RADIATION AND INFANT MORTALITY—SOME HAZARDS OF METHODOLOGY

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A decade ago, in a paper presented at the 1960 State of California Department of Public Health Air Pollution Research Conference, it was suggested by this speaker that an attempt be made to determine whether the distribution of mortality within a city was related in some meaningful way to the geographic distribution of the air pollution within the same geographic area. I said [9],

It may surprise you to have me suggest that one should start with the youngest age group. For many years infant mortality decreased rapidly; very recently this trend has been altered, and no obvious reasons have been found. Could air pollution be the culprit? Therefore, one highly recommended step is the determination of the geographic distribution of infant mortality. The study preferably should include only the postneonatal period; i.e., deaths during the first year of life but excluding the first month to minimize the effect of birth injuries and the like.

Soon after this simplistic view that an environmental factor, air pollution, was implicated in the leveling off in the decline of the infant mortality rate in the United States was presented, the possible hazards of another etiologic agent, radiation, specifically, radioactive fallout from nuclear weapons were cited by Sternglass. He mentioned the need at this time to study the incidence of childhood leukemia and cancer deaths among children born in areas which had received heavy fallout doses six to nine months earlier [15].

In the meantime, some attempt had been made to assess the hazards of extremely low levels of ionizing radiation in the United States, largely by means of the published vital statistics. Grahn and Kratchman in 1963 [8] summarized the studies as follows. "The results of the (bone) 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."

In their article, they examined the relationship between the neonatal death rate for the eight-year period, 1950–57 and estimated natural or background radiation exposure in the United States for the white population, by county of residence. The total population of a county was used in place of the white population

when the nonwhite portion constituted a small fraction of the total population in the county. The environmental data included radiation estimates based on the distribution of uranium ore deposits obtained from the Atomic Energy Commission and altitude data based primarily on the U.S. Geologic Survey. For some of the analysis, 80 counties with uranium ore reserves, principally in the Mountain States, were compared with 180 counties not containing such reserves in the same states.

The mean county altitude values which were used were in reality mean population-altitude figures. State altitude figures were mean population-altitudes weighted by the live births at risk. To take account of differences in socioeconomic factors, as reflected by median family income, county values were adjusted to a common income. Differences in maternal age were "controlled" by adjusting individual county mortality ratios to a constant maternal age. This adjustment was based on a limited special study of live births conducted in the first quarter of 1950. Since Utah had significantly lower neonatal death rates than the other Mountain States, it was excluded from the subsequent analysis. We will come back to this matter of exclusions later.

A highly significant positive correlation ($r = 0.90$) was found between cosmic ray intensity and neonatal death rates for 11 states in the western portion of the United States, but now excluding Idaho, Montana, and Utah. These death rates were adjusted for age of the mother and family income level. Another highly significant negative correlation ($r = -0.91$) was found when atmospheric pressure was correlated with these death rates.

To ascertain if any relationship would exist between mortality and the presence of uranium ore reserves in the absence of the altitude variable, the authors adjusted the neonatal mortality rates for the 57 counties with ore reserves (excluding Utah) to a constant altitude and then plotted these adjusted death rates against tons of uranaium oxide per 1000 square miles. Since no correlation was found, the authors stated: "*Thus, it can be concluded that the quantity of uranium ore reserves is unassociated with the probability of neonatal mortality*" (authors' emphasis). Yet, they did add the following caution, "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." With reference to altitude, they concluded that historical, experimental and clinical evidence supported the role of the reduced partial pressure of oxygen in causing a reduced fetal growth rate and an increased neonatal death rate.

In his article presented in 1963, published two years later, Grahn made reference to the fact that interest in the possible relationship between infant mortality and environmental radiation had increased due to the testing of nuclear weapons [7]. Also, the increased use of nuclear energy for peaceful purposes had contributed to public concern. He suggested, "Both genetic and somatic endpoints can be studied with equal pertinence to the problem, but genetic endpoints are preferred because they are not confounded by a lifetime's accumulation of environ-

mental experiences." However, the study of infant mortality would not appear to be significantly affected by this consideration.

Later Sternglass expressed his belief that radiation due to nuclear testing had increased the incidence of leukemia in the Albany-Troy area of New York State. He stated that deposition of strontium 90 on the ground in the New York area was associated with excess fetal deaths in New York State. Also, fallout was correlated with excess mortality in the United States for children under one year of age [17]. According to his interpretation, the changing pattern of infant mortality resulted in a large excess of these deaths over that expected. The assumption made is that the rate of infant mortality would have continued to decline without interruption were it not for the effects of fallout due to weapons testing in the United States and overseas. He has noted that the rate of decline of infant mortality, beginning two or three years following the termination of atmospheric testing in 1963, was again approaching that from 1935 to 1950 [18].

