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Serum Magnesium Pattern in Apparently Healthy Israeli Population

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Abstract. 69 apparently healthy probands, 40 males, aged 21–45 ($\bar{x}$ 29.9, SD 5.6) and 29 females, aged 19–50 ($\bar{x}$ 31.9, SD 8.4) were carefully selected to exclude the presence of history of past serious disease, concomitant disease, ongoing medication, intercurrent infection, alcohol or drug abuse, and a cigarette consumption exceeding 10 cigarettes/day. These probands were screened for inter- and intra-individual and circannual variation of serum Mg concentration (S-Mg). The mean S-Mg of all probands was 0.808 mmol/l, SD 0.058, range 0.70–0.98. The mean S-Mg and the degree of intra-individual variation did not differ significantly with age, sex, or season, but hypomagnesaemia was 3 times more frequent in females than in males. The results were compared with those of apparently healthy Swedish probands matched for age, sex, season and the length of the interval between two estimations, which were carried out by the same laboratory procedures. The means of the Israeli and Swedish population samples did not differ ($p > 0.05$) but the intra-individual variation differed significantly ($z = 3.84$; $p < 0.001$; Wilcoxon rank sum test). The estimated intra-individual variation of the Israeli population (SD 0.043) was found to be virtually the same as that found for the *sick* Swedish population (SD 0.046) calculated from the source data of patients suffering from various viral diseases [*Stendig-Lindberg* et al., 1980].

Introduction

Several workers reported that the inter-individual variation in serum magnesium concentration (S-Mg) was very small in healthy subjects [*Wacker,* 1980]. The intra-individual variation was found to be remarkably small in apparently healthy subjects [*Henrotte and Durlach,* 1971; *Petersen* et al., 1977; *Stendig-Lindberg* et al., 1980]. While attempting to establish reference values for the Israeli population, we wished, therefore, to examine both the inter-individual and the intra-individual S-Mg variation. We also

wanted to follow the circannual variation, since the heavy heat load of the Israeli summer, causing excessive sweating, could result in excessive Mg loss through sweat [*Consolazio* et al., 1963] and a subsequent fall of S-Mg during the hot season.

Material and Methods

The probands were selected from the staff of Tel-Aviv University and Ichilov Hospital, Tel-Aviv. A standard interview inquiry served as a basis for selection. Past diseases, present diseases – including common cold and influenza – current medication, if any, possible alcohol and/or drug abuse and cigarette consumption were probed. Only probands with no past diseases characterized by lasting sequels, no concomitant disease, including intercurrent infection, no ongoing medication, no alcohol or drug abuse and little or no cigarette consumption (< 10 cigarettes/day) were included in the investigation. Using these stringent criteria, a total of 69 apparently healthy probands were selected. Since S-Mg is not related to age [*Danielsson* et al., 1979] we examined only probands aged 20–50; 40 males (aged 21–45, $\bar{x}$ 29.9, SD 5.6) and 29 females (aged 19–50, $\bar{x}$ 31.9, SD 8.4). For the assessment of the intra-individual variation, a second sample was collected from 51 probands (29 males and 22 females), following an interval of 10–21 days from the time of the first sampling.

In order to detect the presence of a possible circannual variation, 40 probands (22 males and 18 females) were examined in the summer and 29 probands (18 males and 11 females) in the winter. The summer probands were examined at peak heat in August, with the exception of 11 men, examined in April. Although in Israel the temperature may be already quite high in April, we shall refer to the latter group, for accuracy, as the spring probands.

