Sudden Infant Death Syndrome: The Bradford Hill Criteria and the Evaluation of the Thyroxine Deficiency Hypothesis

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Abstract

In the United States, SID Sis approximately twice as common in infants in the Pacific and Mountain Regions as in the Atlantic States. These spatial differences appear unlikely to be due to chance and their analysis ought to provide insights into the etiology of this syndrome. A data bank was developed, therefore, from published government and academic sources that contained 132 incidence and/or prevalence and/or mortality patterns for 84 disorders and diseases, including SIDS mortality for each of the years 1983 to 1987 and for the period as a whole. This bank also contained information on the spatial distribution of 221 environmental variables, including a wide range of climatic and geo chemical data and information on air and water pollutants and a variety of industrial, commercial and agricultural activities.

Pearson correlation was then used to compare SIDS mortality in each of the five years 1983 to 1987. This analysis established that regardless of cause(s), mortality from SIDS produced a very repetitive spatial pattern. SIDS mortality was then compared with incidence, prevalence and/or mortality from the 83 other diseases and disorders. These analyses indicated that, during the five-year period under study, SIDS mortality in the USA had a very similar distribution to the prevalence of goiter among males examined for military service during World War I ($r = 0.75774$, $p < 0.0001$). SIDS also showed repetitive negative associations with various cancers, especially those of the digestive tract and with diseases of the heart. There is considerable evidence that all these health problems may be exacerbated by selenium deficiency. Pearson correlation also was used to compare SIDS mortality with the 221 environmental variables. It was concluded that SIDS was less likely to occur in industrial states, but was found most often in those states with soils that contained elevated levels of selenium, calcium, strontium and sodium. In contrast, states with soils that were very high in mercury, the selenium antagonist, had depressed SIDS mortality rates. Stepwise multiple regression was then conducted for each year and for the entire five-year period using those data that had correlated with SIDS mortality, either negatively or positively at the $p < 0.001$ level. In all six regressions, male recruit goiter was the first independent variable to enter the initial equation; where it could explain between 57.4 percent and 42.2 percent of the SIDS variance.

On the basis of these analyses and a review of the literature, it is suggested that the fundamental cause of SIDS may be a maternal iodine deficiency accompanied by an excess or a deficiency of selenium. This is thought to result in a thyroid hormone imbalance, which probably includes a thyroxine deficiency. This imbalance seems to result in a variety of subtle developmental neurological, cardiorespiratory and metabolic defects in the fetus and subsequently in the infant. Stresses, such as a prone sleeping position, low temperatures or cigarette smoke either increase the infant's need for thyroxine, or reduce this hormone's availability. When this occurs, the developmental defects previously listed may result in sudden infant death.

The Bradford Hill criteria, commonly used to establish cause and effect, are applied to assess the validity of this hypothesis, which is found to meet eight of Hill's nine principles. The thyroid hormone imbalance hypothesis' inability to fulfil Hill's ninth criterion, that of specificity of association, is not thought to be crucial, since several authors previously have questioned the validity of this particular principle. The evidence, therefore, suggests that maternal hormone imbalance during the development of the fetus is the fundamental

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cause of many SIDS deaths. If this is the case, the implementation of simple preventive measures could significantly reduce losses from this cause of infant mortality.

Key words

Sudden Infant Death Syndrome (SIDS), thyroid hormone imbalance, thyroxine deficiency, selenium, iodine, Bradford Hill criteria.

Abbreviations

SIDS, Sudden Infant Death Syndrome; En 18, prevalence of goiter in military recruits (1917-1918); En39, ratio of land disturbed by strip mining to undisturbed land; En 65, number of Superfund listed toxic waste sites in the state divided by the state's area; PVH, percentage of soil samples from a state for a particular element that were in the highest 20 percent collected in the conterminous USA.

Introduction

Sudden Infant Death Syndrome (SIDS), also known as crib or cot death, is the leading cause of mortality in the United States in the postneonatal period. As a consequence, it is the eighth most significant cause of years of potential life lost.[1] SIDS involves "the sudden death of any infant or young child, which is unexpected by history, and in which thorough postmortem examination fails to demonstrate an adequate cause of death."[2] Each year, in the United States, there are approximately 5,300 such SIDS fatalities.[3] Their distribution is not geographically random, rather SIDS is more common in the west of the United States than in the east and in the north than the south. In consequence, SIDS is approximately twice as likely to occur in infants in the Pacific and Mountain Regions than it is in the Atlantic States (Table 1 and Figure 1). These spatial differences in SIDS mortality are unlikely to be due to chance and their analysis, therefore, may provide insights into the etiology of this syndrome.

Methodology

Any attempt to identify associations between SIDS and possible geographical variables requires medical and environmental data from both the same spatial units and time

Table 1. A Comparison of SIDS (1983) and Male Goiter (1917-1918) in the United States

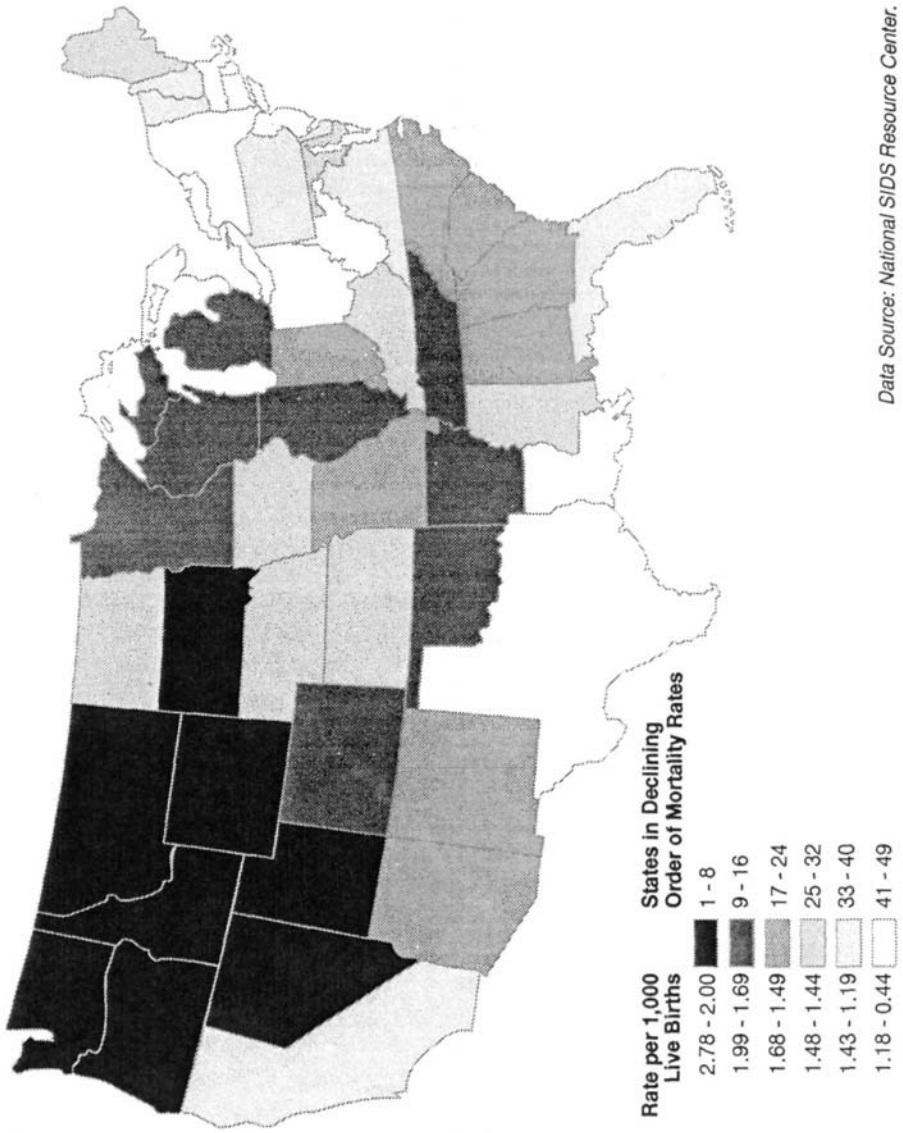
Area	SIDS Rate (1983-87)	Goiter Prevalence in Male Recruits (1917-1918)
NEW ENGLAND	1.02	0.88
Maine	1.48	0.66
New Hampshire	1.26	0.70
Vermont	1.19	2.14
Massachusetts	0.89	0.32
Rhode Island	0.44	0.55
Connecticut	0.87	0.89
MIDDLE ATLANTIC	1.11	1.91
New York	1.12	1.19
New Jersey	0.94	0.43
Pennsylvania	1.27	4.10
EAST NORTH CENTRAL	1.54	9.06
Ohio	0.97	5.59
Indiana	1.49	6.48
Illinois	1.76	7.79
Michigan	1.69	11.43
Wisconsin	1.79	14.02

