Variation in Neonatal Death Rate and Birth Weight in the United States and Possible Relations to Environmental Radiation, Geology and Altitude

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THE POTENTIAL BIOLOGICAL HAZARDS for man exposed to extremely low levels of ionizing radiation continue to be the subject of much debate. Ideally, the hazards are best evaluated in man himself, though there are many difficulties inherent in any survey or study of a human population. The United States population, for example, contains widely different social customs, economic levels, educational attainments, racial origins, and health practices. In addition, the age structure varies among the different regions and states, and a high degree of mobility is a population characteristic. In spite of these variables, there have been several attempts to evaluate the effects of environmental radiation on man, largely by means of the published vital statistics records. These have included the study of bone tumor incidence (Bugher and Mead, 1958), congenital malformations (Gentry, Parkhurst and Bulin, 1959; Kratchman and Grahn, 1959; Wesley, 1960), and leukemia incidence (Court Brown *et al.*, 1960; Craig and Seidman, 1961). The results of the tumor and leukemia incidence studies have all been negative. The malformation studies have been suggestive of a radiation effect, though alternative explanations and hidden biases were not entirely accounted for.

The present study is a more detailed follow-up of our previous preliminary report (Kratchman and Grahn, 1959). This study is not restricted to congenital malformation deaths, as these are not believed to be uniformly diagnosed in all regions. In addition, deaths from this cause are not presented in the vital statistics by age intervals. The calculation of comparative mortality rates would therefore require the age-standardization of all population groups. The neonatal death rate (deaths occurring within the first 28 days of life) is used instead, since it is normally based on the number of live births and therefore avoids the difficulties of a shifting population base. About 10 to 15 per cent of the neonatal deaths are attributed to malformations, and in addition, there is a sufficient variety of causes of death to permit the measure to reflect the effect of a number of intrinsic and extrinsic factors. The birth weight parameter was examined because of the high negative correlation that exists between it and the neonatal death rate.

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METHODS

Vital Statistics Data

The published vital statistics data of the U.S.A. (U. S. Department of Health, Education and Welfare) for the eight years 1950 through 1957 have been the source of all neonatal mortality and birth weight data, though the latter were not available for the years 1950 and 1951 in the form employed. The neonatal deaths and live births were tabulated by county of residence for the white population. The published listings are separated into "white" and "non-white" whenever 10 per cent of the population or 10,000 of their number are non-white. This category includes Negro, American Indian and Oriental races. When the 10 per cent or 10,000 criteria are not met, no separation is given, and therefore tabulations by county contain a small, but variable, proportion of non-white births and deaths. The sum effect of this is to raise the death rates a little above those published for the white population of a given state or region.

The birth weight data are published, by county, in two broad categories: "2,500 grams or less" and "2,501 grams or more." County tabulations for this study were re-expressed in terms of the percentage of births weighing 2,500 grams or less. Births of this category are classed as "immature," according to the Sixth Revision of the International Lists of Diseases and Causes of Death; therefore the weight parameter expresses the frequency of immature births in the population. The same breakdown of racial information pertains to both the weight and mortality data.

Several additional tabulations were made for selected states, regions, or years. These include: gestation length, mean birth weight, per cent born in hospitals, cause of death, and time of death. For the states of Delaware, Illinois, Indiana, Idaho and Montana, which contain virtually no uranium ore reserves, neonatal mortality rates were tabulated on a state-wide basis rather than by summation of individual counties for the purpose of rough comparison across an array of geologic environments.

Census Data

Certain characteristics of the surveyed population groups were tabulated to evaluate differences in age and socio-economic level. Median family income and median age values were tabulated, by county, from the published 1950 U. S. census data (U. S. Bureau of the Census, 1953). Where needed, other characteristics, such as median school years completed, per cent non-white, total population number, and population growth figures were also derived from the census reports.

Geologic Data

The geologic provinces of the U. S. were carefully defined in order that every county in the study could be assigned to a province. Where geologic borders did not coincide with political boundaries, assignment was made according to the location of the majority of the land area of the county.

Data as of January 1, 1962, on the location and magnitude of known uranium ore reserves in terms of tons of U_3O_8 were obtained from the Division of Raw Materials, U. S. Atomic Energy Commission.

Altitude estimates were drawn from several sources, such as road maps and commercial atlases. However, most of the available figures, regardless of immediate source, are drawn from the accumulated data of the U. S. Geological Survey.

The mean county-altitude values finally employed are not mean values for the total physical topography, but are better classed as "mean populated altitude" figures. Individual locality elevations were multiplied (weighted) by the population number for the given locality. These were summed within the county and divided by the total population number to yield a weighted mean altitude. When county values are assembled into larger units, as states or provinces, the county altitudes were weighted by the number of live births. Thus, state altitude values are, for example, mean populated altitudes weighted by the number of live births at risk. The above procedure is critical for the present survey since mean physical elevations are nearly always well above the populated elevations.

Radiation Data

In the absence of detailed radiation dosimetry data, the preliminary report (Kratchman and Grahn, 1959), relied on the geographical distribution of uranium ore deposits as an indication of higher than average concentration of radioactive material in the natural environment. Although this presumption recognized the fact that most uranium reserves are highly localized, frequently deeply-buried, and in remote unpopulated areas, it was selected as a preliminary hypothesis on the assumption that an area containing large uranium deposits was presumed to be an environment which has a greater amount of disseminated uranium than an area which lacks deposits.

Since the publication of the preliminary report, additional studies have indicated that the assumption that uranium ore reserves are indicative of higher radiation levels may not be entirely appropriate. Nevertheless, there is a generally higher terrestrial radiation level in the mountain areas than in the midwestern region (Solon *et al.*, 1959). The average of 27 independent readings of environmental radiation (excluding terrestrial beta rays) is 11.7 microroentgens per hour or 103 milliroentgens per year for Ohio, Indiana, Illinois and Wisconsin. Of this, 66 mr is terrestrial, 37 cosmic. Forty-nine readings in Colorado, Wyoming, Utah and New Mexico averaged 20.2 μr per hour or 177 mr per year. Of this, 104 mr is terrestrial and 73 cosmic. The terrestrial gamma radiation is therefore about 50 per cent and cosmic radiation nearly 100 per cent higher in the sampled regions of the mountain states.

These data of Solon *et al.* are the only direct measures available for the regions of interest and provide only a broad definition of the differences in radiation intensity. In view of the above remarks concerning the probable lack of close correlation between radiation levels and uranium reserves, Solon's data are probably sufficient for the question of external radiation levels. Radiation levels from the deposition of internal emitters have not been measured.

The dose rate from cosmic radiation was also measured and reported by Solon *et al.* (1959, 1960) for altitudes up to 17,000 feet after adjustment to a latitude of about 41° N, which very nearly bisects the continental U. S. No attempt was made to correct for latitude variation since the cosmic flux rises only 14 per cent between 30° and 50° N at an altitude of 6,500 feet and less than 10 per cent at sea level. The altitude effect on radiation intensity is considerably greater and the majority of the populations studied reside in the more limited latitude range between 35° and 45° N.

Geographic Areas Selected for Study

Table 1 presents the number of counties in the study with and without known ore reserves by geologic province and state west of the Mississippi River. Fig. 1 outlines the geologic provinces in the U. S. and Fig. 2 indicates the states and counties included in the study. The map does not encompass the Texas Coastal Plain counties of Colorado, DeWitt, Fayette, Gonzales, Karnes and Lavaca.

Only portions of some states are included. These are:

(1) California and Washington: Counties containing large granite batholiths and including several ore deposits.