Stewart has called our attention to the fact that fetal and infant mortality are the resultant of a number of forces in operation [19]. She said "The most likely explanation of the observed change in trend is that it is a reversion towards normality of a death rate which had, for 20 years, been experiencing booster effects—first from the introduction and dissemination of sulphonomides and then from the introduction and dissemination of antibiotics." She concluded: "In practice, infection deaths are so strongly correlated with sex, age, wealth, climate, density of population, chemotherapy, and so on, that any deviation from normality of related death rates and prevalence rates (for example infant mortality, leukemia mortality and leukemic clusters) can only be regarded as significant *after* these effects have been eliminated" (author's emphasis).

Most recently, Sternglass has postulated that infant mortality has increased around nuclear power plants [18]. I believe that the methodology, and its limitations, if any, will be discussed in greater detail by the next speaker, Mrs. Tompkins.

For those who do not have sufficient exposure to mortality data, it is appropriate to present some definitions of terms and some pitfalls. This will be followed by a discussion of demographic factors affecting infant mortality. Finally, some possible mechanisms of radiation effects will be outlined so that their relevance to possible epidemiologic studies can be examined.

Let us get some perspective on the deceleration in the rate of decline in the infant death rate by looking at selected infant mortality rates. Moriyama had first called our attention to the basic change in the infant mortality trend beginning about 1949 or 1950 [10].

In 1935, there were 55.7 deaths under one year of age per 1000 live births. By 1950, the rate was about half—29.2. By 1964, the rate had declined further but at a much slower pace. It was then 24.8 deaths under one per 1000 live births. Since 1933, the 48 continental states and the District of Columbia have been included in the registration system and so it seemed appropriate to select 1935 as the base year.

Chase has provided in summary fashion an evaluation of the basic data used in infant mortality analysis [2]. She has noted that a distinction between live birth and fetal death is one of the major decisions which has to be made for vital registration statistics. This is significant not only in international comparisons but also in terms of interstate comparisons. A live birth as defined by the World Health Organization (WHO) in 1950 is "the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born" [22]. Fetal death, as defined by WHO at the same time to complement that of live birth, above, is "death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation, the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles" [22]. It should be emphasized that these definitions deliberately omitted any mention of duration of pregnancy or the terms abortion, miscarriage or stillbirth.

Registration of live births, fetal deaths and deaths is required throughout the United States. However, registration requirements for fetal deaths varies widely. Except for Kansas and New York City, registration is based on length of gestation. The minimum period of gestation at which fetal deaths are required to be registered varies. Most national tabulations of fetal deaths include fetal deaths of 20 weeks or more gestation and those with period of gestation unspecified. This is so because this gestation period is common to all States and presumably all States provide complete data for gestations of this period. Nonetheless, any deficiencies in registration data for a state will be reflected in the national data. Special studies have demonstrated there is gross underregistration of fetal deaths in the United States [4], [6], [13]. The difficulties that may be encountered because of varying registration practices of fetal deaths even in a single state are well illustrated by the remarks of Tamplin, Richer, and Longmate [20] on the use of fetal death data for New York State by Sternglass [20].

Tamplin's comments about the differences in reporting procedures for New York City and for the remainder of the state are especially pertinent. In 1939, reporting of early fetal deaths was promoted energetically in New York City and, as a result, an increase in fetal deaths occurred due to the better reporting that resulted.

Attention has already been called to the change in definition of live birth and fetal death which occurred in 1950. These nuances in definition may represent a problem of interpretation as the points in time at which changes may have happened to take place may have been affected by the differences in definition [2]. This is so despite the relatively small effect resulting from the variation in definition.

Also, neonatal deaths were earlier defined as those occurring during the first month of life. Now, they are restricted to those within the first 28 days of life. The difference due to this reason, however, is believed to be relatively slight inasmuch as the risk of death declines rapidly throughout the first month following birth. Postneonatal deaths are those occurring during the remainder of the first year, that is, the 28 days of age to the first anniversary. Death registration is probably more complete for this period than for the neonatal period.