Table 1. (continued)

WEST NORTH CENTRAL	**1.61**	**4.99**
Minnesota	1.72	8.04
Iowa	1.45	6.68
Missouri	1.54	3.99
North Dakota	1.48	8.73
South Dakota	2.16	4.09
Nebraska	1.46	2.14
Kansas	1.45	1.25
SOUTH ATLANTIC	**1.42**	**1.97**
Delaware	1.34	0.59
Maryland	1.48	0.94
District of Columbia	1.43	1.39
Virginia	1.32	3.38
West Virginia	1.18	7.89
North Carolina	1.59	1.81
South Carolina	1.49	0.94
Georgia	1.57	0.52
Florida	1.36	0.25
EAST SOUTH CENTRAL	**1.57**	**1.14**
Kentucky	1.44	1.41
Tennessee	1.74	1.96
Alabama	1.46	0.56
Mississippi	1.62	0.64
WEST SOUTH CENTRAL	**1.32**	**0.51**
Arkansas	1.70	0.40
Louisiana	0.86	0.62
Oklahoma	1.75	0.72
Texas	0.95	0.30
MOUNTAIN	**2.07**	**11.60**
Montana	2.54	21.00
Idaho	2.45	26.91
Wyoming	2.37	15.37
Colorado	1.82	5.29
New Mexico	1.49	0.88
Arizona	1.53	1.21
Utah	2.00	15.72
Nevada	2.39	6.38
PACIFIC	**2.14**	**18.05**
Washington	2.61	23.40
Oregon	2.78	26.31
California	1.39	4.45
Alaska	2.91	no data
Hawaii	1.03	no data

Sources: National SIDS Resource Center and Pendergrast, Milmore and Marcus[6] (1961).

Figure 1. SIDS (Sudden Infant Death Syndrome): 1983-1987



periods. Elsewhere, the author has described establishing such a data bank, at the state level, for the conterminous United States.[4,5] This consists of two discrete components. The first section contains medical data, whilst the second is devoted to environmental information. Included in the medical section are 132 incidence and/or prevalence and/or mortality rate distribution patterns for 84 disorders and diseases (including SIDS mortality, for each of the years 1983 to 1987 and for this period as a whole). The diseases and disorders included in this data bank range from diabetes mellitus, goiter[6] and schizophrenia to Creutzfeld-Jacob disease and monocytic leukemia. They have been described in detail elsewhere.[5]

Environmental variables included in the second section of the data bank include average annual precipitation and sunlight, air pollution levels, groundwater use, hardness and sodium content of public water supplies and the percentage of the population drinking fluoridated water. In addition, the data bank includes information on the presence of dieldrin, lindane, cadmium, chromium, arsenic, mercury and lead in surface waters. Other variables include the use of deicing salts by highway departments and the amount of water utilized by both industry and agriculture. The data bank also contains information on the harvested acreage of 59 principal crops, with additional detail concerning the number of bushels of barley, corn grain, oats, rye and wheat produced. Data on hay, cotton, potato and tobacco production also are included. So too are the levels of 35 soil elements, established by the US Geological Survey. These range from aluminum, arsenic and barium to ytterbium, yttrium, zinc and zirconium. In summary, the environmental base includes details of a very wide range of climatic and geochemical variables, air and water pollutants and a variety of industrial, commercial and agricultural activities. In total, the data bank contains 221 geographical variables.

Pearson correlation was used to compare the spatial distribution of SIDS in each of the five years both with themselves and with that of all other diseases in the data bank. This analysis was undertaken because it is possible that diseases or disorders with very similar distribution patterns may have (a) risk factor(s) in common.[5] Pearson correlation was subsequently used to determine whether there were significant associations between SIDS mortality and any of the data bank's 221 environmental variables. Strong statistical links between SIDS mortality rates and particular environmental variables, of course, would not prove causality. However, they would be suggestive and could be used to generate hypotheses that might stimulate late new lines of enquiry.[7-9] Those geographical variables that were either positively or negatively correlated with SIDS mortality at the $p < 0.001$ level in any year were then used in a series of stepwise multiple regressions. The number of such variables differed from year to year but ranged from 27 to 16, with a mean of 22. This technique permitted the identification of variables that could explain the largest percentage of the variance demonstrated by SIDS mortality patterns in the conterminous United States.

Results

Step 1

To determine whether the spatial variations in mortality from SIDS, during the period 1983 to 1987, were relatively permanent, Pearson correlation was used to compare distribution patterns for the five years involved and for the mean mortality rate for the period as a whole (Table 2). The strongest correlations were found to have occurred between the mean SIDS rate for the entire period and SIDS mortality in the years 1984 ($r = 0.93687$) and 1985 ($r = 0.92940$). There were also very strong correlations between SIDS mortality in 1984 and the years 1983 ($r = 0.86072$); 1985 ($r = 0.80240$); 1986 ($r = 0.78215$) and 1987 ($r = 0.86873$). Indeed, correlations between all years were significant at the $p < 0.0001$ level. Clearly, regardless of the cause(s) of mortality from SIDS, the resulting spatial distribution patterns, in the United States, remained extremely constant over the five years under investigation.

Step 2

In the second stage of the analysis, the six measures of the spatial distribution of mortality from SIDS were statistically compared with 126 mortality and/or incidence and/or prevalence data for 83 other disorders, diseases or disease groups. This analysis resulted in the identification of numerous correlations

Table 2a. A Comparison of SIDS Mortalities in the United States, at the State Level, for the Years 1983 to 1987

	SIDS 1983	SIDS 1985	SIDS 1986	SIDS 1987	SIDS 1983-1987 (Mean Rate)
SIDS 1983	0.86072 0.0001 51	0.84786 0.0001 51	0.78369 0.0001 51	0.74793 0.0001 51	0.91601 0.0001 51
SIDS 1984		0.80240 0.0001 51	0.78215 0.0001 51	0.86873 0.0001 51	0.93687 0.0001 51
SIDS 1985			0.85414 0.0001 51	0.76373 0.0001 51	0.92940 0.0001 51
SIDS 1986				0.79434 0.0001 51	0.91335 0.0001 51
SIDS 1987					0.90908 0.0001 51

Table 2b. A Comparison, at the State Level, of SIDS Mortalities for the Years 1983 to 1987 with Goitre Prevalence in Potential Male Military Recruits, 1917 to 1918

SIDS 1983	0.62372 0.0001 49
SIDS 1984	0.73482 0.0001 49
SIDS 1985	0.71774 0.0001 49
SIDS 1986	0.64964 0.0001 49
SIDS 1987	0.73062 0.0001 49
SIDS 1983-1987 (Mean Rate)	0.75330 0.0001 49

Table 3. Associations Between United States Sudden Infant Death Syndrome Mortality for the Period 1983 to 1987 and other Disease Distributions, at the State Level (n=48)