The blood was sampled after an overnight fast between 8 and 9 a.m. to avoid the possible effects of circadian variation [*Touitou* et al., 1978; *Guillard* et al., 1979] and drawn without stasis, so that correction for a constant serum protein level was not necessary [*Christiansen* et al., 1975; *Petersen* et al., 1976]. S-Mg was determined by atomic absorption spectrophotometry, at the Department of Chemistry, Tel-Aviv University, using a Perkin-Elmer spectrometer No. 403. The blood was collected in polypropylene test tubes and centrifuged within 2 h. The samples were examined in duplicate. 0.25% $SrCl_2$ was used as a diluent. The coefficient of variation for intra-assay variability was 0.8%, and for inter-assay 1.3%. The inverse 99% confidence interval was 0.019 [*Wacker* et al., 1981]. Calcium, creatinine, total protein, albumin and globulin were determined in the Clinical Chemistry Laboratory of Ichilov Hospital. The Mg content of the diet of 10 female probands was estimated. The Mg content of tap water in Tel-Aviv was measured.

Statistical Methods

Simple correlations, Wilcoxon sign test, Wilcoxon rank sum test and Student's t test were used where applicable. To see whether there was any effect of sex and season, analysis of variance and F test were carried out on paired observations.

Results

The S-Mg of the first sampling of all probands is seen in table I and figure 1. In the former, the data of a Swedish population sample [*Stendig-Lindberg* et al., 1980] matched for age, sex and season with Israeli group 1, are included as well. The results of both sampling occasions are shown in table II and figures 2 and 3. The Swedish and the Israeli population samples matched for age, sex, season and sampling interval, are shown in figure 4. On comparing *the means* of the Israeli group 1 with the Swedish sample (table I, fig. 4), there is no statistically significant difference ($p > 0.05$, Student's t test). The means of the Israeli samples (first sampling; table I) did not differ from one another ($p > 0.05$, Student's t test).

The Wilcoxon sign test shows no statistically significant difference between the means of the first and means of the second sampling within any of the groups examined. On analysis of variance we found that the *in-*

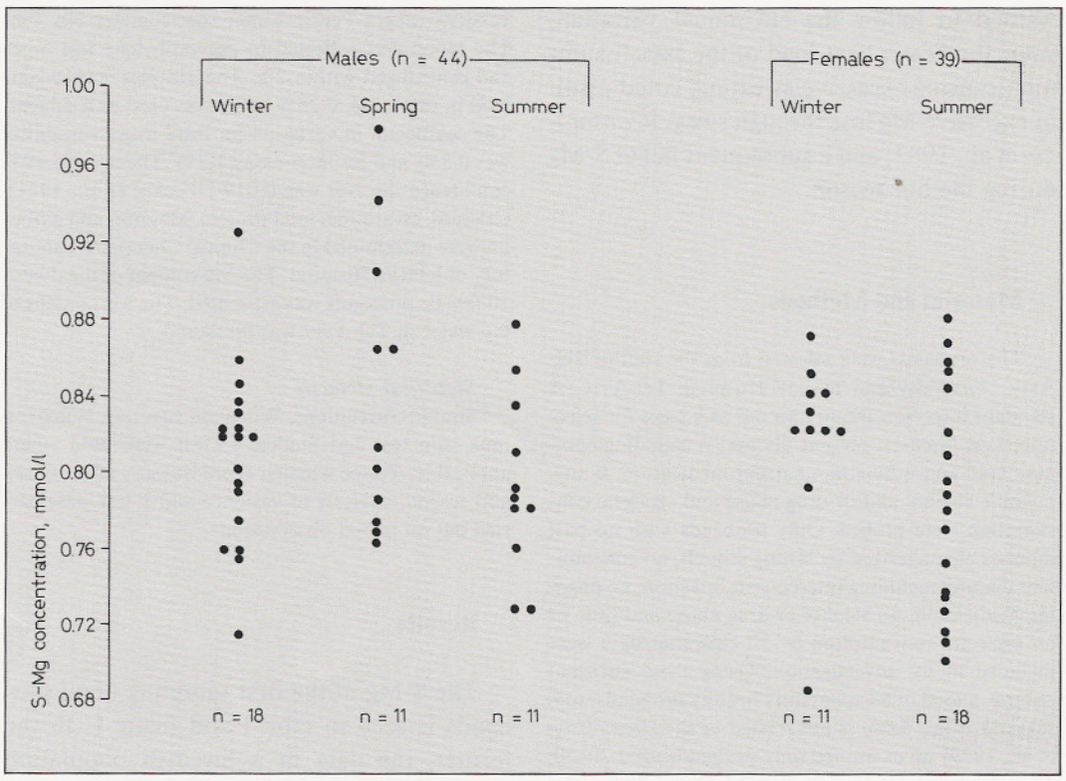

Fig. 1. S-Mg values of all probands (first sampling).