(2) North and South Dakota: Limited ore bearing areas with non-uranium areas for controls.

(3) Nebraska: A non-uranium control area at moderate altitude.

TABLE 1. GEOLOGIC PROVINCES AND STATES INCLUDED IN THE ANALYSIS OF NEONATAL MORTALITY RATES

Geologic Province	State	No. of counties	
		With U_3O_8 reserves	Without U_3O_8 reserves
Colorado Plateau	Arizona	3	0
	Colorado	6	5
	New Mexico	3	2
	Utah	7	7
Rocky Mountains	Colorado	9	18
	New Mexico	1	2
	Utah	0	5
	Washington	2	2
	Wyoming	4	9
Basin and Range	Arizona	3	8
	Nevada	4	13
	New Mexico	3	5
	Utah	2	8
Western Stable Region	Colorado	1	24
	Kansas	5[a]	9[b]
	Nebraska	0	11
	N. Dakota S. Dakota	5	7
	New Mexico	0	16
	Texas	9[a]	8[b]
	Wyoming	5	5
Coastal Plain	Texas	6	7
Coast Ranges	California	2	9
		80	180

[a]With known helium reserves.
[b]Without known helium reserves.

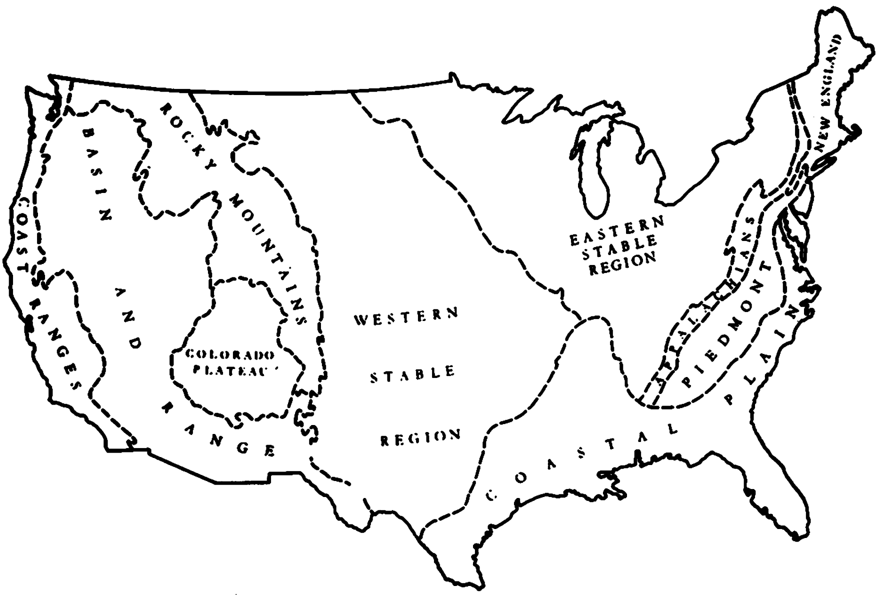

FIG. 1. Geologic provinces of the Continental United States.

(4) Kansas and Texas Panhandle: Helium reserve area with non-helium areas as controls.

(5) Texas Coast: Limited ore-bearing area with non-uranium areas as controls.

Control counties, in the specified instances, were chosen from geologic maps according to two criteria; contiguity with an ore bearing county and similarity of the geology.

RESULTS

Neonatal Mortality: Standardization of the Population

During the eight-year study period, a 15 per cent decline in neonatal mortality has occurred. The rate of change is essentially the same for the mountain states as for the whole U. S. (Fig. 3). This suggested that the time trend could be ignored and the data were pooled across the eight years.

An analysis of socio-economic factors was done for the years 1951-1954 for the nine geographic census divisions of the U. S. (these do not coincide with the geologic provinces and are defined in Volume II, Part 1, U. S. Summary, 1950 census). The eight states of the Mountain Division were also separately evaluated. The data for this analysis are given in table 2.

Several assumptions can be made concerning these measures of the socio-economic characteristics of the population: (a) median income reflects educational attainment and age, (b) neonatal mortality decreases as the probability of being born in a hospital increases and the latter is in turn positively related to income, (c) neonatal mortality decreases with increasing income. Income

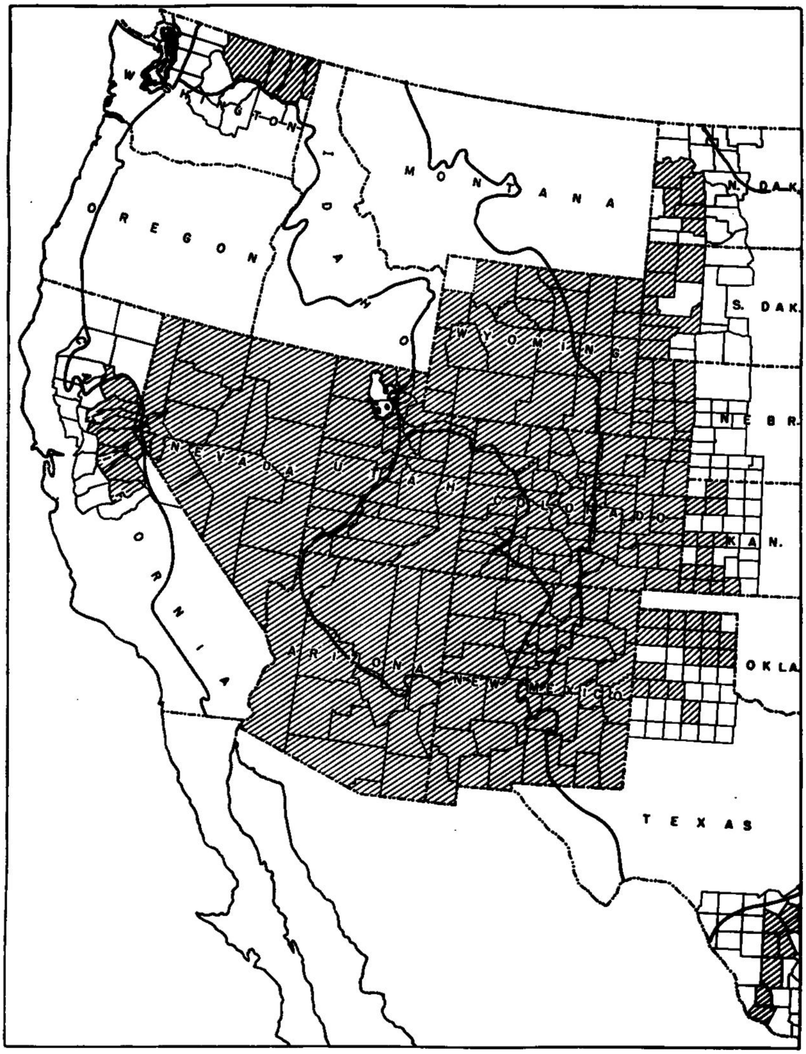

FIG. 2. Western portion of United States. Counties included in survey indicated by cross hatch. Heavy lines outline geologic provinces defined in Fig. 1.

therefore appears to characterize the general educational and social attainments and level of medical care in the population. Variation in median family income has consequently been used to account for the effect of differences in socioeconomic level on neonatal mortality among the individual counties and states. The regression is —2.0/1000 live births per $1,000 median income, and all county values were adjusted to a common income of $3,000.

