Ischemic heart disease, water hardness and myocardial magnesium

T.W. Anderson,* BM, B CH, PH D; L.C. Neri,† MD, DPH, M SC; G.B. Schreiber,‡ MS HYG; F.D.F. Talbot,§ PH D; A. Zdrojewski,¶ DIP AG SCI

Summary: In 54 cases of accidental death in cities with water hardness of 60 parts per million (ppm) or less, the mean myocardial magnesium concentration was 918 μg/g of dry tissue. This was 7% lower than the corresponding figure of 982 μg/g among 29 cases of accidental death in cities with water hardness of 300 ppm or more, and this difference was significant (P < 0.01). There were no significant differences between the cities with soft and hard water in the mean myocardial concentrations of calcium, zinc, copper, chromium, lead or cadmium. These results are compatible with the belief that the relatively high death rates in some soft-water areas may be due to a suboptimal intake of magnesium, and that water-borne magnesium exerts a protective effect on the residents of hard-water areas.

Résumé: Dans 54 cas de mort accidentelle survenue dans des villes où l'eau de boisson contenait 60 parties de sels minéraux par million (ppm) ou moins, la concentration moyenne de magnésium dans le myocarde était de 918 μg/g de tissu sec. Cette concentration était 7% plus faible que celle de 982 μg/g parmi 29 personnes mortes accidentellement dans des villes où la teneur de l'eau potable était au moins de 300 ppm. Cette différence était significative (P < 0.01). Par contre, en ce qui concernait les concentrations moyennes de calcium, de zinc, de cuivre, de chrome, de plomb ou de cadmium dans le myocarde on ne notait guère de différences significatives entre les villes à eau dure et celles à eau douce. Ces résultats corroborent la théorie que les taux de mortalité relativement élevés constatés dans certaines régions à eau douce pourraient être attribués à une ingestion suboptimale de magnésium et que le magnésium contenu dans l'eau de boisson exerce un effet protecteur sur les résidents des régions dont l'eau est dure.

A number of investigators have reported an association between the hardness* of municipal water supplies and local mortality rates, particularly (but not exclusively) those ascribed to ischemic heart disease (IHD).[1,2] In some areas the association between higher IHD mortality and water hardness appears to be due to a higher frequency of "sudden deaths" in the communities with softer water.[3-6]

If there is indeed a causal relation between water composition and IHD mortality, the factor responsible is presumably something toxic in soft water or something beneficial in hard water. If the latter, two of the most likely factors are calcium and magnesium, since they are mainly responsible for the hardness of most water supplies and have been shown to have some of the strongest correlations with regional mortality patterns.[2,4,7] In a previous study we therefore examined serum concentrations of these two elements in residents of soft- and hard-water communities in Ontario, but were unable to find any difference in serum values and thus had no reason to believe that residents of soft-water areas were suffering from an intake of either calcium or magnesium that was less than optimal.[8]

However, it seemed possible that a comparison of heart-muscle concentrations of these elements might be more rewarding. Crawford and Crawford demonstrated some years ago that the walls of the coronary arteries of young residents of a soft-water area had relatively low concentrations of both calcium and magnesium, although the higher IHD death rate in the soft-water area appeared to be due to an increased susceptibility of the myocardium to infarction rather than to a difference in the severity of coronary artery disease.[9] Furthermore, in the case of magnesium at least, tissue concentration could well be a more appropriate indicator of adequate intake than serum concentration since magnesium is (unlike calcium) predominantly an intracellular ion.

Other reasons for believing that magnesium may be the

*Professor, department of preventive medicine and biostatistics, faculty of medicine, University of Toronto
†Bureau of epidemiology, laboratory centre for disease control, Health and Welfare Canada, Ottawa
‡Planning and evaluation directorate, health protection branch, Health and Welfare Canada
§Professor, department of chemical engineering, University of Ottawa
¶Chemistry division, air pollution control directorate, Department of the Environment, Ottawa

Reprint requests to: Dr. T.W. Anderson, Department of preventive medicine and biostatistics, Faculty of medicine, University of Toronto, Toronto, Ont. M5S 1A8

