Effectiveness of Food Fortification in the United States: The Case of Pellagra

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ABSTRACT

Objectives. We evaluated the possible role of niacin fortification of the US food supply and other concurrent influences in eliminating the nutritional deficiency disease pellagra.

Methods. We traced chronological changes in pellagra mortality and morbidity and compared them with the development of federal regulations, state laws, and other national activities pertaining to the fortification of cereal-grain products with niacin and other B vitamins. We also compared these changes with other concurrent changes that would have affected pellagra mortality or morbidity.

Results. The results show the difficulty of evaluating the effectiveness of a single public health initiative such as food fortification without controlled experimental trials. Nonetheless, the results provide support for the belief that food fortification played a significant role in the elimination of pellagra in the United States.

Conclusions. Food fortification that is designed to restore amounts of nutrients lost through grain milling was an effective tool in preventing pellagra, a classical nutritional deficiency disease, during the 1930s and 1940s, when food availability and variety were considerably less than are currently found in the United States. (*Am J Public Health.* 2000;90:727–738)

Mortality statistics for the United States[1] indicate that pellagra was perhaps the most severe nutritional deficiency disease ever recorded in US history. Pellagra is a classical nutrient deficiency disease characterized by dermatitis, diarrhea, inflammation of mucous membranes, and, in severe cases, dementia. Death can occur if treatment is not received. Pellagra is associated with diets low in the B vitamin niacin, flares up when skin is subjected to strong sunlight. Niacin intakes and requirements are generally expressed as niacin equivalents. Dietary sources of niacin equivalents include preformed dietary niacin and the metabolic conversion of the amino acid tryptophan to niacin (approximately 60 mg of tryptophan are equivalent to 1 mg of niacin).[2]

In the early 1900s, when it was prevalent, pellagra occurred to some extent in every state in the United States.[1] It was, however, most serious in the southern states, where income was low, most of the available land was used for nonfood crops such as cotton and tobacco, and corn products were a major dietary staple. With the advent of motorized corn mills, the corn used as a dietary staple was particularly low in niacin. Annual deaths from pellagra far outnumbered deaths from other nutritional deficiency diseases. During the peak incidence years of 1928 and 1929, it was the eighth or ninth highest cause of death, exclusive of accidents, in many southern states.[3] The early history of pellagra is covered in detail by Harris[4] and summarized by Sebrell.[5]

Pellagra is one of the few deficiency diseases for which there are records of annual deaths in the United States from the beginning of the 20th century to the present. The availability of mortality statistics and the relatively high rates of mortality and morbidity for pellagra in the United States make pellagra a useful model for examining the complex interrelationships between the decline of a nutritional deficiency disease and possible contributing factors to this decline.

A brief comparison of the total number of deaths from pellagra and voluntary bread enrichment has been published previously.[6,7] In this report, we present a more in-depth evaluation of the effects of various contributing factors, including food fortification, on the eventual elimination of pellagra in the United States. The effects on this evaluation of several changes in the recording system for pellagra deaths are also discussed.

Methods

To examine contributions made by various factors, we chronologically compared the recorded annual cases, deaths, and death rates from pellagra for selected critical years with the development of federal regulations, state laws, and other national activities pertaining to the fortification of cereal–grain products (hereafter referred to as grain products) and with changes in other contributing factors at critical points in the history of pellagra. Other possible contributing factors examined included changes in factors that could affect (1) niacin nutriture (i.e., personal income, food availability, and use of vitamin supplements), (2) treatment of the disease (i.e., evolution of the understanding of the etiology and role of foods in the disease), and (3) the nutritional/health status of people that would make them more susceptible to pellagra or deaths

