiality of the data regarding individuals will be maintained.

Assurances on safeguarding the rights of INTERSALT participants

INTERSALT centres will follow a common set of procedures in regard to protecting and safeguarding the rights and welfare of all examinees in the study. These include: informing participants of the nature and aims of INTERSALT (an investigation of multiple factors possibly influencing BP); the above described guarantee of confidentiality, and the timely transmission to participants of clinically relevant findings.

In keeping with common practice in ethical research worldwide, there should be local review by an independent body of the INTERSALT protocol and local research plans, including any proposed ancillary studies. This body, which could be an existing Institutional Review Board or an ad hoc committee established for this review, should consist of a group of competent men and women independent of the local research team. Their assurances, based on their review on safeguarding and protection of the rights and welfare of the human beings at the local centre, should be forwarded to the Chicago Coordinating Centre.

1.9 Equipment and Materials

To be provided centrally

1. All forms (to be reproduced locally).

2. Participant files (plastic).

3. Jars for 24-hour urine collection: 96 1-litre plastic reusable jars with screwtop lids (4-5 per participant).

4. Funnels: 20 large reusable plastic funnels for use during urine collection (1 per participant for 24-hour collection, mainly for women).

5. Sticky labels, printed, for spot urine receptacle, collection jars, file, aliquot tubes, FORM U.

6. Marking pens: black indelible oil-based pens for use on labels.

7. Aliquot tubes and tops: push-top leakproof, 9 ml polypropylene.

8. Refrigerated packing boxes and cooling elements.

9. Measuring platform and scale for urine jars.

10. Transparent tape and packing tape.

11. Dipsticks: 300 N-Labstix for testing in freshly voided spot urines.

To be provided locally:

1. Clinic appointment diary.

2. Outdoor/indoor thermometer.

3. Large reusable receptacles for collecting spot urine samples (with lid to prevent spillage when placed in refrigerator before taking aliquots).

4. Loose-fitting gown for BP measurement, if participant's clothing restricts arm.

5. Littmann stethoscopes: two of model 2100 or 2101 (3M Company).

6. Stopwatch for measurement of pulse.

7. Height ruler (plus short ruler for extreme heights).

8. Beam balance or other weighing scale.

9. Boric acid crystals analytic reagent quality (minimum 99.5% pure), for preserving urine; 10 to 15 kg.

10. Carrier bags or cases (or equivalent) for use during urine collection (1 per participant for 24-hour collection). Number of bags or cases should be sufficient for the number of participants expected over 3-4 days.

11. Pair of rubber gloves for handling urine specimens.

12. 5-litre bucket for mixing 24-hour urine collection prior to taking aliquots.

13. Stirring rod for mixing urine.

14. Small beaker or pipette for transferring urine to aliquot tubes.

15. Scissors.

16. Laboratory racks for storing aliquots upright for freezing.

17. Refrigerator (4°C) or freezer (-20°C) on site at clinic. This should have a backup electric supply.

18. Access to a freezer (-20°C) if none on site.

19. Access to photocopier.

Ordering by local centres from a central supplier

In addition to the material being supplied centrally (forms, LOG BOOK, etc. from London, equipment for standardised urine collection from the Central Laboratory), standardised equipment for measuring BP is essential.

1. The machine to be used is the Hawksley random zero sphygmomanometer, 0-20 mm variation in the random zero, without the constant release valve. Two machines per centre are required.

2. A selection of different size Baumanometer Calibrated V-Lok cuffs with latex bags, bulb and valve:

   Number and sizes: 2 adult (Number: 1820)
   1 large adult (Number: 1825)
   1 child (Number: 1821)

3. The above items are to be ordered by the individual centres, directly from Hawksley who will advise as to total cost (including shipping), which is dependent on whether mercury is shipped together with the sphygmomanometer.

2. Methods for the London Coordinating Centre

This section summarises the methods of the London Coordinating Centre and is an edited version of the London Coordinating Centre Manual. It was used to document procedures of the Coordinating Centre and to train its staff.

2.1 Summary of Coordinating Centre Responsibilities

The functions of the London Coordinating Centre can be summarised as follows:

Joint responsibility with the Chicago Coordinating Centre

1. Standardise methods so that data are collected in a similar manner by all centres.

2. Organise and conduct regional training meetings to train each centre in INTERSALT methods, to hold individual consultations with local investigators, and to ensure that all documentation has been received and is up-to-date.

3. Plan and carry out site-visits to selected centres.

4. Take urgent policy decisions as necessary between meetings of the Executive Committee.

5. Periodically review finances, staffing levels, and progress of the study to enable a high level of supervision and quality control to be maintained.

6. Prepare the main final paper for publication, and advise on further publications.

London Coordinating Centre responsibilities

1. Allocate the centre code and staff numbers for each local centre.

2. Distribute Log Books, Dry Run material, documentation and forms, and update them where and when necessary (for example "corrections and additions" to the Field Manual of Operations), based on training meeting and field-work experience.

3. Back-translate and approve questionnaire and forms for local use.

4. Receive necessary documentation from each centre prior to data collection, including population description, social scale, alcohol equivalents, and education levels.

5. In conjunction with the Central Laboratory, arrange for the bulk purchase of INTERSALT supplies and materials and ensure that payment is made.

6. Invoice local centres for the costs of the INTERSALT supplies, or alternatively ensure that these costs are met from central funds.

7. Ensure that all supplies and equipment are shipped to local centres in time.

8. Receive and review completed Dry Run forms and feed-back urgently to local centres.

9. Approve local ancillary study requests.

10. Communicate with local centres before and during data collection, and clarify problem areas that may arise.

11. Set up and maintain a computer file for each centre.

12. Ensure that forms are sent regularly to London, and that urine aliquots are shipped as required to Leuven.

13. Review forms as they arrive for important errors and omissions, and take appropriate action.

14. Advise centres when necessary on the need to recruit supplementary participants.

15. Monitor progress so that the exact status of each centre is known as to the number of forms and urine aliquots shipped and processed.

16. Communicate regularly with the Central Laboratory and monitor the arrival, completeness, and integrity of urine shipments.

17. Receive and review copies of the daily working sheets from the Central Laboratory.

18. Oversee Central Laboratory procedures, including internal quality control, making site visits as necessary.

19. Carry out data handling procedures: receive, edit, code, punch, verify, and check completed forms.

20. Prepare a weekly report of the number of forms received, edited, coded, punched, verified, and checked.

21. Hold regular staff meetings to discuss progress and problems.

22. Communicate regularly with all centres, in the form of Newsletters, reports, etc.

23. Inform the Executive Committee and funding agencies of the progress of the study.

24. Carry out data quality control procedures: re-code a random sample of forms, and determine error rate in coding; verify (double punch) all forms, or a random sample of forms, and determine error rate in data entry; carry out range and consistency checks on the data; and monitor the technical error of the Central Laboratory (12% of the samples will be split and sent blind to the Central Laboratory for analysis).

25. Receive the necessary documentation from each centre after completion of data collection, including the Recruiting Record, Recruiting Summary, Log Book, Urine Collection Register, and local centre Report.

26. Prepare a summary of data received (excluding urine data) for each local centre.

27. Arrange transfer of computerised data from the Central Laboratory, and merge the data for each centre with the appropriate computer file in London.

28. Transfer data to the University mainframe computer for analysis.

29. Perform the data analysis in preparation for the main INTERSALT publication, in consultation with the Chicago Coordinating Centre.

30. Suggest and perform other data analyses, in collaboration with the Chicago Coordinating Centre and other INTERSALT investigators.

2.2 Central Training

Venue

The central training of investigators was organized jointly by London and Chicago, in a series of regional training meetings. In all, 5 regional meetings were held and 105 investigators were trained centrally. The regional meetings were held in London (2), Houston, East Berlin, and Singapore. The first took place in December 1984, and the last in September 1985.

Content

The training sessions were held over 3 days (4 days in Singapore) and consisted of lectures and slide presentations in the mornings, and practical sessions and individual consultations in the afternoons. Training was based around the Manual of Operations, and covered all aspects of the Study, from sampling and recruiting, BP measurement, instruction on the 24-hour urine collection, etc., to the role of local Principal Investigators, and ethical concerns.

The practical sessions involved filling out of all forms, including the questionnaire (with feedback), and detailed instruction, training, and certification in BP and the urine collection, the key variables under study.

Overall, BP training consisted of:

1. Slide/lecture presentation, outlining the INTERSALT BP procedures, and introducing the forms and equipment to be used.

2. Lecture giving definitions of the BP sounds (phase I - systolic; phase V - diastolic) and introducing the London School of Hygiene and Tropical Medicine BP - audio tape.

3. Recognition and timing of the BP sounds on the audio training tape, using individual cassette recorders and headphones.

4. Certification on the audio test tape, by defined criteria.

5. Practice (in groups of three, and under supervision) in the use of the random zero sphygmomanometer, application of cuffs, etc.

6. Use of double-headed stethoscopes to train and test investigators against the INTERSALT BP trainers. Investigators were certified by defined criteria using live readings on the random zero sphygmomanometer.

7. Instruction on the maintenance of the random zero device, and on emptying and filling with mercury.

Training in the urine collection was as follows:

1. Lectures and slide/lecture presentations covering all aspects of the urine collection, including timing, participant instruction, ensuring complete collections, labelling procedure, aliquoting, refrigerating, and shipping.

2. Collection for 24 hours and aliquoting of investigators' own urine during the meeting:

   a. Jars had to be prepared (with boric acid) and labelled.

   b. Spot urines were collected, the dipstick test carried out, boric acid added, and the urines refrigerated overnight.

   c. Instructions for the 24-hour urine collection were given.

   d. Relevant forms were filled out (Form G - General, Form U - Urine Collection, Urine Collection Register).

   e. Urine volume (heights) was measured.

   f. Aliquots were taken, labelled, and taped together in the prescribed manner.

   g. The refrigeration box was packed ready for shipping, and the shipping form was filled out.[13]

2.3 Review of Local Centres

Centre Identification

Each centre is identified by name and unique 2-digit centre code, assigned at one of the regional training meetings. The centre code is incorporated as the first 2 digits of each ID number listed on the LOG BOOK and on the corresponding pre-printed labels sent from the Central Laboratory.

Back translation of forms

The questionnaire and data forms for the Study were prepared in English by the London and Chicago Coordinating Centres. For languages other than English, local translations of the forms were made and sent for approval to London (and to Chicago, for a few centres). Native or fluent speakers of the language (usually from within the University) are contacted to back-translate the forms into English without reference to the original. Comparison is then made with the original English version, and discrepancies referred back to the local centre for clarification.

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[13] Urine aliquots from the meetings were analysed and individual results were sent to participating investigators. At the end of each training meeting, the training materials (including the training slides and the BP audio tape) were made available to investigators to allow them to train their own staffs locally.

All approach letters to participants, extra questions, etc. must also be translated and back-translated, and local field work should not begin until all the necessary forms and documentation have been approved.

To minimize errors in coding, it is particularly important that translated versions of the forms and questionnaire maintain the structure of the English originals, and efforts are made to ensure that questions line up correctly with the boxes in the right-hand coding columns. Where possible, common versions of the forms and questionnaire are agreed for centres which share a common language (for example, Italian, Spanish, German). Translations into 22 languages and dialects are approved for use in the INTERSALT study.

Preliminary information (See Appendix 3)

Before data collection begins, each centre is asked to send preliminary information to the London Centre. A check-list is filled out by one of the London coding staff, to document whether the following has been received from each centre:

1. Population description. A detailed account to characterise the base population is prepared: urban/rural status; main type of economic activity; economic level; weather; usual diet pattern, including any information on salt use; general level of health; ethnic composition; and, where available, size of the population and age-sex distribution.

2. Social scale. Where possible, a four-point social scale (1 = lowest, 4 = highest) is constructed to classify participants broadly into social groups. The scale chosen might be based on accepted national criteria (for example, Registrar General's social class in England and Wales), or be particular to the population under study.

3. Alcohol equivalents. A list of alcoholic drinks consumed in the population and the equivalent volumes (in ml) of absolute alcohol are necessary to allow data on alcohol intake to be quantified. During the study, centres need specify only the type of alcohol consumed (beer, wine, whisky, etc.) and the volume (in ml); conversion to ml of absolute alcohol is then calculated by computer.

4. Education levels. A brief description of the education system, and the expected time spent at each level (primary, secondary, higher education) is needed to interpret answers to questionnaire queries on education.

5. Clinic hours. Days and times that local clinics are open are entered on to the computer, and checked against those filled out on the data forms.

6. Certification of local staff. At least one member of staff from each centre is trained at a regional training meeting. If other members of staff are taking part in the study (in any capacity) they are trained locally, and certified in the appropriate tasks by the local Principal Investigator. For BP, observers not trained at regional training meetings must be certified against an INTERSALT trained and certified observer.

   The local Principal Investigator completes and returns a "Certification of Staff Member" form for each of his or her staff, indicating those aspects of the Study for which each staff member is certified. Staff numbers (starting at "01" in each centre) are assigned by London, and a computer check of staff number against study tasks (as recorded on the data forms) is carried out.

7. Methods of sampling. Sampling in each centre is achieved by one of three methods:

   a. Age-sex stratified random sampling when age and sex are known.

   b. Simple random sampling if names and locations are known, but not age and sex.

   c. House-to-house contact, if there is no list of names.

   These are to be discussed with London in advance. During the study, London is on hand to advise on sampling where necessary (for example, if a shortfall is apparent in one of the age-sex groups).

Ancillary studies

INTERSALT policy is to encourage ancillary studies by local centres, providing that: funding is arranged locally; an INTERSALT investigator is a principal investigator or co-investigator on the ancillary study, and is responsible for presenting it to the INTERSALT Executive Committee; and that the ancillary study does not interfere significantly with the conduct and goals of the main study. Interference may take a variety of forms, for example, the collection of fasting blood samples, too much additional examination time, or the inclusion of procedures which would make the examination less acceptable to participants.

The local Investigator submits the "Ancillary Study Approval Request Form" and any relevant documentation to London for approval. In general, requests meeting the conditions above are approved.

Communications

It is the responsibility of the London Centre to maintain close contact with participating centres throughout the study. This takes the form of regular general communications (e.g., updates to the Manual of Operations, Newsletters, etc.), and direct contact at different stages of the study locally. Two separate files and a "local centre book" are kept to record details of communications with each centre.

1. Planning for the Study. Once initial contact is made, letters are exchanged on details of the local study, and relevant INTERSALT documents are sent out, including the Protocol and Manual of Operations .

2. Regional Training Meeting. Local investigators were sent invitations to attend one of the regional training meetings, and were required to fill out and return Registration Forms for the meeting. Any missing documentation, and the training and Dry Run materials, were distributed at training meetings.

3. Preparation for the Study. Prior to data collection, contact is established with each centre by letter, telephone, and if possible by telex, and the preliminary materials are requested, including translations of the data forms and questionnaire. A date is set for the Dry Run and the study proper, and despatch of the central supplies is organized.

4. Dry Run. Where possible, the Dry Run is discussed with the local investigator by telephone after review of the completed Dry Run forms in London. Arrangements for the study proper are also discussed, and a follow-up letter is sent.