Other Diseases or Disorders	1983	1984	1985	1986	SIDS 1987	1983-7 (mean)
Prevalence of Goitre (1917-18) (in male recruits)	0.65326 0.0001	0.74416 0.0001	0.71066 0.0001	0.64939 0.0001	0.73903 0.0001	0.75778 0.0001
Thyroid Disturbances (World War II)	0.28781 0.0473	0.46103 0.0010	0.37289 0.0090	0.36313 0.0112	0.54503 0.0001	0.45303 0.0012
Suicide (1976)	0.45869 0.0010	0.50282 0.0003	0.41432 0.0034	0.36054 0.0118	0.48527 0.0005	0.48313 0.0005
Suicide (1977)	0.40510 0.0043	0.44574 0.0015	0.30901 0.0326	0.30268 0.0365	0.46677 0.0008	0.41753 0.0032
Suicide (1980)	0.42170 0.0028	0.46285 0.0009	0.42035 0.0029	0.39596 0.0053	0.46574 0.0009	0.47284 0.0007
Diabetes mellitus Mortality(1976)	-0.28959 0.0459	-0.35745 0.0126	-0.42001 0.0030	-0.31305 0.0303	-0.37012 0.0096	-0.38334 0.0072
Diabetes mellitus Mortality (1977)	-0.44233 0.0016	-0.46974 0.0008	-0.47052 0.0007	-0.47083 0.0007	-0.42103 0.0029	-0.49519 0.0003
Diseases of the Heart Mortality (1976)	-0.36960 0.0097	-0.35025 0.0147	-0.40156 0.0047	-0.34235 0.0172	-0.40228 0.0046	-0.40472 0.0043
Diseases of the Heart Mortality (1977)	-0.37807 0.0081	-0.37061 0.0095	-0.43814 0.0018	-0.36944 0.0098	-0.40996 0.0038	-0.42772 0.0024
Diseases of the Heart Mortality (1978)	-0.41421 0.0034	-0.40092 0.0047	-0.47062 0.0007	-0.40129 0.0047	-0.42814 0.0024	-0.45854 0.0010
Diseases of the Heart Mortality (1979)	-0.41284 0.0035	-0.41547 0.0033	-0.47834 0.0006	-0.4092 0.0039	-0.43763 0.0019	-0.46808 0.0008
Diseases of the Heart Mortality (1980)	-0.42943 0.0023	-0.42232 0.0028	-0.46848 0.0008	-0.40502 0.0043	-0.44388 0.0016	-0.47017 0.0007
Malignant neoplasms Mortality (1976)	-0.39491 0.0055	-0.35958 0.0121	-0.46532 0.0009	-0.41191 0.0036	-0.44174 0.0017	-0.45249 0.0012
Malignant neoplasms Mortality (1977)	-0.39997 0.0049	-0.32947 0.0222	-0.46314 0.0009	-0.42433 0.0026	-0.42583 0.0025	-0.44410 0.0016
Malignant neoplasms Mortality (1978)	-0.41626 0.0033	-0.40341 0.0045	-0.50764 0.0002	-0.45539 0.0011	-0.46349 0.0009	-0.48836 0.0004

Table 3. (continued)

Malignant neoplasms	-0.44618	-0.41954	-0.52497	-0.46282	-0.47326	-0.50667
Mortality (1979)	0.0015	0.0030	0.0001	0.0009	0.0007	0.0002
Malignant neoplasms	-0.44896	-0.41889	-0.54184	-0.49002	-0.49214	-0.52028
Mortality (1980)	0.0014	0.0030	0.0001	0.0004	0.0004	0.0002
Tumor of the Mouth	-0.62971	-0.58250	-0.69648	-0.75408	-0.65525	-0.71785
in White Males	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
Mortality (1950-1967)						
Tumor of the Eye	0.54504	0.50391	0.43657	0.48817	0.46726	0.52549
in White Females	0.0001	0.0003	0.0019	0.0004	0.0008	0.0001
Mortality (1950-1967)						

that were statistically significant at the $p < 0.01$ level. Table 3 identifies these diseases or disorders that correlated, in three years or more, either positively or negatively at the $p < 0.01$ level with SIDS mortality. Certain trends are immediately obvious. SIDS mortality in the conterminous United States clearly demonstrates spatial patterns that are very similar to both those of the prevalence of male goiter and of thyroid disturbances[6] and to suicide. In contrast, repeated strong negative correlations are apparent between SIDS mortality and death from diabetes mellitus, diseases of the heart, and malignant neoplasms. When the latter category of diseases is further subdivided, it becomes obvious that numerous specific cancer mortality patterns strongly negatively correlate with SIDS. With the exception of mortality from cancer of the mouth in White males, which demonstrates the strongest and most repetitive negative correlations, for the sake of brevity, these specific cancers are not included in Table 3. Mortality from cancer of the eye in White females, however, appears to be an exception to this general rule, being strongly positively correlated with SIDS mortality in every year analysed (Table 3).

Step 3

In the third stage of the analysis, using Pearson correlation, the six measures of the spatial distribution of SIDS mortality were compared using Pearson correlation with the 221 environmental variables previously described. Table 4 identifies those variables that correlated, in three or more years, either positively or negatively at the $p < 0.01$ level with SIDS mortality. Certain trends are obvious from this illustration. Clearly, SIDS was relatively uncommon in densely populated, polluted states even if they supported extensive mining and industrial sectors. In contrast it occurred most frequently in states with soils that contained elevated levels of selenium, strontium, calcium and sodium, but little mercury.

Step 4

Stepwise multiple regression was then conducted as the final stage of the analysis, with SIDS mortality being used as the dependent variable. Environmental data that had correlated, either negatively or positively with SIDS mortality at the $p < 0.001$ level, were utilized as independent variables. In addition, because of its repetitive highly significant correlations with SIDS mortality (Table 3), the prevalence of goiter in World War I military recruits also was used as an independent variable. Only those variables that met the 0.1500 significance level entered the resulting models.

In all six regression analyses, male military recruit goiter prevalence was the first independent variable to enter the initial equation. In 1986, for example, this was able to explain 42.2 percent of the variance involved in SIDS mortality. For the five year period as a whole, goiter prevalence was capable of accounting for 57.4 per cent of SIDS variance. In all other years, the variance accounted for by goiter prevalence lay somewhere between these two extremes. In step one of the six stepwise

Table 4. Associations Between United States Sudden Infant Death Syndrome and Environmental Variables During the Period 1983 to 1987, at the State Level (n=48)

				SIDS		1983-7
Environmental Variable	1983	1984	1985	1986	1987	(mean)
Population density	-0.51683	-0.46913	-0.52019	-0.60852	-0.58536	-0.59005
	0.0002	0.0008	0.0002	0.0001	0.0001	0.0001
Precipitation	-0.36997	-0.46455	-0.54030	-0.52128	-0.53391	-0.53027
	0.0096	0.0009	0.0001	0.0001	0.0001	0.0001
Air pollution (summer	-0.43902	-0.51667	-0.46725	-0.47640	-0.53860	-0.53399
suspended particulates)	0.0018	0.0002	0.0008	0.0006	0.0001	0.0001
Iodine deficient soils	0.43336	0.50129	0.57711	0.51898	0.56345	0.56409
	0.0021	0.0003	0.0001	0.0002	0.0001	0.0001
Egg production	-0.38144	-0.43818	-0.51423	-0.54433	-0.53035	-0.52985
	0.0075	0.0018	0.0002	0.0001	0.0001	0.0001
Sand and gravel (land	-0.50277	-0.44394	-0.47098	-0.56132	-0.55599	-0.55312
disturbed)	0.0003	0.0016	0.0007	0.0001	0.0001	0.0001
Strip mining (area	-0.41413	-0.48418	-0.44966	-0.49512	-0.50942	-0.51570
requiring reclamation)	0.0034	0.0005	0.0013	0.0003	0.0002	0.0002
Rural water use	-0.43894	-0.42556	-0.42282	-0.53698	-0.50737	-0.50863
	0.0018	0.0026	0.0028	0.0001	0.0002	0.0002
Industrial	-0.46527	-0.48928	-0.46194	-0.59421	-0.59012	-0.57098
water withdrawal	0.0009	0.0004	0.0009	0.0001	0.0001	0.0001
Toxic waste site density	-0.51537	-0.46528	-0.49869	-0.60561	-0.52220	-0.56835
	0.0002	0.0009	0.0003	0.0001	0.0001	0.0001
Very high soil mercury	-0.48112	-0.37247	-0.52143	-0.53282	-0.53856	-0.53143
levels	0.0005	0.0091	0.0001	0.0001	0.0001	0.0001
Very low soil mercury	0.54348	0.46494	0.50360	0.54399	0.50109	0.54886
levels	0.0001	0.0009	0.0003	0.0001	0.0003	0.0001
Very high soil selenium	0.52657	0.54360	0.39443	0.51730	0.55595	0.54627
levels	0.0001	0.0001	0.0055	0.0002	0.0001	0.0001
Very high soil strontium	0.53375	0.60046	0.53613	0.51182	0.57242	0.59482
levels	0.0001	0.0001	0.0001	0.0002	0.0001	0.0001
High soil strontium	0.31945	0.33539	0.47544	0.47451	0.46247	0.45036
levels	0.0269	0.0198	0.0006	0.0007	0.0009	0.0013
Medium soil strontium	-0.50890	-0.28670	-0.47860	-0.46385	-0.33921	-0.43627
levels	0.0002	0.0482	0.0006	0.0009	0.0183	0.0019

Table 4. (continued)

Very high soil calcium levels	0.42107 0.0029	0.43747 0.0019	0.57429 0.0001	0.58729 0.0001	0.52332 0.0001	0.55265 0.0001
Very high soil sodium levels	0.49068 0.0004	0.56921 0.0001	0.49513 0.0003	0.43159 0.0022	0.53897 0.0001	0.54613 0.0001
Very low soil zirconium levels	0.38127 0.0075	0.43371 0.0021	0.45582 0.0011	0.41852 0.0031	0.50959 0.0002	0.47722 0.0006
High soil barium levels	0.29927 0.0388	0.42117 0.0029	0.49712 0.0003	0.51836 0.0002	0.48431 0.0005	0.48542 0.0005

regression equations, goiter prevalence was able to explain 50.5 percent of the mean variance.

