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Relationship Between Mercury in Blood and 24-h Ambulatory Blood Pressure in Greenlanders and Danes

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Background: Intake of mercury with food items from sea mammals and fish has been suggested to be involved in cardiovascular disease, but the relationship between mercury in blood and 24-h ambulatory blood pressure (BP) has never been studied.

Methods: We measured mercury in blood and 24-h BP in four groups of healthy subjects: group 1, Danes living in Denmark consuming European food; group 2, Greenlanders living in Denmark consuming European food; group 3, Greenlanders living in Greenland consuming European food; and group 4, Greenlanders living in Greenland consuming mainly traditional Greenlandic food.

Results: Mercury in blood was highest in Greenlanders and increased when they lived in Greenland and consumed traditional Greenlandic food (group 1: 2.2 μg/L (median), group 2: 4.8 μg/L, group 3: 10.8 μg/L, and group 4: 24.9 μg/L). The 24-h BP was the same in all three groups of Greenlanders. However, 24-h diastolic BP was lower among Greenlanders than Danes (71 *v* 76 mm Hg, $P < .000$) and 24-h pulse pressure was higher (54 *v* 50 mm Hg, $P < .000$). Mercury in blood was significantly and positively correlated to pulse pressure ($\rho = 0.272$, $P < .01$).

Conclusions: Pulse pressure was higher and diastolic BP was lower in Greenlanders than Danes. Pulse pressure increased with higher mercury content in the blood. Although genetic factors must be responsible to some extent for the difference in pulse pressure between Greenlanders and Danes, the present results seem to support the hypothesis that mercury intake from maritime food is involved in cardiovascular disease. Am J Hypertens 2005;18:612–618
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Key Words: Blood mercury, blood pressure, Danes, diet, Greenlanders, pulse pressure.

The toxicity of mercury in humans is well documented and the risk is due to exposure to methyl mercury from fish and predatory sea mammals, to mercury vapor from amalgam tooth fillings, and to ethyl mercury added as an antiseptic to many vaccines.[1,2] Methyl mercury affects primarily the central nervous system. The greatest susceptibility seems to be in the prenatal period.[1,2] However, accumulation of mercury in the body has also been associated with an excess risk of acute myocardial infarction,[3,4] death from coronary heart disease and cardiovascular disease,[3] and accelerated progression of carotid atherosclerosis.[5] In mercury poisoning blood pressure (BP) has been reported to be elevated,[6] and methyl mercury treatment of rats resulted in an increased systolic BP.[7] In humans, analyses have so far been based on casual BP measurements, which is a much less reliable method than 24-h ambulatory BP measurement. No information is available about the relationship between the mercury content in the body and 24-h BP.

The purpose of the present study was 1) to determine blood mercury levels and 24-h ambulatory BP in Greenlanders and Danes stratified according to ethnicity, type of food consumption, and residence, and 2) analyze whether an association existed between mercury in blood and BP.

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The BP data from the present study have been published previously to analyze the relationship between 24-h ambulatory BP on the one hand and lifestyle and vasoactive hormones on the other.[8,9] The present study is the first to report the relation between 24-h BP and mercury in blood.

Methods

Study Subjects

The inclusion criteria were 1) Greenlanders in Greenland and Denmark, and Danes in Denmark, 2) aged 20 to 60 years, and 3) both genders. The exclusion criteria were 1) a history of or clinical signs of disease in the heart, lungs, liver, kidneys, brain, or endocrine organs, 2) arterial hypertension, 3) neoplastic disease, 4) daily use of medicine, 5) alcohol abuse defined as more than 21 drinks a week for men and more than 14 drinks a week for women, 6) abnormal laboratory screening including B-hemoglobin, plasma-creatinine, plasma-aspartate-amino-transaminasis, urine-albumin, urine-glucose, urine-hemoglobin, and an electrocardiogram, and 7) unwillingness to participate.

The study was approved by the local Medical Ethics Committees in Greenland and Denmark and carried out according to their rules.

Design

The study was designed as a comparison between four groups of study subjects based on 1) ethnicity, 2) diet composition, and 3) place of residence. Group 1 included Danes consuming European food and with residence in Denmark; group 2 included Greenlanders consuming European food and with residence in Denmark for at least during the past 2 years; group 3 included Greenlanders consuming European food and with residence in Greenland; and group 4 included Greenlanders consuming traditional Greenlandic food and with residence in Greenland.