Moriyama has cautioned us to be concerned about the statistical problems involved in trying to correlate changes in trends of infant mortality with presumed etiologic agents [11]. According to him three factors must be taken into account: (1) the mortality level at which the change takes place; (2) the differences in the rate of change; and (3) the time when the change takes place.

Let us now look at the role of demographic characteristics in infant mortality analysis. There are a number of demographic factors which are associated with differences in infant mortality rates in the United States as well as in other countries. Sometimes, however, there are statistical artifacts present. Thus, Norris cites the case where the Japanese in California were stated to have a very low infant death rate [12]. Yet, in actuality, their rate was almost as high as the white population. The explanation was in the coding process. For infants born of mixed marriages, race was coded differently on the death certificate from that on the birth certificate. Births were assigned to the race of the nonwhite parents, while deaths were assigned to the race of the child, which was recorded as white. Therefore, small area comparisons must be made with caution and with detailed consideration being given to possible sources of statistical bias.

What are some of the demographic factors which appear to be important? One is geographical variation and, in the United States, the highest rates for fetal, neonatal and postneonatal deaths are found in the southeastern part of the United States. There are differences between urban and rural rates also. With the advent of the greater availability of hospital and medical facilities, urban experience had tended to become more favorable than rural in the 1930's and 1940's. However, during the 1950's the character of most major cities of the country changed. There had been an inmigration to the central city of low income individuals accompanied by an outmigration to the suburbs of the middle class. Accordingly, it is not surprising to find that neonatal mortality in the largest cities in the United States is higher than among infants living elsewhere in the states containing these cities.

A major concomitant of infant mortality is color or race. For nonwhite infants, fetal death ratios covering 20 weeks or more gestation, per 1000 live births have remained about twice that of white infants since data have been available by color in 1945. Postneonatal death rates are about three times as high for the nonwhite infants while their neonatal death rates are about 1.5 times the mortality experience of white infants.

Maternal age is an important component of relative risk. Thus, fetal and neonatal and postneonatal deaths are lowest when the mother is between 20 to

29 at the time of delivery. Accordingly, the age distribution of women giving birth affects the infant mortality pattern significantly.

Parity or birth order is another significant variable. High birth orders are associated with higher neonatal death rates. But, probably the most important factor is that of birth weight. This, of course, reflects the physical development and maturation of the infant. Neonatal mortality for each sex-color group demonstrates a rate for infants under 2500 grams or less at birth which was at least ten-fold that of heavier infants. Limited data for fetal deaths show that for these as for infant deaths there is an increase in risk for these smaller infants. Any difference in weight distribution for population groups is thus of critical importance.

A replication of the matched birth-death records study in England and Wales which had been carried out initially in 1949–50 was conducted in 1964–65 to determine the changes which had taken place in the 15-year period. The new analysis by Spicer and Lipworth concentrated mainly on regional and social effects on infant mortality [14]. The effects of maternal age and parity mentioned previously were again confirmed in this study. These authors point out that all of the main variables affecting infant mortality are correlated with each other and some process of standardization is required. Moreover, there is interaction in that the effect of one variable is different in the presence of various categories of the others. Thus the relationship of infant mortality to age of mother is different in the lowest social class than in the highest.

One review of this publication, I believe, is particularly germane. In accounting for the differences in infant mortality rates by area, the reviewer said: "We cannot help suspecting that of all possible factors which influence the continuance of the unfavorable rates in the North and in Wales by comparison with other regions that of implementation of the Clean Air Act may still be the most obvious. The other main factor may be assumed to be housing and the greater concentration of Social Classes I and II in the regions with better rates, but here one is entering into the more speculative realm of receptivity to health education" [21].

Before I close this section, I should like to call attention to the findings of trends in late fetal deaths and neonatal mortality as related to birth weight in England and Wales from 1956–65. In this study, Ashford and co-workers found a decrease in the proportion of low birth weight between 1956 and 1965 was associated with a steady reduction of infant and perinatal mortality, in England and Wales during the decade [1]. (Perinatal mortality includes fetal deaths of 20 or more weeks gestation and neonatal deaths.)

They said "Since the changes which have occurred are of multiple causation and since the factors involved are not clearly understood, the use of standard methods of predicting future patterns, such as linear or polynomial interpolation, should be treated with caution. It is unfortunate that information about many of the factors which may be involved is not generally available in England and Wales. A system of monitoring temporal changes in the ethnic, economic, and

sociological structure of the population would be an invaluable aid to the interpretation of epidemiological data, including studies of perinatal mortality."