The relationship between maternal age and neonatal mortality is shown in Fig. 4. This is based upon data from a limited special study of live births that occurred during the first quarter of 1950 (U. S. Department of Health, Education and Welfare, 1958). Individual county mortality ratios were

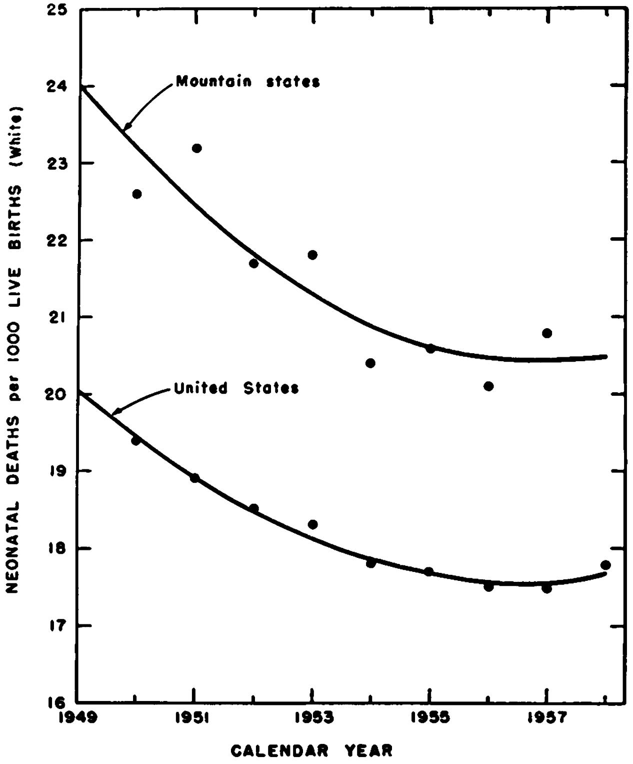

FIG. 3. Regression of neonatal death rate on time in years for U. S. and mountain states.

TABLE 2. SOCIO-ECONOMIC VALUES FOR U. S. CENSUS DIVISIONS AND MOUNTAIN STATES

Division or State	Neonatal[a] Death Rate per 1,000	Median[b] School yrs.	Median Family[b] Income-Thous.	Median[b] Age yrs.	% Born in[a] Hospitals
New England	17.58	10.4	$3.25	32.4	98.8
Middle Atlantic	17.43	9.5	3.40	33.0	98.3
E. North Central	17.85	9.7	3.43	31.4	98.1
W. North Central	17.88	9.1	2.90	31.2	97.0
South Atlantic	18.90	9.2	2.41	28.3	93.6
E. South Central	20.93	8.7	1.79	27.0	87.0
W. South Central	19.68	9.3	2.36	28.2	89.6
Mountain	20.98	10.9	3.10	27.8	95.1
Pacific	17.68	11.6	3.55	32.0	98.8
United States (Total)	18.37	9.7	3.07	30.8	95.9
Arizona	22.05	10.6	2.85	27.8	95.2
Colorado	22.40	10.9	3.07	29.6	96.2
Idaho	18.63	11.0	3.05	27.5	98.6
Montana	18.83	10.3	3.26	30.2	98.9
Nevada	20.80	11.7	3.61	32.1	99.4
New Mexico	25.03	9.5	2.65	24.4	82.1
Utah	16.63	12.0	3.26	25.0	98.9
Wyoming	22.25	11.1	3.48	28.0	98.9

[a] Based on 1951-54 data for white population only.

[b] From 1950 U. S. census data; income for 1949.

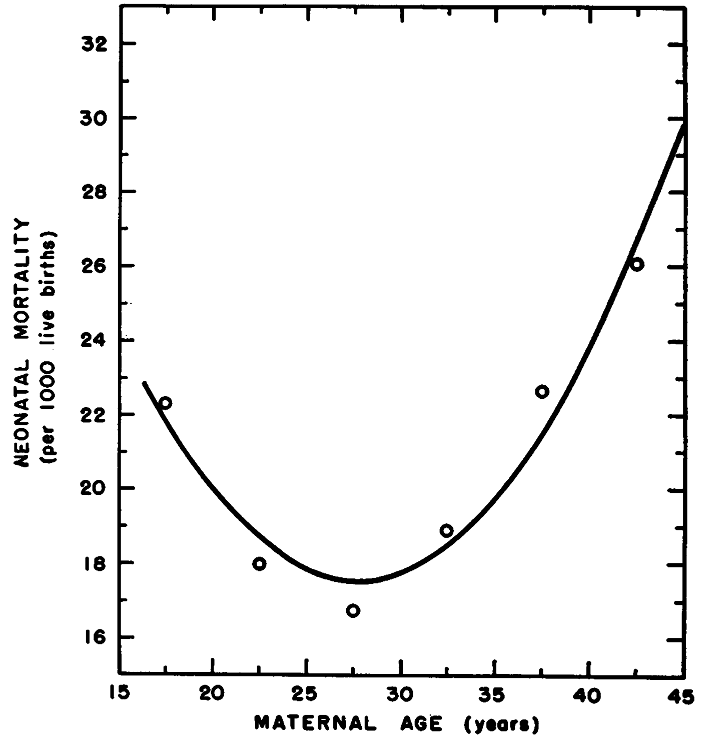

Fig. 4. Regression of neonatal death rate on maternal age, 1950 white population.

adjusted to a constant maternal age of 27.5 years by means of the equation: $Y = 49.8 - 2.33A + 0.042A^2$ where A is the maternal age. At 27.5 years, $Y = 17.5$, and is at a minimum value. For ages above or below 27.5, the mortality rate, Y_X, is always greater and the difference, $Y_X - 17.5$, is subtracted from the observed county value for adjustment purposes.

Comparison of States and Geologic Provinces

The age and income adjusted neonatal mortality figures for the individual states, or portions thereof, are given in table 3. Significant differences exist between Colorado, for example, and the Texas Coastal Plain counties, sampled regions of Washington and California, or the states of Delaware, Illinois and Indiana. The most striking difference involves the state of Utah, which has the lowest neonatal death rate in the U. S., significantly below its neighboring states. This is not associated with a high fetal death rate, so it apparently cannot be attributed to a classification difference for perinatal mortality. The individual county values in Utah are uniformly low but do vary from about 10/1000 to 24/1000, though this is a more limited range as compared to other states. A further analysis of the Utah data will be given below and it will be shown that Utah, though an exception, does adhere to certain basic relationships to be brought out. However, because of its unexplained deviation from other states, Utah is not included in subsequent analyses.

A comparison of geologic provinces (table 4) reveals differences that were already evident from the examination of their composite states. Significant differences do exist, but these are associated with the extremes of geographic location. The data in both tables 3 and 4 point to altitude as an important variable. However, ore reserves also are larger in the provinces and states at the higher altitudes where the higher mortality rates prevail, even though there appears to be no consistent effect that can be associated with the presence of uranium ore within the geologic provinces.