5. Data Collection. Lines of communication between London and local centres are established in advance of data collection to allow for early detection and correction of errors. In all cases, London is on hand to answer queries arising in the field. Urgent problems discovered during the edit procedure are dealt with by telephone, telegram, or telex (including the need to recruit supplementary participants). Other queries are normally made by air-mail letter, and a standard form for this purpose has been prepared. London also

advises local centres on whether shipment of forms and urines are received in London and Leuven, and whether back-up urines are required.

6. Completion of the local Study. After completion of data collection, a request is made for copies of the Log Book, Urine Collection Register, Recruiting Record, and Recruiting Summary (without the names) together with answers to any outstanding queries. The local Investigator is also asked to make out a report of the centre's experiences during data collection, along the lines of a pro-forma prepared in London. Once all data have been entered onto the microcomputer in London, checked and verified, a summary report of data received (excluding urinary data) is prepared and sent to the local Investigator.

7. Publications. The main paper by the INTERSALT Cooperative Group is to be circulated for comment to local investigators in advance of publication.

Site visits

The INTERSALT Protocol made provision for site visits to be made to selected centres to coincide with local training and the Dry Run. The size of the study and the distances involved do not permit this to be a primary means of contact.

2.4 Review of the Central Laboratory Procedures

Delivery of central supplies

Central supplies (tubes, tops, etc.) for the INTERSALT study are purchased in bulk by Leuven for shipment to local centres, and a set of numbered and blank labels are printed for each centre. After receiving word from London (for example, once payment for central supplies has been made), boxes of supplies and labels are packed and despatched, and the details discussed with London so that local centres can be informed.

London and Leuven have worked closely together to ensure that central supplies have been delivered to centres in time. This has necessitated overcoming many local and international difficulties in the shipping of supplies around the world, including airline and customs regulations.

Notification of local shipments

According to protocol, both the London Coordinating Centre and the Central Laboratory are to be advised of incoming shipments from local centres at least 2 weeks in advance. This has not always been feasible, and occasionally contact with either London or Leuven has not been made until near the time of shipment. In all events, London and the Central Laboratory discuss the shipping details by telephone, and arrangements are made in Leuven to collect the shipment as soon after arrival as possible.

Once the shipment has been retrieved, the boxes are opened, an inventory of the aliquots is taken and compared with the shipping list from the local centre, and an assessment is made of the state of the urines (whether thawed, whether the aliquot tubes are cracked, etc.). Details are discussed with London by telephone, and appropriate feedback to the local centre (usually by London) is agreed. Forms documenting the date of arrival of each shipment, the IDs of urines received, and the state of the urine samples are sent on to London by post.

The shipment of the first 25 urines from each centre is analyzed quickly by the Central Laboratory and the results discussed with London by telephone. This identifies any problems in labelling (particularly of the split samples) or in the allocation of ID numbers, and if necessary the local centre is contacted urgently by London for a review of local procedures.

Receipt of laboratory data

Photocopies of the laboratory working sheets are sent regularly to London by post. In addition, plots of the internal quality control samples and addition curves for sodium and potassium are periodically reviewed. Computerised laboratory data are being sent on 8" floppy disks (one or two per centre), and are transferred onto microcomputer in London. Thus both uncorrected data (working sheets) and data corrected to baseline control values (floppy disks) are being received.

Communications

Regular site visits are being made to the Central Laboratory enabling laboratory quality control procedures, transfer of data, etc., to be reviewed. Several visits to the London Coordinating Centre have also been made by Central Laboratory staff, with detailed Minutes of such meetings.

A close working relationship has been established with the Central Laboratory, and frequent communications are made by telephone, telex, and letter. Details of telephone conversations are recorded in a separate book for the Central Laboratory, and files are maintained for correspondence, for invoices related to central supplies and shipping costs, and for routine Laboratory data received in London.

Quality control procedures

An extensive system of internal quality control for the INTERSALT Study has been developed by the Central Laboratory in collaboration with the London Coordinating Centre. Regular review of the quality control procedures is carried out by post and on the telephone, and during site visits. External quality control is by means of the split samples.

1. Quality Control Charts and Addition Curves. Results of the daily quality control samples (High, Medium, and Low for each analysis of interest) are displayed and outliers investigated. Addition curves for Na and K are also produced to check for systematic errors in the Laboratory.

2. Laboratory Working Sheets. Copies of the daily working sheets for the Central Laboratory are sent to London by post. These are reviewed and kept as a working record of Laboratory performance.

3. Participant IDs. Participant initials from the aliquot labels are entered onto the Laboratory working sheets when the urines are analyzed. They are entered onto computer in Leuven and checked against initials listed on the urine Shipping Forms.

   A list of IDs (with initials) is prepared in London for each centre, and comparison is made with the IDs received in Leuven. Any discrepancies are investigated in London and in Leuven, and if necessary checked with the local centre. Finally, the full 7-character ID for each participant in the Study is agreed, so that Laboratory data can be merged with the data file in London.

4. Split Samples. The analysis of split samples is reviewed in London, and any discrepancies are checked first for mislabelling in the Laboratory and then for mislabelling in the field. A formal analysis of laboratory technical error is undertaken once computerised laboratory data have been received in London.

Finances

Bulk purchase of the INTERSALT central supplies sent from Leuven is organised by the Central Laboratory. The Laboratory is also liable for the costs of shipping supplies and for customs duties when incoming shipments are picked up from Brussels airport. Detailed invoices are sent periodically to London for payment from central INTERSALT funds.

2.5 Processing Data from Local Centres

Introduction

The London Coordinating Centre has several microcomputers for use in INTERSALT. Data are stored on double-sided double-density (720 K) 3.5" diskettes with one diskette per centre. Each diskette contains participant data from the data forms, laboratory data, and data characterising the local centre. Data are additionally stored on hard disk (10 Mb) which is used for up-dating the data set and copying local centre data back to the corresponding diskette. Some data analyses are also carried out on microcomputer.

Participant and local centre data are entered on computer in London, while laboratory data are entered and checked in the Central Laboratory in Leuven and transferred to London on 8" floppy disks. The data are then merged in London using the 7-character participant ID as identifier.

Planning the workload

The workload of the London Centre is unpredictable from week to week, depending on a variety of factors beyond control of either London or the local centre (availability of photocopying facilities, the state of the postal services, etc.). Nevertheless, efforts are made to plan ahead and keep abreast of the workload (for example, by employing part-time coding staff). Regular timetables are produced of expected starting dates of centres not yet in the field, and a summary is made each week of the number of data forms received, edited, coded, entered onto the computer, checked, and verified.

Local centre data

A number of general files are prepared for each local centre. These contain identity numbers of participants and staff and information on the centre's working hours and

rest days. Further files contain coding information on alcohol use and dietary changes.

Logging in data forms

When a shipment of forms is received, the Shipping List is date-stamped, and the shipment passed onto the appropriate staff member for editing and coding. In most cases, one coder will be responsible for a centre until the completion of the study locally. The Field Coordinator or Data Manager decides (usually at the time of the Dry Run or first shipment) which member of staff to allocate to a given centre; their decision depends on the current and expected workload of each staff member.

When a Shipping List is not enclosed and a copy has not been received under separate cover, a list of IDs included in the shipment is prepared by the coder and date-stamped. The Shipping Lists are kept together with the data forms during editing and coding. They are then filed along with copies of the Urine Shipping Forms.

The coders keep a tally of the number of forms received, edited, and coded each week, and this is passed on to the Data Manager or Computer Operator. A weekly summary for the London Centre is then prepared.

Initial edit procedure

As soon as possible after receipt of a shipment of forms, the initial edit procedure is carried out. The purpose of the edit procedure is to check that all the forms have been received for each participant included on the Shipping List, and that no systematic errors are being made on the variables of most interest (BP and the urine collection). In addition, a decision is taken as to whether supplementary participants are required.

Following the initial edit procedure, the local centre is contacted by telex or telegram. In urgent cases, where the protocol has not been followed or has been misunderstood, the Field Coordinator gets in touch with the local investigator by telephone. Follow-up letters are also sent where necessary. Once the initial edit is complete, forms are ready for coding.

Coding of data forms

1. Training and instruction of coders. Instruction of full-time INTERSALT coding staff was organized by the Field Coordinator and Data Manager, using

a detailed schedule of coding rules. Part-time coding staff are trained by one of the full time coders, but problem areas and areas of disagreement are referred to the Field Coordinator for clarification.

The Field Coordinator is on hand to advise on interpretation of existing coding rules or on new rulings, and decisions are recorded in a book kept for this purpose. In addition, regular meetings are held at the London Centre during which coding problems can be discussed and new coding rules can be communicated to other INTERSALT staff.

2. The Dry Run. A full coding of the Dry Run is made as soon as possible after the forms have arrived in London, and the local centre file and check-list are inspected to see whether all the preliminary information has been received. A complete list of errors, inaccuracies, and omissions on the Dry Run and a note of any missing documentation, are recorded in the local centre book, which is passed to the Field Coordinator. Efforts are then made to contact the local Principal Investigator by telephone to discuss the Dry Run and any outstanding problems or queries. In all cases, a follow-up letter is sent.

3. Coding Methods. While INTERSALT data forms are in general precoded, some variables need central coding (e.g., ml of alcohol, type of diet change). Coding boxes are located in the right-hand coding column. In addition, mock-up data forms with prompts and coding boxes have been set up on the computer using dBase II.

4. Coding Quality Control. A 5% sample of forms from each centre (excluding repeats) has been randomly selected for double-coding. Staff who code the forms the first time round are unaware of which forms have been selected. The second coding is carried out by a different member of staff, but to ensure that the second coding is "blind" to the first, the forms are photocopied with blank boxes substituted into the right hand coding columns. Both sets of forms are entered onto the computer and compared. Any discrepancies are investigated, and an "error rate" (for the first coding) is calculated. Feedback on the double-coding is given to the coding staff, and action is taken if error rates are too high or if a systematic error by one of the staff is detected. Double-coding is also used to train part-time staff, and their performance is compared with that of the established coders.

5. Data Entry. Data are entered either directly from the forms (without a separate coding stage) or from coded information in the right hand coding

boxes. If the data do not need coding, the digits are transferred to the right hand coding boxes, to enable the data entry technician to proceed efficiently. Whether data in the right hand column are from direct transfer or from coding, the data are verified by double entry (by the same individual, on a separate day), and an entry "error rate" is established. Double entry is also used when data are corrected and up-dated.

Data checking

Checking programs are run once data have been entered onto the computer and verified. These test whether identity numbers are valid, missing, or duplicated; whether fields are within acceptable ranges, and whether data are internally consistent. In addition, a list of unknown or missing fields (coded 9 and 7) is produced.

Communication of errors to local centres

Local centre errors are detected by the London Centre at various stages of the review procedure. These include the Dry Run, the initial edit, the coding stage, and computer checking of the data. All errors detected in the Dry Run are reported back to the local centre, by telephone if possible. In addition, a telex or telegram is sent after the initial edit to advise centres on whether supplementary participants are required.

In general, errors are of two types:

1. Major (systematic) errors. These arise from misinterpretation of the protocol, and result in incorrect recording of the data. They are usually discovered either at the Dry Run, or during the initial edit procedure. In all cases, contact with the local centre is made immediately by telephone, telegram, or telex, so that corrective action can be taken.

2. Minor errors. These occur when information is missing, incorrectly entered, out of range, or illegible on particular forms. They are generally found at the coding stage or by the data checking program, and are reported to the local centre by air mail. A standard form for this purpose has been prepared. A list of outstanding problems is stored on computer until a response has been received from the field.

Error correction

When corrections are received from the local centre, the necessary amendments are made to the data set using the data entry program. The disk file with the problems outstanding for the centre is also amended, so that an updated list of queries is kept on file. Corrections are verified by copying the original file and updating it twice (double entry).

Additional procedures

When data correction in a centre is complete, a number of additional procedures are carried out.

1. Local Centre Documentation. Copies of the Log Book, Recruiting Record, Recruiting Summary, and Urine Collection Register are requested, with names removed to preserve confidentiality. They are checked for completeness and examined to determine whether the protocol was carried our correctly (for example, in recruiting the sample in the order of the age-sex lists). In addition, ID numbers and initials from the Log Book and Urine Collection Register are compared with those received in London and Leuven. Any queries are referred back to the local Principal Investigator for clarification.

   Response rates in each age and sex group are calculated from the Recruiting Record and Recruiting Summary, where possible. The numerator is all age-sex eligible participants (including supplementaries), with eligible participants plus refusals as the denominator. (Noneligibles and those above the required numbers per age-sex group from the initial lists are excluded from the calculations.) A printout of those participants for whom supplementaries were required is also made.

2. Computer Checks. In addition to the range and consistency checks of participant data, programs are run to check that only certified staff carried out clinic tasks and that clinic opening times were consistent with those indicated in the preliminary information received from each centre.

3. Summary of Data Received. Once all the data from a local centre have been entered onto computer, verified, and checked, and replies have been received to outstanding queries, a report is prepared of data received in London (excluding urinary data) and sent to the local investigator.

2.6 Processing Central Laboratory Data

Introduction

Definitive data from the Central Laboratory are sent to London in computerised form on floppy disks. The laboratory records results, enters them into its computer, and verifies the data (by 10% random double entry). In addition, a number of checking programs are run to give range and consistency checks on the data, and to detect transcription errors by laboratory technicians.

In addition, for day-to-day management of the study, a variety of non-computerised data are received from the Central Laboratory.

1. Results on first 25 urine aliquots. The first 25 urine aliquots from a centre are analysed soon after receipt in Leuven, and results are transmitted to London by telephone. Split samples are identified by London and if gross discrepancies are apparent, the Laboratory is asked to reanalyse the samples to help determine whether the error was in analysis, recording, or mislabelling.

2. Laboratory working sheets. These are filed for reference and are periodically reviewed (for results on split samples, to check participant initials, etc.).

3. Quality control charts and addition curves.

4. Inventory of urine aliquots. Lists of urine aliquots received in the Central Laboratory, giving date of arrival, state of arrival, etc., are sent to London as shipments arrive. A comparison of IDs is made with those on the data forms, and any discrepancies are investigated.

Processing computerized data

When a floppy disk from the Central Laboratory is received, it is read on an 8" disk drive within the Department of Epidemiology and the data are transferred to microcomputer. The data are merged on hard disk with the corresponding participant data, using the seven-character participant ID as identifier, and copied onto the local centre's diskette.

At the end of the Study, a magnetic tape of all the Central Laboratory results will be prepared and transferred to London. Comparison will be made with the data received on floppy disk.

External quality control

External control of the Central Laboratory is being monitored by computation of the technical error. This is calculated by analysing paired results on the split samples, as follows:

$$TE = \Sigma^{N}_{i=1} \quad \frac{(X_{i1} - X_{i2})^2}{2N}$$

where TE = technical error

N = number of paired split samples,

and X_{i1}, X_{i2}, X_{21}, X_{22}, etc are split-sample pairs.

The technical error is also expressed as a percentage of the mean:

$$\%TE = 100 \times TE/\Sigma^{N}_{i=1} (X_{i1} + X_{i2})/2N$$

2.7 Other Procedures

Staff meetings

Meetings of London Coordinating Centre staff are held regularly to review the day-to-day running of the Coordinating Centre. In addition, meetings are held from time to time with staff from the Chicago Coordinating Centre and the Central Laboratory, and progress and policy issues are discussed. Detailed minutes of the meetings are distributed to INTERSALT staff.

