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REDUCTION IN MORTALITY FROM CORONARY HEART DISEASE IN MEN RESIDING AT HIGH ALTITUDE

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Abstract In New Mexico, where inhabited areas vary from 914 to over 2135 m above sea level, we compared age-adjusted mortality rates for arteriosclerotic heart disease for white men and women for the years 1957–1970 in five sets of counties, grouped by altitude in 305-m (1000-foot) increments. The results show a serial decline in mortality from the lowest to the highest altitude for males but not for females. Mortality rates for males residing in the county groups higher than 1220 m in order of ascending altitude were 98, 90, 86 and 72 per cent of that for the county group below 1220-m altitude ($P<0.001$). The results do not appear to be explained by artifacts in ascertainment, variations in ethnicity or urbanization.

A possible explanation of the trend is that adjustment to residence at high altitude is incomplete and daily activities therefore represent greater exercise than when undertaken at lower altitudes. (N Engl J Med 296:581-585, 1977)

RATES of coronary-heart-disease mortality vary according to geographic region within the continental United States.[1] In 1949–1951 and in 1959–1961 all the Rocky Mountain states except Nevada showed rates for whites below the national average among both males and females. Among the 48 continental states, New Mexico exhibited the lowest rates for white males in both time periods; rates for white females in New Mexico were the lowest in 1949–1951 and the second lowest in 1959–1961.

One explanation for this observation might be that a protective effect is associated with residence at high altitude. Anecdotal information suggests such a possibility,[2,3] but a study of variation in coronary-disease mortality within Colorado demonstrated no differences associated with high altitude.[4] The present report consists of a study of death rates from arteriosclerotic heart disease related to altitude of residence in the state of New Mexico.

MATERIALS AND METHODS

The state of New Mexico is approximately square, measuring about 540 km in each direction. The Rio Grande River, flowing north to south, roughly bisects the state. West of the Rio Grande the land rises to the Continental Divide, which lies within the state's western border. East of the Rio Grande are higher land and mountain ranges, which separate the Rio Grande valley from the Pecos River valley, also running from north to south. Inhabited areas in New Mexico vary in altitude from about 914 m above sea level in the southeast corner of the state to over 2135 m in the north.

The population of the state was 951,000 in 1960 and 1,016,000 in 1970.[5,6] Slightly more than 90 per cent of the population are white, about 2 per cent are black, and nearly all the remainder are American-Indian. Of the white population, 31 per cent were estimated to be of Spanish-American descent in 1960 and 44 per cent in 1970; unfortunately, the methods of designation of Spanish-American origin differed in the two censuses.[5,6]

The New Mexico Regional Medical Program assembled computerized death-certificate data as coded by the state for 14 years, 1957 through 1970. From this source, tabulations of mortality from arteriosclerotic heart disease as the underlying cause of death were obtained for the white residents of each county according to age and sex. Deaths coded by the state as ICD #420 from 1957 through 1968 and ICDA #410-414 and #428 in 1969-1970 were included. Estimated populations during each of the 14 years in each county were calculated in a Regional Medical Program project in which populations for between-census years were estimated, with consideration of births, deaths and migrations for each county. We computed person-years at risk for residents aged 25 and above by summing the estimated county populations in each year over the 14-year period.

Each of the 32 counties was assigned to one of five altitude groups determined by increments of 305 m (1000 ft). When portions of a county's population resided at different altitude levels, the county was assigned to the group appropriate for the majority of its residents, as determined by the populations of county divisions in the 1960 and 1970 censuses. Table 1 shows the altitude groups and populations at risk during the 14-year period. For brevity the five groups have been assigned numbers from 1 (lowest) to 5 (highest) altitude. For example, county Group 1 consists of counties the majority or all of whose residents live between 914 and 1219 m above sea level. The largest city, Albuquerque (Bernalillo County), is located in altitude Group 3, and this group is therefore separated into Bernalillo County (3B) and the remaining counties in that altitude range (3A).

Mortality rates from arteriosclerotic heart disease for each altitude group were computed in 10-year age groups between 25 and 74 years and for 75 years and older. Age adjustment was to the age distribution of the New Mexico population, 1957–1970.