*"Hardness" reflects the mineral content of water as measured by its capacity to prevent the lathering of a standard soap solution. It is conventionally expressed in terms of parts per million (ppm) (≈mg/l) of calcium carbonate equivalent.

elusive "water factor" are the following:

1. Highly refined Western diets may supply barely adequate amounts of magnesium, so that the additional water-borne magnesium could be critical.[10,11]

2. Myocardial magnesium concentrations have been found to be abnormally low in persons dying from myocardial infarction, even in the uninfarcted parts of the myocardium, suggesting that a low concentration may predispose to infarction or to a fatal outcome thereof.[12-15]

3. One of the manifestations of magnesium deficiency in experimental animals is an increased tendency to cardiac arrhythmias[16] — possibly analogous to the increased frequency of sudden death reported in some soft-water areas.[3-5]

We therefore investigated samples of myocardial tissue taken during autopsies of local residents in two areas at the extremes of the water-hardness range in Ontario for their concentrations of seven elements. In addition, samples were taken from the diaphragm (as an example of another continuously active muscle) and the pectoralis major. All three muscle samples were then analysed for magnesium and calcium, as well as for zinc, copper, chromium, cadmium and lead.

The data were subsequently examined in three groups according to the cause of death — IHD, accidents and all other causes. Because our primary interest was in the tissue electrolyte concentrations of "normal" residents in the two areas, the accidental deaths were of particular importance, for although we recognize that these cases are not a random sample of the general population, they are the closest available approximation to such a sample.

Method and material

This study, conducted over a 4-month period, was carried out with the cooperation of pathologists in eight Ontario cities. Five of these cities (North Bay, Pembroke, Sault Ste. Marie, Sudbury and Thunder Bay) have municipal water supplies of less than 60 ppm total hardness, while three (Brantford, Guelph and Stratford) have water supplies with a hardness of more than 300 ppm.

The pathologists were asked to obtain samples approximately 3 x 3 cm in size from the apex† of the heart, the muscular part of the diaphragm and the midsection of the pectoralis major. These were to be placed in separate plastic containers, labelled and transferred promptly to a deep-freeze. Brief information on age, sex, cause of death, duration of final illness and place of usual residence was also requested for each subject, and this information was subsequently augmented when necessary by reference to death certificates, coroner's reports and hospital records.

Samples were obtained from 161 autopsies. The cause of death was accident or suicide in 83 and acute IHD in 40, but loss or spoilage reduced the number of samples from a potential maximum of 123 to 122 (myocardium), 116 (diaphragm) and 117 (pectoralis). The remaining 38 deaths were due to a variety of other causes and the data from these cases will not be examined in detail in this report.

Most of the accidental deaths were due to trauma (notably motor vehicle accidents), while among the suicides approximately half were due to trauma (gunshot wounds or hanging) and half were "chemical" (carbon monoxide, drug overdose, etc.). (Note: Here, as in some other parts of this report, the accident and suicide cases are, for convenience, referred to simply as accidents.)

All muscle samples were analysed in a central laboratory under the supervision of one of us (G.B.S.). Each specimen

was stripped of all visible fat, blood vessels and fibrous or necrotic tissue, then dried at 110°C to constant weight in a Kjeldahl flask. Wet ashing was carried out in the same flask; 15 ml of a 2:1 mixture of nitric and perchloric acids was used. After standing overnight the mixture was heated gradually to approximately 220°C until a clear solution was obtained. Analyses for magnesium, zinc and copper were carried out using a Pye Unicam SP90 atomic absorption spectrophotometer, with either an air/acetylene flame (magnesium) or an air/propane flame (zinc and copper). For magnesium determinations a 1% solution of lanthanum chloride was added to overcome interference from other ions. For determinations of the other metals a Perkin-Elmer 403 atomic absorption spectrophotometer was used, with a nitrous oxide/acetylene flame for calcium and a

Table I—Characteristics of soft- and hard-water areas and of autopsy series from which muscle samples were obtained