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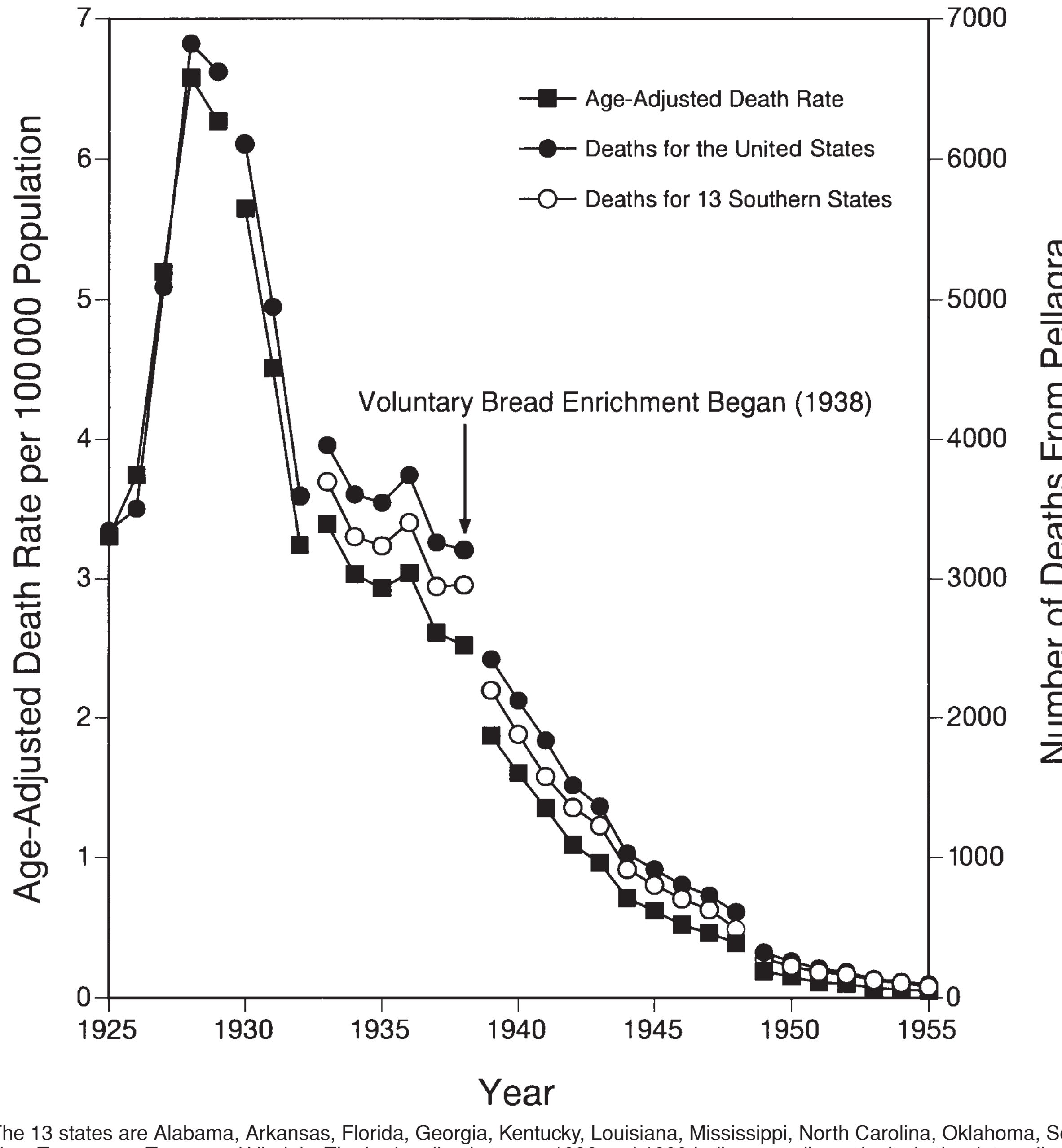
from pellagra (i.e., epidemics of infectious diseases such as influenza and pneumonia [IP]).