In subsequent steps a variety of other variables entered the equations. Very high soil mercury and potassium and medium soil strontium appeared in several equations, as did industrial water use and land disturbed by strip mining. However, none of these additional variables could explain more than a further 21.6 percent of SIDS variance, in any particular year.

To illustrate the procedure, and some of the results obtained, the stepwise multiple regression equations for mean SIDS mortality during the period 1983-1987 are given below:

At this point all variables left in the model are significant at the 0.1500 level; no other variables met this criterion for entry.

Where:

- En 18 is the prevalence of goiter in military recruits examined for service during World War I (1917-18).
- En 39 is the ratio of land disturbed by strip mining to undisturbed land.
- En 65 is the number of toxic waste sites in the US Superfund list, divided by the area of the state.
- PVH Na is the percentage of soil samples taken from the state that contained sodium levels that were in the highest 20 percent of those collected in the conterminous United States.
- PVH Hg is the percentage of soil samples taken from the state that contained mercury levels that were in the highest 20 percent of those collected in the conterminous United States.

Step 1 R-square = 0.574
SIDS (1983-87) = 1.271 +(0.0523 En 18)

Step 2 R-square = 0.733
SIDS (1983-87) = 1.456 + (0.0455 En 18) - (0.0370 En 65)

Step 3 R-square = 0.766
SIDS (1983-87) = 1.518 + (0.0448 En 18) - (0.0235 En 65) - (0.00450 PVH Hg)

Step 4 R-square = 0.801
SIDS (1983-87) = 1.587 + (0.0429 En 18) - (0.0133 En 65) - (0.00484 PVH Hg) - (0.532 En 39)

Step 5 R-square = 0.811
SIDS (1983-87) = 1.572 + (0.0391 En 18) - (0.0133 En 65) + (0.00416 PVH Na) - (0.00478 PVH Hg) - (0.0476 En 39)

Discussion: SIDS, A Possible Etiology

Pregnancy results in subtle changes in maternal thyroid function that increase the need for iodine. Total serum thyroxine, triiodothyronine and reverse triiodothyronine, for example, are elevated in pregnant women because of the influence of estrogen-induced increases in thyroxine-binding globulin.[10] Some of the increased thyroxine appears to cross the placenta because it is necessary for the development of the fetus.[10] As a consequence, in iodine deficient regions, the majority of pregnant women develop goiter.[10] This is the case, for example, in Scotland" and Ireland[12] where goiter, as assessed by a visible and palpable gland, has a prevalence rate of 70 percent amongst pregnant women. Comparable studies in Iceland, Canada and California[11,13-14] reveal goiter prevalence rates of between 5 and 20 percent. This suggests that many pregnant women are deficient in iodine.

The Pearson correlations and stepwise multiple regressions just described demonstrate that, in the United States during the years 1983 to 1987, SIDS mortality had a spatial pattern that was extremely similar to goiter, prior to the introduction of iodine prophylaxis.[6] These relationships are also obvious from Table 1 and Figures 1 and 2.

The possibility of a role for iodine deficiency in the etiology of SIDS is also supported by the significant positive correlations between the distribution of iodine deficient soils and SIDS mortality in every one of the years examined. To illustrate, for the years 1983 to 1987 the correlations were 0.43336 ($p = 0.0021$); 0.50129 ($p = 0.0003$); 0.57711 ($p = 0.0001$); 0.51898 ($p = 0.0002$) and 0.56345 ($p = 0.0001$) respectively.

Beyond this, both Table 3 and Table 4 strongly indicate that SIDS mortality was elevated in states where soils contain very high selenium levels. The author has argued in detail elsewhere[4-5] that selenium is protective against diseases of the heart and against some malignant neoplasms, especially those of the digestive tract. The strong negative correlations between SIDS mortality and death from diseases of the heart and from cancer are suggestive of a potential role for elevated selenium in the etiology of SIDS (Table 3). There are also strong positive correlations between SIDS mortality and soils that contain very high levels of selenium. This possibility is further supported by the strong negative correlations that occur between SIDS mortality and soils that contain very high levels of mercury, the selenium antagonist. In addition, selenium is very bioavailable in calcium enriched soils which again also show strong positive correlations with SIDS mortality (Table 4).

On the basis of this analytical evidence and an extensive literature review, the author postulates that SIDS tends to occur in the infants of mothers who developed a thyroid hormone imbalance during pregnancy. Such subclinical hypothyroidism may have occurred because of an iodine and selenium imbalance, or the excess consumption of goitrogens, or for some other reason. It is further hypothesized that this maternal hormone imbalance probably denies adequate thyroxine to the fetus which, as a consequence, develops the subtle developmental defects described by Barnet and Hunter.[15] When stressed by events such as cold weather, or difficult breathing conditions, which increase the demand for thyroxine and hence for iodine, these developmental defects converge in early infancy to cause death. In the United States, this process seems to occur most often when environments, and hence diet, are selenium enriched. However, this is not the case in regions like the South Island of New Zealand where SIDS mortality is high (Table 5) yet the environment is both iodine and selenium deficient.[16,,18] It should be pointed out, however, that in China the relationship between goiter and iodine is bimodal. Goiter is common, for example, where the iodine content of drinking water is either below 5 or above 300 micrograms per litre.[19] It is possible, therefore, that selenium may also have a bimodal impact on thyroid hormone metabolism, with imbalances occurring in both selenium elevated and selenium depressed environments. Such a relationship would help to explain why internationally SIDS appears to be commonest in iodine deficient regions which also have either abnormally high, or very low soil selenium levels.

Testing the Hypothesis: The Bradford Hill Criteria

The geographical evidence, therefore, appears to suggest that SIDS is yet another iodine deficiency disorder,[20-22] exacerbated by either elevated or depressed selenium levels.

Figure 2. Prevalence rates of simple goiter among males examined for potential military service: 1917-1918.