Interim reports

INTERSALT Newsletters are sent regularly by the London Coordinating Centre to all participating investigators and to members of the Executive Committee. In addition, it is the responsibility of the London Centre together with Chicago to provide updated reports as necessary for the Executive Committee and funding agencies.

Filing

Two filing systems are in use in the London Coordinating Centre: a working file and a permanent file. As forms are received from a local centre, they enter the working filing system. Data forms for a given participant are kept within the participant's

plastic file, and all the files for a given centre are filed together in five or six filing boxes per centre. Once all the data for a centre have been coded, punched, entered into the computer, verified, and checked (i.e., the data set is complete and correct), the centre's filing boxes and data forms are transferred to permanent storage.

Data security

To preserve confidentiality of the individuals participating in INTERSALT, identification is made by means of the study ID only and names are not held in London. Efforts are made to ensure that no data are mislaid or go missing. As forms are received in London, they are checked against the Shipping List prepared in the local centre and discrepancies are queried. Data forms, microcomputers, and diskettes are locked up outside working hours.

Once data have been entered into the computer, a number of copies are kept to guard against loss through faulty media. One copy is kept on hard disk, a second copy on diskette, and a third copy on a diskette stored in a safe place outside the building. This is locked up, and provides a backup should the others be lost through fire, etc.

3. Methods for the Central Laboratory

This section summarises the methods and procedures of the Central Laboratory (excluding biochemical procedures) which were developed jointly by the Laboratory and the London Coordinating Centre. It was part of a larger Laboratory Manual used by the Laboratory staff and technicians.

3.1 Procedures for Shipping Urine Aliquots

There is one Central Laboratory for all chemical analyses, at the Sint-Rafael University Hospital, Capucijnenvoer 33, B-3000, Leuven, Belgium.

Local centre to Brussels airport

These procedures are described in detail in Section 3, Field Methods.

Brussels airport to Central Laboratory

As urine shipments arrive at Brussels airport, the Central Laboratory makes contact with the appropriate air freight handling department (either Sabena or Belgavia, depending on which airline is used for the shipment). If the samples arrive before 6

p.m. on a weekday, they are collected on the day of arrival in Brussels. Shipments arriving after 6 p.m. are collected the next morning.

The local centres have been advised not to send any shipments scheduled to arrive in Brussels over a weekend. In the event that this occurs, however, shipments can be collected only on the Monday morning, since there is no customs service over the weekend. If shipments have to stay overnight at the airport, the airline handlers are advised to store them in a deep-freeze until collection. Import duties are invoiced to the London Coordinating Centre.

Upon arrival in the Central Laboratory, the urine aliquots are unpacked, counted, checked, and stored in a deep-freeze at -30°C (aliquot numbers 1, 3, 4, and 5), and at -80°C (aliquot number 6). Aliquot numbers 1 (spot) and 3 (full, 24-hour) are analyzed for cations and creatinine; numbers 4 and 5 are stored for future analyses and number 6 is kept for long-term central storage. If for some reason less than four aliquots of the 24-hour urine collection are received, the following priority rules apply: irrespective of the aliquot number, the first aliquot is taken for immediate analysis, the second one for long-term central storage, and the remainder for future analyses.

Shipping information is entered on the Urine Inventory. This information includes the local centre number, airway bill number, invoice number, import duties, date of shipment, date of arrival in Brussels, whether first or repeat collection, whether or not the aliquots are backups, and whether or not aliquots are thawed (s= only spot thawed; f= at least one full sample thawed; a= both spot and full samples thawed). The participant initials are also copied onto this form from the urine Shipping List sent by the local centre.

The Central Laboratory informs the London Coordinating Centre by telephone of the number of samples received, the ID numbers, the condition in which they were received, and of any discrepancies noted (e.g., when at least one of the five urine aliquots for a given participant is missing). The London Coordinating Centre informs the local centre accordingly and instructs the Central Laboratory of actions to be taken.

As far as possible, the Central Laboratory analyses the first shipment of urine from a centre on the first working day after arrival in Leuven. Results of these analyses are immediately telephoned to the London Coordinating Centre, and the labelling, the allocation of ID numbers, and the results for any split samples are checked there.

At the end of each week, the Central Laboratory sends copies of the Inventory Forms (if any shipment arrived during the preceding week) and of the laboratory working sheets (crude data) to the London Coordinating Centre. Once all the aliquots for a particular centre have been analysed, data are transferred to London on a 3740 formatted 8" floppy disk; separate data files are used for first and for repeat collections.

3.2 Quality Control Procedures

An extensive quality control programme is used to ensure high-quality urine analyses. This includes internal control by analysis of a commercially available urine standard, addition curves, procedures for monitoring daily laboratory performance, and external control by means of split samples.

Internal quality control

1. INTERSALT Reference Samples. At the beginning of the study, before any sample had been analysed, a number of urine pools were collected and subdivided into 4 ml aliquots. They were stored in a deep-freeze at -30°C for use throughout the study for internal laboratory control.

   For each of the analyses of interest (sodium, potassium, calcium, magnesium, chloride, and creatinine) two low, two medium, and two high concentration pools of urine were prepared.

   For a given substance and concentration (i.e. sodium, medium) the two pools were designed to differ by about 2.5%. This was done in order to blind the technicians as to the "true" value of concentration for a given quality control sample.

   About 250 aliquots were taken from each pool. Assuming that the chemical analyses will last about 2.5 years, that is 500 working days, a sufficient number of aliquots were prepared for the duration of the study.

   Each working day is randomly assigned an INTERSALT reference sample from either pool for each substance and concentration and the technicians have no prior knowledge of which of the two pools a specific INTERSALT reference sample has been drawn.

Analysis of the INTERSALT reference samples is by visual display and control charts.

2. Visual display. Plots of the INTERSALT reference samples Low (1,2), Medium (1,2), High (1,2) are made periodically and reviewed with the London Coordinating Centre. Outlying points are investigated.

3. The Levey-Jennings Control Chart. For each INTERSALT reference sample, estimates of the mean (X), the standard deviation (s) and the range (R) were calculated from results obtained over a period when the laboratory was judged to be at a good level of control. Each day, the average of repeated estimates of a given INTERSALT reference sample is calculated to determine whether it lies within a 3 standard error (S.E.) confidence interval of X. Points lying outside 3 S.E. give a warning of a possible out-of-control situation. Such a warning also occurs when at least seven consecutive values fall either below or above the nominal value, or when seven consecutive values show a positive or negative trend.

4. Commercially Available Urine Standard. Throughout the study, a commercially available urine standard is analyzed periodically for external comparison of results obtained in the Central Laboratory with target values as given by the company from which the standard is obtained. The primary objective here is to test whether or not the analytical system provides accurate results.

   For an analytical system to be accurate, the obtained results should fall within the designated range.

5. Addition Curves. This method is also applied for testing the accuracy of the analytical system, and may provide more reliable conclusions than by analysing commercial standards.

   This method consists of analysing a set of urine samples obtained by mixing specified amounts of an unknown sample (x), of a urine standard (y) with known concentration, and of distilled water (z), according to the formula:

$$x + n*y + z = t \; (n = 0,..., 10)$$

   If the samples are prepared carefully following detailed instructions, the results obtained after analysis should follow a straight line.

The accuracy of the analyzing system is evaluated using linear regression techniques. Empirically, the linear correlation coefficient r should be at least 0.999 for the accuracy to be acceptable. The slope b should not be significantly different from one ($p<0.01$). The intercept a is to be interpreted as the concentration of the unknown urine sample.

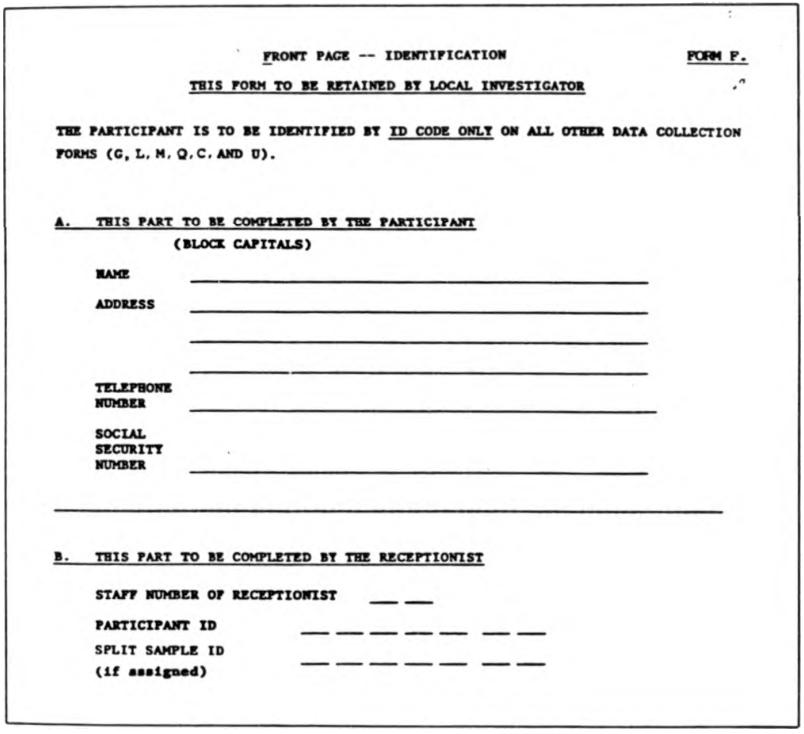
Addition curves are made periodically throughout the study.

External quality control: split samples

External validation of the Central Laboratory is through analysis of the 12% split samples.

Appendix 2: Forms and Questionnaire

Data Collection Forms



FRONT PAGE -- IDENTIFICATION FORM P.

THIS FORM TO BE RETAINED BY LOCAL INVESTIGATOR

THE PARTICIPANT IS TO BE IDENTIFIED BY ID CODE ONLY ON ALL OTHER DATA COLLECTION FORMS (G, L, M, Q, C, AND U).

A. THIS PART TO BE COMPLETED BY THE PARTICIPANT
(BLOCK CAPITALS)

NAME _____

ADDRESS _____

_____

_____

TELEPHONE NUMBER _____

SOCIAL SECURITY NUMBER _____

B. THIS PART TO BE COMPLETED BY THE RECEPTIONIST

STAFF NUMBER OF RECEPTIONIST __ __

PARTICIPANT ID __ __ __ __ __ __ __ __

SPLIT SAMPLE ID (if assigned) __ __ __ __ __ __ __ __

GENERAL PREPARATION FOR MEASUREMENT

FORM G.

PLEASE DO NOT WRITE HERE

GENERAL

STUDY CENTRE _____ (Name)

PARTICIPANT ID __ __ __ __ __ __ __ 1-7

0 1 8-9

APPOINTMENT: FIRST ☐ 1 REPEAT ☐ 2 10

STAFF NUMBER OF PERSON COMPLETING THIS FORM __ __ 11-12

1. WAS PARTICIPANT ASKED TO FAST IN PREPARATION FOR THIS VISIT?

YES ☐ 1 NO ☐ 2 13

(IF YES, RE-SCHEDULE CLINIC APPOINTMENT)

2. DATE __ __/__ __/__ __ (Day / Month / Year) 14-19

3. DAY OF WEEK MON ☐ 1 TUES ☐ 2 WED ☐ 3

THUR ☐ 4 FRI ☐ 5 SAT ☐ 6 SUN ☐ 7 20

4A. IS TEMPERATURE RECORDED IN:

DEGREES CENTIGRADE? ☐ 1 DEGREES FAHRENHEIT? ☐ 2 21

4B. OUTSIDE TEMPERATURE __ __ __ (DEGREES) 22-24

ABOVE ZERO? ☐ 1 BELOW ZERO? ☐ 2 25

4C. ROOM TEMPERATURE __ __ __ (DEGREES) 26-28

ABOVE ZERO? ☐ 1 BELOW ZERO? ☐ 2 29

(CONTINUED ON NEXT PAGE)

GENERAL PREPARATION FOR MEASUREMENT

APPOINTMENT: FIRST ☐ REPEAT ☐

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PAGE 2 - FORM G.

PLEASE DO NOT WRITE HERE

5A. HAS PARTICIPANT VOIDED AND HAS SPOT URINE BEEN COLLECTED?

YES ☐ 1 NO ☐ 2 ☐ 30

5B. START OF 24-HOUR URINE COLLECTION (RIGHT AFTER VOIDING SPOT URINE)

TIME OF DAY (24-hour clock) ___ ___ : ___ ___ Hours Mins. ☐☐:☐☐ 31-34

5C. HAS PARTICIPANT BEEN GIVEN FUNNEL, URINE CONTAINERS, AND INSTRUCTIONS FOR 24-HOUR URINE COLLECTION?

YES ☐ 1 NO ☐ 2 ☐ 35

IN THE PAST HALF HOUR

HAS PARTICIPANT BEEN:

6A. EATING? YES ☐ 1 NO ☐ 2 ☐ 36

6B. DRINKING ANYTHING OTHER THAN WATER? YES ☐ 1 NO ☐ 2 ☐ 37

6C. SMOKING? YES ☐ 1 NO ☐ 2 ☐ 38

6D. TAKING STRENUOUS EXERCISE? (INCLUDING TRAVELLING TO THE CLINIC IF STRENUOUS) YES ☐ 1 NO ☐ 2 ☐ 39

IF 'YES' TO ANY OF QUESTIONS 6A-6D ABOVE, WAIT HALF AN HOUR BEFORE PROCEEDING TO MEASUREMENT

LABSTIX

FORM L.

STUDY CENTRE _____ (name)

PARTICIPANT ID _ _ _ _ _ _ _ _ _ 1-7

8-9 0 9

APPOINTMENT FIRST ☐ 1 REPEAT ☐ 2 10

NOTES: USE DIPSTICK IN FRESHLY VOIDED SPOT URINE ONLY (NO PRESERVATIVE). COMPLETELY IMMERSE ALL REAGENT AREAS IN THE URINE, THEN IMMEDIATELY REMOVE THE STICK. TAP EDGE OF DIPSTICK TO REMOVE EXCESS URINE, AND HOLD IN A HORIZONTAL POSITION. COMPARE THE TEST AREAS WITH THE CORRESPONDING COLOUR CHARTS ON THE BOTTLE LABEL, AT THE TIMES SPECIFIED FOR EACH AREA.

1. NITRITE (40 secs) ☐ 1 Neg ☐ 2 Pos — 11

2. BLOOD (40 secs) ☐ 1 Neg ☐ 2 Trace ☐ 3 + ☐ 4 ++ ☐ 5 +++ — 12

3. KETONES (15 secs) ☐ 1 Neg ☐ 2 Trace ☐ 3 Small ☐ 4 Mod ☐ 5 Large ☐ 6 — 13

4. GLUCOSE (30 secs) ☐ 1 Neg ☐ 2 Trace ☐ 3 + ☐ 4 ++ ☐ 5 +++ ☐ 6 ++++ — 14

5. PROTEIN* ☐ 1 Neg ☐ 2 Trace ☐ 3 + ☐ 4 ++ ☐ 5 +++ ☐ 6 ++++ — 15

6. pH* ☐ 1 5.0 ☐ 2 6.0 ☐ 3 6.5 ☐ 4 7.0 ☐ 5 7.5 ☐ 6 8.0 ☐ 7 8.5 — 16

*Time not critical

STAFF NUMBER _ _ 17-18

MEASUREMENTS

FORM M.