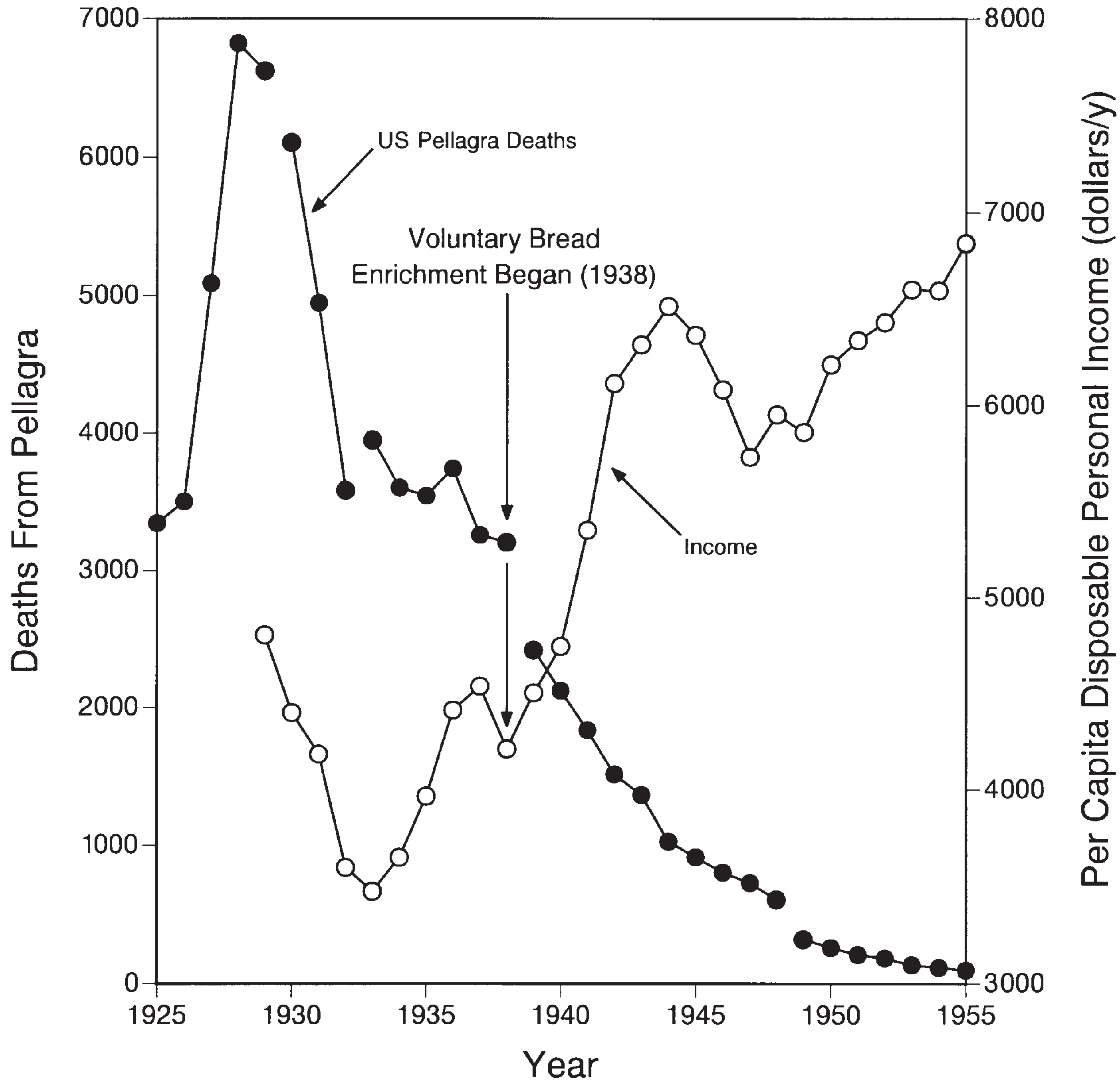
The number of deaths from pellagra came from the mortality statistics published by the National Center for Health Statistics (NCHS) of the US Department of Health and Human Services.[1] Mortality data were gathered by each state department of health and were compiled by the NCHS. Annual age-specific numbers of deaths from pellagra came from the yearly volumes of *Vital Statistics of the United States,* published by the NCHS. Age-adjusted death rates for pellagra were calculated with the direct method of applying the age-specific rates to the total US population in 1940.[8,9] Age-adjusted death rates for influenza and pneumonia were obtained from NCHS publications.[9,10] Mortality data before 1933 are for states in the death registration system; from 1933 on, they are for the entire United States[8] (Figures 1–4, Tables 1 and 2).

Information on federal regulations concerning the fortification of grain products was obtained from the *US Federal Register.* Information on state fortification activities was obtained through literature and personal com-



Note. The 13 states are Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, and Virginia. The broken line between 1932 and 1933 indicates a discontinuity in the data collection system for pellagra deaths: mortality data before 1933 are for states in the death registration system, and those from 1933 on are for the entire United States. Other broken lines indicate changes in the coding system for the *International Classification of Diseases.*

FIGURE 1—Pellagra deaths in the United States from 1929 to 1955 and in the 13 southern states, and age-adjusted death rates in the United States per 100 000 population from 1933 to 1955.