TABLE 3. AGE AND INCOME ADJUSTED NEONATAL DEATH RATES AND ASSOCIATED PHYSICAL VARIABLES BY STATE; 1950-57
WHITE POPULATION ONLY

State	Altitude (feet)	U_3O_8 Reserves (tons)	Atm. Press (mm Hg)	Cosmic rad. (mr/yr)	No. of Live Births	Neonatal Deaths ± SE (Per 1,000 births)
Texas (Coast)	310	570	752	35.1	37.216	18.13 ± 0.98
Washington	1,440	[a]	721	41.9	11,078	18.01 ± 1.80
California	1,490	40	720	42.1	26,203	18.33 ± 1.17
Arizona	2,080	2,240	703	46.4	179,659	20.67 ± 0.47
Kansas	3,080	(Helium)	678	53.6	15,007	20.90 ± 1.65
Dakotas	3,180	2,680	676	54.2	33,975	20.10 ± 1.08
Texas (Panhandle)	3,370	(Helium)	672	55.3	35,192	21.26 ± 1.09
Nevada	3,690	190	664	58.0	40,360	22.64 ± 1.04
Nebraska	3,920	—	657	60.2	22,790	21.72 ± 1.37
New Mexico	5,010	80,330	632	69.6	189,242	23.41 ± 0.49
Colorado	5,390	11,670	623	73.1	306,818	22.19 ± 0.38
Wyoming	5,390	60,830	623	73.1	66,728	22.65 ± 0.82
Delaware	60	—	758	34.0	63,648	17.10 ± 0.73
Illinois and Indiana	630	—	744	36.8	2,285,385	17.40 ± 0.12
Idaho	3,320	—	673	55.1	131,306	18.25 ± 0.52
Montana	3,490	50	668	56.7	127,660	18.66 ± 0.54
Utah	4,590	12,190	642	65.6	191,042	16.63 ± 0.41

[a] Data not available for publication.

TABLE 4. AGE AND INCOME ADJUSTED NEONATAL DEATH RATES BY GEOLOGIC PROVINCE

Geologic Province	U_3O_8 Reserves (tons)	Altitude (feet)	No. of Live Births	Neonatal Death Rate ± SE
Basin and Range	670	3,550	74,180	20.96 ± 0.74
	Non-Ur.	2,700	213,699	21.89 ± 0.45
	Total	2,920	287,879	21.65 ± 0.38
Coastal Plain	570	330	20,024	18.74 ± 1.36
	Non-Ur.	280	17,192	17.43 ± 1.41
	Total	310	37,216	18.13 ± 0.98
Coast Ranges	40	2,390	2,371	19.51 ± 4.02
	Non-Ur.	1,400	23,832	18.21 ± 1.23
	Total	1,490	26,203	18.33 ± 1.17
Colorado Plateau	104,230	5,670	38,921	21.65 ± 1.05
	Non-Ur.	6,240	18,098	21.19 ± 1.52
	Total	5,850	57,019	21.51 ± 0.86
Rocky Mountains	62,580	5,440	66,864	21.30 ± 0.79
	Non-Ur.	6,100	59,827	21.56 ± 0.84
	Total	5,750	126,691	21.42 ± 0.58
Western Stable Region	2,700	4,320	37,127	21.04 ± 1.05
	Non-Ur.	4,790	341,934	22.81 ± 0.36
	Helium	3,220	27,508	21.04 ± 1.22
	Non-Helium	3,360	22,691	21.28 ± 1.36
	Total	4,570	429,260	22.46 ± 0.32

Altitude is not a simple variable. There is an increase in cosmic ray intensity, a decrease in oxygen partial pressure, an increase in ultraviolet radiation, and a decrease in average humidity and temperature accompanying altitude increase. Although a search for radiation effects underlies this study, oxygen tension is one environmental factor that cannot easily be dismissed, since it has long been recognized as a factor in the disturbed reproductive physiology seen at high altitudes (Monge, 1948). Fig. 5 presents the mortality data from table 3 plotted against cosmic ray intensity and atmospheric pressure in terms of mm of mercury. The latter can be re-expressed as the partial pressure of oxygen by multiplying the abscissal values by 0.2096. The equations for the two relationships are:

$$Y_1 = 13.42 + (0.1343 \pm 0.0205)D \text{ and}$$
$$Y_2 = 48.92 - (0.415 \pm 0.0058)P$$

where Y_1 and Y_2 are the predicted neonatal death rates per 1,000 live births, D is annual cosmic ray dose in milliroentgens, and P is atmospheric pressure in millimeters of mercury. Both regressions are highly significant ($r_{Y\cdot D} = +0.900$; $r_{Y\cdot P} = -0.914$) and the regression on atmospheric pressure is slightly, but not significantly, the better fit. The values of Y at sea level are:

$$Y_1 = 17.89, \quad D = 33.3 \text{ mr}$$
$$Y_2 = 17.38, \quad P = 760 \text{ mm}$$

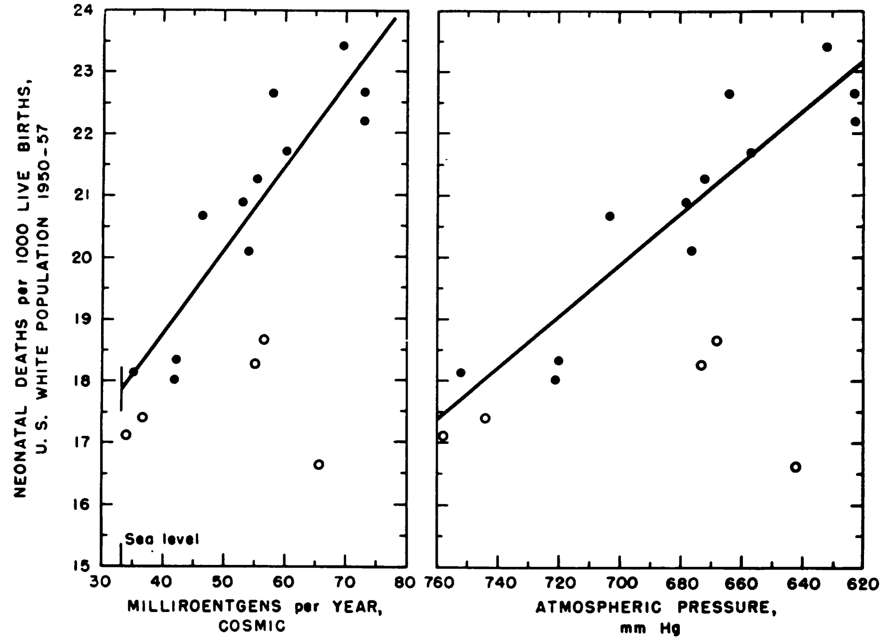

FIG. 5. Regressions of age and income-adjusted neonatal death rate on annual cosmic radiation dose and atmospheric pressure. Open circles not included in calculation (see text and table 3). To facilitate comparison, values for atmospheric pressure are plotted from high to low.

The regression of mortality rate (Y_3) on altitude in feet (A) is

$$Y_3 = 17.51 + (1.04 \times 10^{-3} \pm 0.15 \times 10^{-3})A.$$

This regression fits the data about as well as that for atmospheric pressure and is used for certain data adjustments and comparisons. It should be noted that neither cosmic radiation intensity nor atmospheric pressure is linearly related to altitude.

In all three cases, the regression coefficient is the least squares estimate from the data in the upper portion of table 3. Data for the states of Delaware, Illinois, Indiana, Idaho and Montana are not employed since, as noted previously, these data are not summarized by county and therefore do not include the small portion of non-white births and deaths which invariably elevate the final mortality rates. Utah is the exception, but within the state the data are consistent with the relationships noted in Fig. 5. Individual counties in Utah range from 3,500 to 7,000 feet and a progressive increase in mortality rate is detectable across this range. The rate of change is similar to the above noted regressions and the equation for Utah is

$$Y = 7.78 + (1.83 \times 10^{-3} \pm 0.79 \times 10^{-3})A.$$

Comparison of Areas with and without Uranium Ore

The data in table 4 also present the mortality rates in the six provinces according to the presence or absence of uranium ore and, for western Kansas and the Texas Panhandle, the presence or absence of helium reserves. The helium reserves are considered since, as Kratchman and Grahn (1959) indicated, these reserves may be the result of the disintegration of localized disseminations of uranium and therefore reflect a higher than average level of environmental radiation. The differences within provinces are not significant and uranium-bearing counties are as likely to have mortality rates above as below their control areas. There is, however, a small confounding of altitude in these comparisons.