Characteristic	Soft-water area (five cities)	Hard-water area (three cities)
Ischemic heart disease, SMR*		
Male	129	98
Female	119	103
Tap-water composition (mg/l)†		
Magnesium	2.8	29.4
Calcium	8.9	119.4
Zinc	0.41	0.20
Copper	0.74	0.34
Chromium	0	0
Cadmium	0.001	0.002
Lead	0.010	0.014
Clinical details		
Accident and suicide (total no.)	54	29
Accident	42	22
Suicide	12	7
Traumatic	49	24
"Chemical"‡	5	5
Age (yr)		
Mean	38.9	37.0
Range	15-78	18-83
Sex (% male)	85	83
Ischemic heart disease (total no.)	28	12
Age (yr)		
Mean	61.4	60.7
Range	42-85	44-73
Sex (% male)	79	58
Duration§ (% under 24 hours)	87	84

*SMR = standardized mortality ratio, based on deaths ascribed to ischemic heart disease, 1970-72 (Ontario = 100).
†Mean values were calculated in a simple (unweighted) manner.
‡Carbon monoxide, drug overdose, etc.
§Interval between onset of symptoms and death.

Table III—Mean* myocardial magnesium concentration (μg/g, dry weight) by various characteristics in accident and suicide cases

	Myocardial magnesium		Soft/hard (%)
Characteristic	Soft-water area	Hard-water area	
Total group	918 (54)	982 (29)	93
Age (yr)			
< 40	926 (30)	999 (16)	93
40+	909 (24)	962 (13)	94
Sex			
Male	924 (46)	992 (24)	93
Female	887 (8)	934 (5)	95
Alcohol abuse			
Yes	913 (25)	986 (14)	93
No	923 (29)	979 (15)	94
Cause of death			
Accident	928 (42)	983 (22)	94
Suicide	883 (12)	982 (7)	90
Mechanism of death			
Trauma	921 (49)	980 (24)	94
"Chemical"	890 (5)	992 (5)	90

*Numbers of cases on which means were based are given in parentheses.

†The apex of the heart was chosen as the part least likely to be involved in a recent but inapparent myocardial infarction.

PE HGA-70 graphite furnace for chromium, lead and cadmium. Quality control was maintained by standard additions and by replicate analysis using anode-stripping voltametry.

Concentrations were calculated in $\mu g/g$ of both the wet and dry weights of the tissue samples. Initial comparisons were carried out using both wet and dry values and yielded identical conclusions. For simplicity, only the dry-weight concentrations will be given in this report. (Wet-weight concentrations were approximately 25% of the dry values.) Extreme outlier values were adjusted by a modification of the method suggested by Snedecor and Cochran,[17] so that each outlier was then plus or minus two standard deviations from the mean. Three magnesium values (two diaphragm, one pectoralis) and four calcium values (three myocardium, one pectoralis) were thus treated. In each case there was a slight effect on the mean, but the main effect was to reduce the size of the standard error of the mean. In no case did this manipulation change the interpretation of the results.

Scatter diagrams of the data, subdivided by region, cause of death and type of tissue, demonstrated approximately normal distributions of magnesium, calcium, zinc and copper concentrations, but many of the chromium and cadmium values were close to zero, resulting in very skewed distributions. A log transformation was therefore carried out on the chromium and cadmium values before means and standard errors were calculated, making the few zero values equal to 0.01 $\mu g/g$ (the lower limit of detection).

Results

Some of the characteristics of the five soft-water and three hard-water communities and of the autopsy material therefrom are shown in Table I. Water analyses were based on samples from 4 to 20 household tap-water samples in each city.

The results of the tissue analyses are summarized in Table II. To facilitate comparisons of the mean concentrations by type of water supply and by cause of death, certain ratios were calculated; these are presented in Figs. 1 and 2. Lead values were omitted because of the large proportion of zero (undetectable) values.