MEASUREMENTS

PLEASE DO NOT WRITE HERE

STUDY CENTRE _____

PARTICIPANT ID __ __ __ __ __ __ __ 1-7

0 2 8-9

APPOINTMENT: FIRST ☐ 1 REPEAT ☐ 2 10

BLOOD PRESSURE OBSERVER NUMBER __ __ 11-12

1. PREPARATIONS FOR MEASUREMENT

1A. HAS PARTICIPANT REMOVED HEAVY OUTER GARMENTS AND EXPOSED ARM?

YES ☐ 1 NO ☐ 2 13

1B. WHICH ARM? RIGHT ☐ 1 LEFT ☐ 2 14

1C. HAS BLOOD PRESSURE CUFF BEEN APPLIED CORRECTLY?

YES ☐ 1 NO ☐ 2 15

(NB: USE LARGE ADULT CUFF FOR OBESE ARMS AND CHILD CUFF FOR SMALL ARMS)

1D. CUFF SIZE?

ADULT ☐ 1 LARGE ADULT ☐ 2 CHILD ☐ 3 16

1E. HAS PARTICIPANT RESTED, SEATED, WITH CUFF APPLIED FOR FIVE MINUTES?

YES ☐ 1 NO ☐ 2 17

1F. TIME OF DAY (24-hour clock) __ __:__ __ 18-21

ENSURE STANDARD PREPARATIONS FOR MEASUREMENT 1A, 1C, 1E ABOVE HAVE BEEN CORRECTLY COMPLETED BEFORE PROCEEDING

(CONTINUED ON NEXT PAGE)

MEASUREMENTS

APPOINTMENT: FIRST ☐ REPEAT ☐

PLEASE DO NOT WRITE HERE

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

2. PULSE AND BLOOD PRESSURE

RESTING PULSE (30 seconds) ___ ___ ___ ☐☐☐ 22-24

PULSE OBLITERATION PRESSURE ___ ___ ___ ☐☐☐ 25-27

PEAK INFLATION PRESSURE
(PULSE OBLITERATION PRESSURE + 10 mm
OR 180 mm, WHICHEVER IS GREATER) ___ ___ ___ ☐☐☐ 28-30

MEASUREMENT I: PULSE (30 seconds) ___ ___ ___ ☐☐☐ 31-33

RZ SYSTOLIC ___ ___ ___ ☐☐☐ 34-36

RZ DIASTOLIC ___ ___ ___ ☐☐☐ 37-39

RZ ZERO ___ ___ ☐☐ 40-41

MEASUREMENT II: PULSE (30 seconds) ___ ___ ___ ☐☐☐ 42-44

RZ SYSTOLIC ___ ___ ___ ☐☐☐ 45-47

RZ DIASTOLIC ___ ___ ___ ☐☐☐ 48-50

RZ ZERO ___ ___ ☐☐ 51-52

WAS BLOOD PRESSURE MEASUREMENT DIFFICULT?

YES ☐ 1 NO ☐ 2 ☐ 53

IF YES, GIVE DETAILS BELOW
(please write legibly, in English, if possible)

IF FIRST APPOINTMENT, PROCEED TO MEASURE HEIGHT AND WEIGHT (next page). IF REPEAT APPOINTMENT, THIS ENDS THE MEASUREMENTS.

(CONTINUED ON NEXT PAGE)

MEASUREMENTS

PAGE 3 — FORM M.

PLEASE DO NOT WRITE HERE

PARTICIPANT ID _ _ _ _ _ _ _ _ _

1. HEIGHT AND WEIGHT

HEIGHT AND WEIGHT OBSERVER NUMBER _ _ — 54-55

HAVE PARTICIPANT'S SHOES BEEN REMOVED?

YES ☐ 1 NO ☐ 2 — 56

HEIGHT I _ _ _ (CENTIMETRES) — 57-59

HEIGHT II _ _ _ — 60-62

WEIGHT I _ _ _ . _ (KILOS, TO THE NEAREST HALF KILO) — 63-66

WEIGHT II _ _ _ . _ — 67-70

OR I _ _ _ (POUNDS, TO THE NEAREST ONE POUND) — 71-73

II _ _ _ — 74-76

QUESTIONNAIRE

FORM Q.

PLEASE DO NOT WRITE HERE

STUDY CENTRE _____
(Name)

PARTICIPANT ID _ _ _ _ _ _ _ _ _ _

1-7

0 3
8-9

QUESTIONNAIRE

PAGE 2 FORM Q.

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

PLEASE ANSWER ALL QUESTIONS THAT APPLY TO YOU. MARK AN 'X' IN THE BOX OR PRINT INFORMATION WHERE REQUESTED. ASK THE INTERVIEWER FOR ASSISTANCE IF REQUIRED

1. WHAT IS YOUR DATE OF BIRTH? ___/___/___ (Day)(Month)(Year) ☐☐☐☐☐☐ 10-15

2. WHAT WAS YOUR AGE LAST BIRTHDAY? _____ (Years) ☐☐ 16-17

3. WHAT SEX ARE YOU? MALE ☐ 1 FEMALE ☐ 2 ☐ 18

4. ARE YOU:

NOW MARRIED ☐ 1 DIVORCED OR SEPARATED? ☐ 2

WIDOWED? ☐ 3 NEVER MARRIED? ☐ 4 ☐ 19

5. DO YOU NOW SMOKE CIGARETTES?

YES ☐ 1 IF YES, PLEASE ANSWER QUESTIONS 6 AND 7

NO ☐ 2 IF NO, PLEASE SKIP QUESTIONS 6 AND 7 AND THEEN ANSWER QUESTIONS 8, 9 AND 10 ☐ 20

ONLY FOR CURRENT CIGARETTE SMOKERS

6. ABOUT HOW MANY CIGARETTES A DAY DO YOU SMOKE?

_____ (Number) ☐☐ 21-22

7. ARE THESE:

MANUFACTURED CIGARETTES? ☐ 1

'ROLL YOUR OWN' CIGARETTES? ☐ 2 ☐ 23

SMOKERS, PLEASE SKIP QUESTIONS 8,9 AND 10 AND PROCEED TO QUESTION 11

QUESTIONNAIRE

PARTICIPANT ID _ _ _ _ _ _ _ _ _ _

PLEASE DO NOT WRITE HERE

ONLY FOR PEOPLE NOT NOW CIGARETTE SMOKERS

8. IF YOU ARE NOT A CIGARETTE SMOKER NOW, DID YOU EVER SMOKE 5 OR MORE CIGARETTES A DAY?

YES ☐ 1 NO ☐ 2 — 24

9. DO YOU NOW SMOKE A PIPE?

YES ☐ 1 NO ☐ 2 — 25

10. DO YOU NOW SMOKE CIGARS OR CIGARILLOS?

YES ☐ 1 NO ☐ 2 — 26

FOR EVERYONE

11. HAVE YOU EVER BEEN TOLD BY A DOCTOR (OR HEALTH WORKER) THAT YOU HAVE HIGH BLOOD PRESSURE?

YES ☐ 1 NO ☐ 2 — 27

12. ARE YOU NOW TAKING ANY MEDICATION FOR HIGH BLOOD PRESSURE?

YES ☐ 1 NO ☐ 2 — 28

IF YOU ARE TAKING SUCH MEDICINE, WRITE THE NAME (OR NAMES)

_____

_____

_____

QUESTIONNAIRE

PARTICIPANT ID ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

13. PLEASE WRITE THE NAMES OF ANY OTHER MEDICINES YOU ARE NOW TAKING

_____

_____

(IF YOU ARE TAKING ANY MEDICINES NOW BUT YOU DON'T REMEMBER THEIR NAMES, PLEASE SHOW US THE MEDICINES THE NEXT TIME WE SEE YOU)

14. AS FAR AS YOU KNOW, DOES YOUR MOTHER, FATHER OR ANY SISTERS OR BROTHERS NOW HAVE HIGH BLOOD PRESSURE, OR DID THEY HAVE HIGH BLOOD PRESSURE IN THE PAST?

YES ☐ 1 NO ☐ 2 ☐ 29

IF YES, PLEASE LIST WHICH FAMILY MEMBERS WERE AFFECTED

_____

_____ ☐ 30

15. HAVE YOU EVER BEEN TOLD BY A DOCTOR THAT YOU HAVE HAD A HEART ATTACK?

YES ☐ 1 NO ☐ 2 ☐ 31

16. HAVE YOU EVER BEEN TOLD BY A DOCTOR THAT YOU HAVE HAD A STROKE?

YES ☐ 1 NO ☐ 2 ☐ 32

17. OVER THE LAST TWELVE MONTHS, HAS YOUR WEIGHT GENERALLY BEEN:

THE SAME? ☐ 1 INCREASING? ☐ 2

FALLING? ☐ 3 ☐ 33

QUESTIONNAIRE

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

ONLY FOR THOSE OVER 25 YEARS OLD

18A. DO YOU WEIGH MORE NOW THAN YOU DID WHEN YOU WERE 25?

YES ☐ 1 NO ☐ 2 DON'T KNOW ☐ 3 → ☐ 34

18B. ABOUT HOW MUCH DID YOU WEIGH WHEN YOU WERE 25? _____ → ☐☐☐ 35-37

IS THIS IN: KILOS ☐ 1 POUNDS ☐ 2 STONES & POUNDS ☐ 3 → ☐ 38

FOR EVERYONE

THE NEXT FEW QUESTIONS ARE ABOUT WHAT YOU USUALLY EAT, AND ANY CHANGES YOU MAY HAVE MADE.

19. HAVE YOU CHANGED HOW MUCH YOU USUALLY EAT?

NO ☐ 2 YES, I EAT MORE ☐ 3

YES, I EAT LESS ☐ 4 → ☐ 39

IF "YES", ABOUT HOW LONG AGO DID YOU MAKE THIS CHANGE? _____ → ☐☐ 40 41

20. HAVE YOU CHANGED THE AMOUNT OF SALT IN YOUR FOOD?

NO ☐ 2 YES, I EAT MORE SALT ☐ 3

YES, I EAT LESS SALT ☐ 4 → ☐ 42

IF "YES", ABOUT HOW LONG AGO DID YOU MAKE THIS CHANGE? _____ → ☐☐ 43 44

QUESTIONNAIRE

PAGE 6 - FORM Q.

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

21. DID YOU MAKE SOME OTHER CHANGES IN YOUR DIET?

YES ☐ 1 NO ☐ 2 ☐ 45

IF YES, PLEASE LIST CHANGES HERE

_____

_____

_____ ☐☐ 46 47

22. IF YOU HAVE MADE CHANGES IN YOUR DIET, WERE ANY OF THESE MADE ON THE RECOMMENDATION OF A DOCTOR (OR HEALTH WORKER)?

YES ☐ 1 NO ☐ 2 NO CHANGES MADE ☐ 3 ☐ 48

QUESTIONNAIRE

PLEASE DO NOT WRITE HERE

PARTICIPANT ID _ _ _ _ _ _ _ _

FOR EVERYONE

23. IN THE LAST FEW YEARS, HAVE YOU MADE ANY CHANGES IN THE AMOUNT OF ALCOHOL YOU USUALLY DRINK?

NO ☐ 2 YES, I DRINK MORE ALCOHOL ☐ 3

YES, I DRINK LESS ALCOHOL ☐ 4

24. THIS PAST WEEKEND, HOW MUCH ALCOHOL DID YOU DRINK?

	TYPE (BEER, WINE, WHISKY, ETC)	HOW MUCH?
FRI.		
SAT.		
SUN.		

☐☐☐☐☐☐☐ 1-7

0 ☐ 8-9

☐ 10

☐☐☐☐☐☐ 11-16

☐☐☐☐☐☐ 17-22

☐☐☐☐☐☐ 23-28

☐☐☐☐☐☐ 29-34

☐☐☐☐☐☐ 35-40

☐☐☐☐☐☐ 41-46

☐☐☐☐☐☐ 47-52

☐☐☐☐☐☐ 53-58

☐☐☐☐☐☐ 59-64

QUESTIONNAIRE

PAGE 8 – FORM Q.
PLEASE DO NOT WRITE HERE

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

25. FOR WEEKDAYS THIS PAST WEEK, HOW MUCH ALCOHOL DID YOU DRINK?

	TYPE (BEER, WINE, WHISKY, ETC)	HOW MUCH?
MON.		
TUES.		
WED.		
THUR.		

1–7

8–9 0 5

10–15

16–21

22–27

28–33

34–39

40–45

46–51

52–57

58–63

64–69

70–75

76–81

QUESTIONNAIRE

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

26. FOR ALL OF LAST WEEK, WAS THE AMOUNT OF ALCOHOL YOU DRANK

ABOUT AVERAGE FOR A WEEK? ☐ 1

LESS THAN AVERAGE FOR A WEEK? ☐ 2

MORE THAN AVERAGE FOR A WEEK? ☐ 3 — ☐ 82

27. HAVE YOU HAD AN ALCOHOLIC DRINK WITHIN THE LAST TWENTY-FOUR HOURS?

YES ☐ 1 NO ☐ 2 — ☐ 83

THE FOLLOWING QUESTIONS ARE ABOUT YOUR WORK.

28. WHAT IS YOUR USUAL WORK, OR JOB?

_____

29. WHICH OF THE FOLLOWING BEST DESCRIBES YOUR USUAL WORK, OR JOB?
(MARK 'X' IN ONE BOX ONLY)

HOUSEWORK	☐ 01	FARM	☐ 02
OFFICE, CLERICAL	☐ 03	SALES	☐ 04
MANUAL LABOUR	☐ 05	SERVICE WORKER	☐ 06
FOREMAN, SUPERVISOR	☐ 07	SKILLED WORKER	☐ 08
MANAGER, PROPRIETOR PROFESSIONAL	☐ 09	OTHER	☐ 10

☐☐ 84 85

QUESTIONNAIRE

PARTICIPANT ID _ _ _ _ _ _ _ _ _

PLEASE DO NOT WRITE HERE

ONLY FOR MARRIED PEOPLE

30. WHAT IS THE USUAL WORK OR JOB OF YOUR HUSBAND OR WIFE?

_____

31. WHICH OF THE FOLLOWING BEST DESCRIBES YOUR HUSBAND OR WIFE'S USUAL WORK, OR JOB? (MARK 'X' IN ONE BOX ONLY)

HOUSEWORK	☐ 01	FARM	☐ 02
OFFICE, CLERICAL	☐ 03	SALES	☐ 04
MANUAL LABOUR	☐ 05	SERVICE WORKER	☐ 06
FOREMAN, SUPERVISOR	☐ 07	SKILLED WORKER	☐ 08
MANAGER, PROPRIETOR PROFESSIONAL	☐ 09	OTHER	☐ 10

☐☐ 86 87

FOR EVERYONE

32. ARE YOU NOW EMPLOYED?

YES	☐ 1	NO, UNEMPLOYED	☐ 2
NO, RETIRED	☐ 3	NO, OTHER	☐ 4

☐ 88

ONLY FOR PEOPLE NOW EMPLOYED

33. IF YOU ARE NOW EMPLOYED, IS THIS YOUR USUAL WORK, OR JOB?

YES ☐ 1 NO ☐ 2

☐ 89

33B. IF NO, DESCRIBE YOUR PRESENT WORK OR JOB.