Sample Size

The number of subjects needed in each group was calculated at a significance level of 5% and with a power of 90%. The minimum relevant differences were estimated to be 7 mm Hg, 5 mm Hg, and 3.5 mm Hg for systolic BP, diastolic BP, and pulse pressure, respectively, and the corresponding SDs were estimated to be 10, 7, and 5 mm Hg. The number of subjects in each group could then be calculated to 40 to 45.

Enrollment

The study was carried out in Nuuk, Greenland, and Aarhus, Denmark. A structured interview with a questionnaire was completed. The subjects underwent a clinical examination, blood sampling, urine collection, and 24-h ambulatory BP measurement.

Questionnaire

The questionnaire contained information on ethnicity, place of residence, and food consumption. The participants were categorized as Danes, if they were born in Denmark and had Danish parents who were also born in Denmark, and considered themselves as Danes. The participants were categorized as Greenlanders if they were born in Greenland, had Greenlandic parents who were also born in Greenland, and considered themselves as Greenlanders. Residence for Greenlanders in Denmark requested that they had lived in Denmark for at least during the past 2 years. Residence for Greenlanders in Greenland and Danes in Denmark requested that they had lived their whole life in Greenland and Denmark, respectively. Information about food consumption was based on a 3-month recall interview with specifications of certain traditional Greenlandic food items (eg, seal, whale). Diet was characterized as traditional Greenlandic when it contained seal or whale meat one to three times a week, and as western when it contained a maximum intake of seal and or whale meat two to three times a month. Participants with intakes in-between were excluded from the study.

Mercury in Blood

Mercury was determined by "flow injection" atomic absorption spectrometry after reduction with sodium borohydride. The detection limit of the method is 0.001 mg/kg and the precision (95% confidence) is 12% relative.[10]

Twenty-Four-Hour Ambulatory BP Measurement

Twenty-four hour ambulatory BP measurement of systolic and diastolic BP was performed with Takeda TM-2421 equipment (Takeda Chemical Industries, Ltd., Tokyo, Japan), which uses both the oscillometric and Korotkoff's method. Blood pressure was measured every 15 min during daytime and every 30 min during night-time.

Statistics

Statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, IL). Data are presented as means $\pm$ SD or medians with 25 to 75 quartiles. A log transformation was done if data did not show normality. ANOVA was used for comparison of means between several groups, and a *t* test, for comparison of means between two groups. Pearson coefficient of correlation was calculated for correlation analysis between variables, which showed normality, and Spearman's test for data not fulfilling this criterion. Kruskal-Wallis test and Mann-Whitney's test were used for nonparametric comparison between several groups and two groups, respectively.

Results

Demographics

A total of 198 subjects were recruited for the study, and 186 fulfilled the criteria to be included. Group 1 comprised

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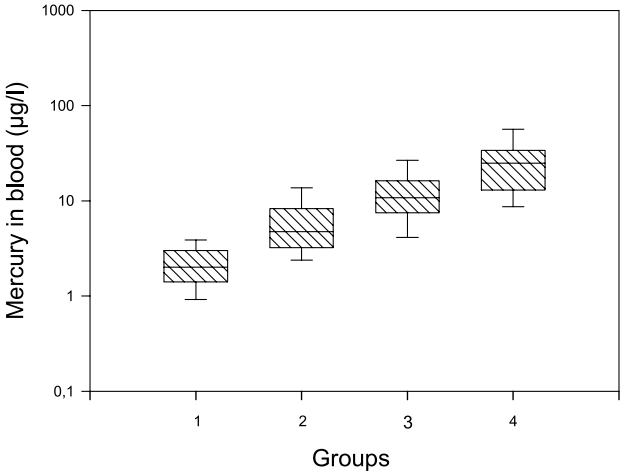

FIG. 1. Blood mercury concentration (log-scale) in Danes consuming European food with residence in Denmark (Group 1), Greenlanders consuming European food with residence in Denmark (Group 2), Greenlanders consuming European food with residence in Greenland (Group 3), and Greenlanders consuming traditional Greenlandic food with residence in Greenland (Group 4). Medians with 25–75 and 5–95 percentiles.