In Fig. 1 only accident cases are considered. Magnesium was the only element with a significant difference in myocardial concentration between the two areas ($t = 2.43$). Since this difference was in the direction predicted by the hypothesis under examination, a one-tailed t test was appropriate and gave a P value of less than 0.01. To ensure that this finding was not due to an abnormal distribution

Table II—Tissue concentrations ($\mu g/g$, dry tissue) of elements in autopsy samples, by muscle, water supply and cause of death

Water supply and cause of death	No. of autopsy samples	Element						
		Mg*	Ca*	Zn*	Cu*	Cr†	Cd†	Pb‡
		Myocardium						
Soft								
IHD§	27	697	282	101	13.0	0.047	0.159	0.01
		28	*16*	*3.5*	*0.70*	*0.012*	*0.012*	*(93)*
Accident	54	918	224	103	15.7	0.087	0.143	0.23
		15	*6*	*1.9*	*0.30*	*0.012*	*0.011*	*(74)*
Hard								
IHD	12	744	301	98	13.3	0.134	0.097	0.41
		59	*25*	*4.3*	*0.76*	*0.014*	*0.013*	*(58)*
Accident	29	982	232	102	16.4	0.102	0.136	0.16
		23	*9*	*3.3*	*0.45*	*0.012*	*0.012*	*(79)*
		Diaphragm						
Soft								
IHD	28	561	296	128	6.0	0.064	0.454	0.19
		21	*29*	*7.6*	*0.61*	*0.013*	*0.012*	*(89)*
Accident	50	721	241	159	6.7	0.079	0.282	0.33
		18	*11*	*4.1*	*0.30*	*0.012*	*0.011*	*(76)*
Hard								
IHD	12	693	266	154	6.6	0.058	0.371	1.02
		34	*16*	*9.5*	*0.56*	*0.013*	*0.012*	*(83)*
Accident	26	738	231	178	6.6	0.068	0.301	1.02
		18	*9*	*7.3*	*0.26*	*0.012*	*0.012*	*(77)*
		Pectoralis						
Soft								
IHD	28	757	188	193	4.2	0.040	0.352	0.07
		25	*10*	*8.3*	*0.32*	*0.012*	*0.012*	*(82)*
Accident	51	869	191	221	4.8	0.081	0.163	0.09
		16	*8*	*5.3*	*0.17*	*0.011*	*0.012*	*(78)*
Hard								
IHD	12	816	184	210	3.8	0.050	0.247	0.03
		52	*12*	*13.1*	*0.30*	*0.014*	*0.012*	*(83)*
Accident	26	852	176	230	4.5	0.065	0.160	0.10
		29	*6*	*8.6*	*0.31*	*0.012*	*0.012*	*(73)*

*Mean values (arithmetic) and SE (in italics) for tissue, type of water supply and cause of death.
†Values are antilogarithms of the logarithmic (geometric) means and SE (in italics).
‡Mean values (arithmetic) only, because large proportion of tissues contained undetectable concentrations of lead; percentages of zero values in each group are given within parentheses in italics.
§IHD = ischemic heart disease

of values within a single subgroup, the means were recalculated after classification according to various characteristics (Table III). In each case the direction and magnitude of the difference in myocardial magnesium concentration were similar.

The only other significant difference between the accident means was that for diaphragm zinc concentration ($t = 2.44$). Since there was no reason to anticipate this difference, a two-tailed t test was appropriate and gave a P value between 0.05 and 0.01.

In Fig. 2 a comparison is made between IHD deaths and accidental deaths, using the combined results from both water-hardness areas. The accident means (forming the 100% axis) were adjusted to allow for the more than 20-year difference in mean age between the subjects who died accidentally and those who died from IHD (Table I). Linear regressions on age found to be significant (based on the total accident cases), together with the sign of the relation ($+$ = direct correlation; $-$ = inverse correlation) were as follows: myocardium, Ca($+$), Cu($-$); diaphragm, Mg($-$), Cd($+$); pectoralis, Mg($-$), Zn($-$), Cd($+$). Adjustment was carried out within each muscle subgroup by using the appropriate regression coefficient to bring the mean concentration for each subject who died accidentally to what it would have been at the mean age of those who died from IHD, then recalculating the mean value. In most of the subgroups this adjustment reduced the size of the difference between the IHD and accident means and in no case did it create a significant difference where none had previously existed.

There were significant differences (both before and after age-adjustment) in the myocardial concentrations of magnesium, calcium and copper, the diaphragm concentrations of magnesium and zinc, and the pectoralis concentrations of chromium.