_____

QUESTIONNAIRE

PAGE 11 -- FORM Q

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

34. IN REGARD TO YOUR PRESENT WORK, IS IT MOSTLY INDOORS OR OUTDOORS?

INDOORS ☐ 1 OUTDOORS ☐ 2 MIXED ☐ 3 ☐ 90

35. HOW MUCH PHYSICAL ACTIVITY OR HEAVY LABOUR IS INVOLVED IN YOUR PRESENT WORK?

VERY HEAVY, LOTS OF PHYSICAL ACTIVITY ☐ 1 MEDIUM PHYSICAL ACTIVITY ☐ 2

LIGHT OR VERY LITTLE PHYSICAL ACTIVITY ☐ 3 ☐ 91

FOR EVERYONE

36. IN YOUR LEISURE TIME, HOW MUCH PHYSICAL ACTIVITY ARE YOU ENGAGED IN?

A LOT ☐ 1 MODERATE ☐ 2 LITTLE OR NONE ☐ 3 ☐ 92

37. WHAT TYPE OF SCHOOL (OR COURSE OF EDUCATION) DID YOU LAST ATTEND?

NO SCHOOL ATTENDED ☐ 1 ELEMENTARY SCHOOL ☐ 2

SECONDARY OR HIGH SCHOOL ☐ 3 HIGHER EDUCATION ☐ 4 ☐ 93

38. ABOUT HOW MANY YEARS OF SCHOOLING OR FORMAL EDUCATION HAVE YOU COMPLETED? _____ ☐☐ 94-95

FOR MEN: THIS ENDS THE QUESTIONS. THANK YOU

FOR WOMEN: PLEASE TURN TO THE NEXT PAGE.

QUESTIONNAIRE

ONLY FOR WOMEN
PLEASE ANSWER THE REMAINING QUESTIONS.

PLEASE DO NOT WRITE HERE

PARTICIPANT ID __ __ __ __ __ __ __ __ 1-7

0 6 8-9

39. HOW MANY CHILDREN WERE BORN TO YOU?
(INCLUDE BOTH LIVE BIRTHS AND ANY FULL TERM STILLBIRTHS) _____ (NUMBER) 10-11

40. ARE YOU NOW TAKING ANY BIRTH CONTROL PILLS?

YES ☐ 1 NO ☐ 2 12

40A. IF NO, HAVE YOU TAKEN ANY BIRTH CONTROL PILLS WITHIN THE LAST YEAR?

YES ☐ 1 NO ☐ 2 13

41. ARE YOU NOW PREGNANT?

YES ☐ 1 NO ☐ 2 14

42. ARE YOU MENSTRUATING (HAVING A PERIOD) TODAY?

YES ☐ 1 NO ☐ 2 15

43. ARE YOU:

BEFORE THE MENOPAUSE (CHANGE OF LIFE)? ☐ 1

NOW IN THE MENOPAUSE? ☐ 2

PAST THE MENOPAUSE? ☐ 3 16

THIS ENDS THE QUESTIONS. THANK YOU.

CHECKLIST

CHECKLIST

FORM C.

PLEASE DO NOT WRITE HERE

STUDY CENTRE _____ (Name)

PARTICIPANT ID __ __ __ __ __ __ __ 1-7

0 7 8-9

STAFF NUMBER OF QUESTIONNAIRE INTERVIEWER __ __ 10-11

1. HAS APPOINTMENT BEEN MADE TO COLLECT FINAL URINE SPECIMEN AND END 24-HOUR COLLECTION AT THE CLINIC?

YES ☐ 1 NO ☐ 2 _____ Reason 12

2. ETHNIC GROUP PARTICIPANT:

WHITE ☐ 1 BLACK ☐ 2

AMERINDIAN ☐ 3 ASIAN-INDIAN ☐ 4

CHINESE/JAPANESE/KOREAN ☐ 5

OTHER ☐ 6 _____ (Describe) 13

THE QUESTIONNAIRE

3. HOW WAS QUESTIONNAIRE COMPLETED?

PARTICIPANT COMPLETED, INTERVIEWER REVIEWED ☐ 1

PARTICIPANT FILLED OUT PART, INTERVIEWER HELPED COMPLETE ☐ 2

INTERVIEWER ASKED ALL OR MOST QUESTIONS ☐ 3 14

4. REFER TO QUESTIONS 12 and 13 OF QUESTIONNAIRE. IS THE PARTICIPANT TAKING:

A. POTASSIUM SPARING DIURETIC? YES ☐ 1 NO ☐ 2 ☐ 15

B. OTHER DIURETIC? YES ☐ 1 NO ☐ 2 ☐ 16

C. POTASSIUM SUPPLEMENT? YES ☐ 1 NO ☐ 2 ☐ 17

(Continued on next page)

CHECKLIST

PLEASE DO NOT WRITE HERE

PARTICIPANT ID __ __ __ __ __ __ __

4. D. OTHER ANTIHYPERTENSIVE? YES ☐ 1 NO ☐ 2 ☐ 18

Specify _____

_____

(See MANUAL OF OPERATIONS, Appendix)

5. REFER TO QUESTION 13 OF QUESTIONNAIRE. IS THE PARTICIPANT TAKING:

A. OESTROGENS, OTHER THAN THE 'PILL'? YES ☐ 1 NO ☐ 2 ☐ 19

B. SYSTEMIC STEROID PREPARATION? YES ☐ 1 NO ☐ 2 ☐ 20

C. OTHER MEDICATION AFFECTING BLOOD PRESSURE? YES ☐ 1 NO ☐ 2 ☐ 21

Specify _____

_____

D. ANY OTHER MEDICATION? YES ☐ 1 NO ☐ 2 ☐ 22

Specify _____

_____

(See MANUAL OF OPERATIONS, Appendix)

6. SOCIAL SCALE OF PARTICIPANT:

(LOWEST = 1; HIGHEST = 4) ☐ ☐ 23

URINE COLLECTION INFORMATION

FORM U.

24 HOUR URINE COLLECTION

PLEASE DO NOT WRITE HERE

STUDY CENTRE _____ (Name)

PARTICIPANT ID __ __ __ __ __ __ __ 1-7

0 8 8-9

APPOINTMENT: FIRST ☐ 1 REPEAT ☐ 2 10

1. END OF 24-HOUR COLLECTION

A. DAY OF WEEK: MON ☐ 1 TUES ☐ 2 WED ☐ 3

THURS ☐ 4 FRI ☐ 5 SAT ☐ 6 SUN ☐ 7 11

B. TIME OF DAY (Right After Voiding Final Sample)

(24-HOUR CLOCK) __ __ : __ __ 12-15
Hours Minutes

C. WAS THE COLLECTION COMPLETED AT THE CLINIC?

YES ☐ 1 NO ☐ 2 16

EXPLAIN _____

2. COMPLETENESS

ASK THE PARTICIPANT THE FOLLOWING QUESTIONS AFTER COMPLETION OF THE URINE COLLECTION

A. "DURING THE 24-HOUR PERIOD, DID YOU ALWAYS VOID INTO ONE OF THE URINE COLLECTION JARS?"

YES ☐ 1 NO ☐ 2 17

B. "WERE ALL JARS CONTAINING URINE RETURNED?"

YES ☐ 1 NO ☐ 2 18

IF NO, EVERY EFFORT SHOULD BE MADE TO RETRIEVE MISSING URINE

(CONTINUED ON NEXT PAGE)

URINE COLLECTION INFORMATION

PAGE 2 - FORM U.

APPOINTMENT FIRST ☐ REPEAT ☐

PARTICIPANT ID ___ ___ ___ ___ ___ ___ ___

PLEASE DO NOT WRITE HERE

2. COMPLETENESS (CONTINUED)

C. "IS ANY URINE MISSING FROM THE COLLECTION FOR ANY OTHER REASON - FOR EXAMPLE, FROM SPILLING?"

YES ☐ 1 NO ☐ 2 ☐ 19

IF YES TO 2C, ASK QUESTION 2D;

D. WAS THE AMOUNT OF URINE LOST

ONLY A FEW DROPS? ☐ 1

MORE THAN JUST A FEW DROPS? ☐ 2 ☐ 20

3. FOR WOMEN:

ASK THE FOLLOWING QUESTION:

"WERE YOU MENSTRUATING, THAT IS, HAVING A PERIOD, AT ANY TIME IN THE LAST 24 HOURS?"

YES ☐ 1 NO ☐ 2 ☐ 21

THIS ENDS THIS CLINIC VISIT.

**REMEMBER TO SCHEDULE APPOINTMENT FOR REPEAT BP AND 24-HOUR URINE IF THIS PARTICIPANT HAS DUMMY ID

STAFF PERSON SUPERVISING END OF 24-HOUR COLLECTION

___ ___ ☐☐ 22-23

(CONTINUE ON TO PAGE 3)

URINE COLLECTION INFORMATION

PAGE 3 - FORM U.

APPOINTMENT: FIRST ☐ REPEAT ☐

PARTICIPANT ID __ __ __ __ __ __ __

PLEASE DO NOT WRITE HERE

AFFIX 'FORM' LABEL HERE

☐☐☐☐☐☐☐ 24-30

IF SPLIT SAMPLE ID IS ASSIGNED AFFIX SPLIT SAMPLE FORM LABEL HERE

☐☐☐☐☐☐☐ 31-37

24-HOUR URINE COLLECTION: HEIGHT IN EACH JAR

MEASURE HEIGHT IN cms TO THE NEAREST 0.1 cm USING SCALE ATTACHED TO THE MEASURING PLATFORM. ENTER RESULTS BELOW. PUT A DASH IF A JAR WAS NOT USED. THERE IS ROOM FOR A POSSIBLE 6 JARS. NOTE EACH LINE ON THE SCALE REPRESENTS 0.1 c.m.

JAR 1 __ __.__ (cms) ☐☐☐ 38-40

JAR 2 __ __.__ (cms) ☐☐☐ 41-43

JAR 3 __ __.__ (cms) ☐☐☐ 44-46

JAR 4 __ __.__ (cms) ☐☐☐ 47-49

JAR 5 __ __.__ (cms) ☐☐☐ 50-52

JAR 6 __ __.__ (cms) ☐☐☐ 53-55

STAFF NUMBER OF PERSON MEASURING URINE HEIGHT __ __ ☐☐ 56-57

Participant Instruction Forms

PREPARING PARTICIPANT FOR VISIT

FROM:

CLINIC ADDRESS:

TELEPHONE:

ATTENDING THE CLINIC APPOINTMENT

Thank you for taking part in this study on blood pressure. An appointment has been made for you to attend the clinical centre (address and telephone number above) at _____ am / pm on _____.

For at least one-half hour before your appointment, please avoid strenuous exercise, and refrain from eating or drinking anything other than water, or smoking.

Blood pressure, height, and weight will be measured, and you will be asked to answer a questionnaire. You will also be asked while at the clinic to start a collection of urine. This will be completed 24 hours later. You will be asked to return to the clinic to complete the urine collection at the same time the day following your first clinic appointment.

If for any reason you find that you are unable to attend your clinic appointment, or the return visit 24 hours later, please let us know in advance so that substitute clinic and return appointments can be made.

Thank you once again for your cooperation.

FORM I

INSTRUCTIONS FOR 24-HOUR URINE COLLECTION

1 You will be asked to collect all urine passed during one day (24 hours).
You will be given urine collection jars, and a carrier. You may also receive a funnel.
The jars have screw-top lids to avoid spillage.
You will already have been asked to pass a sample of urine.
This was the start of the 24-hour collection.
COLLECTION STARTED ON: _____ _____
(Day) (Date)
AT: _____ (am / pm)

2 COLLECT ALL (EVERY DROP!) OF YOUR URINE for the complete 24 hours. If you feel the need to have a bowel movement, first try and pass urine into one of the collection jars so that no urine is lost during the bowel movement.

3 If you have been given a funnel, always use it to avoid spillage or loss of urine.

4 Always hold the jar while urinating, to avoid tipping.

5 Once the jar is two-thirds full, start a new jar to avoid running over.

6 Do not add anything but urine to the jar, and do not rinse it.

7 BEFORE LEAVING THE CLINIC make sure you have an appointment to return to the clinic AT ABOUT THE SAME TIME TOMORROW to complete the 24-hour collection.

8 BRING WITH YOU all collection jars, the funnel (if given), the carrier, and this form when you return to the clinic tomorrow.

OUR NEXT APPOINTMENT WITH YOU IS TOMORROW:
at _____ (time)

BE SURE TO USE THE JARS TO COLLECT ALL URINE VOIDED UNTIL WE SEE YOU AGAIN.
THANK YOU FOR YOUR COOPERATION!

PREPARING PARTICIPANT FOR

REPEAT VISIT

FROM:

CLINIC ADDRESS:

TELEPHONE:

ATTENDING THE REPEAT CLINIC APPOINTMENT

Thank you for taking part in this study on blood pressure. An appointment has been made for you to attend the clinical centre (address and telephone number above) at _____ am / pm on _____.

For at least one-half hour before your appointment, please avoid strenuous exercise, and refrain from eating or drinking anything other than water, or smoking.

Blood pressure will be measured again. You will also be asked while at the clinic to start another collection of urine. This will be completed 24 hours later. You will be asked to return to the clinic to complete the urine collection at the same time the day following you first clinic appointment.

If for any reason you find that you are unable to attend your clinic appointment, or the return visit 24 hours later, please let us know in advance so that substitute clinic and return appointments can be made.

Thank you once again for your cooperation.

CERTIFICATION OF STAFF MEMBER

The following individual has been trained in INTERSALT procedures and is able to carry them out in the standardized way defined in the INTERSALT Manual of Operations:

CENTRE _____

NAME OF STAFF MEMBER _____

Procedures which staff member is certified to perform:
(check any that apply)

Blood pressure observer _____
Height, weight _____
Questionnaire interviewer _____
Laboratory _____
Editing forms _____
Recruiting _____
Reception _____
Other: Describe _____
_____
_____

Staff Number ___ ___
(To be assigned by London)

_____
Signature: Local Investigator

Date: _____

RECRUITING RECORD

(For Centres with List of Known Names)

PART I.