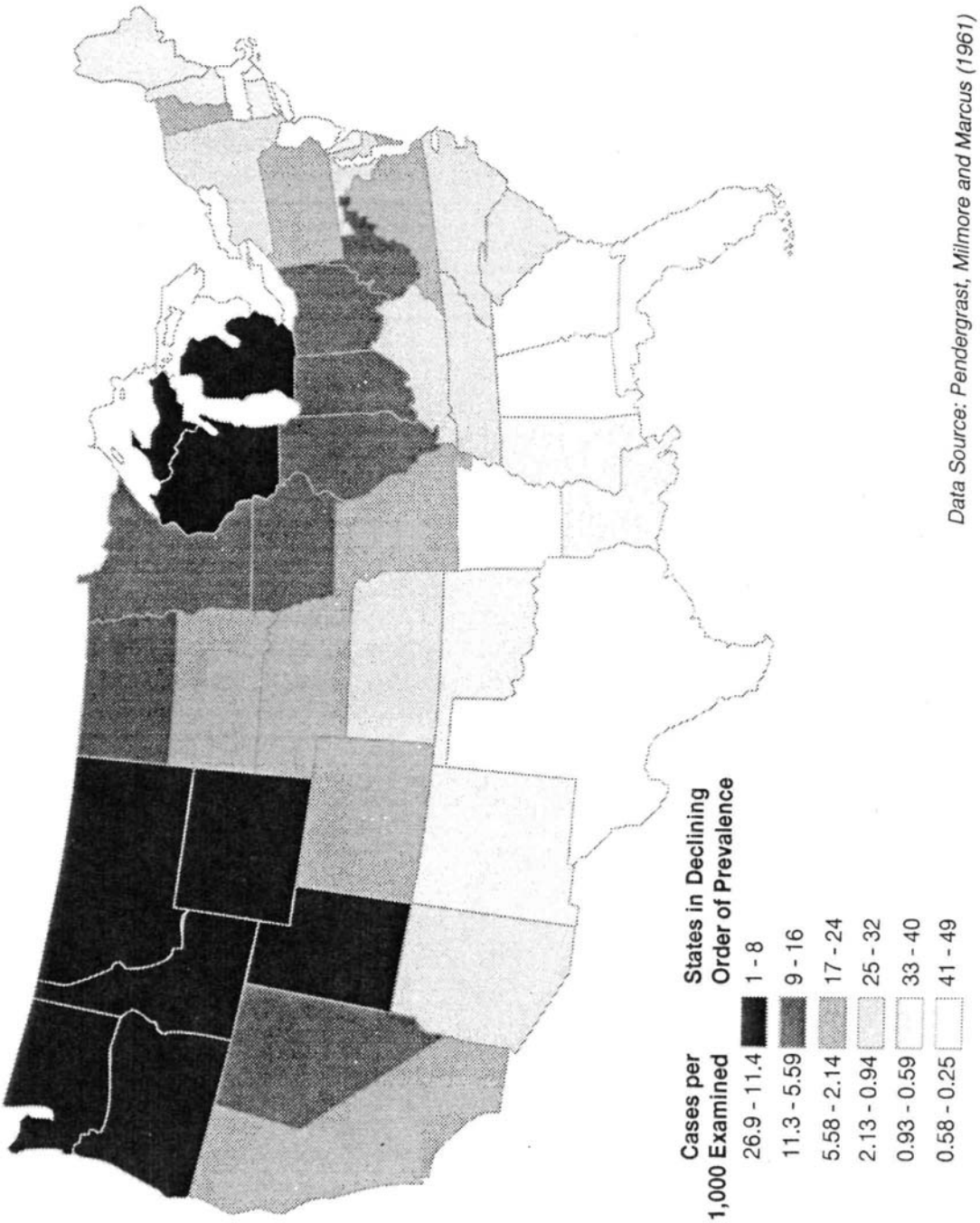


Table 5. International Rates of Sudden Infant Death Syndrome

Year	Location	Rate/1000 Live Births
1974	Stockholm, Sweden	0.06
1980-1987	Upper Austria	0.3
1973	Ashkelon District, Israel	0.31
1974	Netherlands	0.42
1983-1987	Rhode Island, USA	0.44
1979	Northern Territories, Australia	0.7
1983-1985	Sweden	0.7
1970	Czechoslovakia	0.8
1983-1987	Connecticut, USA	0.87
1979	Queensland, Australia	1.1
1988	Denmark	1.3
1990	Southern New Zealand	1.3
1978-1987	Wisconsin (Whites), USA	1.4
1972	California, USA	1.55
1980-1983	Denmark	1.66
1973	Sacramento, California, USA	1.7
1972	South Australia	1.7
1990-1991	Avon, England	1.7
1987	Denmark	1.9
1974	Auckland, New Zealand	1.9
1972	Philadelphia, USA	1.92
1970	Great Britain	2.0
1974	Cuyahoga Country, Ohio, USA	2.08
1980-1987	Salzburg, Austria	2.2
1985-1987	Victoria, Australia	2.2
1979-1983	Hamburg, Germany	2.3
1972	King County, Washington, USA	2.32
1975	Western Australia	2.5
1983-1987	Montana, USA	2.54
1973	Oxford Linkage Area, Great Britain	2.78
1971	Northern Ireland	2.8
1983-1987	Alaska, USA	2.91
1970	Ontario, Canada	3.0
1987-1989	Avon, England	3.5
1978-1987	Wisconsin, (Blacks), USA	3.6
1985-1987	Tasmania, Australia	3.8
cl989	New Zealand	4.0
1981	Tasmania, Australia	4.6
1979-1984	Southern New Zealand	6.3
1978-1987	Wisconsin (Native Americans), USA	6.7

Source: Data derived from numerous original sources.

However, geographers and epidemiologists are well aware of the ecological fallacy[23] and the difficulties implicit in generalizing from one scale of analysis to another.[5-23] Statistical abberations also can produce spurious relationships between disease distributions and the environment, which may tend to suggest causal links where none exist. To address this problem, a set of principles, often referred to as the Bradford-Hill[24] criteria after that author, have been developed to further identify probable cause and effect relationships.[23,25] They are similar to those used, for example, by the Surgeon General's expert committee to evaluate the postulated causal relationship between smoking and lung cancer.[25] In the remainder of this paper, these nine criteria are used to evaluate this author's hypothesis that a maternal thyroid hormone imbalance, often caused by sub-optimal dietary iodine and selenium intake, is the root cause of SIDS.

(1) Coherence

Hill[24] argued that an association is more likely to be causal if it agrees with the "known facts," or with the "established scientific truth" of a particular discipline. This is a confusing criterion to apply since it ignores the reality that some novel concepts cause paradigm shifts that invalidate the conventional wisdom. As Jones and Moon[23] point out, if coherence was always insisted upon "we would never discover anything new; coherence supports existing theory while incoherence potentially generates new theory."

However, the current author does not claim that the hypothesis that iodine-selenium induced maternal and hence fetal thyroid hormone imbalances are the ultimate cause of SIDS requires a paradigm shift. Rather, it is argued that the existing literature supports the view that SIDS is largely the result of a maternal nutritional deficiency and that the deficient nutrient is most likely to be iodine. To illustrate, SIDS is more common amongst twins than singletons.[2627] Its occurrence is particularly frequent in infants from multiple pregnancies, especially if they weigh less than 2 kg at birth.[28] When the birth weights of two twins in a pair are significantly different, it is usually the lighter of the two, if any, that dies of SIDS.[29] As Beal[27] has pointed out, a possible explanation for these phenomena "is that some factor is at a critical supply level from the mother during pregnancy. A twin receives only half of this supply, and a smaller twin probably receives less than half." Obviously, if this is true, the resulting nutritional deficiency may render the lighter infant even more susceptible than usual to SIDS.

If Beal[27] is correct, such a maternal dietary deficiency appears to result in a wide range of developmental abnormalities in the susceptible infant. In 1983, for example, Barnett and Hunter[15] pointed out that "There is a growing body of evidence that SIDS victims are not completely normal and healthy, as was once believed. A variety of new information from several disciplines strongly suggests that the infant who dies suddenly and unexpectedly may do so because of subtle developmental, neurology, cardiorespiratory and metabolic defects that converge at a particularly vulnerable time."

Since this observation was made, evidence has continued to accumulate to confirm that SIDS victims display diverse subtle abnormalities, many of which often are apparent only at autopsy.[30,,35] It is clear, therefore, that if maternal dietary deficiency is the fundamental cause of SIDS, it must involve nutrient(s) for which there are widespread developmental requirements.

It is obvious from the literature that SIDS deaths also tend to occur more frequently after cold weather,[3638] or when a child has been placed in a prone sleeping position.[39,40] Bottle feeding[41] and exposure to tobacco smoke[42] also appear to elevate SIDS risk. It seems very improbable that any of these factors are the fundamental cause of SIDS, rather they appear to be triggers. That is, they result in the death of infants which previously have been weakened by subtle developmental neurological, cardiorespiratory and metabolic defects,[15,30-35] which in themselves were caused by a maternal dietary deficiency(ies). Removing these triggers, however, can result in a decline in SIDS mortality,[40,43] indicating that is possible for an infant suffering from the effects of such a maternal nutritional deficiency(ies) to survive, provided it is not unduly stressed.

The evidence suggests, therefore, that the nutrient(s) involved as the basic cause(s) of SIDS is critical for the development of a wide range of organs and is required to maintain both respiration and body temperature. Iodine

appears an obvious candidate for this role since it is necessary for all these purposes.[20,44] Similarly, selenium is an essential trace element that is linked to birth defects in animals at both ends of its dose-response curve.[45-46] Deficiencies of selenium also cause congenital malformations in humans.[47] It is not too difficult, therefore, to accept that selenium imbalance also may be involved in the subtle abnormalities found in SIDS victims.

(2) Biological plausibility

Biological plausibility is also a useful criterion for the evaluation of possible cause and effect relationships. It is necessary to know, for example, whether a postulated relationship makes biological sense; that is whether it is possible to elaborate the biological and biochemical links between the suspected causal variable(s) and the disease.[24] In the present case, the question to be asked must be "is it possible to sketch biological mechanisms by which a lack of iodine and selenium excess, or deficiency, might interfere with the normal development of the fetus, so causing the subtle abnormalities which can culminate in SIDS when the infant is stressed?" It will now be demonstrated that this appears to be the case.