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Table 1. Person-Years at Risk According to County Altitude Group, 1957–1974.

Group	Altitude (M)	Counties	Person-Yr*	
			Male	Female
1	914–1219	Chavez, Dona Ana, Eddy & Lea	687,929	686,652
2	1220–1523	Curry, De Baca, Guadalupe, Harding, Hidalgo, Luna, Otero, Quay, Roosevelt, Sierra, Socorro & Valencia	579,964	571,773
3	1524–1828		1,213,256	1,269,992
3A		Grant, Rio Arriba, Sandoval, San Juan & Union	(312,323)	(311,202)
3B		Bernalillo	(900,933)	(958,790)
4	1829–2133	Colfax, Lincoln, McKinley, San Miguel & Torrance	222,994	227,680
5	>2133	Catron, Los Alamos, Mora, Santa Fe & Taos	280,384	289,773
Totals			2,984,527	3,045,870

*Persons <25 yr of age excluded.

Results

Table 2 shows age-adjusted and relative age-adjusted death rates from arteriosclerotic heart disease for white males and females according to county altitude group. For males the data show a distinct decline in rates associated with residence at increasing altitude; the age-adjusted rate above 2135 m is 72 per cent of the rate between 914 and 1219 m. The differences in these age-adjusted rates for males are statistically significant (chi-square = 94 with 4 degrees of freedom, $P<0.001$). The decline in mortality with increase in altitude is reasonably regular except for the relatively high rates seen in Bernalillo County (Albuquerque). Rates for females do not exhibit the same association, although county Group 5 for females has the lowest rate of all the altitude groups.

Several analyses were undertaken to determine whether these results might be attributable to artifacts in reporting or coding of causes of death. First of all, mortality rates from all causes were compared and indicated that the county group at lowest altitude had higher rates than the counties at highest altitude in approximate proportion to the fraction attributed to arteriosclerotic heart disease. Secondly, the possibility was investigated that in the high-altitude counties deaths from this cause were more frequently attributed to other causes, such as "symptoms, senility, etc." (ICD #780-795 and ICDA #780-789) or to other cardiovascular-renal diseases. We determined age-adjusted death rates for major causes for all races and both sexes for county Groups 1 and 5 for the years 1958–1967 using published vital statistics.[7] An excess of deaths in county Group 5 was ascribed to "symptoms, senility, etc." If all the excess in this group represented arteriosclerotic heart disease, the difference in mortality from that cause between county Groups 1 and 5 would be reduced by about half. The national vital statistics, however, include all races, and the higher proportion of American-Indians in county Group 5 might account for the greater proportion of deaths attributed to ill defined causes. Deaths from arteriosclerotic heart disease did not appear to have been assigned to other cardiovascular-renal diseases, since death rates from these causes are slightly lower in county Group 5 than in county Group 1. Moreover, if, through a diagnostic or reporting artifact, deaths were less frequently attributed to arteriosclerotic heart disease in the high-altitude counties, the same trend with altitude would be expected for females as for males. Thirdly, comparison of mortality rates for three periods (1957–1962, 1963–1967 and 1968–1970) showed that, if anything, the decrease in mortality with residence at altitude was more evident in recent years when reporting might be expected to be more precise.

Table 2. Age-Adjusted Death Rates Attributed to Arteriosclerotic Heart Disease by County Altitude Group.

Altitude Group	Deaths/100,000*		Relative Death Rates†	
	Male	Female	Male	Female
1	403.2	195.7	100	100
2	396.2	196.9	98	101
3	363.3	195.6	90	100
3A	311.0	168.7	77	86
3B‡	380.9	204.3	94	104
4	346.8	203.6	86	104
5	291.0	165.0	72	84
New Mexico (total)	370.5	194.0	92	99

*Age ≥25 yr, white males & females only.

†Relative to an arbitrary rate of 100 in lowest altitude group.

‡Bernalillo County (Albuquerque).