Name of Person Randomly Selected	Sex	Age	Not Age Eligible	Contact Results			
				Unable to Contact 1st Time	Unable to Contact 2nd Time	Contacted	
						Agreed	Refused

RECRUITING RECORD

(For Centres Without List of Known Names)

Part 1

Household Identification (Address, etc.)	Spoke with Occupant		No One Age Eligible	Age Eligibles Invited - Results				
	Yes	No		Name	Age	Sex	Refused	Agreed

RECRUITING RECORD

SUMMARY OF RECRUITING, BY AGE-SEX STRATA

PART II. Number with Appointments

Date	Men: Age 20-29	30-39	40-49	50-59	Women: Age 20-29	30-39	40-49	50-59

LOG BOOK STUDY CENTER LONDON

MEN AGE 20-29

PARTICIPANT ID		NAME	FOR THOSE WITH SPLIT SAMPLE REPEAT VISIT
			SPLIT SAMPLE ID / ATTENDED? (YES OR NO)
Number	Initials		
66001			
XXXXX (NUMBER USED FOR SPLIT SAMPLE)		XXXXX	XXXXX
66003			
66004			
66005			66014 SR
66006			
66007			
66008			
XXXXX (NUMBER USED FOR SPLIT SAMPLE)		XXXXX	XXXXX
66010			
66011			
66012			
66013			
XXXXX (NUMBER USED FOR SPLIT SAMPLE)		XXXXX	XXXXX
66015			
66016			66002 IS
66017			
66018			

PAGE 1 OF 2

LOG BOOK STUDY CENTER LONDON

MEN AGE 20-29

PARTICIPANT ID		NAME	FOR THOSE WITH SPLIT SAMPLE REPEAT VISIT ATTENDED? (YES OR NO)
Number	Initials		SPLIT SAMPLE ID
66019			
66020			
66021			
66022			
66023			
66024			
66025			66009 LP
66026			
66027			
66028			

SUPPLEMENTARY

66029			
66030			
66031			
66032			

URINE COLLECTION REGISTER

_____ Centre Name

NAME	Participant ID	Split Sample ID if assigned	Split done	Spot	# Jars given	Start 24 hr Date	Start 24 hr Time	End 24 hr Date	End 24 hr Time	# Jars returned	# Jars used	Aliquots: Refrig date	Aliquots: Freeze date	Aliquots: Ship date

FORM R

REPEAT VISIT REMINDER

1. This participant (ID Code ___ ___ ___ ___ ___ ___ ___ ___) should be invited for a repeat visit 1 to 3 weeks after the first visit.

2. Explain that 1 out of 8 participants is being asked to return to see how much people vary over time on those things we have measured.

3. When making the appointment, be sure it is on a day when the participant can begin the 24-hour urine collection and return the following day for its completion.

4. Remember that for those attending REPEAT VISITS, all will have blinded split urine aliquots, identified by his or her split sample ID code.

SHIPPING FORM

THIS FORM IS TO BE SENT TOGETHER WITH SPECIMENS LISTED BELOW, TO CENTRAL LABORATORY. BE SURE SHIPPING CARTONS ARE CORRECTLY ADDRESSED, AND MARKED PROPERLY FOR PRESERVATION.

A COPY OF THIS FORM IS TO BE MAILED TO LONDON AND A COPY KEPT IN THE LOCAL CLINIC.

LIST ID CODES IN NUMERICAL ORDER

DO NOT INDICATE WHICH ARE SPLIT SAMPLE IDs

ID CODE	NUMBER OF TUBES	ID CODE	NUMBER OF TUBES	ID CODE	NUMBER OF TUBES

Appendix 3: Description of Study Centres

Study centre: **Argentina**, Buenos Aires

Principal Investigators: E, Balossi, J Hauger-Klevene

Study dates: 18.11.85 - 17.2.86

Study population and sampling:

The population was staff of the National Institute of Agricultural Research (INTA), located 26 kms. from Buenos Aires. The staff work on major agricultural research. Offices are located throughout the country, but the study was done in the Castelor Centre where there are 612 employees aged between 20-59 years.

A complete list of names, age and sex was available and random sampling was done. People were contacted at work by telephone and asked to participate.

Social scale:

1 =) Based on education and income,
2 =) e.g., no or incomplete education and
3 =) unemployed is social scale 1, and higher
4 =) or university education with large income
) is social scale 4.

Education:

State schools:
Primary school from 6-12 years
Secondary school 13-18 years
University 18-25 years

There are also private schools organised by religious groups, community groups and non-profit organisations. These can teach subjects other than those indicated by the State.

Study centre: **Belgium**, Charleroi

Principal Investigator: M Kornitzer

Study dates: 10.12.85 - 13.1.87

Study population and sampling:

Charleroi is a city located in the south, and part of the French speaking community. On 1.1.1983 the population was 216,144 people.

A random sample was selected from the MONICA Study register dated January 1984 (ages 25-59) and a random sample of the population of Charleroi added for those aged 20-24.

A home visit and three telephone calls were made before the contact was considered as a refusal.

Social scale: Based on level of education:

1 = No school
2 = Primary
3 = Secondary
4 = Higher

Education:

Elementary school, age 6-12 years
Secondary inferior, age 12-15 years
Secondary superior, age 15-18 years
Secondary professional, age 15-19 years
Secondary technical, age 15-19 years
University, age 18-25 years
Technical superior, age 18 to 22 or 23 years

Study centre: **Belgium**, Ghent

Principal Investigator: G de Backer

Study dates: 4.11.85 - 22.5.86

Study population and sampling:

A sex/age stratified random sample was selected from the population register of the city of Ghent which is in the north, and is part of the Dutch speaking community. Except for those aged 20-24, all participants were also eligible for the MONICA study.

Sampling was undertaken centrally for the Ghent and Charleroi Centres at Brussels University. Eligible subjects were informed by letter requesting a home visit (at least 3 attempts were made to establish contact).

Social scale: Based on level of education:

1 = No school
2 = Primary
3 = Secondary
4 = Higher

Education:

Elementary school, age 6-12 years
Secondary inferior, age 12-15 years
Secondary superior, age 15-18 years
Secondary professional, age 15-19 years
Secondary technical, age 15-19 years
University, age 18-25 years
Technical superior, age 18 to 22 or 23 years

Study centre: **Brazil**, Yanomamo Indians

Principal Investigator: **J J Mancilha Carvalho**

Study dates: 3.6.86 - 8.7.86

Study population and sampling:

Yanomamo Indians, Amazon Jungle: Approximately 18,000 individuals occupy a region of 100,000 square miles located between Brazil and Venezuala. Four villages were chosen for study, in the Surucucu Plateau area. Sampling was of all adults identified by house-to-house survey. The Yanomami live under primitive conditions, with banana as the main staple, no access to alcohol and a salt-free diet. The diet is supplemented by game, fish, insects, sugar cane, roots and wild vegetable foods. Access is from the Funai Health Station, 30-40 kilometres or 5-10 hours walking distance through the jungle. A Funai interpreter was used by the Portuguese speaking investigators. Adults use 'penene' (leaves of tobacco and ashes).

Social scale:

1 = All women
2 = All other men (not 3 or 4)
3 = The Xamens (Xabores)
4 = The Chiefs (Tuxquas)

Education: Not applicable

Study centre: **Brazil**, Xingu Indians

Principal Investigator: R G Baruzzi

Study dates: 17.7.85 - 5.5.86

Study population and sampling:

Native tribes of the Parque Indigena do Xingu (PIX) in Central Brazil, 1600 km from Sao Paulo, were studied; access to the region is only by air. There is a complete medical file on every Indian - including age, sex and village.

Random sampling was done, stratified by age, sex, and Indian group to get proportional representation of the 3 Indian groups: Upper Xingu, Je Indians and "other" Indians.

Social scale:

1 =) Based on degree of leadership
2 =) within the tribe.
3 =) Not concisely defined.
4 =)

Education: Not applicable

Study centre: **Canada**, Labrador

Principal Investigator: **M Baikie**

Study dates: 22.4.85 - 21.5 85

Study population and sampling:

Three villages were chosen in Labrador, Newfoundland, Canada's most easterly province.

Nain is an isolated community with an air strip and a good telephone service. Total population is 938, predominantly Innuit. Major employment is fishery. In summer, 300 people go north to the fishing grounds. In winter, there is dependence on insurance, welfare, and government projects. Fresh food is in short supply in winter. Half of calorie intake is 'native food', i.e., fish, caribou, partridge, berries.

Northwest River The population is 515 (35% under 20), mainly white settlers speaking English only. There is limited local employment: hunting, trapping, fishing. The majority of the workforce travels to Goose Bay daily to government related jobs. Alcohol abuse is a problem.

Sheshashit The population is 550, almost exclusively Innuit. Housing is in poor repair. There is no running water or sewage facilities. Many are fluent in English. The standard of living is one of the lowest in the area. Alcohol abuse is a problem.

Names of all men and women aged 20-59 were extracted from the census list and sent to the University of Newfoundland for random sampling. Recruitment was by a public health aide, fluent in English and Innutituk, undertaken partly by telephone and partly by 'skidoo' visiting subjects at home.

Canada, Labrador, cont.

Social scale:

1 = Unskilled, unemployed, low income, poor housing

2 = Partly skilled, occasional manual, seasonally employed or traditional employment, low income, adequate housing

3 = Skilled manual, involved with and well regarded in the community, good income and housing

4 = Professional, skilled, community leader or elder, good income and housing

Education:

Grades 1-9
Grades 9-13 with or without secondary certificate
Trade schools/vocational centres do not require secondary school graduation.

Nain 55% of those over age 15 years have less than grade 9 education, but there are 30 people with university degrees and 15 with a university education but no degree.

Northwest River Aged over 15 years, 28% have less than grade 9. 29% have some secondary and 16% some university education.

Sheshashit Most have not completed secondary school.

Study centre: **Canada**, St Johns

Principal Investigators: J Martin, G Fodor

Study dates: 16.4.85 - 21.6.86

Study population and sampling:

Inhabitants of 3 coastal fishing villages with harbours on the west coast of Newfoundland. The climate is subarctic with the sea frozen from January to May. Random sampling was done using a census based on a household census drawn up 10 years earlier for a different study. It was updated by age and reference to the electoral polling list of 1983. A letter about the study was posted to each householder and also put up in the local community centre. Two attempts were made to contact potential participants before considering them as refusals. There are only a few surnames in this region - hence a number of participants had the same first and surname (but had different ages).

Social scale:

1 = Seasonally employed
2 = Permanently employed
3 = Skilled
4 = Professional

Education:

Education became compulsory in 1949 when Newfoundland joined Canada. Until 1969 every religious denomination had its own school system, but now only 3 remain (Roman Catholic, Pentecostal and non-religious integreated). Each "grade" is one academic year.

Kindergarten
Elementary school grades 1-7
High school grades 8-11
Grade 12 was added in 1984
University, or college of trades and technology

Study centre: **Columbia**, Tuquerres

Principal Investigator: G Montes

Study dates: 9.7.86 - 5.12.86

Study population and sampling:

Participants were randomly selected from the population of the small town of Tuquerres (30,000 people). The urban zone with 13,000 inhabitants and rural zone with 17,000 were both included in the study. It is in the Andes mountains 3,051 metres above sea level, and therefore cold. There is no large industry - most of the people are involved in agriculture or small family craft workshops. Most inhabitants are mixed race ("mestizo") and indigenous ethnic groups with few white people. Approximately 70% are graded 1 in the social scale below.

Social scale:

1 = Occasional jobs - small plot owners
2 = Field work, crafts traders
3 = Farmers, store owners, transport workers
4 = Professionals, large landowners with cattle

Education:

Elementary school for 5 years
Secondary school for 6 years
University for 5 years

Study centre: **Denmark**, Glostrup

Principal Investigators: K Klarlund, M Schroll

Study dates: 11.3.85 - 14.5.85

Study population and sampling:

Random sampling was done from the Central Registry of all inhabitants of the town of Glostrup aged 20-59 years old. Non-responders were contacted twice and some three times.

Social scale:

1 = Unskilled workers
2 = Semi-skilled workers, smallholders
3 = Skilled workers, farmers, employees with degrees (non-professional), subordinates
4 = Professionals, landed proprietors

Education:

Primary education for less than 7 years
Secondary education for less than 7 years
University or Institute of Dentistry/Engineering etc.

Education is interwoven with work and training in Denmark. Apprenticies in the winter attend school for 3-4 hours each afternoon. Many young skilled workers attend one year of school at the start of apprenticeships.

Study centre: **Finland**, Joensuu

Principal Investigators: P Pietinen

Study dates: 6.11.85 - 22.1.86

Study population and sampling:

A stratified random sample was selected from the 'population' register of the Health Centre in Joensuu, a town in North Karelia.

Social scale:

1 = Unskilled
2 = Semi-skilled
3 = Skilled
4 = Professional

Education:

Pre-school care for 5 and 6 year olds
Primary school from age 7
Lower secondary for 3 years
Upper secondary for 3 years
University or higher education, 4-6 years
Vocational or in-service training after secondary school

Study centre: **Finland**, Turku

Principal Investigator: O Impivaara

Study dates: 3.9.85 - 13.11.85

Study population and sampling:

A stratified random sample was drawn from the population register of Turku City (situated on the SW coast of Finland). Subjects were contacted by letter and extra participants recruited to allow for refusals and cancellations. Main areas of employment are in industry, public services, commerce, transport and construction. The general educational and economic level are relatively high.

Social scale:

1 = Unskilled
2 = Semi-skilled
3 = Skilled
4 = Professional

Education:

Pre-school care for 5 and 6 year olds
Primary school from age 7
Lower secondary for 3 years
Upper secondary for 3 years
University or higher education, 4-6 years
Vocational or in-service training after secondary school

Study centre: **Germany**, Bernried

Principal Investigator: H Hofmann

Study dates: 9.9.85 - 28.7.86

Study population and sampling:

An urban population was selected in Bernried, Bavaria. The sample was drawn from a municiapl list of all men and women aged 20-59, giving sex, age (decades only) and addresses of each person.

The first attempt to contact individuals was by home visit. Refusals at this stage were contacted by letter from the local Investigator, followed by another visit or telephone call.

The study was publicised in the local press.

Social scale:

1 = Blue collar
2 = White collar
3 = Employed in family shop
4 = Self-employed, professionals

Education:

From ages 3-6, attendance at kindergarten is voluntary
Primary school 6-9 years
Grammar school for 4 years
Common school for 5-6 years, or
"Gymnasium" which usually leads to university.
Usually there is a 3-year apprenticeship
after common school with "part-time" lessons as well.

Study centre: **Germany**, Cottbus (formerly in the G.D.R.)

Principal Investigator: L Heinemann

Study dates: 6.11.85 - 28.1.86

Study population and sampling:

Cottbus is a County Capital town in East Germany, population 120,000; main industries are open-cast mining, engineering, and textiles. In co-operation with the local Registration Office an initial list was drawn up of names and addresses of 700 Cottbus inhabitants, born on certain days of the year. A stratified random sample was then selected from this list.

Subjects were approached by letter (answer letter pre-paid), and two follow-up reminders were sent if necessary.

Social scale: Based on years of education:

1 = 0-10 years
2 = 11-13 years
3 = 14-15 years
4 = 16+ years

Education: The system was introduced in 1965 but was not a major change from the old system:

Creche
Kindergarten from about 4 years
Primary school from 7-9 years
Intermediate from 10-12 years
Secondary from about age 13-16
Vocational training leading to:
Adult education, technical school,
University or college

Study centre: **Germany**, Heidelberg

Principal Investigator: U Laaser

Study dates: 23.9.85 - 27.2.86

Study population and sampling:

A random sample was selected from a list of staff at the Rehabilitation Centre in Heidelberg, and young men (20-29) who were doing their "civil service" in the Centre.