In 1820, Coindet began recommending the use of iodine for the treatment of goiter.[20] It is now well established that iodine is essential to the functioning of the thyroid gland, being an integral component of both thyroxine and triiodothyronine. These hormones play key roles in energy production, growth, metabolism and the burning of fat. They also are involved in mentality, the conversion of carotene to vitamin A, the synthesis of ribosomes and the absorption of carbohydrates from the intestines.[44] It is not surprising, therefore, that the offspring of iodine deficient women often display a wide range of abnormalities, which at their worst culminate in cretinism.[20-22]

Selenium also appears to play a role in the operation of the thyroid gland, since it has been known for many years that in areas where the soils are selenium deficient tend to suffer from elevated goiter.[48] Researchers at the Hahn-Meitner Institute in Berlin have discovered that this is because selenium plays a key role in deiodinase, an enzyme which catalyzes the conversion of thyroxine to triiodothyronine. If there is a selenium deficiency, this enzyme is present in insufficient quantities to create triiodothyronine.[48-51] However, it may be dangerous to use selenium supplementation alone in an attempt to correct this problem. Why was demonstrated by Contempre and colleagues[49-50] in an area of northern Zaire, which is both selenium and iodine deficient and suffers from excessive hypothyroidism. These researchers discovered that selenium supplementation in isolation caused a dramatic fall in the already impaired thyroid function, in patients who were clinically hypothyroid. They argued, therefore, that selenium supplementation alone in iodine deficient pregnant patients may lead to brain damage in the fetus, by causing a decline in available thyroxine. They further suggested that to some degree, selenium deficiency may be protective in iodine deficient patients because it tends to lessen the severity of their hypothyroid condition. In the fetus, selenium deficiency may tend to reduce the degenerative process of the thyroid gland leading to myxedematous cretinism.[49] They suggest, therefore, that selenium supplementation should only *follow* iodine prophylaxis. The essential role of selenium in the functioning of the thyroid may explain why SIDS is particularly common in the United States where iodine levels are depressed and selenium levels elevated. It may also explain why SIDS mortality also is elevated in southern New Zealand, where the food chain is depressed in both iodine and selenium.[51] It seems biologically plausible, therefore, that iodine deficiency and selenium excess, or deficiency, may play key roles in the etiology of SIDS, since either combination clearly compromises thyroid function.

(3) The temporal relationship of the association

Any suspected putative cause must precede, or at least be simultaneous with, its effect(s).[24] That is, cause cannot follow effect. This principle of temporality, therefore, implies that if the thyroid hormone imbalance hypothesis is correct, SIDS victims should display abnormal hormonal levels prior to their deaths. The evidence on this crucial point is somewhat contradictory, but does support thyroxine deficiency in at least some SIDS cases.

To illustrate, in 1981 Chacon and Tildon[52]

described elevated serum triiodothyronine levels in autopsied SIDS victims. They reported that 88 percent of 50 cases had serum triiodothyronine values greater than 2.5 ng/ ml, with a mean level of 4.06 ng/ml. These values compared with the 1.8 ng/ml mean serum triiodothyronine level displayed by a control group of infants that had died from known causes. The significance of elevated triiodothyronine in SIDS victims is apparent from the following quotation from Lewin:[53]

> An ingenious shift occurs in the nature of the thyroid output when the body is deficient in iodine. Iodine is actually incorporated into the structure of the thyroid hormones, but thyroxine has four atoms of iodine per molecule while triiodothyronine has only three. When, therefore, iodine stocks are low in the body, the thyroid produces more triiodothyronine than normal and less thyroxine. The reserves of iodine are therefore used more economically.

The elevated triiodothyronine found in SIDS victims by Chacon and Tildon[52] would suggest, therefore, that these infants had been iodine deficient prior to death. However, Schwarz and coworkers[54] refuted Chacon and Tildon's results, claiming that thyroxine, free thyroxine, reverse total triiodothyronine and thyroid-stimulating hormone were not useful in differentiating SIDS victims because an appropriate control group of infants had not been autopsied. However, Peterson and colleagues[55] also demonstrated that elevated triiodothyronine levels could be detected in SIDS cases and suggested that this hormone might serve as a useful port-mortem diagnostic marker for crib death. In addition, comparable results were obtained by Riss and his research colleagues[56] who reported on blood samples taken from 53 infants within 18 hours of their deaths. They noted a 3.7 fold increase in triiodothyronine in the blood of 11 SIDS victims, compared to 32 infant controls that had died from known causes. These researchers denied that this significant difference could be the result of post-mortem conversion of thyroxine to triiodothyronine, a suggestion that had been made elsewhere in the literature. Indeed, Riss and coworkers[57] claimed that increased triiodothyronine in the blood, within 18 hours of death could be used as a diagnostic characteristic of SIDS. If the current author is correct, this may only be true in infants short of iodine but with elevated selenium. It seems less likely to be true of iodine deficient infants dying with a deficiency of selenium, since as has been pointed out this trace element is an essential component of deiodinase, an enzyme required to catalyze the conversion of thyroxine to triiodothyronine.

It appears, therefore, that the medical and biochemical evidence, although somewhat contradictory, tends to demonstrate that the thyroid hormone imbalance hypothesis meets Hill's[24] principle of temporality. That is, many SIDS victims do appear to develop thyroxine deficiency and triiodothyronine excess prior to their deaths. Beyond this, the thyroid hormone imbalance hypothesis also appears to explain the virtual immunity from SIDS that occurs during the first three weeks after birth.[358] Originally it was believed that there was no transplacental thyroid hormone transfer.[59] However, experimental evidence has established that it occurs in rats[60] and probably also in sheep.[61] It seems likely, therefore, that the developing human fetus also receives both iodine and thyroxine from its mother.[1062] It is probable, therefore, that in the first few weeks after birth, newborns utilize iodine stores that were provided by their mothers during pregnancy.[63] These, however, seem likely to be depleted rapidly, especially if prone sleeping position or cold weather increase demands for iodine. In addition, in both cows and humans, colostrum (the thin milky fluid secreted by the breast during the first few days after birth) contains more iodine than does true breast milk. Salter[64] quotes values of 50 to 240 micrograms per litre for human colostrum, compared with 40 to 80 micrograms of iodine in mother's milk, once lactation is established fully. The evidence suggests, therefore, that the human breast fed infant receives more iodine from its mother immediately after birth than it does once lactation peaks. If the thyroxine deficiency hypothesis is correct, these two phenomena, the building up of thyroxine stores by the fetus and the elevated levels of iodine in colostrum, could account for the SIDS peak which occurs at age two to four months.[3,58]

(4) Dose-response curve

A dose-response relationship is a highly

significant criterion for establishing cause and effect. As exposure to the suspended causal agent increases, its deleterious effects are expected to become more extreme. If iodine deficiency and selenium imbalance are involved in the etiology of SIDS, it is to be anticipated, therefore, that both birth defects and infant mortality would be especially common in very iodine deficient environments, especially if they are selenium enriched or depleted.

This appears to be the case. In its most extreme form iodine deficiency is known to lead to both myxedematous and neurological cretinism, both of which involve a wide range of birth defects.[20,22] Interestingly, severe iodine and selenium deficiencies have been demonstrated in eastern Zaire on Idjwi Island and in the Ubangi in Northern Zaire, which are African endemias of myxedematous cretinism.[65] In addition, in China individuals suffering from the Kaschin-Beck disease, which is known to involve selenium deficiency, are retarded, dwarfed and very similar in appearance to the myxedematous cretins, who are endemic in low iodine environments.[66] Clearly, either extreme deficiencies of iodine or selenium can cause major birth defects and it is probable that together they play key roles in myxedematous cretinism.[65]

Infant mortality rates also appear to rise as iodine deficiencies increase. The relationship between severe iodine deficiency and stillbirths and neonatal deaths has been examined in detail by Dulberg.[67] Subsequently, that author and his coworkers[68] reviewed iodine deficiency's impact on the eight countries of the WHO South-east Asia region. They argued that, in the region as a whole, iodine deficiency was responsible for an average late reproductive loss (stillbirths and neonatal deaths) of 5.0 per 1000 live births. However, its effects were greatest in Bhutan and Nepal, which are still areas of extremely depressed iodine intake.[20] Here the loss rates were 70.2 and 40.3 per 1000 live births respectively.[68] These figures are far in excess of any recorded SIDS mortality rates (Table 5) and seem to indicate a clear dose-response relationship between iodine deficiency and infant mortality. The greater the deficiency, the higher the resulting infant death rate.