Discussion

These results are compatible with the belief that the higher cardiac death rate in the soft-water areas of Ontario is due to the relative lack of magnesium in the water supply.

Among those who died accidentally the mean myocardial magnesium concentration in the soft-water area was 93% of that in the hard-water area (Fig. 1, Table II). It is unlikely that this difference was due to chance. Not only was the difference significant, but differences of similar direction and magnitude were present in samples from both those who died from IHD (94%) and those who died from "other causes" (88%). Data for the latter group have not been examined in any detail in this paper because in most cases there was a prolonged period of failing health (e.g. cancer) or metabolic disturbance (e.g. diabetes) that might have affected tissue electrolyte concentrations. However, for the 20 individuals who died from other causes in the soft-water area the mean myocardial magnesium concentration was 828 $\mu g/g$, some 88% of the corresponding value of 943 $\mu g/g$ in the 18 such individuals in the hard-water area.

The fact that the diaphragm and pectoralis muscles did not have the same sort of soft:hard differential in magnesium concentrations as the myocardium would seem at first to argue against the myocardial differential being due to a deficient magnesium intake by the residents of the soft-water areas. However, animal experiments have shown that a prolonged mild restriction of magnesium intake can depress the magnesium concentration of the myocardium while having little effect on the magnesium content of skeletal muscle.[19]

The regional difference in these results could have arisen as a result of an imbalance between the two groups in the frequency of other conditions associated with abnormally low magnesium concentrations. Although a number of such conditions exist,[20] the only two that are common enough to pose a problem in the present context are alcoholism and the prolonged use of diuretics. We did not have a detailed clinical history for each subject, but "normal" persons (i.e. those who died accidentally) under the age of 40 are unlikely to have been taking diuretics, and the regional difference in this age group was actually slightly greater (93%) than in those aged 40 or more (94%) (Table III). Acute or chronic alcohol abuse was recorded in almost half of the accident cases, but the proportion was almost identical in the two areas (soft, 46%; hard, 48%). Furthermore, the regional difference in myocardial magnesium concentration was essentially the same in those with and those without
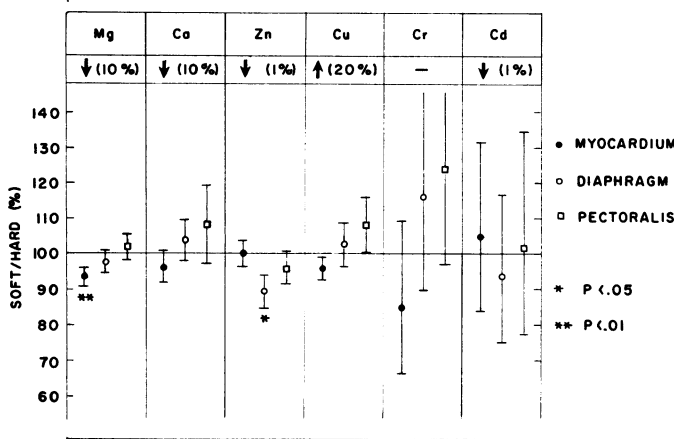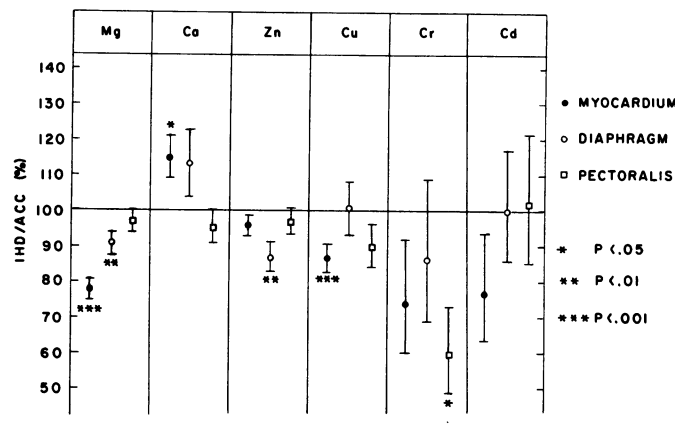