Social scale:

1 = Manual workers
2 = Tradesmen
3 = Office workers
4 = Professionals

Education:

From ages 3-6 attendance at kindergarten is voluntary
Primary school 6-9 years
Grammar school for 4 years
Common school for 5-6 years; or
"Gymnasium" which usually leads to university.
Usually there is a 3-year apprenticeship
after common school with "part-time"
lessons as well.

Study centre: **Hungary**, Porcsalma village

Principal Investigator: J Kishegyi

Study dates: 25.11.85 - 9.1.86

Study population and sampling:

A stratified random sample of the population of Porcsalma village in N.E. Hungary was selected - most are agricultural workers but 60% of them also work part-time in a shoe factory or canning factory; 40% work in an agricultural co-op. A population list by age and sex was compiled by the local council in 1985. Invitations were delivered to participants by the local council messenger. Non-responders were sent a second letter, but generally residents were keen to take part.

Social scale:

1 =) Dependent on 5 factors: occupation
2 =) income, housing circumstances and
3 =) positions held in organisations like
4 =) trade union or youth club.

Education:

Until 1947 elementary schools had 6 grades (now 8 grades). People who did not aim at higher education went through all grades. Those who worked to become clerks and sales personnel went to a 4 grade lower middle school (i.e., higher elementary school) after finishing the 4th grade of elementary school. Children aiming for universiy went to a lower plus upper middle school, 8 grades altogether, taking 12 years until university.

Study centre: **Iceland**, Reykjavik and district

Principal Investigator: J Ragnarsson

Study dates: 12.2.85 - 28.1.86

Study population and sampling:

A random sample for the study was drawn from the MONICA population, which includes the city of Reykjavik and its 5 surrounding towns. Two letters were sent to each person and where there was no response the person was telephoned before registering a refusal. There were problems recruiting the youngest age group (20-29) of both sexes because the MONICA population had tended to move away, often out into the country. Therefore a new additional sample in this age range was selected randomly from the National Register using pre-defined birthdates.

Social scale:

1 = Manual workers without higher training, e.g., drivers/cleaners, invalided workers and the unemployed

2 = Salaried workers - e.g. clerks, waiters, nurses

3 = Workers with higher education, professionals scientists, registered nurses

4 = Managers, doctors, judges, those with an education of 18 years or more

Education:

At age 15, students can choose technical schools, business schools or marine school; there are also 4-year apprenticeships. Some people in the oldest age group could have had only 3 years total formal schooling if they lived in the remote areas.

Elementary school from age 6 to 15 years
High school from age 15 to 19 years
University from age 19 years

Study centre: **India**, Ladakh

Principal Investigator: K S Reddy

Study dates: 14.7.86 - 30.7.86

Study population and sampling:

A stratified random sample was selected from a list of the residents of Stok (population 857), Ladakh, situated on a high altitude plateau 11,600 ft above sea level. The people of Ladakh are mostly Buddhist, linked ethnically and culturally to the people of Tibet but Asian-Indian in terms of geo-political integration into India. The people are mostly farmers (men and women) - there is periodical movement to the mountains with livestock for grazing. Additional work includes bricklaying, civilian labour for army construction projects and a travel camp for tourists. There are few other forms of employment - school teachers, medical/paramedical personnel, revenue clerks etc. (although these people still tend to farm part-time). The Lamas (Buddhist monks) reside in monasteries and lead a life of prayer, worship and religious teaching. They are literate, as they undergo 8-15 years training in Buddhist schools of religion. The staple crops are barley and wheat. Fresh vegetables are not available in winter and fresh meat is scarce. Salted tea, prepared with tea leaves, milk, yak butter and salt is drunk often during the day, up to 30 or more cups per day.

Social scale: Based on yearly income:

1 = Less than RS 6000 per year
2 = RS 7600-12000 per year
3 = RS 12000-18000 per year
4 = More than RS 18000 per year

Education:

The majority of the people have no formal education, being mostly farmers. The Lamas are trained Buddhist monks (and have no formal education in the usual sense but they have between 8-15 years of religious education and are therefore highly literate). However, there is primary, secondary and high school education. There is now a school in Stok for primary and secondary education. High school is only available in Srinagar, the capital city.

Study centre: **India**, New Delhi

Principal Investigator: K S Reddy

Study dates: 10.3.86 - 9.6.86

Study population and sampling:

The population of study was employees of the All India Institute of Medical Sciences (A.I.M.S.) including medical/professional, administrative, engineering (technical) staff and their families, resident on campus. Lists were compiled from the 1984 electoral rolls, housing records and registration records of A.I.M.S. health service. Age/sex stratified groups were randomly selected using random number tables.

Social scale: Based on monthly income:

1 = Less than RS 500 per month
2 = Between RS 500-999 per month
3 = Between RS 1000-1999 per month
4 = More than RS 2000 per month

Education:

There are usually 10 years of education from 5 to 15 years of age, class 1 to class 10, often preceded by 1 or 2 years of nursery pre-school. Then:

Junior college (pre-university) for 2 years
(class 11-12)
University education - 3 years, bachelors course
Professional course (medicine, engineering, etc.)

Study centre: **Italy**, Bassiano

Principal Investigator: G Urbinati

Study dates: 18.2.86 - 23.4.86

Study population and sampling:

Bassiano is a small hill town, 500 metres above sea level, 60 miles south of Rome, with 1535 inhabitants. Main activities are agriculture, stock-raising, and services. Commuters represent a substantial percentage of the male working population. The economic level is lower than the average for Italy.

A stratified random sample was selected from the Bassiano electoral register. Potential participants were invited by letter to a general meeting organised by clinical and municipal staff to explain the study aims and procedures. A letter was sent confirming the invitation to attend the clinic; some contacts were made by telephone.

Social scale: Based on employment and education:

1 = Manual and unemployed - illiterate
2 = Farming/skilled/services - primary school
3 = Sales/office/clerical/craftsmen - secondary high school
4 = Managers/students/professional -university or postgraduate

Education: Elementary school 6-20 years
Junior school 11-13 years
High school 14-18 years
University 19-22 years

Study centre: **Italy**, Gubbio

Principal Investigators: M Laurenzi

Study dates: 10.4.86 - 4.7.86

Study population and sampling:

Stratified random sampling was done from the census list of the population of the historical centre of the town of Gubbio. At least 3 attempts were made to contact individuals before considering them as refusals.

Social scale:

1 =) No detailed information on income,
2 =) therefore based on educational
3 =) achievement and job. For housewives and
4 =) students, social scale of spouse or parents
) was used.

Education:

Elementary school 6-20 years
Junior school 11-13 years
High school 14-18 years
University 19-22 years

Study centre: **Italy**, Mirano

Principal Investigators: C Dal Palu, S Zamboni

Study dates: 1.4.86 - 4.6.86

Study population and sampling:

Stratified random sampling was done among the population of Mirano, a small town in the Veneto region, 30 kilometres from Padua, population approximately 25,183. Sampling was compiled from the cesus list of the Mirano Health District. Letters were sent to general practitioners advising them of the INTERSALT aims and the proposal to recruit patients. Explanatory letters were then sent to individuals inviting them to attend the clinic; some were contacted by telephone.

The Chernobyl nuclear accident affected the diet during the study since the radioactive cloud passed over Italy in early May. Sale of leafy vegetables was stopped. Many people refrained from using fresh milk for the whole period of risk.

Social scale: Based on education:

1 = Illiterate, or primary school only
2 = Secondary school 1st level
3 = Secondary school 2nd level
4 = University

Education: Elementary school 6-20 years
Junior school 11-13 years
High school 14-18 years
University 19-22 years

Study centre: **Italy**, Naples

Principal Investigator: E Farinaro

Study dates: 29.5.85 - 17.10.85

Study population and sampling:

Stratified random sampling was carried out from the list of employees at the Olivetti factory. Since few women are employed at the factory, wives and daughters were also included in the study.

Social scale: Based on employment:

1 = Unemployed
2 = Retired/housewife
3 = Employed
4 = Professional/manager

Education: Elementary school 6-20 years
Junior school 11-13 years
High school 14-18 years
University 19-22 years

Study centre: **Japan**, Osaka

Principal Investigator: H Ueshima

Study dates: 1.4.85 - 23.10.85

Study population and sampling:

Employees of the Daidon Life Insurance Company, Osaka, and their wives were selected by stratified random sampling. Participants live in Osaka City and 'satellite' cities in the Osaka area, and were mainly white office workers and their wives (mostly housewives). Osaka is the second largest city in Japan. Diet is typically middle-class Japanese: older people eat more fish; younger people eat more meat.

Social scale:

This was based on age and work experience, which is indicated by job number. Wives have the same job number as their husbands. The social scale is confounded by age, since jobs become more senior with age.

1 = Lowest class (newcomer to job, job no. 1-2)
2 = Middle class (job no. 3-4)
3 = Upper middle class (job no. 5-6)
4 = Highest class (job no. 7-9, executives)

Education: Primary school at age 6 years (until 12 years old)
Junior high school for 3 years (until 15 years old)
Senior high school for 3 years

University for either 4 years or (mainly for girls) 2 years, or after senior high school students go to a professional school to be trained for jobs in computing, nursing, etc. There are also cramming schools to prepare for university entrance.

Study centre: **Japan, Tochigi**

Principal Investigator: T Hashimoto

Study dates: 26.8.85 - 9.12.85

Study population and sampling:

A stratified random sample was selected of inhabitants of Minamikawachi-machi town and its surrounding communities, in Tochigi prefecture. The list was drawn from people who have national insurance, but some non-insured people in the youngest age range (20-29) were accepted. Tochigi is a rural area; 50% of the participants were farmers.

Social scale: Based on bicycle/car ownership:

1 = No bicycle or car
2 = One bicycle
3 = One car
4 = Two or more cars

Education: Primary school at age 6 years (until 12 years old)
Junior high school for 3 years (until 15 years old)
Senior high school for 3 years

University for either 4 years or (mainly for girls) 2 years, or after senior high school students go to a professional school to be trained for jobs in computing, nursing, etc. There are also cramming schools to prepare for university entrance.

Study centre: **Japan**, Toyama

Principal Investigator: S Kagamimori

Study dates: 21.10.85 - 4.12.85

Study population and sampling:

The study population was all employees of a zip fastener company - YKK. Stratified random sampling was done from a complete list of employees.

Social scale: Based on occupation:

1 = Manual worker
2 = Non-manual
3 = Foreman and supervisor - manual
4 = Manager

Education: Primary school at age 6 years (until 12 years old)
Junior high school for 3 years (until 15 years old)
Senior high school for 3 years

University for either 4 years or (mainly for girls) 2 years, or after senior high school students go to a professional school to be trained for jobs in computing, nursing, etc. There are also cramming schools to prepare for university entrance.

Study centre: **Kenya**, Rambugu and Ndori villages

Principal Investigator: N Poulter

Study dates: 13.1.85 - 14.2.85

Study population and sampling:

The study population was inhabitants of Rambugu village, Western Kenya, which has a population of about 1500 persons, from 320 households. Five men aged (50-59) were also randomly selected from Ndori, a similar village nearby. The study population was exclusively from the Luo tribe. Approximately 90% of adults are engaged in subsistence farming.

Sampling was carried out using a pre-exisitng census list (by individual and household). Households were randomly selected and eligible subjects listed. Subjects were studied at home.

Social scale:

1 = Subsistence farmer
2 = Subsistence farmer & sells produce
3 = Subsistence farmer and urban source of funds
4 = Other

Education:

Begins at age 5. Primary school until the "Kenyan Primary Exam" is passed. Secondary education leads to O and A levels which are (or were) based on the English system. Fees are paid in secondary schools. In practice, children are often in primary school until their late teens although secondary school begins at about age 12 years.

Study centre: **Malta**, Dingli village

Principal Investigators: J M Cacciottolo, A Amato Gauci

Study dates: 3.6.86 - 11.7.86

Study population and sampling:

A stratified random sample was drawn from inhabitants of the village of Dingli, using the latest electoral register (October 1985). People were recruited by a Health Inspector calling at their homes to give an invitation and explain the procedures. Those who failed to attend were contacted by telephone. Those who were working were given a letter for their employers written by the Chief Medical Officer.

Social scale:

1 =) Based on the
2 =) Registrar General's
3 =) classification
4 =) of England and Wales.

Education:

Education has changed radically in Malta over the last 30 years. Malta was a colony until 1964 when a full scale education system began, on U.K. lines, with comprehensive schools, etc. This system has since been adapted several times. Prior to 1964, it was not compulsory to stay at school until age 16. There was a literacy campaign in the 1950s when people were obliged to attend a government scheme "school" for three years to learn reading and writing. It is therefore possible for people such as nurses to have only 3 years education and yet do important skilled jobs. Now, nurses are educated to age 16 and then follow a 3 year training course.

Study centre: **Mexico**, Tarahumara Indians

Principal Investigator: W E Connor

Study dates: 6.6.85 - 25.6.85

Study population and sampling:

The study was conducted among the Tarahumara Indians of Sierra Madre in Chihuahua. The altitude is about 2240 metres above sea level. The recruitment method was to invite participants by radio, through bilingual school teachers and through local authorities to a local meeting place in the main school where the study was explained and participants recruited.

Social scale:

Depends on economic situation of the head of the household together with the education level and and social standing of both husband and wife (includes the ability to read, write, travel and take part in religious ceremonies).

Education:

Kindergarten (not obligatory)
Primary school for 6 years
Secondary school for 2 or 3 years
Several types of high school depending on pupils
Options: preparation for natural sciences,
Correra Tecnica, technical training, etc.
for 3-4 years
University for minimum of 4 years

Study centre: **The Netherlands**, Zutphen

Principal Investigator: D Kromhout

Study dates: 18.3.85 - 8.5.85

Study population and sampling:

Stratified random sampling was carried out among the population of the small commercial town of Zutphen. The sampling list was provided by the Department of Population. Several attempts were made to contact non-responders by letter and telephone.

Social scale: Based on employment:

1 = Manual/unskilled
2 = Lower administrative professions/ skilled manual
3 = Small businessmen/shopkeepers/students
4 = Professionals/managers

Education:

Primary school for 6 years
Lower vocational training 3-4 years, or
Lower level high school for 4 years, leading to vocational training; or
Higher level high school 5 years, leading to high vocational training, or
Grammar school for 6 years, leading to University.

Study centre: **Papua New Guinea**, Asaro Valley

Principal Investigators: P Howard, M Alpers

Study dates: 18.11.85 - 20.2.86

Study population and sampling:

The study population comprised two groups of villages in the Asaro Valley of the Eastern Highlands Province, about 18 miles from Goroka:

> the Kamus group is more traditional and depends on subsistence agriculture. Few women attend school.
>
> the Gimisave group are more acculturated - more women attend school and more "store food" is eaten. There is a primary school in the village.

In June/July 1985 a complete census of the communities was drawn up allocating house numbers and drawing maps. Few adults knew their year of birth, therefore it was estimated (and is probably accurate to within 5 years). Data from the census forms were entered onto computer and two population listings drawn up, stratified by age and sex. Because of the differences in lifestyle and economy of the two communities, the two populations were sampled separately and slightly more weight was given to the more traditional community (Kamus).