41 Danes aged 43 ± 8.6 years (mean ± 1 SD), 20 men and 21 women; group 2 comprised 53 Greenlanders aged 43 ± 10 years, 21 men and 32 women; group 3 comprised 45 Greenlanders aged 39 years ± 9.2 years, 15 men and 30 women; and group 4 comprised 47 Greenlanders aged 42 years ± 9.9 years, 24 men and 23 women. The total group of Greenlanders comprised 145 subjects aged 42 ± 8.9 years, 60 men and 85 women.

Mercury in Blood

The mercury content in blood was seven- to eight-fold higher in Greenlanders than Danes (16.2 *v* 2.2 μg/L (medians), $P < .000$). Fig. 1 shows that blood mercury was highest in the group who consumed traditional Greenlandic food (group 4) and significantly higher than in the groups who consumed European food (groups 2 and 3). Blood mercury was also higher among Greenlanders when the residence was in Greenland (groups 3 and 4) than in Denmark (group 2).

Twenty-Four-Hour Ambulatory BP Measurement

Table 1 shows that 24-h ambulatory systolic BP was the same in Greenlanders and in Danes. The 24-h ambulatory diastolic BP was significantly lower in Greenlanders than in Danes ($P < .000$). The 24-h ambulatory pulse pressure was significantly higher in Greenlanders than in Danes ($P < .000$). These data are for the entire 24-h period and during daytime using both oscillometric-based measurements and Korotkoff's method. During night-time the differences remained significant using Korotkoff's method, but not using the oscillometric measurements. Fig. 2 shows that there was no significant difference between the three Greenlandic groups with regard to 24-h systolic and diastolic BP either during the enture day or in the day and night periods using the oscillometric data. The same information was obtained using Korotkoff's method.

Association Between Mercury in Blood and BP

The values for mercury in blood did not follow a normal distribution, thus a nonparametric test was used for correlation analysis. Blood-mercury (B-mercury) was negatively and significantly correlated to diastolic BP for determinations using both the oscillometric method ($\rho = -0.170$, $P < .05$) and the Korotkoff's method ($\rho = -0.249$, $P < .01$), but not for systolic BP. B-mercury was positively and significantly correlated to pulse pressure for both oscillometric ($\rho = 0.272$, $P < .01$) and Korotkoff's methods ($\rho = 0.203$, $P < .01$) as shown in Fig. 3.

Data for mercury in blood followed the criteria for normality after log transformation, and log B-mercury was

Table 1. 24-h ambulatory systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) during the entire period, daytime and night-time using the oscillometric and Korotkoff's methods

	Oscillometric Method			Korotkoff's Method		
	SBP	DBP	PP	SBP	DBP	PP
24-h						
Danes	126 ± 9	76 ± 7	50 ± 5	123 ± 10	75 ± 7	51 ± 5
Greenlanders	126 ± 10	71 ± 7	54 ± 7	122 ± 12	69 ± 7	56 ± 7
P	NS	< 0.000	< 0.000	NS	< 0.000	< 0.005
Daytime						
Danes	131 ± 9	80 ± 7	47 ± 5	129 ± 11	77 ± 7	49 ± 6
Greenlanders	130 ± 11	74 ± 8	50 ± 8	126 ± 13	71 ± 8	53 ± 8
P	NS	< 0.000	< 0.000	NS	< 0.000	< 0.009
Night-time						
Danes	110 ± 9	63 ± 7	51 ± 7	105 ± 11	65 ± 6	40 ± 7
Greenlanders	112 ± 11	63 ± 8	55 ± 9	106 ± 14	62 ± 7	43 ± 10
P	NS	NS	< 0.058	NS	< 0.011	< 0.021

Mean ± SD.