This author is uncertain of infant mortality rates in those areas of China which are extremely selenium deficient or enriched. However, it is clear that in China, selenium deficiency plays a major role in Keshan disease, which is associated with myocardial damage and inadequate heart function. However, most resulting deaths take place post-weaning and amongst pre-school children.[66]

(5) Experimental support

It is rarely possible, for ethical reasons, to perform strictly controlled experiments on humans in an effort to establish causal relationships. Normally, one must rely on animal models or quasi-experiential or simply observational studies.[25] However, in the case of iodine there is impressive experimental evidence, from both animals and humans, which demonstrates this trace element's impact on the incidence of birth defects and on infant mortality.[20]

In one such experiment, ewes were fed an iodine deficient diet for a period of six to twelve months and then mated with normal rams.[69] A control group of ewes eating the same diet, but given sodium iodide and iodized oil supplements was used as a control. Lambs from the iodine deficient ewes showed a wide variety of birth defects, including numerous neurological problems. Similar abnormalities have been observed in the offspring of iodine deficient marmosets[20] and rats.[70] In the experiment with sheep, a retrospective review of pregnancies demonstrated that there had been a 21 percent loss in iodine deficient ewes, compared with a 4 percent mortality in controls.[69]

Iodine deficiency also causes increased human infant mortality. The first experiment to demonstrate that iodine prophylaxis could reduce the incidence of cretinism whilst lowering human infant mortality rates took place in the Jimi River District of the Western Highlands of Papua New Guinea.[71] Here alternate families were given injections of iodized oil or saline. Eight thousand individuals in total were so treated. In the eight villages for which there were good records, women receiving saline gave birth to 26 cretins during the next five years. In contrast, there were only seven cretins born to women who had received iodized oil. This difference was statistically significant at the $p < 0.001$ level. Since it was very probable that the seven women who received iodized oil, but

still gave birth to cretins, were already pregnant at the time of the injection, it was concluded that iodized oil prevented cretinism. It was noted also that infant mortality rates fell amongst those families that had received the iodized supplement. During the succeeding five years, infant mortality in untreated families was some 18.2 percent, compared with only 13.3 percent in those families receiving iodine injections. This decline in infant mortality was significant at the $p < 0.05$ level. In a comparable experiment conducted in Zaire, Thilly[72] showed that the injection of iodized oil during pregnancy reduced perinatal mortality per 1000 from 250 to 167.

Hetzel[20] has summarized evidence from Ecuador, Papua New Guinea, Peru and Zaire, arguing that the effects of iodine deficiency on the fetus, which include spontaneous abortion, stillbirth, congenital anomalies and various manifestations of cretinism, probably occur because of depressed thyroxine in the blood of its iodine deficient mother. He suggests that the more severe this reduction in the level of maternal thyroxine, the greater the threat to fetal integrity. The reverse also appears true, since Romaguera and colleagues[73] have demonstrated in more than 140 patients that intra-amniotic thyroxine injection will accelerate fetal maturation.

Numerous animal experiments also have been conducted with selenium to examine the effects of a deficiency of this trace element on reproduction.[74] It has been established, either by experiment or by observation, that selenium deficient diets result in white muscle disease in lambs and calves,[75] muscular dystrophy and pancreatic impairment in chickens,[76] growth hormone insufficiency in rats[77] and myocardial degeneration in dogs.[78] Why animals respond in such different ways to selenium deficiency is still uncertain.

There is also a synergistic relationship between iodine and selenium. Rats deficient in both of these trace elements have significantly lower thyroidal triiodothyronine, thyroxine and total iodine than those deficient in iodine alone. In contrast, levels of plasma thyroid-stimulating hormone and thyroid weight are significantly elevated in rats that have been deprived of both elements.[79]

There is also an impressive experimental literature linking elevated selenium levels to reproductive problems and congenital malformations in animals.[45] In the seleniferous regions of Western South Dakota and Northern Nebraska many chicken eggs would not hatch.[80] Embryos were badly deformed with malformations of legs, toes, wings, beaks or eyes. Disturbance in the normal process of bone and cartilage formation also occurred. Those chicks that did hatch were greasy or wiry and never became fluffy. They were weak and often died soon after hatching. In an effort to determine whether such congenital malformations were due to selenium toxicity, Franke and colleagues[81] injected Selenite into eggs from normal chickens, before incubation. The resulting embryos developed abnormalities of beaks, eyes and legs, establishing that such deformities were the result of excessive selenium. Adverse effects of elevated selenium have been noted in numerous other animals. Female rats receiving high levels of selenium, for example, produced young that could not feed and were emaciated at birth.[82] In swine, high selenium diets lowered conception rates, decreased the number of surviving piglets and reduced their weight.[83] Congenital malformations of the limbs and eyes have also been recorded in the lambs of ewes feeding on seleniferous pastures.[45]

Obviously no experiments have been conducted to study the effect of toxic doses of selenium in humans. However, in China this element has been added to soils and fertilizers in deficient regions.[47,66,84] As a result, in many regions the incidence of both Kaschin-Beck and Keshan diseases have fallen markedly. Clearly, therefore, an increase in selenium in the food chain of deficient regions reduces the frequency of the congenital malformations, such as dwarfism, necrosis of cartilage and dystrophy of skeletal muscles. This may explain, in part, the dramatic fall in SIDS rates in Southern New Zealand[85] where losses have declined from 6.3 deaths per 1000 live births in the period 1979 to 1984 to 1.3 in 1990. Infants in southern New Zealand had been shown to be extremely prone to selenium deficiency[17,86] and, as a consequence, awareness of the need to supplement diet with this element has increased.

In summary, it seems clear that the hypothesis, that SIDS is due to iodine deficiency, exacerbated by selenium excess or deficiency, meets Hill's[24] criterion of experimental support. The evidence reviewed demonstrates

that in both animals and humans iodine deficiency is a major cause of both congenital malformations and elevated mortality in the young. In addition, the literature illustrates that both selenium deficiency and excess are associated with numerous birth defects and with elevated mortality in the offspring of a variety of animals. Beyond this, selenium deficiency also has been linked to congenital malformations and elevated childhood mortality, the frequency of which can be greatly reduced by adding this trace element to the food chain.[87-88]

(6) Consistency of the association

The consistency principle stresses the need for repetition, arguing that an association between a suspected cause and its effect is more likely to be true if it has been observed in different populations, places, circumstances and times.[24] If the thyroid hormone imbalance hypothesis is correct, therefore, one would expect particularly low SIDS rates in countries that either had conducted vigorous iodine supplementation programs, or in which soil iodine levels were naturally very high. In addition, one might expect depressed SIDS rates in ethnic or social groups that ate diets rich in iodine. Conversely, elevated SIDS mortality might be anticipated in groups that were consistently exposed to goitrogens, or that lived in regions of naturally depressed soil iodine.

Certainly there appears to be evidence that SIDS rates are low in countries with very successful iodine supplementation programs. To illustrate, Hetzel[20] has pointed out that the four Scandinavian countries, Norway, Sweden, Finland and Denmark now have virtually no goiter because of impressive eradication programs. The success of iodine prophylaxis in Scandinavia is reflected in the elevated iodine concentrations found in the urine of its full-term infants. To illustrate, Delange and colleagues[89] recorded urinary iodine levels in infants from 14 European cities and from Toronto, Canada. Results demonstrated that there was a marked difference, with the highest iodine urinary levels being recorded in Rotterdam, Helsinki and Stockholm, and the lowest in Gottingen, Heidelberg, Freiburg and Jena. Depressed urinary iodine concentrations were least common in Stockholm, where only 5.9 percent of infants provided samples which measured below 5 micrograms per deci-litre. This figure compared with 11.9 percent in Toronto and 100 percent in Freiburg and Jena.

If thyroid hormone imbalance, especially thyroxine deficiency, leading to subtle developmental abnormalities, is the fundamental cause of SIDS, one might expect such infant mortality, therefore, to be extremely uncommon in Stockholm. A search of the literature provided SIDS rates for 40 cities, states, regions, ethnic groups or countries (Table 5). Interestingly, the lowest known rate, at 0.06 per 1000 live births, was recorded in Stockholm.[90] SIDS mortality for Sweden as a whole was only 0.7 per 1000 live births. Clearly, therefore, high infant urinary iodine concentrations seem consistent with the low SIDS mortality in Sweden.