Social scale:

1 = Immigrants, subsistence farmer, unskilled workers, income less than K500

2 = Subsistence farmer with income K500-K1000/ salaried workers/average villager with low income from small coffee holdings

3 = Younger average villager with primary education or a salaried job or with a bigger coffee holding

4 = Owners of extensive coffee estates/ other business interests/ professionally qualified people

Education: Some schooling was available in the village

Study centre: **People's Republic of China**, Beijing

Principal Investigator: H Da Xien

Study dates: 13.3.86 - 5.5.86

Study population and sampling:

A list of all 2,000 people living in and around the military hospital quarters in Beijing was drawn up. A stratified random sample was then drawn.

Social scale:

1 =) Classified according to education,
2 =) salary and living conditions.
3 =)
4 =)

Education:

Elementary school for 6 years
Middle school for 3 years
High school for 3 years
Higher education for 5 years

Technical school after middle school for 3 years. Graduate program after university for 3 years for Masters degree.

Study centre: **People's Republic of China**, Nanning

Principal Investigator: Z Long

Study dates: 17.4.86 - 12.5.86

Study population and sampling:

Participants were residents/staff of Guangxi Medical College. A list of names, sex, and ages (20-59 years) was obtained from the security section of the college and a stratified random sample was drawn.

Social scale:

1 = Manual worker, farmer
2 = Skilled worker
3 = Nurse, technician, teching assistant
4 = Teacher, doctor, official

Education:

Elementary school for 6 years
Middle school for 3 years
High school for 3 years
Higher education for 5 years

Technical school after middle school for 3 years. Graduate program after university for 3 years for Masters degree.

Study centre: **People's Republic of China**, Tianjin

Principal Investigator: L Liu

Study dates: 20.3.86 - 4.4.86

Study population and sampling:

The study was done in Zhao Ku Li village, east of Tianjin. The population includes both peasants working in agriculture and people in industry, mostly working 7 days a week. A complete list of names with age/sex was available and a random sample selected.

Social scale:

1 =) Based on work type, education
2 =) and living conditions.
3 =)
4 =)

Education:

Elementary school for 6 years
Middle school for 3 years
High school for 3 years
Higher education for 5 years

Technical school after middle school for 3 years. Graduate program after university for 3 years for Masters degree.

Study centre: **Poland**, Krakow

Principal Investigator: J Sznajd

Study dates: 15.4.86 - 12.6.86

Study population and sampling:

The study population was the 2500 employees of the POLKABEL cable factory in Krakow. A stratified random sample was taken from the list of employees. The factory officer was responsible for scheduling the clinic appointment times.

Social scale:

1 = Unskilled
2 = Skilled, farmers, craftsmen
3 = Clerical, administration
4 = Executives, professionals, managers

Education: The education system was ill-defined between 1939-45

Before 1939
Elementary school 7 years
Gymnasium 8 years
University 4-6 years

After 1945
Elementary school 7 years (8 years after 1960)
Secondary school (4 years)
Engineering school (5 years) or
Technical schools (3 years)
College (2 years), for those not going to university
University 4-6 years

Study centre: **Poland**, Warsaw

Principal Investigator: S L Rywik

Study dates: 16.4.86 - 11.6.86

Study population and sampling:

This was a study of the general population of Warsaw, based on the MONICA survey. A list of 32,629 people aged between 20-59 was obtained from the 1985 voters' list and a stratified random sample was selected.

Social scale:

1 = Unskilled
2 = Skilled, farmers, craftsmen
3 = Clerical, administration
4 = Executives, professionals, managers

Education: The education system was ill-defined between 1939-45

Before 1939
Elementary school 7 years
Gymnasium 8 years
University 4-6 years

After 1945
Elementary school 7 years (8 years after 1960)
Secondary school (4 years)
Engineering school (5 years) or
Technical schools (3 years)
College (2 years), for those not going to university
University 4-6 years

Study centre: **Portugal**, Cartaxo Village

Principal Investigator: J G Forte

Study dates: 2.5.86 - 23.7.86

Study population and sampling:

A random sample was drawn of inhabitants of the town of Cartaxo, about 65 kms east of Lisbon, using the electoral census list. The population is about 10,000, half of whom work in rural activities (farming, vineyards and cattle farming).

Social scale:

1 =) Based on income and
2 =) education.
3 =)
4 =)

Education:

Primary school 4 years
Ordinary level 5 years
High level 3 years
University level 4-6 years

Study centre: **South Korea**, Pusan

Principal Investigator: B C Park

Study dates: 27.6.86 - 11.8.86

Study population and sampling:

Personnel of the Kosin Medical College (excluding medical doctors) were studied, as well as some relatives of patients in the hospital.

Social scale: Based on household income:

1 = Monthly household income under 300,000 won

2 = Monthly household income between 300,000-500,000 won

3 = Monthly household income between 500,000-900,000 won

4 = Monthly household income above 900,000 won

Education:

Kindergarten 5-7 years old
Primary school 7-13 years old
Middle school 13-16 years old
High school 16-19 years old
University or college 19-23 years old

Study centre: **Soviet Union**, Moscow

Principal Investigator: R Oganov

Study dates: 5.3.86 - 30.6.86

Study population and sampling:

The study population comprised blue and white collar workers in the automobile industry, Moscow. Employees of 3 engineering plants were studied, including engineers, technicians, lab personnel, foremen, managers and service staff. A random sample was drawn from the list of employees.

Social scale:

1 = Blue collar
2 = White collar
3 = Foreman
4 = Manager

Education:

Elementary school age 6-10 years
Secondary school age 10-17 years
Higher education 17+ years

Secondary specialised school can be attended after secondary school or as its continuation instead of high school. Higher education means a completed university or institute course after the age of 17.

Study centre: **Spain**, Manresa

Principal Investigator: S Sans

Study dates: 9.5.85 - 30.7.85

Study population and sampling:

A random sample was drawn from the general population of Manresa, an industrial town of 66,000 inhabitants 60 kilometres north of Barcelona, using an updated 1981 municiapl census list.

Personal letters were sent to individuals inviting them to participate in the study. Two nurses paid domicilliary visits to participants who did not keep their appointments after a letter of telephone call. (An average of 4 contacts was attempted.)

Social scale:

1 = Unskilled
2 = Skilled
3 = Services
4 = Professionals

Education:

From age 6 to 16 years:
Primary school
Secondary school
Polytechnic/high school, age 14-16 years
University at age 17

Study centre: **Spain**, Torrejon

Principal Investigator: M Luque-Otero

Study dates: 19.2.86 - 22.4.86

Study population and sampling:

A stratified random sample was selected from the population of Torrejon de Ardoz, an industrial town 20 km to the west of Madrid. There are 80,000 inhabitants, most of whom migrated there in the 1960s from the south and central parts of Spain. The main employment is a factory in the town.

Social scale: Based on monthly income:

1 = Unemployed
2 = Salary up to 50,000 pesetas a month
3 = Salary up to 51-100,000 pesetas a month
4 = Salary more than 100,000 pesetas a month

Education: From age 6 to 16 years:
Primary school
Secondary school
Polytechnic/high school, age 14-16 years
University at age 17

Study centre: **Taiwan**, San Chilo village area

Principal Investigator: W P Tseng

Study dates: 19.9.85 - 25.10.85

Study population and sampling:

The population sample was the San Chilo village, one hour from Taipei. Total population is 17,000, 40% of whom are farmers.

Social scale:

1 =) Devised on a points-system based on
2 =) education, occupation and economic status.
3 =) The higher the number of points scored,
4 =) the higher the social scale.

Education:

Elementary school for 6 years
Junior school for 3 years
Senior high school for 3 years
College/university for 4 years
Law school for 5 years
Medical school for 7 years

Study centre: **Trinidad and Tobago**, Plymouth-Bethesda

Principal Investigator: A Patrick

Study dates: 14.3.85 - 10.8.86

Study population and sampling:

The 1976 censused adult population of Plymouth-Bethesda in Tobago of 826 respondents was used. The population was aged 20 and over in 1976 and so was now aged 30 years or more. Therefore, 149 people aged 20-29 also were sampled. Many people from the 1976 census had migrated. Many additional house visits were necessary. A second survey was carried out to repeat the 24-hour urine collections, because of problems in the first survey.

Social scale: Based on employment:

1 = Unemployed
2 = Labourer
3 = Clerk, waiter, sales or service
4 = Professional, landowner

Education: Preparatory school, ages 3-6 years
Elementary school, ages 7-10 years
Secondary school system, ages 11-19 years

Study centre: **United Kingdom**, Belfast

Principal Investigator: G Scally

Study dates: 17.6.85 - 10.4.86

Study population and sampling:

The study was based on the MONICA project in Belfast. Patients were selected randomly from the age-sex lists of general practitioners practising in Belfast, obtained from the Central Services Agency.

Social scale: Based on Registrar General's classification:

1 = Farming/manual
2 = Foreman supervisor
3 = Office, public service, sales
4 = Managerial, professional

Education:

Kindergarten
Primary school, ages 5-7 years
First/junior school, ages 7-11 years
Secondary school, ages 11-18 years
College/University, age 18+ years

Study centre: **United Kingdom**, Birmingham

Principal Investigator: G Beevers

Study dates: 18.4.85 - 26.11.85

Study population and sampling:

A stratified random sample was selected from the workforce of Lucas Electrical (manufacturer of car headlights), Hockley, Birmingham. There are over 3000 employees of whom approximately 1000 are office workers. The women are mostly office workers, clerks and cleaners. About 90% of the workforce are white, but there are also Caribbean blacks and Asians (Indian or Pakistani born).

Social scale: Based on Registrar General's classification:

1 = Farming/manual
2 = Foreman supervisor
3 = Office, public service, sales
4 = Managerial, professional

Education:

Kindergarten
Primary school, ages 5-7 years
First/junior school, ages 7-11 years
Secondary school, ages 11-18 years
College/University, age 18+ years

Study centre: **United Kingdom**, South Wales

Principal Investigator: P Elwood

Study dates: 26.3.85 - 19.4.85

Study population and sampling:

A stratified random sample was selected from the age/sex register of a general practice in Bridgend, a market town in mid-Glamorgan. Letters of invitation were sent out and telephone calls and home visits made as necessary.

Social scale: Based on Registrar General's classification:

1 = Farming/manual
2 = Foreman supervisor
3 = Office, public service, sales
4 = Managerial, professional

Education:

Kindergarten
Primary school, ages 5-7 years
First/junior school, ages 7-11 years
Secondary school, ages 11-18 years
College/University, age 18+ years

Study centre: **United States**, Chicago

Principal Investigator: J Stamler

Study dates: 20.11.85 - 5.6.86

Study population and sampling:

A stratified random sample was drawn from the list of employees aged 20-59 of the Chicago Peoples Gas Co (about 1200 people were eligible). Letters of invitation were sent and if no reply was received within ten days, the person was contacted by telephone and the invitation repeated.

Social scale:

1 = Unskilled labourer/service worker
2 = Skilled labourer/semi skilled/secretary, clerk
3 = Foreman, salesman, supervisory
4 = Executive, managerial, professional, technical

Education:

Elementary school 1-8 years
High school 9-12 years
Higher education 13+ years

A college graduate would have 16 years of education; a masters degree student, 17 or 18 years; an MD, 20 years and a PhD, 19-20 years of education or more.

Study centre: **United States**, Goodman (2 centres)

Principal Investigators: D A Frate, H Langford

Study dates: 24.4.86 - 27.8.86

Study population and sampling:

The population sampled was a rural settlement, 51% black and 49% white. There were two centres: one for black, and one for white participants. The sample was drawn from a pool of age, sex and race eligible individuals identified from a series of 5% random population surveys conducted in the project area. Home visits and telephone calls were used to recruit people from the sample. Refusal on initial contact or one missed appointment constituted a "refusal".

Social scale: Based on employment, income and home ownership:

1 = Unemployed or wage under $5000, none home owner

2 = Unemployed or wages under $5000, but owns home, and/or garden, livestock

3 = Employed, salary over $5000, rents or owns home

4 = Employed, professional or agricultural, income more than $25000, owns home

Education: Elementary school 1-8 years
High school 9-12 years
Higher education 13+ years

A college graduate would have 16 years of education; a masters degree student, 17 or 18 years; an MD, 20 years and a PhD 19-20 years of education or more.

Study centre: **United States, Hawaii**

Principal Investigator: D Curb

Study dates: 13.6.85 - 1.8.85

Study population and sampling:

The study was conducted on the island of Molokai. 250 people (67% of population) 20-59 years old were seen. These people live in extended family dwellings or small groups of houses on "homestead" lands which are allocated by state law for long term low-cost housing for native Hawaiians. It is a mobile community, but a census of individuals was completed and thought to be reasonably accurate. There were difficulties getting people to come to the clinic. One solution was to have the clinic and the study itself blessed by a local religious figure, a Kahuna.

Social scale: Based on education:

1 = Elementary school
2 = Secondary/high school
3 = College
4 = Advanced degree

Education: Elementary school 1-8 years
High school 9-12 years
Higher education 13+ years

A college graduate would have 16 years of education; a masters degree student, 17 or 18 years; an MD, 20 years and a PhD 19-20 years of education or more.

Study centre: **United States**, Jackson (2 centres)

Principal Investigators: H Langford, R Watson

Study dates: 7.3.86 - 17.12.86

Study population and sampling:

A stratified random sample was selected from the list of employees of the University of Mississippi Medical Center (about 4000 people). There were two centres: one for black and one for white participants.

Social scale: Based on the highest grade completed in high school:

		Black	White
1	=	1-8 grade	1-11 grade
2	=	9-11 grade	12 grade
3	=	12 grade	13-16 grade
4	=	13+ grade	17+ grade

Education: Elementary school 1-8 years
High school 9-12 years
Higher education 13+ years

A college graduate would have 16 years of education; a masters degree student, 17 or 18 years; an MD, 20 years and a PhD 19-20 years of education or more.

Study centre: **Zimbabwe**, Harare

Principal Investigators: J Matenga

Study dates: 10.12.85 - 25.2.86

Study population and sampling:

A stratified random sample was selected from the list of non medical workers of Parirenyatwa Teaching Hospital (secretaries and hospital clerks were excluded).

Social scale:

1 = Unskilled, semi-skilled (no training), servants, labourers
2 = Semi-skilled (some training) police, lorry drivers, etc.
3 = Skilled (requiring 0 levels)
4 = Professional

Education:

Based on the British system except for a change in number of years at primary school in 1970:
Primary school for 7 years (was 8 years)
Secondary education:
Zimbabwe Junior Certificate, 2 years
British 0 levels, 2 years
A levels, 2 years
University, same as the British system
After secondary education it is also possible to do technical training in various colleges.

Appendix 4: INTERSALT Methods and Main Results (Published Papers)

INTERSALT Co-operative Research Group. INTERSALT Study. An international co-operative study on the relation of blood pressure to electrolyte excretion in populations. 1. Design and Methods. *J Hypertens* 1986; 4: 781-787.

INTERSALT Co-operative Research Group. INTERSALT: an international study of electrolyte excretion and blood pressure. Results for 24-hour urinary sodium and potassium. *Br Med J* 1988; 297: 319-328.