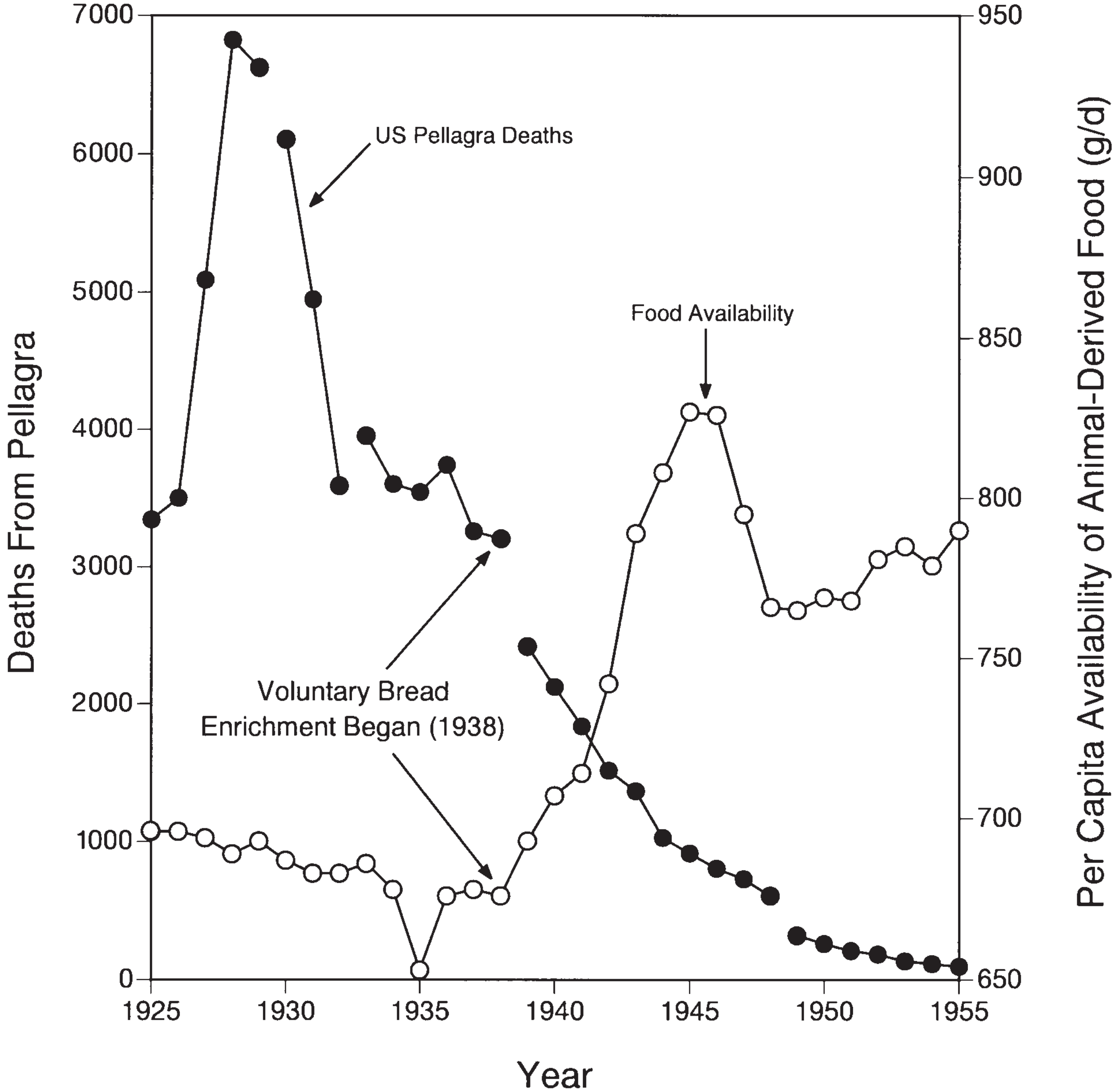


Note. To adjust for inflation, income data are expressed in 1987 dollars. The broken line between 1932 and 1933 indicates a discontinuity in the data collection system for pellagra deaths: mortality data before 1933 are for states in the death registration system, and those from 1933 on are for the entire United States. Other broken lines indicate changes in the coding system for the *International Classification of Diseases.*

FIGURE 2—Pellagra deaths and per capita disposable income in the United States from 1929 to 1955.