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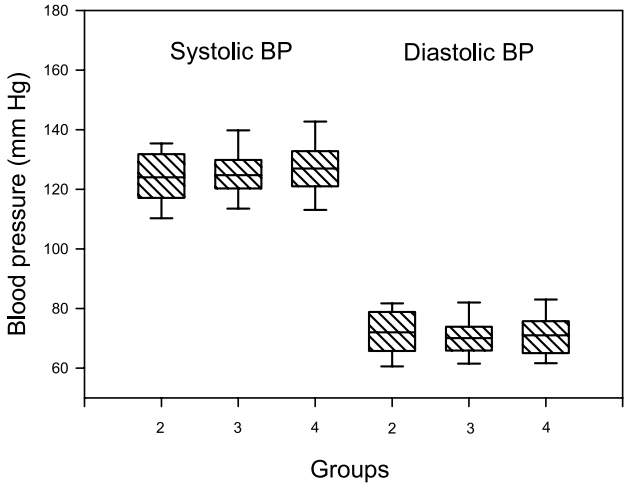

FIG. 2. 24-hour ambulatory systolic and diastolic blood pressure in Greenlanders consuming European food with residence in Denmark (Group 2), Greenlanders consuming European food with residence in Greenland (Group 3), and Greenlanders consuming traditional Greenlandic food with residence in Greenland (Group 4). Medians with 25–75 and 5–95 percentiles.

negatively and significantly correlated to diastolic BP for the Korotkoff measurements ($r = -0.184$, $P < .05$), but the correlation did not reach statistical significance for the oscillometric measurements ($r = -0.141$, $P =$ not significant). However, log B-mercury was positively and significantly correlated to pulse pressure for both oscillometric ($r = 0.255$, $P < .01$) and Korotkoff determinations ($r = 0.167$, $P < .05$).

Regression analyses showed that pulse pressure was significantly dependent of mercury in blood (log transformation) during the entire 24-h period and daytime (for the oscillometric method: 24-h period, $P < .001$; daytime, $P < .000$; night-time, $P < .108$; and for Korotkoff method: 24-h period, $P < .033$; daytime, $P < .009$; and night-time, $P < .070$). The significance of these relations remained after inclusion of age and body mass index in the analysis.

Association Between Mercury in Blood and BP

Table 2 shows systolic and diastolic BP and pulse pressure in relation to blood mercury. The blood mercury was divided in quartiles, and the BP values were calculated for each quartile. For both pulse pressure during 24-h and daytime, and diastolic BP during 24-h and daytime the levels in the quartiles were significantly different (Kruskal-Wallis test). There was a clear and gradual increase in pulse pressure with increasing blood mercury level, whereas a larger variation was measured for diastolic BP.

Association Between BP, Mercury in Blood, Age, Body Mass Index, Gender, and Residence

The association between BP on the one hand and mercury in blood and selected variables on the other was analyzed using multiple regression. Blood pressure was dependent variable, and as predictors we used the concentration of mercury in blood, age, body mass index, gender, and residence. Table 3 shows the standardized coefficients (β), t, and the significance level for systolic BP, diastolic BP, and pulse pressure. For 24-h systolic BP a significant association was demonstrated only for body mass index. For 24-h diastolic BP significant associations were demonstrated to mercury in blood and age. Twenty-four-hour pulse pressure was significantly associated to mercury in blood, also after adjustment for significant associations to mercury intake and body mass index. No significant association was found between mercury in blood and BP when the groups from Denmark and Greenland were analyzed individually. The association between blood mercury and BP was pronounced in women (pulse pressure, women: $\beta = 0.285$, $t = 2.951$, $P = .004$, and men: $\beta = 0.195$, $t = 1.585$, $P = .119$; diastolic BP, women: $\beta = -5.780$, $t = -3.175$, $P = .02$, men: $\beta = -2.396$, $t = -1.512$, $P = .135$).

Discussion

In the present study we have shown that Greenlanders have a higher level of mercury in blood, a higher pulse pressure, and a lower diastolic BP than Danes. In addition, mercury in blood was positively correlated to pulse pressure and negatively to diastolic BP.

The higher level of mercury in the blood of Greenlanders is attributed to their intake of the traditional Inuit diet, which is characterized by special food items from the sea such as predatory sea mammals containing high concentrations of mercury due to biomagnification of environmental contaminants in the marine food web. Traditional Greenlandic food cannot be obtained in Denmark. Thus, it is evident from our study that even after a stay in Denmark of at least 2 years, blood mercury levels remain considerably elevated in Greenlanders. Mercury's toxic effect is well documented on the central nervous system,[1,2] and recent studies have shown that mercury can also induce cardio-