We examined the possibility that migration of ill persons from high-altitude to low-altitude counties contributed to these results. If such an explanation were true, it should be reflected by deaths at the only United States Veterans Administration Hospital in New Mexico, located in Albuquerque. Review of deaths at this hospital, 1968–1970, indicated that substantial migration of patients with cancer did occur, and that this migration to Albuquerque was more than twice as frequent from high-altitude as from low-altitude counties. In contrast, migration of patients with arteriosclerotic heart disease was infrequent, and differences in migration among county groups were negligible.

The data were also examined to determine whether differences in proportions of urban and rural residents among the county groups might explain the altitude trend, since urbanization is associated with increased mortality from arteriosclerotic heart disease.[8] Such an effect is evident in county Group 3, which, except for Bernalillo County, is predominantly rural (Table 2). The effects of differences in urban and rural residence could not be examined directly because deceased persons could not be classified according to residence without examination of individual death

certificates. Accordingly, death rates from arteriosclerotic heart disease for white males were combined in predominantly rural counties at different altitudes and, similarly, for more urban counties. The 12 counties with one or more communities inhabited by 5000 or more white males according to the average of the 1960 and 1970 censuses were considered to be urban counties. In these "urban" counties the proportions of the total white male population of the county residing in such communities ranged from 48 to 94 per cent. The remaining 20 counties were classified as rural. Age-adjusted death rates for white males due to arteriosclerotic heart disease were determined separately for rural and urban counties within each altitude group; to achieve adequate numbers the five county groups were compressed into three. Table 3 shows that the same decline in mortality with altitude occurs in rural and urban populations as in the total white male population, even though rates in rural counties were lower than in urban counties.

Table 3. Death Rates from Arteriosclerotic Heart Disease for White Males in Urban and Rural Counties According to County Altitude Group.

GROUP	% URBAN*	URBAN COUNTIES†		RURAL COUNTIES†
		RATES‡	% URBAN	RATES‡
1 & 2	44	407.8	65	383.3
3	76	371.3	90	320.3
4 & 5	49	321.9	73	312.7

*All counties.
†Classification of counties as urban or rural is explained in text.
‡Rates are for ages ≥25 yr, age-adjusted as described in text.

We also examined available data to determine whether different distributions of ethnic groups among white males might account for the apparent effect of altitude. The 1970 census indicates that the proportions of Spanish-American white males increased from 34 per cent in county Group 1 to 64 per cent in county Group 5. Thus, if mortality rates from arteriosclerotic heart disease are lower among Spanish-American than non-Spanish-American whites, ethnic distribution could account for the association with altitude. Because of underestimation of Spanish-American populations in the 1960 census and overestimation in 1970, this possibility could not be tested directly. However, as with the question of urban-rural differences, it is possible to assign the counties to sets with large and small proportions of Spanish-Americans. Table 4 shows mortality rates from arteriosclerotic heart disease for white males according to altitude groups, with counties separated according to the proportion of Spanish-Americans as estimated in the 1970 census. Table 4 shows the same tendency to decreasing mortality with altitude, regardless of the proportions of Spanish-American males in the population. Because of the previously noted urban-rural effects, sets of counties at different altitude levels were also examined to determine whether the decline in

Table 4. Death Rates from Arteriosclerotic Heart Disease for White Males According to Proportions of Spanish-Americans and County Altitude Group.

GROUP	% SPANISH-AMERICAN*	PROPORTIONS OF SPANISH-AMERICANS†					
		LOW			HIGH		
		rates‡	*% Spanish-American*	*% urban*	*rates‡*	*% Spanish-American*	*% urban*
1 & 2	35	415.8	26	52	354.6	58	30
3	45	371.7	39	90	309.9	81	14
4 & 5	63	350.8	25	46	312.6	71	50

*All counties. †Calculations are described in text.
‡Rates are for white males ≥25 yr, age-adjusted as described in text.

mortality with increasing altitude in counties with high and low proportions of Spanish-Americans might be related to more rural residence in counties with more Spanish-Americans. Therefore, Table 4 also includes the per cent of the white males in each grouping residing in rural circumstances as previously defined, and shows no relation between more rural residence and higher proportions of Spanish-Americans. Thus, even if males of Spanish descent exhibit lower mortality rates from arteriosclerotic heart disease, those rates appear to be similarly affected by altitude.