munications with state governments. Annual national per capita disposable income in 1987 dollars came from a report by the Bureau of Economic Analysis of the US Department of Commerce.[11] State-specific annual per capita disposable income in 1987 dollars was obtained from the Bureau of Economic Analysis (unpublished data, 1989). Data on per capita disappearance of food were obtained from an agricultural economic report by the US Department of Agriculture.[12] The food disappearance data provide per capita estimates of food available for potential consumption by the US population. For most commodities, these data are derived by subtracting exports, nonfood uses, military uses, and end-of-the-year inventories from the sum of production, imports, and beginning-of-the-year inventories and then dividing by the US civilian population. In the absence of time-trend data for actual food intakes, we used the per capita disappearance data as a surrogate for examining trends in food intake. Foods that would be expected to affect pellagra rates by increasing the intake of niacin equivalents because of their high niacin or tryptophan content and the magnitude of consumption were included in the analysis; these are meats, poultry, fish/shellfish, eggs, and dairy products excluding butter (hereafter referred to as animal-derived foods).

Using SAS procedures,[13] we statistically analyzed the relationship between various



Note. The broken line between 1932 and 1933 indicates discontinuity in the data collection system for pellagra deaths: mortality data before 1933 are for states in the death registration system, and those from 1933 on are for the entire United States. Other broken lines indicate changes in the coding system for the *International Classification of Diseases.*

FIGURE 3—Pellagra deaths and per capita availability of animal-derived food in the United States from 1929 to 1955.

contributing factors and the decline in the pellagra mortality/morbidity rate for the years 1933 to 1950. We limited statistical analysis to these years because information on pellagra deaths was not available for all 13 southern states before 1933 and pellagra was under control by 1950. Because pellagra rates changed by orders of magnitude, log rates were used for pellagra mortality and morbidity rates. Two types of analysis were done: (1) simple correlation analysis to examine the relationship of each possible contributing factor and the decline in the pellagra rate and (2) multiple regression analysis to examine the relationship between food fortification and the pellagra rate after other contributing factors were adjusted for (i.e., knowledge about the cause of pellagra, availability of animal-derived food, and IP rate). Income is expected to affect the pellagra rate, because high income is associated with an improved diet—that is, increased intake of animal-derived foods—which results in a decreased rate of pellagra. It is unknown what percentage of income was used to improve the diet or if the percentage was the same over the years. Per capita availability of animal-derived foods better reflects the trends in the intake of these foods over the years. Thus, we chose to adjust for the availability of animal-derived foods rather than for income.

Statistical analyses were done for 13 southern states combined (Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, and Vir-