Table I. S-Mg of Swedish and Israeli population samples (first sampling; mmol/l)

	Group, sex, and season					
	Swedish male winter	1 Israeli male winter	2 Israeli male spring	3 Israeli male summer	4 Israeli female winter	5 Israeli female summer
$\bar{X}$	0.797	0.809	0.843	0.796	0.820	0.788
SD	0.037	0.047	0.075	0.048	0.049	0.059
SEM	0.011	0.011	0.023	0.014	0.015	0.014
n	11	18	11	11	11	18
Range	0.73–0.87	0.76–0.93	0.76–0.98	0.73–0.88	0.69–0.87	0.70–0.88

ter-individual variation in Israel did not differ with age and season, and there was no statistically significant difference between the intra-individual variation within any of the 5 Israeli groups on either sampling occasion ($p > 0.05$). The S-Mg of all the probands, regardless of season, are shown in table III. Although neither the means, the inter- nor the intra-individual variation differed significantly between the sexes, or between the seasons, the incidence of hypomagnesaemia in the Israeli females was 3 times more frequent than in the males (table III).

The Wilcoxon rank sum test was used *to compare the magnitude of intra-individual variation between the first and the second sampling* (i.e. the absolute variation; either a rise or a fall of S-Mg) of the Swedish and of the matched Israeli group 1 and within the 5 Israeli groups. Although the intra-individual variation of the 5 Israeli groups did not differ significantly from one another ($p > 0.05$), we found a highly significant difference between the intra-individual variation of the Swedish sample and that of the Israeli matched group 1: $z = 3.84$, $p < 0.001$ (table I, fig. 4).

In each Israeli group, an *estimate of the intra-individual variation* was developed; the variance ranged from 0.0012 to 0.0024. The *estimated variance,* which is a measure of intra-individual variation in the Israeli population was calculated and compared with that of the intra-individual variation of the apparently healthy Swedish population, as well as with that of a *sick* Swedish population (table IV).

Calcium, creatinine, total protein, albumin and globulin values were all within normal reference value. S-Mg was significantly correlated to serum creatinine concentration in group 2 ($r = +0.832$, $n = 9$, $p < 0.01$) and in group 5 ($r = +0.552$, $n = 17$, $p < 0.05$), to calcium in group 3 ($r = -0.765$, $n = 8$, $p < 0.05$) and to globulin in group 1 ($r = +0.479$, $n = 18$, $p < 0.05$). Food Mg content estimated in 10 female probands (group 4) was: $\bar{x}$

Table II. Intra-individual variation in Israeli population samples (mmol/l)

Group-No.	Sample	$\bar{X}$	SD	SEM	n	Range	Range of difference between the 2 samplings
1	males winter I	0.809	0.047	0.011	18	0.76–0.93	0.02–0.14
	males winter II	0.799	0.056	0.017	11	0.72–0.89	
2	males spring I	0.843	0.074	0.023	11	0.76–0.98	0.01–0.14
	males spring II	0.853	0.058	0.022	7	0.79–0.96	
3	males summer I	0.796	0.048	0.014	11	0.73–0.88	0.003–0.07
	males summer II	0.777	0.037	0.011	11	0.72–0.85	
4	women winter I	0.820	0.049	0.015	11	0.69–0.87	0.01–0.13
	women winter II	0.834	0.054	0.018	9	0.76–0.92	
5	women summer I	0.788	0.059	0.014	18	0.70–0.88	0–0.14
	women summer II	0.784	0.065	0.018	13	0.72–0.91	