In order to ascertain if any relationship may exist between mortality and the presence of uranium ore in the absence of the altitude variable, the 57 counties with ore reserves (excluding Utah) were adjusted to a constant altitude of 3,000 feet. These adjusted mortality rates were plotted against a crude measure of ore concentration; tons of U_3O_8 per 1,000 square miles. No correlation was evident even across six log cycles of difference in ore concentration. The regression coefficient of death rate on log ore concentration is $+0.113 \pm 0.625$. *Thus, it can be concluded that the quantity of uranium ore reserves is unassociated with the probability of neonatal mortality.* However, in the absence of direct measurement of radiation levels in the 57 counties, these results cannot be considered as having entirely eliminated an interpretation based on radiation-induced injury.

Birth Weight and Associated Parameters

In the course of the analysis of neonatal mortality, it became increasingly apparent that other measures associated with the birth event had to be examined, since the observed relationship with altitude strongly suggested the existence of an underlying subtle disturbance of reproductive physiology.

Table 5 presents data drawn from the 1956 and 1958 statistics on gestation length and birth weight for the indicated states that were selected for their distribution between sea level and 6,000 feet and the adequacy of sample size for live births. There is a decline in the duration of gestation with increasing altitude, but the maximum difference is only about 1 per cent of the average duration, or about 0.4 weeks. This is not significant and will not explain the birth weight difference of 190 grams between Colorado and Illinois-Indiana. Fig. 6 describes the fetal growth curves for Illinois-Indiana versus Colorado-New Mexico for the years 1950-51. This suggests that during the last 10 weeks of gestation the growth rate of the fetus at 5,000 feet or more progressively falls behind that for the fetus at or near sea level.

TABLE 5. DURATION OF GESTATION AND BIRTH WEIGHT FOR SELECTED STATES; 1956 AND 1958 WHITE POPULATION ONLY

State	Altitude (feet)	Duration of gestation (wks)	Birth weight (grams)
Illinois-Indiana	630	40.40	3,342
Arizona	2,080	40.28	3,300
Idaho-Montana	3,400	40.13	3,290
Utah	4,590	40.23	3,288
New Mexico	5,010	40.17	3,169
Colorado	5,390	40.01	3,152

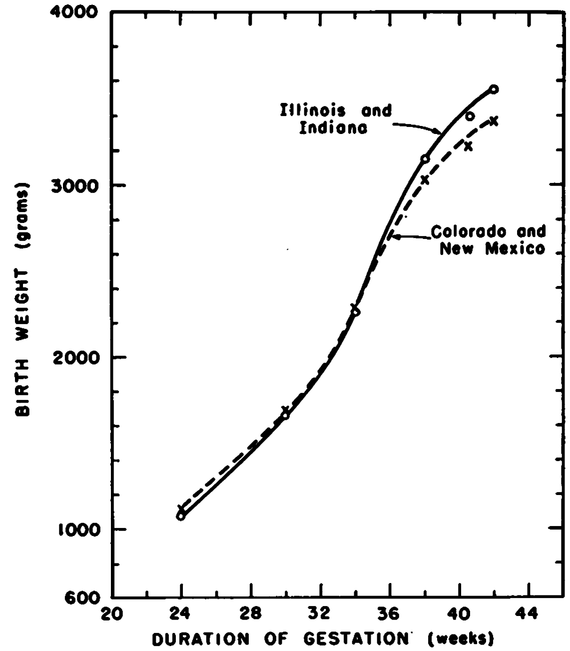

FIG. 6. Fetal growth curves derived from data on live birth weights for 1950-51 white population.

It would thus appear that, all other factors being equal, the duration of gestation may be slightly shorter at higher altitudes. In addition, birth weight is several hundred grams lower, apparently because of a depressed growth rate in the third trimester. With these observations in mind, the 1952-57 birth-weight classification data can be examined as an indication of more extensive physiological perturbation.

The percentage of live births falling in the category, "immature," 2,500 grams or less, is summarized by altitude intervals in table 6. This summary is based upon the county altitude values without regard to state or geologic province, for all states except Utah. In the 1952-57 period, between 3 per cent and 5 per cent of the birth weights were not reported. Although these are generally distributed across all weight categories, failure to report tends to occur more frequently for small infants. If so, there is probably a slightly greater rate of increase in frequency of immaturity with altitude than noted here.

In Fig. 7, the data are fitted with two equations; a first and a second degree polynomial. The equations are:

$$Y_1 = 30.6 - (0.033 \pm 0.003)P \text{ and}$$

$$Y_2 = 83.8 - (0.195 \pm 0.052)P + (0.000122 \pm 0.000039)P^2,$$

where Y is percentage of live births at 2,500 grams or less, and P is atmospheric pressure in mm of Hg.

Sea level values are:

$$Y_1 = 5.6$$

$$Y_2 = 6.4$$

The data for Utah are shown separately in Fig. 7. As noted previously for

TABLE 6. PERCENTAGE OF LIVE BIRTHS AT 2,500 GRAMS OR LESS BY ALTITUDE INTERVAL: 1952-57 WHITE POPULATION ONLY. UTAH NOT INCLUDED

Altitude Interval (feet)	Mean Alt.	Atm. Press (mm Hg)	No. Live Births	% 2,500 grams or less
0-500	263	753	35,166	6.57
501-1,000	633	743	7,147	6.66
1,001-1,500	1,118	729	73,318	6.17
1,501-2,000	1,786	713	13,809	7.97
2,001-2,500	2,286	699	56,570	7.78
2,501-3,000	2,864	684	12,207	7.14
3,001-3,500	3,256	674	50,933	8.24
3,501-4,000	3,756	662	60,226	8.46
4,001-4,500	4,287	649	63,160	8.67
4,501-5,000	4,824	636	100,420	9.47
5,001-5,500	5,237	627	133,617	10.37
5,501-6,000	5,661	617	28,011	9.80
6,001-6,500	6,149	605	53,899	10.74
6,501-7,000	6,767	591	26,619	11.54
7,001-7,500	7,213	582	10,712	11.17
7,501-8,000	7,721	570	9,427	13.04
8,001-9,000	8,519	553	2,474	12.93
9,001-10,000	9,568	532	887	16.57
10,001-11,000	10,410	513	1,697	23.7

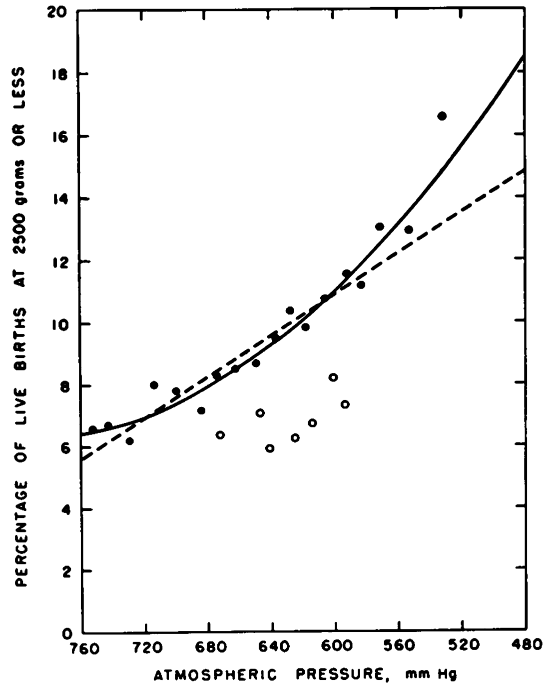

FIG. 7. Regression of percentage of "immature" births on atmospheric pressure. Dotted line: $Y = 30.6 - 0.033\ P$; solid line: $Y = 83.8 - 0.195\ P + 0.000122\ P^2$. Open circles: Utah. Solid circles: All other surveyed counties.

the neonatal death rate, the values lie below the trend but conform to it. Thus, the basic environmental factor, or factors, associated with altitude has the same effect on all fetuses and newborn. The "intercept" of the relationship can be shifted, however, by other undefined aspects of the general environment.