FIG. 1—Mean muscle-electrolyte concentration of subjects from soft-water areas who died accidentally, as percentage of corresponding values from hard-water areas. Each standard error of the difference between the means is also expressed as a percentage of the hard-water mean; vertical bars above and below the mean represent 1 SE. Arrows indicate direction above or below the 100% axis in which percentage value should lie if relative tissue concentrations were a direct reflection of difference in drinking water concentrations in the two areas. In parentheses is the approximate magnitude of difference between the two areas in intake per litre of water as percentage of daily intake from average Canadian diet.[10,18]

FIG. 2—Mean muscle-electrolyte concentrations for all those dying from ischemic heart disease (IHD) ($\pm$ 1 SE difference) as percentage of corresponding values for all those dying from accidents (hard- and soft-water areas combined).

a history of alcohol abuse (Table III). Greater use of alcohol or diuretics by the individuals who had lived in soft-water areas can therefore not explain their lower concentrations of myocardial magnesium.

Since we carried out no dietary studies we are unable to rule out the possibility that the residents of the soft-water areas may consume a diet that contains less magnesium than the diet of the hard-water-area residents, but this is unlikely since the availability of different types of food is relatively uniform throughout Ontario. In any case, if there is such a difference in the dietary intake of magnesium it will be accentuated by the difference in water-borne magnesium, particularly since the latter is ionized and therefore likely to be more readily available than the magnesium in food. Furthermore, if magnesium deficiency is the cause of the higher cardiac mortality in the soft-water area, prevention could presumably be achieved by oral magnesium supplementation, whether the deficiency was originally in the food-borne or water-borne supply.

The mean myocardial magnesium of those who died from IHD was 22% lower than the age-adjusted mean of those who died accidentally (Fig. 2). This value was well within the 19 to 32% range reported by other investigators in the "normal" (i.e. uninfarcted) myocardium of persons dying from myocardial infarction,[7] and was highly significant. Those who died from IHD were also characterized by a relatively low magnesium concentration in both the diaphragm and pectoralis muscles, a finding that is consistent with the hypothesis that myocardial infarction may be in part the manifestation of a generalized muscle disorder.[21,22]

Calcium, the element that, together with magnesium, is responsible for most of the hardness of Ontario water supplies, also was found in a slightly lower myocardial concentration in the subjects from the soft-water area. However, the difference did not reach statistical significance ($t = 0.7$, $P > 0.2$) and, furthermore, death from IHD was associated with a significantly higher concentration of myocardial calcium than normal (Fig. 2) — a difference opposite to that which would be expected if fatal IHD was associated with an inadequate calcium intake. In view of the close interrelationship of calcium and magnesium[20,23] it is possible that the elevated calcium values in the IHD subjects were secondary to the low magnesium values. This is also consistent with recent findings in experimental animals.[24]

Zinc was the only metal other than magnesium with a significant difference in concentration in soft- and hard-water areas for those who died accidentally and, although this difference was confined to the diaphragm samples, it was also present (and significant) in the IHD:accident comparison. The implications of these differences are not immediately obvious, since not only were the myocardial zinc comparisons unremarkable, but water supply makes only a limited contribution (approximately 1 or 2%) to total zinc intake.[18]

Myocardial copper concentrations were significantly lower in those who died from IHD (Fig. 2); the soft:hard difference was in the same direction but was not significant. However, the copper content of drinking water was higher in the soft- than the hard-water area (Fig. 2), probably because of a leaching effect on the copper pipes used in the household water distribution system.

Chromium is also unlikely to be the "water factor" since, although myocardial concentrations showed differences that were in the right direction, the differences were nonsignificant and the metal was undetectable in the water supplies of either area.

However, although zinc, copper and chromium do not appear likely to be the water factor, they may contribute more to the modern epidemic of IHD than is generally recognized. It is possible, of course, that each of the low values from subjects who died from IHD may be simply a secondary manifestation of a diseased muscle, but some could equally well be attributable to a dietary deficiency that, if rectified, might improve the health of the muscle and reduce the vulnerability of the myocardium to infarction.