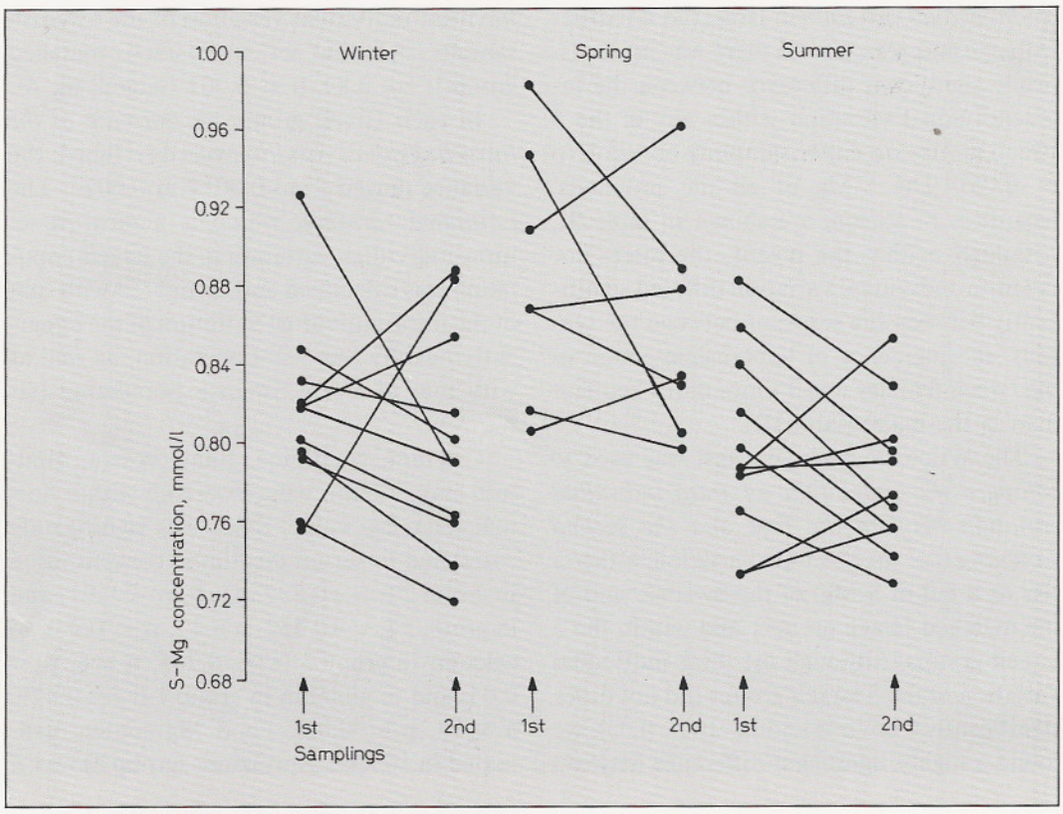

Fig. 2. Influence of season of the year on intra-individual variation of S-Mg in apparently healthy Israeli males.

Table III. S-Mg of all probands, regardless of season (first sampling; mmol/l)

	All apparently healthy males	All apparently healthy females	All probands
$\bar{X}$	0.814	0.800	0.808
SD	0.058	0.057	0.058
SEM	0.009	0.011	0.007
n	40	29	69
Range	0.72–0.98	0.70–0.87	0.70–0.98
±2 SD	0.70–0.93	0.69–0.92	0.69–0.93
Number of hypomagnesaemic cases[1]	3 (8%)	7 (24%)	10 (14%)
Number of hypermagnesaemic cases[1]	4 (10%)	0 (0%)	4 (6%)

[1] Gauged by the criteria of the normal reference value for apparently healthy Swedish subjects.