As birth weight drops below 3,500 grams, the probability of death in the neonatal period increases exponentially (U. S. Department of Health, Education, and Welfare, 1954). In the special study referred to, the neonatal mortality rate was 175.8/1000 live births at 2,500 grams or less and 7.1/1000 at 2,501 grams or more. Although directly applicable statistics are not available, it is possible to combine birth weight distribution data with the mortality — weight data and calculate neonatal death rates for Colorado, for example, that are reasonably close to the observed values. Apparently, most of the excess mortality in the mountain states can be attributed to their lower birth weights. In this regard, it should be noted that the published weight distribution data clearly indicate that the whole distribution of birth weights is shifted downward in the mountain states. The increased frequency of immature births is not due to a skewing of the distribution or to an accumulation of births in a few weight-class intervals below the mean. This is an extremely important factor since it indicates the existence of a generalized phenomenon affecting fetal growth and development, not a factor with a limited effect, such as one causing only an increase in premature delivery of extremely small fetuses.

Age-Specific Mortality and Causes of Death

The time and causes of death have been examined for several selected states with the hope this might reveal differences that could assist in the interpretation of the mortality and birth weight data. It should be emphasized, however, that the cause of death data are subject to considerable difference of diagnostic opinion and can only be evaluated in a broad sense.

Table 7 gives the death rate, by specific cause, for the total neonatal period, of Illinois-Indiana and Colorado-Wyoming. This comparison is emphasized on the assumption that these four states would be more similar in their levels of medical practice and socio-economic status than comparisons involving the border states. About 95 per cent of all deaths are included in the selected categories.

Most of the deaths fall into a few classes: malformations, birth injuries, postnatal asphyxia and atelectasis, and immaturity. The death rate from birth injuries and immaturity is 30 to 50 per cent higher in Colorado-Wyoming than in Illinois-Indiana, while only slight increases are noted for malformations and asphyxia. Other causes vary in the degree of excess, but a few points bear mention. Several causes of death are predominantly of genetic origin; congenital malformation, erythroblastosis, hernia and intestinal obstructions, and possibly asphyxia and atelectasis. These causes are elevated in frequency by only 2 to 18 per cent in the mountain states, while the other causes are elevated by 35 to 137 per cent. Since birth weight is lower at higher altitudes, it is not surprising to find an excess of mortality associated with immaturity as a concurrent qualification or as an unqualified cause.

TABLE 7. MORTALITY RATIOS FOR SELECTED CAUSES OF DEATH; 1950-57 WHITE POPULATION ONLY. ILLINOIS-INDIANA = 1.00

Cause of Death	Ill.-Ind. Death Rate (per 10,000 live births)	Mortality Ratio		
		Colorado-Wyoming	New Mexico	Utah
Hernia; intest. obst.	1.73	1.18	1.14	0.92
Cong. malformation	25.91	1.02	1.05	0.98
Birth injury	26.08	1.48	1.21	0.89
w/o immat.	11.28	1.12	1.24	0.86
with immat.	14.80	1.76	1.19	0.91
Postnatal asphyxia and atelectasis	47.80	1.07	0.81	0.80
w/o immat.	13.92	0.81	0.96	0.79
with immat.	33.88	1.17	0.75	0.81
Pneumonia	6.66	1.44	1.43	0.51
w/o immat.	4.55	1.26	1.48	0.47
with immat.	2.11	1.84	1.35	0.60
Diarrhea	0.88	2.19	5.50	0.72
Matern. toxemia	1.24	1.59	1.59	1.80
Erythroblastosis	6.97	1.06	1.12	1.23
Hemorrhagic dis.	1.73	1.64	0.95	1.19
Ill defined dis.	3.55	2.37	3.89	1.69
w/o immat.	0.66	1.51	4.05	1.60
with immat.	2.89	2.57	3.86	1.71
Immaturity	43.63	1.35	1.81	1.03
Accidents	1.07	1.65	2.59	0.84
All causes	173.03	1.28	1.40	0.95

Data for New Mexico and Utah are also presented in table 7. Although Utah has a total death-rate ratio to Illinois-Indiana of 0.95, there is an array of causes of death that are in excess. These include maternal toxemia, erythroblastosis, hemorrhagic diseases and the ill-defined diseases (largely nutritional maladjustment and congenital debility).

While variation in diagnostic accuracy and completeness certainly exists, immaturity and the ill-defined diseases are definitely excessive as causes of death in New Mexico, Utah, Colorado, and Wyoming. Except for erythroblastosis in Utah, the causes that may be more genetic in origin are not particularly in excess in these states.

During the first 28 days of life, the death rate drops almost exponentially. The mountain states, exclusive of Utah, have a higher rate of mortality throughout the whole time period, but it is not uniformly in excess of the Illinois-Indiana base line. The data in table 8 and Fig. 8 indicate the existence of a sharp increase in the mortality ratio for Colorado-Wyoming during the second and third full days of life. This drops back rapidly in the latter half of the first week, then rises again to a more steady level of excess mortality during the second through fourth weeks of life. This plateau continues throughout most of the first year. The early peak also appears in the data of New Mexico and Arizona though less markedly for Arizona. Since the latter has a mean altitude of about 2,000 feet compared to the 5,000 feet or more in the other states, this early period of high risk may be a characteristic of high altitude populations. Unfortunately, the published data are not reported in a way that permits the calculation of age-specific mortality rates by cause for the individual states, so it is not possible to associate the early period of high risk with specific causes.

The mortality ratios for the state of Utah generally conform to the results for the surrounding mountain states. There is a higher level of mortality during the first week, though it tends to broaden out over most of the week before dropping to a lower stable level. Since the Utah data demonstrate a small mortality excess due to immaturity, the early peak may be the result of a more rapid selection against the immature infant when subject to the additional stress of a lower ambient partial pressure of oxygen.