We obtained further indirect corroboration of a lack of confounding by ethnic group by examining non-Spanish-American male deaths from arteriosclerotic heart disease for the years 1968–1970 according to county group. For these three years, the New Mexico Regional Medical Program provided mortality data in which whites were separated into non-Spanish-Americans and Spanish-Americans according to surname. Indians with non-Spanish-American or Spanish-American surnames were identified by death certificate information (residence and place of death) and classified separately. We estimated non-Spanish-American male populations at risk in 10-year age groups for those years by subtracting the Spanish-Americans in each age group as determined by the 1970 census by county from the total white male population for each year. Because the 1970 census overidentified the Spanish-American proportion of the population and because the counties at higher altitude have larger Spanish-American populations, any bias would increase apparent mortality at altitude by underestimating the non-Spanish-American population at risk. In spite of this increase and the small numbers involved, the same trend toward reduced mortality at higher altitudes was observed.

Cigarette smoking did not appear to exert an effect on these results; examination of state cigarette tax receipts for 1972–1973 showed no statistically significant differences among the county groups per 1000 adults. Furthermore, variations in hardness of water cannot explain these results, since hardness varies inversely with altitude in New Mexico.[9] Other factors that might exert an effect but cannot be examined in-

clude possible dietary variations and occupational differences. Whether some unknown factor predisposes to residence at higher altitude that also selects against arteriosclerotic heart disease cannot be determined.

Discussion

The apparent association between residence at higher altitudes and decreased mortality from arteriosclerotic heart disease in white males in New Mexico differed from the negative results of a somewhat similar study in Colorado.[4] Methodologic differences may have contributed in part to these disparate results, in that rates for the total population were determined in Colorado whereas the present study examined separately only rates for white males and white females. Although non-white populations in Colorado are probably too small to influence total rates significantly, the ratio of males to females in older populations tends to increase with ascending altitude. In 1960, 48.2 per cent of the Colorado residents 45 years and older were male; in the highest and second-highest county altitude groups the proportions were 54.0 and 51.9 per cent respectively. Since mortality rates for arteriosclerotic heart disease for males are approximately twice those for females, the disproportionate numbers of males at higher altitudes in Colorado may explain some of the disparity by masking any reduction in mortality from arteriosclerotic heart disease when rates are combined for both sexes.

There is some information available on mechanisms whereby residence at high altitude may protect against the development of arteriosclerotic heart disease. Hultgren[10] has reviewed several studies indicating that living at altitude deters the development of hypertension. Comparative studies indicate that blood pressure, particularly systolic, is lower at high altitude and that sequential changes with age are less pronounced than at sea level. Acclimatization of hypertensive patients also appears to be associated with reduction in systolic and diastolic pressures. A second effect of high altitude that might exert a protective influence is increased myocardial vascularity. Arias-Stella and Topilsky demonstrated at autopsy that Peruvians resident at altitude exhibit increased vascularity of the myocardium as compared to those at sea level.[3] However, Moret found evidence that coronary blood flow is reduced at high altitude in man.[11] Experimentally, in piglets adapted to simulated high altitude interarterial coronary anastomoses developed that regressed after restoration of sea-level atmosphere, although diameters of coronary arteries were similar at high-altitude and at sea-level pressures in these piglets.[12] One physiologic consequence of residence at high altitude that should predispose to coronary obstruction is the higher hematocrit associated with diminished oxygen tension. If it does, it appears to be outweighed by other influences in the present study.

Regarding the possibility that residence at high altitude protects against acute thrombotic occlusion, even in the presence of underlying arteriosclerotic heart disease, Albrecht and Albrecht have described stepwise increases in prothrombin times in persons ascending to 6200 m above sea level and stopping at intermediate levels for purposes of acclimatization.[13] On the other hand, Genton et al. exposed calves to high altitude and found evidence of hypercoagulability,[14] but this observation might be attributable to exposure to cold.