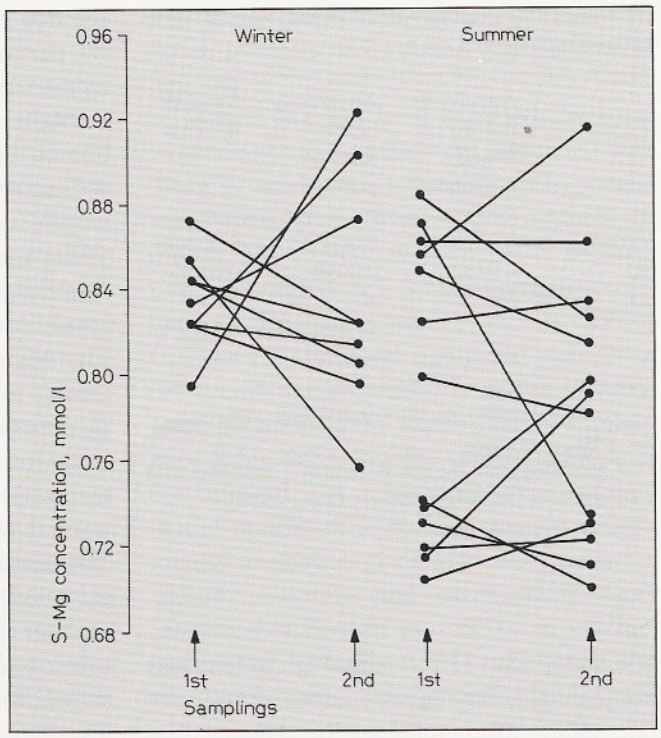

Fig. 3. Influence of season of the year on intra-individual variation of S-Mg in apparently healthy Israeli females.

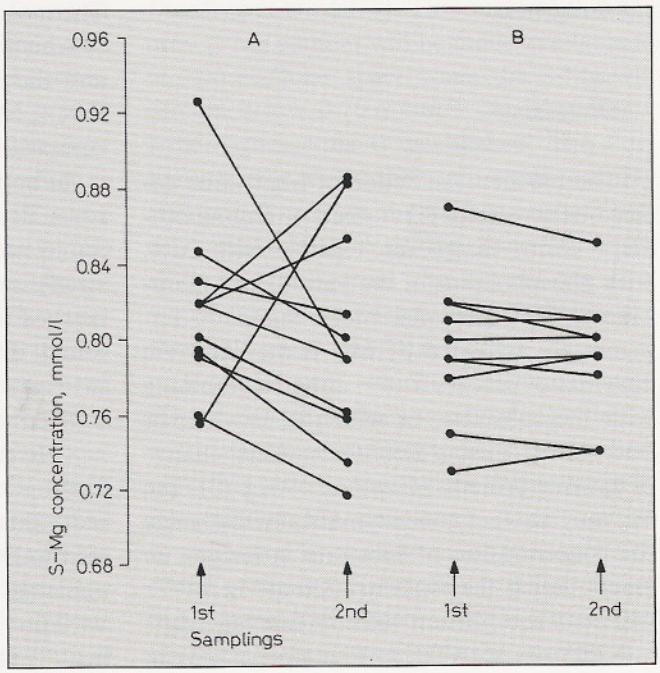

Fig. 4. Comparison of intra-individual variation of S-Mg in the winter season between an (**A**) Israeli and a (**B**) matched Swedish male population sample.

Table IV. Intra-individual Israeli and Swedish variations compared

	Apparently healthy Israeli probands	Apparently healthy Swedish probands	Swedish patients
Variance	0.00187[1]	0.000035	0.00208[2]
SD	0.0432	0.0059	0.0456
d.f.	51	10	26
F	–	$53.43_{(51, 10)}$	$1.11_{(26, 51)}$
p		<0.001	n.s.

[1] Weighted mean of intra-individual variances of the 5 Israeli groups.

[2] Calculated from the source data of 27 patients with viral diseases [*Stendig-Lindberg* et al., 1980].

304.5 mg, SD 132.8 (water Mg content was not included). The mean content of Tel-Aviv tap water was found to be 1.16 mmol/l (28.2 mg/l).