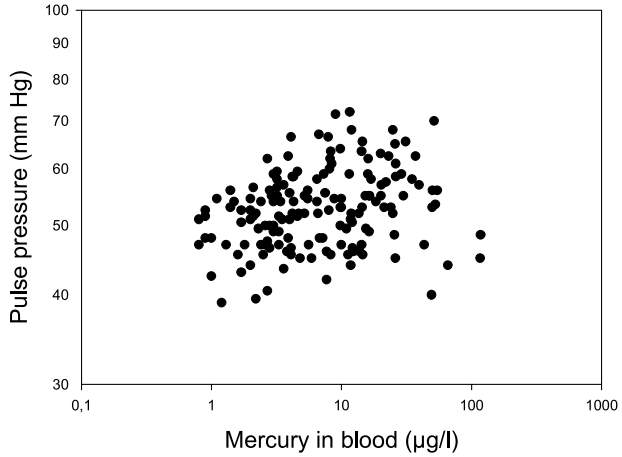

FIG. 3. Relationship between mercury in blood and 24-hour ambulatory pulse pressure in the whole material. Log scales.

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Table 2. 24-h ambulatory SBP, DBP, and PP during the entire period, daytime, and night-time using the oscillometric method in the quartiles of mercury in blood

Blood Hg (μg/L)	1. Quartile 0.8–2.9	2. Quartile 3.0–6.5	3. Quartile 6.6–14.5	4. Quartile 14.6–117.7	P
SBP 24-h (mm Hg)	125 ± 8	126 ± 10	125 ± 11	128 ± 10	.386
SBP day (mm Hg)	129 ± 8	131 ± 11	129 ± 11	133 ± 12	.343
SBP night (mm Hg)	109 ± 8	113 ± 11	113 ± 13	113 ± 10	.164
DBP 24-h (mm Hg)	75 ± 7	73 ± 8	70 ± 8	72 ± 7	.029
DBP day (mm Hg)	79 ± 7	76 ± 9	73 ± 8	76 ± 8	.006
DBP night (mm Hg)	62 ± 7	64 ± 7	63 ± 9	63 ± 8	.851
PP 24-h (mm Hg)	49 ± 5	53 ± 5	55 ± 8	55 ± 7	.001
PP day (mm Hg)	51 ± 5	54 ± 6	56 ± 8	58 ± 8	.001
PP night (mm Hg)	46 ± 4	50 ± 7	50 ± 10	50 ± 8	.143

Abbreviations as in Table 1.
Mean ± SD.

vascular lesions. A relationship has been demonstrated between the intake of fish, mercury content in urine, and mercury content in scalp hair on the one hand and the risk of cardiovascular disease in adult men living in Finland on the other,[3] and toenail mercury level was directly associated with the risk of myocardial infarction among people with residence in eight European countries and Israel.[4] Although the findings from a study from the US[11] did not support an association between the total mercury exposure and the risk of coronary heart disease, a weak correlation could not be ruled out between these variables. Mercury can induce hypertension in animals[7,12] and humans.[6,13] In the Faro Islands, when mercury content in cord blood was increased between 1 and 10 μg/L there was an increase in BP when these children were tested as 7-year olds.[14] In the present study we found a clearly different BP level among Greenlanders than Danes. Pulse pressure was increased and diastolic BP was lower in Greenlanders. This difference could, of course, be attributed to ethnicity and postulated to be independent of environmental factors. However, it is reasonable to speculate that mercury could change BP regulation in Greenlanders: first, due to the relationship between cardiovascular disease and mercury content in the body, as demonstrated previously[3,4,14]; second, due to mercury's capability to induce vascular injury and hypertension demonstrated in animal experiments and humans[6,7,12,13]; and third, due to the high level of mercury in the body of Greenlanders and other populations with a high intake of seafood with high mercury content. Our results support the hypothesis about mercury being a factor involved in the development or maintenance of an abnormal BP regulation.