Cadmium and lead are the only two metals measured in this study that have no known useful biologic function. Both usually tend to be higher in concentration in water from soft-water areas (as a result of corrosion of metal pipes), although in the present study concentrations were actually slightly higher in the hard-water areas. Tissue concentrations of cadmium were not convincingly different between hard- and soft-water areas or between IHD and accident victims. Most of the muscle samples contained no measurable amounts of lead (Table II), and there was no evidence of any systematic differences in those samples that did contain measurable amounts of lead. Neither lead nor cadmium would therefore appear to contribute to the heart disease–water correlations in Ontario, although it is possible that they are important in other parts of the world.

References

1. Neri LC, Mandel JS, Hewitt D: Relation between mortality and water hardness in Canada. *Lancet* 1: 931, 1972
2. Neri LC, Hewitt D, Schreiber GB: Can epidemiology elucidate the water story? *Am J Epidemiol* 99: 75, 1974
3. Anderson TW, le Riche WH, MacKay JS: Sudden death and ischemic heart disease: correlation with hardness of local water supply. *N Engl J Med* 280: 805, 1969
4. Anderson TW, le Riche WH: Sudden death from ischemic heart disease in Ontario and its correlation with water hardness and other factors. *Can Med Assoc J* 105: 155, 1971
5. Peterson DR, Thompson DJ, Nam JM: Water hardness, arteriosclerotic heart disease and sudden death. *Am J Epidemiol* 92: 90, 1970
6. Neri LC, Hewitt D, Mandel JS: Risk of sudden death in soft water areas. *Am J Epidemiol* 94: 101, 1971
7. Seelig MS, Heggtveit HA: Magnesium interrelationships in ischemic heart disease: a review. *Am J Clin Nutr* 27: 59, 1974
8. Anderson TW: Serum electrolytes and skeletal mineralization in hard- and soft-water areas. *Can Med Assoc J* 107: 34, 1972
9. Crawford T, Crawford MD: Prevalence and pathological changes of ischaemic heart-disease in a hard-water and in a soft-water area. *Lancet* 1: 229, 1967
10. Seelig MS: The requirement of magnesium by the normal adult. *Am J Clin Nutr* 14: 342, 1964
11. Hankin JH, Margen S, Goldsmith NF: Contribution of hard water to calcium and magnesium intakes of adults. *J Am Diet Assoc* 56: 212, 1970
12. Iseri LT, Aexander LC, McCaughey RS, et al: Water and electrolyte content of cardiac and skeletal muscle in heart failure and myocardial infarction. *Am Heart J* 41: 215, 1952
13. Heggtveit HA, Tanser P, Hunt B: Magnesium content of normal and ischemic human heart, in *Proceedings of the 7th International Congress of Clinical Pathology*, Montréal, 1969, p 53
14. Chipperfield B, Chipperfield JR: Heart-muscle magnesium, potassium, and zinc concentrations after sudden death from heart-disease. *Lancet* 2: 293, 1973
15. Behr G, Burton P: Heart-muscle magnesium. Ibid, p 450
16. Seller RH: The role of magnesium in digitalis toxicity. *Am Heart J* 82: 551, 1971
17. Snedecor GW, Cochran WG: *Statistical Methods*, 6th ed. Ames, Iowa, Iowa State U Pr, 1967, p 157
18. Kirkpatrick DC, Coffin DE: The trace metal content of representative Canadian diets in 1970 and 1971. *Can Inst Food Sci Technol J* 7: 56, 1974
19. Hunt BJ: Age and magnesium deficiency in the rat with emphasis on bone and muscle magnesium. *Am J Physiol* 221: 1809, 1971
20. Wacker WEC, Parisi AF: Magnesium metabolism. *N Engl J Med* 278: 712, 1968
21. Anderson TW: The changing pattern of ischemic heart disease. *Can Med Assoc J* 108: 1500, 1973
22. Idem: Nutritional muscular dystrophy and human myocardial infarction. *Lancet* 2: 298, 1973
23. Marier JR, Rose D, Belanger LF: Hard waters and heart disease (C). *Br Med J* 2: 686, 1963
24. Silver BB, Sordahl LA: Magnesium modulation of calcium uptake by heart mitochondria. *Physiologist* 3: 452, 1973