Very recently, a study of perinatal mortality in New York City by Fischler and co-workers examined the use of linear models in the analysis of such perinatal data [5]. They found that additive models, as applied to both the mortality rates and their logit transforms gave only a very rough description of the data. First order interactions, and, in particular, the interactions between age and parity, were found to be important.

Moreover, the issues raised in the present paper are to be supplemented by problems in the environmental parameters which may be even worse. We are considering a new battery of variables such as environmental pollutants not considered in the past. New elements of information regarding pollution are being obtained and we are not certain these are meaningful for correlation with health· Which are the exposures which we should be measuring to see their effect on the first year of life? The problems of the environmental contamination from myriad sources and their measurements need further study.

At this point, I should like to introduce a plea for use of a methodology which avoids dealing with selected states which conform to a chosen hypothesis. As scientists, we should examine with equal interest other states which do not con‾ form. We should not be content to report only those instances which mesh with our hypothesis, nor to overlook or to fail to report what happens in other instances. Thus, I am intrigued by the unusually low infant mortality experience of Utah. As noted previously, this was excluded from the analysis of Grahn and Kratchman [8]. A good study of Utah is needed. Since Chase has reported difficulty in linking infant death and birth records for that state, the registration practices might be looked at carefully [3]. Is it possible that there is a statistical artifact involving infant death rates?

The mechanism by which radiation is presumed to affect infant mortality will help determine the methodology which will be used. Which hypothesis is being tested will point to the use of which portion of the mortality curve should be studied, that is, fetal, neonatal or postneonatal. Thus, the Grahn and Kratchman study evaluated the data in terms of three hypotheses: radiation-induced mutations, radiation-induced injury to the fetus, and hypoxic-induced depression of fetal growth [8]. Only the first two will be considered for our purpose at hand. Neonatal death rates were used because the first hypothesis selected was that increased levels of natural environmental radiation would adversely alter neonatal death rates through genetic effects. It was assumed that an increased mutation rate resulting from radiation would express itself, in part, by an increase in early mortality. The authors estimated the proportion of genetic deaths to total neonatal deaths to be about 20 per cent.

The second hypothesis of radiation-induced injury to the fetus was discarded by the authors because "the present data indicate changes far in excess of any chemical and experimental radiation experience." They said there was no evidence for the extremely high level of radiosensitivity which would be required.

Sternglass hypothesized that a genetic effect was due to a low accumulated gonad dose resulting from fallout [16]. The incorporation of strontium 90 into the genetic material of the parents is identified by him as the mechanism of the change in rate of decline of fetal mortality and infant mortality rates. Thus, following exposure to fallout, postneonatal mortality should be affected earlier and neonatal mortality should be affected later. This delayed genetic reaction could be due to the need to accumulate significant radiation to affect the offspring *in utero*.

I should like to conclude by stating that, as yet, there is no simple physical law to explain the rate of change in infant mortality rates. Medical, economic and social factors are clearly important and the possible role of environmental, that is, pollution, factors remains to be uncovered.

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Discussion

Question: E. J. Sternglass, School of Medicine, University of Pittsburgh

How is it possible to explain the sharp rise and decline of fetal mortality rates in St. Louis accompanied by a rise and decline of strontium 90 in the fetal jaw-bone measured by Dr. Harold Rosenthal as an artifact produced by a change in registration requirements?

Reply: E. Landau

Unfortunately, the validity of this apparent association ceases to exist when examined more closely. Although there are serious deficiencies in the presentation of data attempting to correlate strontium 90 levels in the fetal jawbone with fetal mortality, changes in registration practice are not at issue.

On pages 14–19, the 1969 publication of the Bureau of Radiological Health, DBE 69-2, entitled "Evaluation of a possible causal relationship between fallout deposition of strontium 90 and infant and fetal mortality trends" by Tompkins and Brown, discusses the limitations of the analysis by Dr. Sternglass. The authors have noted the use of incomplete data, an error in the estimate for excess fetal deaths for 1963 as well as the use of fetal mortality data for Missouri instead of for St. Louis City and County. They have revised his presentation using his estimating procedure to obtain St. Louis area fetal mortality data and have plotted these revised values against the strontium 90 content of fetal mandibular bone in the St. Louis area for 62 aborted fetuses reported by Dr. Rosenthal. The resulting graph, Figure 16, indicates clearly that the validity of the hypothesis of an association between fetal mortality and fallout as measured by the strontium 90 level of fetal mandibular bone has *not* been substantiated.