TABLE 8. MORTALITY RATIOS FOR ALL CAUSES OF DEATH DURING NEONATAL PERIOD; 1950-57 WHITE POPULATION ONLY. ILLINOIS-INDIANA = 1.00

Age (days)	Ill.-Ind. Death Rate (per 10,000 per day)	Mortality Ratio			
		Colo.-Wyo.	New Mexico	Ariz.	Utah
0	927	1.20	1.26	1.13	0.81
1	250	1.46	1.38	1.28	1.41
2	171	1.27	1.60	1.29	1.00
3	90	1.16	1.42	1.24	1.00
4	51	1.08	1.43	1.20	1.28
5	37	1.19	1.41	1.19	1.00
6	28	1.14	1.32	1.29	0.89
7-13	13.7	1.32	1.80	1.48	0.88
14-20	7.7	1.34	2.17	1.38	0.89
21-27	5.4	1.37	2.38	1.60	0.92

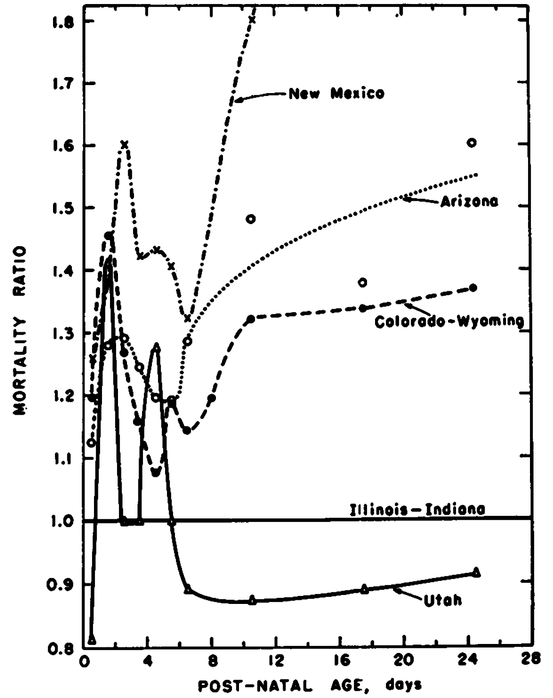

FIG. 8. Mortality ratios for age-specific mortality from all causes. Ratio equals New Mexico/Illinois-Indiana, etc.

DISCUSSION

The neonatal mortality rate is unquestionably higher in most of the mountain states than in the coastal and midwestern regions. The analysis clearly indicates that there is a regular increase in neonatal death rate with increasing altitude and that this relationship is probably independent of the geologic environment. The correlation with altitude, however, may be due to a number of factors, but the associated increase in cosmic ray intensity and decrease in oxygen partial pressure would appear to require special attention.

For the most part, the increased neonatal death rate appears to be a direct function of the lower birth weight that characterizes the higher altitude populations. The proportion of live births classed as immature progressively increases with altitude, and there is evidence that this may be due to a depression of fetal growth. In addition, the age-specific mortality rates indicate the existence of a peak of the mortality-ratio in the first days of life for the infants at higher altitude compared to Illinois and Indiana.

Radiation as a Causative Agent

The original working hypothesis of this study, that increased levels of environmental radiation underlie the higher neonatal mortality rates, is based on genetic concepts. Specifically, it was assumed that higher radiation levels would result in an increased mutation rate that would express itself in part by an increase in early mortality. However, it is extremely difficult either to prove or disprove a genetic argument on the basis of only the published vital statistics data.

Although neonatal mortality is known to have a genetic component (see summary by Stern, 1960), different studies vary in the importance accorded the genotype for the control of perinatal and neonatal deaths. There is apparently no simple way of calculating the proportion of genetic deaths occurring in the neonatal period; we roughly estimate the figure to be about 20 per cent. This assumes that all of the erythroblastosis, one-half of the hernia and malformation, one-fifth of the atelectasis and one-tenth of the pneumonia and immature categories are genetic in origin. Most of these deaths are in the erythroblastosis and congenital malformation categories. Examination of the data revealed that the mortality rates for these two causes of death are very similar in the different parts of the United States that were surveyed. This is particularly true for malformation deaths, which would suggest that a genetic hypothesis to explain the higher neonatal death rates is not appropriate.

Data of the present type have sometimes been employed for the calculation of the genetic doubling dose for man. Such efforts are not appropriate. A brief exploration of the concept will emphasize this and indicate the tenuous nature of any radiation genetic hypothesis to interpret these or similar data reported by Gentry *et al.* (1959) and Wesley (1960). If a doubling dose were to be calculated, two assumptions concerning the population are implicit. One, it is assumed that the population is in genetic equilibrium with respect to the induction and elimination of detrimental genes. Two, it is further assumed that all excess mortality can be attributed to genetic factors. Neither of these assumptions can be met. If one now assumes that excess neonatal death is due to dominant genes, only a single generation would be required to reach equilibrium. However, if this were the case, the Hiroshima-Nagasaki survivorship should have demonstrated tremendous increases in the incidence of early mortality, whereas the actual changes were either negative or insignificantly positive (Neel and Schull, 1956). The average dose to the exposed Japanese population was between 35 to 40 r while that to the U. S. mountain population is only about 2 r/generation/gamete above the sea level exposure.

Certainly, the U. S. population is not in genetic equilibrium. In most of the mountain regions, there have been only about three generations at risk. The average generation number would be less, since these populations have grown by a factor of about 70 in the last 100 years while the balance of the U. S. has grown by a factor of only 6 or 7. Most of this difference must be due to migration, which reduces the rate of approach to equilibrium. Therefore, if one did then assume the population to be in equilibrium for recessive genes, the probability of death of the heterozygote would have to be over 30 per cent, which is about 10 times greater than generally noted (Morton, Crow and Muller, 1956; Fraser, 1962).

Birth weight also has a genetic component (Morton, 1955, 1958; Penrose, 1954), but the amount of genetic variation appears small. If weight is controlled by a polymorphic genetic system where weights in the 2,500 to 4,000 gram interval represent the adaptive norm, as suggested by Stern (1960), then the observed changes in birth weight distribution are contrary to genetic expectation. In this study, the whole distribution of weights is shifted, rather than an increase occurring in only the extreme weight classes, as would be expected if there were an increased segregation of detrimental homozygous gene combinations. A polygenic, additive genetic system under the pressure of an increased frequency of detrimental genes would behave in the manner observed, but again, the 190-gram weight shift is far in excess of any reasonable expectation according to experience (Neel and Schull, 1956; Morton, 1958).

Direct irradiation of the fetus must also be considered as a possible basis for the decreased birth weight and increased mortality rate. In the mountain states, the fetus would receive a dose of 50 to 60 mr over that at sea level, and protracted over the full gestation period. There are no comparative experimental or clinical data at this extremely low dose rate or total dose. There are some data, however, on mice (Russell, Badgett and Saylors, 1960) and rats (Brown *et al.,* 1962) exposed at rates between 2 r and 20 r/day. At doses of 10 r/day or less there is no significant effect on birth weight.

Microcephaly and other deformities have been observed among children exposed *in utero* at Hiroshima and Nagasaki (Plummer, 1952). These were all among the more heavily irradiated as judged by radiation injury and distance from the hypocenter. Doses of several hundred roentgens or more were probably involved. A search for abnormal skeletal development among children irradiated *in utero* was negative (Sutow and West, 1955). Birth weight data are not available on these children.

The observed weight and mortality parameters in the U. S. mountain states are similar to those of radiation-induced injury from exposure *in utero,* but, as with genetic considerations, the present data indicate changes far in excess of any clinical or experimental radiation experience. If radiation were the predominant causative agent through either genetic or somatic pathways, man would be characterized by such an extremely high level of radiosensitivity that it would almost certainly have been detected many years ago, and particularly in the Japanese studies. As the data stand, there is no evidence for the existence of such an extreme radiosensitivity.

Hypoxia as a Causative Agent

It has been mentioned above that a reduced partial pressure of oxygen has a detrimental effect on reproductive physiology. A fascinating report by Monge (1948) portrayed the historical and even evolutionary significance of this problem in the Spanish colonization of Peru. For example, the original Spanish capital city, Jauja, situated at 10,800 feet, was moved to the present location, Lima, near sea level, because of the relative infertility and high neonatal death rate among the livestock.