Further evidence of consistency is apparent from the Southern Hemisphere. In Australia, the mean SIDS mortality rate, during the period 1975 to 1981, was 1.6 per 1000 live births, but ranged from a low of 0.9 in the Northern Territories to a high of 4.4 in Tasmania.[91] Indeed, there was a clear difference between the Australian mainland and the island of Tasmania, with the latter typically experiencing a SIDS death rate some two to three times greater than the former. Interestingly, Tasmania was the only Australian state to undergo extensive glaciation and as a result its soils are often iodine deficient.[92,93] Not coincidentally, Tasmania also has a history of goiter.[63]

There is a similar prominent north to south SIDS gradient in New Zealand, with the intensely glaciated, iodine deficient South Island displaying higher crib death rates than the North.[16] The South Island is also selenium deficient, as displayed by the numerous cases of white muscle disease seen amongst livestock, prior to the introduction of feed supplementation.[94] Much of the South Island, therefore, is deficient in both selenium and iodine and the SIDS mortality rate of 6.3 per 1000 live births for this region, during the period 1979 to 1984. was one of the highest on record (Table 5).[16,85]

Racial differences in SIDS rates also may provide further evidence of consistency of association. It has been established, for example, that in California there are great differences in SIDS rates between various ethnic

groups. Fewest deaths occur amongst Japanese and Chinese American infants, with a SIDS rate of only 0.51 per 1000 live births.[58-90] This contrasts with very elevated SIDS amongst Californian American Indians, who experience a mortality rate of 5.93 per 1000 live births.[90] Abnormally low SIDS losses also are recorded from Japan.[95] These depressed rates of SIDS appear consistent with the thyroxine deficiency hypothesis since seaweeds tend to be a common component of Oriental cuisine. Seaweed, of course, contains extremely elevated amounts of iodine. In addition, Japan has some of the world's most iodine enriched soils,[96] probably because of the use of seaweeds as fertilizers for centuries.[96]

In addition, if the fundamental cause of SIDS is thyroid hormone imbalance, particularly thyroxine deficiency, one would anticipate that the infants of groups routinely exposed to goitrogens also would suffer elevated mortality rates. This certainly appears true of smokers, whose infants are more prone to SIDS than those of non-smokers.[42] This may be due to the adverse effects of cigarette smoke on the fetal thyroid gland. Thiocyanate is a metabolite that is commonly found in the blood of smokers.[42] It is created by the detoxification of cyanide, absorbed from tobacco smoke. In pregnant women it enters the fetal blood circulation.[42] Thiocya-nide is a goitrogen that impairs the production of iodinated thyroid hormones. As a result, it has been established that the thyroid glands of fetuses exposed to their mothers' cigarette smoke are hyperfunctioning, causing an increase in metabolic rate. This results in lower thyrotropin production and greater fetal caloric requirement.[42] The increased SIDS seen amongst the infants of smoking mothers is consistent, therefore, with the thyroxine deficiency hypothesis since such cigarette smoke not only reduces infant birth weight but also interferes with the normal functions of the fetal thyroid gland. Maternal smoking, therefore, has been linked to abnormal development of the fetal nervous system, especially in males, and is thought to reduce intelligence in surviving offspring.[42] Both of these effects have also been noted in infants born to iodine deficient mothers who do not smoke.[63]

(7) Strength of association

Causality is more likely if the magnitude of the relationship between suspected cause and effect is high. A very large relative risk of, say, 10:1 suggests that any association is unlikely to be entirely due to chance.[25] The screening of some 2.5 million potential military recruits during World War I established a national US male prevalence rate for simple goiter of 4.4 per 1000. However, this disorder varied from a high of 26.91 in Idaho to a low of 0.25 per 1000 in Florida.[6] In addition to Idaho, goiter proved most common in recruits from Oregon, Washington, Montana, Utah, Wyoming and Wisconsin. In contrast, its prevalence was lowest in Florida, Texas, Massachusetts, Arkansas, New Jersey, Georgia and Rhode Island (Figure 2). In the five states that formerly had the highest male goiter prevalence rates, the mean SIDS mortality rate per 1000 live births, during the period 1983 to 1987, was 2.48. This contrasts with a SIDS death rate of 1.17 in the five states that used to suffer from the lowest goiter rates. Repeating this procedure for groups of seven states yields SIDS mortalities of 2.36 and 1.12 per 1000 live births respectively. When SIDS deaths in the ten US states which formerly had the most and least male goiter are compared, it can be seen that, in the period 1983 to 1987, deaths per 1000 live births were 2.14 and 1.15 respectively. These three sets of comparisons yield relative risks of 2.1:1,2.1:1 and 1.9:1. It would appear, therefore, that during the five years in question an infant was approximately twice as likely to die of SIDS in a state where goiter was common prior to the widespread use of iodized salt, than it was in one in which goiter has always been relatively rare. Obviously, much has happened to the racial and ethnic mix and to dietary habits in these states between the two periods 1917-1918 and 1983-1987. However, this difference in relative SIDS risk between formerly high and low goiter prevalence states is supportive of the hypothesis that SIDS may be commoner in the infants of mothers who are suffer thyroid hormone imbalances during pregnancy.

Comparisons between countries where prophylaxis has eradicated goiter and those where this disorder is still commonplace yield far higher relative risks. To illustrate, as already discussed, in Sweden where goiter is now virtually unknown, the SIDS mortality

rate is extremely low,[90] probably of the order of 0.7 per 1000 live births (Table 5). In contrast, in Bhutan and Nepal which still suffer severe iodine deficiencies, iodine-related infant mortality is estimated at 70.2 and 40.3 per 1000 live births.[68] While such international comparisons are very suspect, since many other factors also may influence infant mortality, those between Sweden and Bhutan and Nepal yield extremely high relative risks of 100:1 and 57.6:1 respectively.

(8) The specificity of the association

Hill[24] originally argued for specificity of association; that a particular type of exposure should result in one specific disease, and perhaps even to its development at a unique site. The value of this criterion in establishing causality has been criticized by a variety of authors[23,35,98] for several reasons. It has been demonstrated repeatedly, for example, that most disease-producing factors cause more than one observable effect. This is certainly true of both iodine and selenium imbalances in humans. Hetzel,[20] for example, identified 22 iodine deficiency disorders, of which 12 occur in the fetus and two more in the neonate. They vary from spontaneous abortion to dwarfism. Iodine excess also has been implicated in several disorders, including goiter[19-22] and melanoma.[4] Similarly, selenium deficiency is a major risk factor in Keshan and Kaschin-Beck diseases[19-66] and is thought to play a significant role in many cancers[99] and in heart disease.[100] Beyond this, selenium deficiency may be involved in some forms of dementia,[5] schizophrenia[5] and even infertility in males.[101] Selenium excess, in contrast, is known to result in loss of hair and nails, skin lesions, abnormalities of the nervous system, disturbance of the digestive tract and possibly tooth decay.[47]

Houeland[25] considered specificity of association to be an invalid criterion for establishing causality, and argued that it was a relic from the early days of modern disease theory. Similarly, Rothman[98] considered it useless and misleading. The current author agrees with these researchers. Indeed, it seems logical to argue that the lack of specificity of association makes it more, rather than less, likely that iodine and selenium imbalances are the fundamental causes of SIDS. This is because crib death victims tend to display a wide range of subtle abnormalities, many of which are similar to those known to be caused in more extreme form by severe iodine and selenium imbalances.

(9) Analogy

Analogy is the last criterion discussed by Hill[24] for establishing causality. Reasoning from analogy, however, can never produce conclusive supportive evidence; at best it helps generate novel hypotheses that must then be tested further. This is exactly how the current author first became interested in the possibility that iodine and selenium imbalances may be involved in the etiology of SIDS.[7] His interest was awakened by the realization that, in the United States, SIDS had a spatial distribution that was extremely similar to that of goiter, prior to the introduction of iodine supplementation (Figures **1** and 2).

Conclusions

The hypothesis that SIDS is caused by a maternal thyroid hormone imbalance, perhaps brought about by inadequate dietary intake of iodine coupled with either a deficiency or excess of selenium, appears to meet all but one of Bradford Hill's[24] criteria for establishing cause and effect. The exception is specificity of the association. However, this particular criterion itself has been widely criticized and is considered invalid by many authors.[23-25-98]

If the thyroid hormone imbalance hypothesis is correct, SIDS mortality rates can be quickly, cheaply and easily reduced. Preventive measures might include encouraging pregnant women to eat iodine enriched foods, such as seaweeds, or take kelp tablets or other supplements containing this trace element. Pregnant women should not overdose on iodine since an excess leads to goiter in newborns.[22] Dietary selenium enrichment might also reduce SIDS mortality rates but would carry more risk since, when used alone, it can increase thyroid hormone imbalance in iodine deficient women.[102] In addition, in selenium enriched regions, selenium supplements might be expected to exacerbate SIDS. In certain jurisdictions, blood thyroxine level measured in every infant, usually during the fourth or fifth day after birth.[20103] If the level is low, indicating a reduced state of thyroid gland function, further tests are conducted. If

deficiency of thyroxine is confirmed, daily supplements are provided. This treatment is designed to prevent mental retardation. However, if as postulated, thyroid hormone imbalance (especially thyroxine deficiency) is the fundamental cause of SIDS, supplementation of infants with abnormally low blood levels of this hormone ought to result in a decline in mortality. Even if, in the final analysis, the SIDS-thyroxine deficiency hypothesis proves incorrect, such thyroxine supplements seem likely to increase the infant's intelli-gence.[20,22,63,104,105] Such a strategy, therefore, appears to carry no downside risk.

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