The pattern of cardiovascular diseases in Greenland differs from Western Europe and the US. Mortality statistics have shown a considerably lower mortality of ischemic heart disease in Greenlanders, whereas cerebrovascular disease is several times more frequent than in Danes.[15] The age-adjusted mortality rates for diseases of both heart and blood vessels were 2.3- and 2.4-fold higher in Greenland than in Denmark for women and men, re-

Table 3. Association between 24-h ambulatory SBP, DBP, and PP as dependent variables, respectively, and blood mercury (log-B-Hg), age, and body mass index (BMI) as independent variables using multiple regression analysis

	SBP			DBP			PP		
	β	t	P	β	t	P	β	t	P
24-h									
Log-B-Hg	0.516	0.320	.749	−3.112	−2.482	.014	3.627	3.361	.001
Age	0.054	0.662	.509	0.179	2.821	.005	−0.125	−2.289	.023
BMI	0.795	3.290	.001	0.323	1.719	.088	0.472	2.917	.004
Day									
Log-B-Hg	1.170	0.676	.500	−3.312	−2.500	.013	4.482	3.770	.000
Age	0.101	1.156	.250	0.181	2.703	.008	−0.080	−1.329	.186
BMI	0.726	2.797	.006	0.325	1.637	.104	0.401	2.250	.026
Night									
Log-B-Hg	1.085	0.617	.538	−1.047	−0.804	.423	2.132	1.881	.062
Age	−0.059	−0.660	.510	0.167	2.531	.012	−0.225	−3.934	.000
BMI	0.967	3.668	.000	0.269	1.377	.171	0.698	4.108	.000

Other abbreviations as in Table 1.

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spectively.[15] This means that Greenlanders have a considerably higher risk of cardiovascular disease affecting other organs than the heart.[16] Casual measurements of BP among Greenlanders have shown a lower level,[17] or a level similar to Danes.[18–20] A recent study showed that BP was lower among Inuit in Greenland than among Inuit migrants in Denmark, but the difference was absent for systolic BP and reduced for diastolic BP among the better educated population.[21] When surveys of BP from whites in Greenland and the US were compared, similar levels were found up to the age of 64 years,[22] and it appears that pulse pressure was higher in Greenlanders than in US whites at all age levels for both men and women.[22] However, all previous studies have used casual BP in their analyses, and about 30% of casual BP measurements are not reliable due to the white coat effect.[23] The present study is the first in which 24-h BP measurement has been applied to a population of Greenlanders. A total of about 80 measurements of BP were done for each 24-h measurement. Consequently, the evaluation of the BP level is much more reliable than casual BP measurement. The previously measured higher pulse pressure in Greenlanders than in US whites[22] and the lower diastolic BP among Inuit migrants in Denmark,[21] based on casual measurements, might have been a suggestion of what we have documented in the present study, that is, Greenlanders have a higher pulse pressure than Danes.

Mercury can induce lesions in the vascular bed, and mercury accumulation in the human body is associated with accelerated atherosclerosis.[5] The mechanism has been attributed to an enhancement of lipid peroxidation, as mercury generates reactive oxygen species, reduces the antioxidative capacity by binding to sulfhydryl groups, and counteracts the antioxidative effect of selenium.[3,5] We hypothesize that both systolic and diastolic BP were lower in Greenlanders as in other native populations before westernization and before pollution of the environment, and especially of the seas, with mercury during the twentieth century. Because of Greenlanders' consumption of fish and predatory sea mammals as a part of their traditional food items mrcury may have induced vascular injury of the aorta and the large arteries with degenerative processes and stiffening as a consequence. The pathophysiologic sequelae would be an increase in systolic BP to a level not different from the Western populations, and a diastolic BP that remained unchanged and at a lower level than in Western populations, as we measured in the present study. A high pulse pressure has been reported to be a cardiovascular risk factor,[24,25] although pulse pressure data may not be straightforward to interpret.[26]

Blood pressure regulation depends on many factors, both genetic and environmental. It is not possible to include all factors in the analysis. It would have been interesting to include biomarkers for the dietary intake of mercury and n-3 fatty acids in the analysis. Patients with arterial hypertension were not included in the study. Inclusion of these patients would have given a larger range in BP, which might have been an advantage. However, because the duration of hypertensive disease is very difficult to clarify, other analytical problems would have emerged.

In conclusion, Greenlanders have a higher level of mercury in blood, a higher pulse pressure, and a lower diastolic BP than Danes when evaluated with a 24-h ambulatory BP measurement. Pulse pressure was positively correlated to mercury in blood and increased with increasing amount of mercury in the blood. Although genetic factors must be responsible to some extent for the difference in pulse pressure between Greenlanders and Danes, the present results seem to support the hypothesis that mercury intake from maritime food is involved in cardiovascular disease.

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