Reduced viability and an increased probability of early death has been observed in domestic and laboratory animals, as well as in man, and the problem is of some economic importance for poultry breeding in the U. S. mountain states. Smith and Abbott (1961) noted that White Leghorn chickens have only 3 per cent hatchability at 10,150 feet, although 93 per cent of the eggs are fertile. Sixty per cent hatch at sea level, and eggs laid at high altitude but brought to sea level for incubation have a normal hatch rate. Thus, the effect of altitude is transient. Additional evidence of the importance of oxygen was given by Davis (1955) and Moreng and Hartung (1959) who noted the improvement of hatch rate when the incubator air is supplemented with oxygen.

In the Sprague-Dawley rat, exposure to a simulated altitude of 18,000 feet for four hours a day reduces the average litter size by over 40 per cent, and survival between birth and 21 days of age drops from 90 per cent to 60 to 70 per cent (Altland, 1949). Most of the drop in litter size was attributed to fetal resorption. The only persistently noted lesion was marginal necrosis and hemorrhage of the placenta, which was attributed to hypoxia. An additional report by Chiodi (1953) indicated that 35 per cent mortality occurred in the first three days of life among rats born at 12,000 feet. This is prevented by raising the oxygen tension to sea level values.

The most significant data on man were derived from a study of infants born in Lake County, Colorado (10,000 + feet), which is the highest county in the U. S. Lake County infants are 380 grams lighter than Denver infants (Lichty *et al.,* 1957) but congenital defects were no more frequent there than in Denver or New York. There was no effect attributable to race, socio-economic status or diet. Body length and head size were also smaller, but in accordance with normal relations between weight and length or circumference (Howard, Lichty and Bruns, 1957). Thus the reduced birth weight was due to an over-all reduction of growth. These clinical measures conform to the earlier statistical observation that the whole distribution of birth weights is shifted to lower values.

One additional observation in the study by Howard *et al.* is particularly significant. This relates to the infants of mothers who had previously borne children outside of Lake County. For 120 mothers who met this criterion, there were 293 prior children with a mean birth weight of 3,130 grams and 261 children born in Lake County with an average weight of 2,840 grams. The 290-gram difference is more striking when considering that mean birth weight normally rises slightly with increasing maternal age. This observation emphasizes the direct nature of the altitude effect on the maternal-fetal physiological relationships.

The exact physiologic mechanism of the effect of reduced oxygen tension on fetal growth and neonatal mortality is somewhat obscure. An attempt to synthesize the observations and considerations of a number of investigators does offer the following as a possible interpretation (Barcroft, 1938; Boell, 1955; Windle, 1941; Acheson, Dawes and Mott, 1957; Metcalfe *et al.,* 1962). During the period of major differentiation and organogenesis, the oxygen supply is more than adequate as growth of the placenta is in excess of the demand placed upon it. The placenta, however, is structurally limited and therefore the blood volume it can handle is ultimately limited. Although minor fluctuations in oxygen exchange normally occur, there appear to be effective compensating mechanisms for this. When the available oxygen is limited by the physical environment, however, compensation by the fetus will take the form of a reduced oxygen requirement and the amount available for growth must therefore be reduced. In this way, average fetal growth rate in the last trimester could easily be depressed at higher altitudes, where the maternal and uterine environments are unable to provide the normal O_2 requirements.

Since the altitudes in the U. S. are not exceptionally high and the fetal death rates in the mountain states are not excessive, it can be concluded that the lower birth weight and subsequently increased neonatal death rate are an expression of minor adaptive failures detectable only in large populations.

The study has thus touched upon some interesting considerations of human ecology and the adaptive capabilities of man. Neonatal death might well be considered an extended expression of "pregnancy wastage," and of the most expensive form, both biologically and economically. The mountain states have a 20 per cent to 30 per cent higher rate of wastage than the U. S. averages but the pregnancy losses appear to be more than compensated by a greater reproductive activity. The preliminary reports of the 1960 census (U. S. Bureau of the Census, 1961) presented a measure of reproductive performance, the "fertility ratio," for all U. S. regions and states. This ratio is the number of children under 5 years of age per 1,000 women between the ages 15 and 49. The mountain region has the highest fertility ratio in the U. S.; 560, compared to the U. S. average of 488. There is also a generally positive relationship between this ratio and the neonatal death rate across the whole U. S.

Very likely, the non-transient residents of the mountain states become progressively acclimatized and less susceptible to pregnancy loss. However, early death is also a very effective means of natural selection for parent stock of greater adaptability. The existence of what would now be recognized as a genetic basis for resistance to hypoxia was described centuries ago by the Spanish colonists in Peru (Monge, 1948). Intermarriage of Peruvian Indian and Spanish produced offspring more capable of survival at high altitude. It was noted that infants with one parent of pure Indian descent enjoyed greater viability than those with one-quarter, one-eighth or less admixtures of the native genotype. Selection for fertile and fecund breeding stock in sheep has also been successful in the Andes. In this country, selection experiments with poultry have succeeded in improving the viability of standard breeds at elevations above 7,000 feet (Davis, 1955; Smith and Abbott, 1961). Heritability of resistance to the hypoxic environment has been estimated to be between 0.30 and 0.65, comparable to other estimates of heritability of viability in poultry (Lerner, 1950). Thus, the high-altitude environment is an excellent example of a general environmental stress factor to which man and the domestic animals can or have responded in the most classical manner, by selection for the viable genotype.

In conclusion, a word should be said about previous efforts to relate congenital malformation frequency and death rate to environmental radiation. The study by Wesley (1960) hardly deserves mention, since it was inappropriate to accept world-wide figures on malformation deaths as diagnostically accurate and comparable. The study by Gentry *et al.* (1959) was carefully done and relatively complete. Although New York state has some areas with altitudes above 3,000 feet, as in the Adirondacks, the results probably cannot be attributed to altitude, since altitude appears to have little influence on malformation incidence, even though brief periods of severe anoxia are known to induce malformations in mice (Ingalls, Curley and Prindle, 1952). It is difficult to interpret the New York study, but the present study certainly would not support a radiation genetic hypothesis, as put forth by Gentry *et al.* The completeness of ascertainment of malformations is open to question, since the original study detected an under-reporting that may have been as high as 50 per cent. Urban-rural differences in the continuity of medical observation may also be a problem. Lastly, in spite of the existence in the mountain states of local uranium concentrations many times greater than in New York, no detrimental effects could be attributed solely to the geologic environment.

SUMMARY

Variation in the neonatal death rate in selected areas of the Western United States has been evaluated with reference to the geologic environment and the presence or absence of known uranium and helium reserves. While the neonatal death rate is unquestionably higher in the mountain regions, this does not appear to be attributable to higher levels of terrestrial radiation. A significant positive relationship does exist between death rate and altitude. The increased death rate can be largely attributed to a lower birth weight, since the frequency of immature births, on a weight criterion, progressively increases with altitude. The observed correlations with altitude have been evaluated in terms of either the increase in cosmic radiation intensity or the decrease in oxygen partial pressure, or both. The data have been evaluated in terms of three hypotheses; radiation-induced mutation, radiation-induced injury to the fetus, and hypoxia-induced depression of fetal growth. Very little of the excess neonatal death can be attributed to the readily-defined genetic factors, and direct fetal irradiation was concluded to be of no significance. The weight of the evidence—historical, experimental, and clinical—strongly suggests that the reduced partial pressure of oxygen is responsible for the reduced fetal growth and subsequently increased neonatal death rate.

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