Discussion

The biochemical action of Mg can be defined as threefold: (1) A chelate, among others, it forms complexes, together with Ca^{++}, with phospholipids of the various cell membranes. (2) Coenzyme, more than 300 enzymes are activated by Mg. It may activate enzymatic processes by either combining with the substrate, or with the enzyme, or both, or by causing a conformational change of enzyme proteins [*Günther,* 1981]. (3) Free Mg may also act nonenzymatically to change the concentration of substrate in enzymatic reactions, e.g. the concentration of Mg ATP^{2-} will be in equilibrium with the free Mg (Mg^{++} + ATP^{4-} $\rightleftharpoons$ $MgATP^{2-}$). Therefore, shifts in the free Mg may cause change in the rate of the enzymatic reactions which use $MgATP^{2-}$ as the substrate (*Veloso,* 1973].

Mg is, quantitatively, the fourth ion in the human body (after calcium, potassium and sodium) amounting to 3–9 mmol/kg wet weight depending on cell type [*Günther,* 1981] and the major intracellular cation. Its significance in health and disease has been amply reviewed of late [*Wacker,* 1980]. The total Mg body content varies from 20 to 28 g. Of this total, 55% is found in bone and 27% in muscle, and the remainder in decreasing order of concentration in pancreas, brain, connective tissue, spleen and gastrointestinal tract. The Mg:Ca ratio in the bone is about 1:100 and in the soft tissue 3:2 [*Schroeder* et al., 1969]. The mean Mg content of human skeletal muscle (quadriceps femoris) expressed in mmol/100 g fat-free solid is 4.48 (SD 0.08) [*Stendig-Lindberg* et al., 1977]. The extracellular content is about 1% only. The mean S-Mg in man is 0.80–0.90 mmol/l, of which 55% is free, 32% bound to protein and the rest are soluble compounds of Mg HPO_4, Mg citrate and traces of unidentified complexes [*Walser,* 1971].

In apparently healthy nonaddicted Swedish males the intra-individual variation was found to be 0–0.02 mmol/l pointing to a steady state in health. In disease, however, marked intra-individual variation was found, the highest, of the disease populations investigated, was seen in viral disease; up to 0.27 mmol/l [*Stendig-Lindberg* et al., 1980].

Our results show that in an apparently healthy Israeli population sample the intra-individual variation estimate of S-Mg is significantly different from that found in the apparently healthy Swedish population. The variation estimate found in the apparently healthy Israeli population is of the same mag-

nitude as that found in disease in Sweden [*Stendig-Lindberg* et al., 1980].

Whereas evidence is accumulating that Mg might play a role in regulation of intracellular processes [*Wacker,* 1980] it is still not well understood what regulatory mechanism maintains the steady state of S-Mg in health. Still, a possible explanation could be offered to our findings of fluctuating S-Mg. A fall of S-Mg caused by a suddenly increased Mg loss and/or increased Mg demand may offset attempts to mobilize bone and/or muscle Mg pools in an effort to maintain the steady state of extracellular Mg. The fluxes of intracellular Mg into the extracellular space would thus result in a fluctuating S-Mg at the expense of an ongoing depletion of intracellular Mg. This supposition is supported by the following evidence: Of the total bone Mg, 30% is found in a readily available surface limited pool, dissolved in the hydration shell, or absorbed on the surface of the hydroxyapatite crystals, whereas the remainder of bone Mg forms an integral part of the bone crystal. Blood and bone Mg were found to be positively correlated in man [*Alfrey* et al., 1974], and experimental work with animals suggests that there is a blood-bone equilibrium for Mg which is mainly of a physico-chemical nature [*Heaton,* 1981]; however, parathyroid hormone (PTH) may play a role in blood-bone Mg exchange (in Mg deficiency, PTH secretion – which, under physiological conditions, is inversely related to S-Mg – is reduced, together with a reduced response of target organs to the circulating PTH). Nevertheless, the Mg content contained in the hydroxyapatite crystals, which constitutes 70% of the total bone Mg pool, will not be readily available, as its release would probably involve the resorption of the bone [*Heaton,* 1981]. Consequently, 30% of bone Mg content contained in the surface-limited pool might serve as the primary source of Mg fluxes in states of increased Mg loss and/or demand.