Another pathophysiologic explanation for the present results — that residence at high altitude does not protect against the development of arteriosclerotic heart disease but does diminish the likelihood of death if acute coronary obstruction occurs — is suggested by two experiments in rats.[15,16] In brief, excised cardiac muscle fibers from hypoxia-adapted rats retained contractibility in vitro after acute hypoxia better than fibers from rats accustomed to sea-level oxygen tensions, perhaps because of enhanced capability for anaerobic metabolism in cardiac myofibrils of adapted rats. No relevant physiologic observation is available in man.

Also unexplained is why the altitude-associated effect was not observed in females. Whether pathogenic mechanisms for arteriosclerotic heart disease in females differ from those in males is unknown. It is also possible that the association was not evident in females because of a threshold factor; the fact that females in county Group 5 did exhibit lower mortality from arteriosclerotic heart disease than those residing at lower altitudes suggests such a possibility.

It is remarkable that these differences in mortality occurred at altitudes that were moderate in comparison to those in Peru and other areas where high-altitude physiologic studies have been conducted. The partial pressure of oxygen in the atmosphere at 2134 m is 114 mm Hg as compared to 149 at sea level. Grover has indicated that limitations in work capacity at altitude in recently acclimatized men are a consequence of cardiac rather than pulmonary factors[17]; perhaps this limitation of activity stimulates development of an undefined protective mechanism.

The duration of residence at altitudes associated with the apparent protective effect cannot be determined from this study. It is impossible to compare stability of residence among survivors and nonsurvivors in these populations. However, data from the 1970 census for whites 35 years of age and older indicate that 79 per cent of all white males and 89 per cent of Spanish-American males in New Mexico had resided in the same county for five years or more.[6] Therefore, it appears that the population displayed reasonable stability over the five years before 1970. The absence of such stability would be incompatible with the hypothesis of a real relation between altitude and arteriosclerotic heart disease.

Further studies are needed to elucidate the mechanism of this association, if it is confirmed in other data. Such studies might shed light on factors in the genesis of arteriosclerotic heart disease, such as the pro-

tective effect of exercise, as suggested by studies of mortality among longshoremen.[18] A simple explanation for these findings may well be that adaptation to reduced oxygen tension at higher altitudes is never complete, and, therefore, that exertions associated with the activities of daily living represent increased physical exercise.

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EPIDEMIC MEASLES IN A HIGHLY VACCINATED POPULATION

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Abstract During November, 1975, to May, 1976, measles occurred at a rate of 20.3 cases per 1000 in a purported immunized population, of whom historical and serologic survey revealed that 9 per cent had no history of either measles illness or vaccination and 18 per cent did not have detectable measles antibody. Antibody was detectable in 92 per cent of those vaccinated at ⩾13 months, 80 per cent at 12 months and 67 per cent of those vaccinated when less than one year old ($P<0.001$), but no significant differences existed with increasing years since vaccination ($P>0.1$). A second vaccination increased detectable antibody prevalence only in those originally vaccinated when less than nine months old (42 to 80 per cent, $P<0.02$). During a measles outbreak, more cases occurred in those receiving vaccine when less than 12 months old than in those vaccinated at ⩾12 months (37 per cent vs. 9 per cent, $P<0.001$). A second vaccination protected those originally vaccinated at <12 months (35 per cent ill without a second vaccination vs. 2 per cent with, $P<0.001$). Thus, a single measles vaccination of children <12 months old does not protect; a second vaccination will protect this group. (N Engl J Med 296:585-589, 1977)

MEASLES vaccine (live, attenuated virus) was licensed in 1963, and by early 1967, a marked decline in reported cases had occurred. In general, vaccinated youngsters remained free of measles. Scattered outbreaks continued to occur, however, and reports called attention to practices that left vaccinated children susceptible to wild virus. Age of the child at vaccination was found to be important for successful immunization,[1-3] and in 1969 the Advisory Committee on Immunization Practices advised that measles vaccine be administered only to children 12 months or older.[4]

During October-December, 1975, 33 cases of measles occurred in northeast metropolitan Detroit, an area where more than 95 per cent of children entering school in 1975 had a history of measles vaccination. Investigation revealed that many cases occurred in

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