Muscle Mg has been reported, by some workers, not to be positively associated with S-Mg; however, in a later study of hypomagnesaemic subjects (S-Mg $\leqslant$ 0.72 mmol/l) the muscle Mg content was found to be positively correlated with S-Mg and significantly lowered [*Stendig-Lindberg* et al., 1977]. *Günther* [1981] found significant changes in cell membrane permeability and in intracellular metabolism in experimental animals, once S-Mg fell below the threshold value of 0.70 mmol/l. The intracellular changes found in the muscle of hypomagnesaemic experimental animals and of man were a rise in sodium, chloride and extracellular water [*Stendig-Lindberg* et al., 1977], in calcium and cAMP [*Günther,* 1981] together with a small but statistically significant fall in ADP and creatine phosphate content [*Stendig-Lindberg* et al., 1977]. This suggests that the muscle Mg content will be made available to the extracellular space when the S-Mg will remain below 0.70 mmol/l, i.e. when frank hypomagnesaemia is established. The fluctuating state would therefore seem to imply primarily loss from the surface limited, readily available 30% of the bone Mg pool, while an efflux from the muscle Mg pool would take place once S-Mg falls below the threshold value of 0.70 mmol/l.

Regardless of which intracellular pool constitutes the primary source of Mg efflux, it would appear reasonable to view the fluctuating S-Mg as representing the initial stage of intracellular Mg deficiency. This view is strengthened by the finding of *Barnes* [1969] of the presence of intracellular deficit before hypomagnesaemia becomes evident, and the finding of steady state of S-Mg ensuing, fol-

lowing Mg supplementation [*Stendig-Lindberg,* 1974].

The pattern of high intra-individual variation found by us in Israel may be influenced by the climatic factors, prevailing in Israel, causing excessive loss of Mg through sweat [*Consolazio* et al., 1963]. Such a deficit will be sustained and magnified in time in the presence of inadequate intake prevailing in Israel [*Bavli* et al., 1980; *Rozen* et al., 1981] in similarity to that found in western countries [*Seelig,* 1981].

Even though our figures of estimated dietary intake sampled in female Tel-Aviv University employees – which we judged as the relatively most adequately nourished in comparison with other probands – is higher than that reported by *Rozen* et al. [1981] for the Tel-Aviv population ($\bar{x}$ 207.0, SD 65.1, n = 88) and the average intake reported for Israeli adults of 219 mg daily [*Bavli* et al., 1980], it is still below the WHO recommendation and far below what *Seelig* [1981] suggests as daily Mg intake.

It is important to stress that the finding of 1.16 mmol/l Mg in tap water is below the levels found in deep water of the area, suggesting sedimentation of Mg along the water pipes.

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Résumé

69 sujets apparemment en bonne santé (40 hommes âgés de 21 à 45 ans et 29 femmes âgées de 19 à 50 ans) ont été choisis, en excluant les sujets atteints de maladies sévères passées ou présentes, prenant des médicaments, de l'alcool ou de la drogue, ou fumant plus de 10 cigarettes par jour. Ces sujets ont été étudiés pour les variations inter- et intra-individuelles du Mg sérique (Mg S). Le Mg S moyen de tous les sujets est de 0,808 mmol/l. Le Mg S moyen et le degré de variation intra-individuelle ne diffèrent pas significativement avec l'âge, le sexe ou la saison, mais il existe trois fois plus d'hypomagnésémies chez les femmes que chez les hommes. Les résultats ont été comparés avec ceux de sujets suédois en bonne santé, appariés pour l'âge, le sexe, la saison et les délais entre deux examens. Les moyennes de Mg S des deux populations ne sont pas différentes, mais les variations intra-individuelles sont significativement différentes ($z = 3{,}84$; $p < 0{,}001$). La variation intra-individuelle de la population israélienne est virtuellement la même que celle d'une population suédoise malade, atteinte de diverses maladies virales.

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