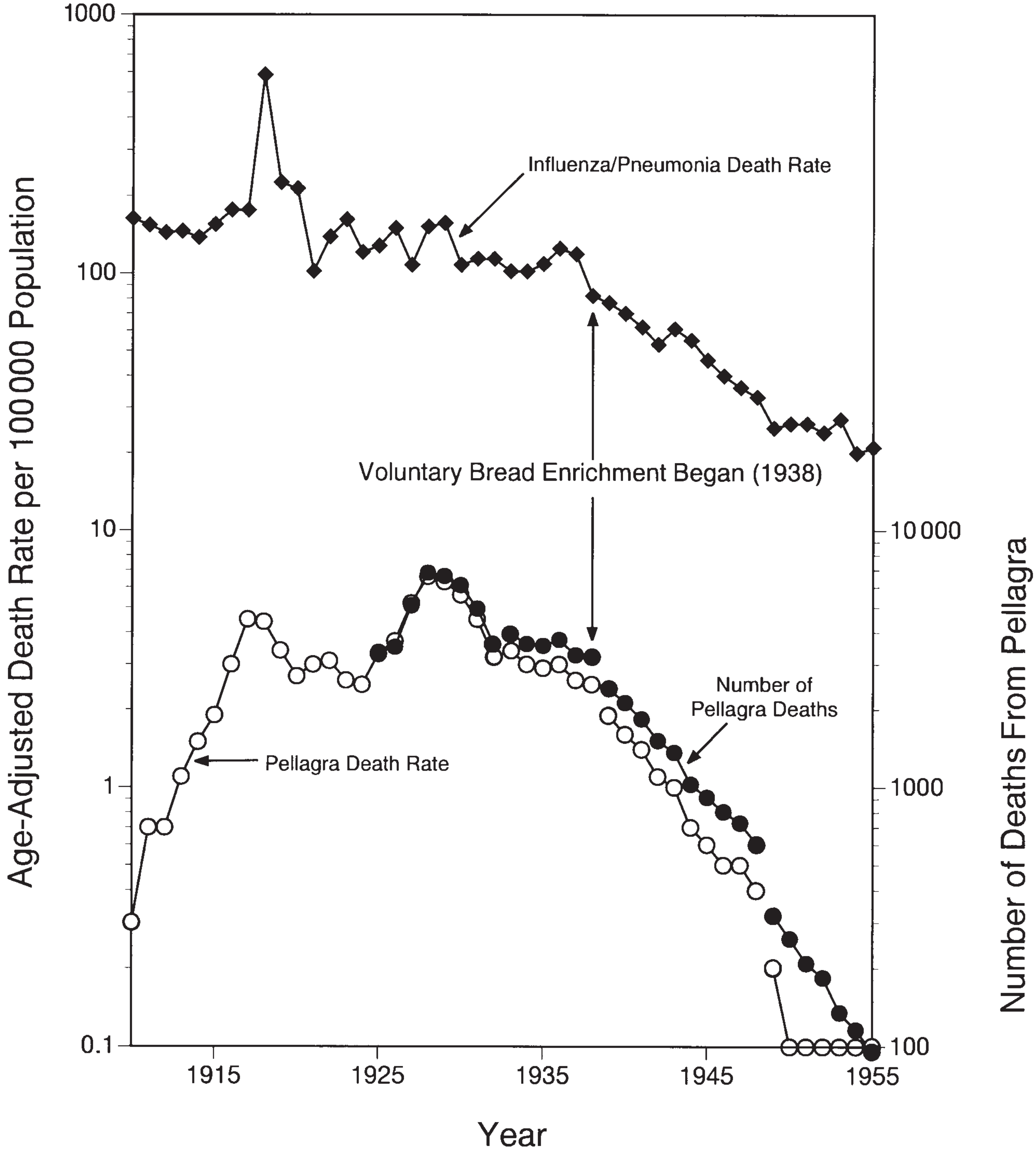


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FIGURE 4—Age-adjusted death rates for pellagra and for influenza/pneumonia from 1910 to 1955.

ginia) and for Mississippi. We used state-specific data for pellagra mortality and morbidity rate, income, and influenza and pneumonia rate. In the absence of state-specific food availability data, we used the national estimates of per capita food availability as a surrogate. Niacin was identified as an antipellagra agent in 1937.[14,15] A value of 1 was assigned to knowledge for years beginning from 1937 (prior years received zero value). To estimate exposure to food fortification, we assigned an annual fortification score of 1 to each year in which a national-level enrichment program was initiated, a federal enrichment regulation became effective, or a state

TABLE 1—Age-Adjusted Pellagra Death Rates in the United States by Sex and Race and Female-to-Male Ratio of Death Rates for Selected Years[a]

Sex and Race	1928[b]	1935	1938	1939	1940
	Death rate per 100 000				
Female					
White	4.1	2.2	1.8	1.4	1.3
Non-White	60.2	21.9	18.2	13.1	11.2
Ratio of non-White to White	14.7	10.0	10.1	9.4	8.6
Male					
White	2.4	1.4	1.2	0.9	0.8
Non-White	25.6	8.7	8.3	6.0	4.9
Ratio of non-White to White	10.7	6.2	6.9	6.7	6.1
	Female-to-male ratio of death rate				
White	1.7	1.6	1.5	1.5	1.6
Non-White	2.4	2.5	2.2	2.2	2.3

[a]Adjusted to the total US population of 1940.
[b]Represents death rates from states in the death registration system.

TABLE 2—Age-, Sex-, and Race-Specific Death Rates per 100 000 and Age- and Race-Specific Female-to-Male Ratios for Pellagra in 1928[a]

	Death Rate				Female-to-Male Ratio of Death Rate	
	Male		Female			
Age Group (y)	White	Non-White	White	Non-White	White	Non-White
<1	0.3	7.1	0.7	2.8	2.3	0.4
1–4	0.4	3.1	0.2	3.5	0.5	1.1
5–9	0.2	3.1	0.1	4.0	0.5	1.3
10–19	0.3	3.5	0.5	16.3	1.7	4.7
20–29	0.6	6.6	2.4	66.7	4.0	10.1
30–39	1.2	9.9	4.6	81.6	3.8	8.2
40–49	2.6	25.9	6.9	85.6	2.7	3.3
50–59	4.9	63.1	7.0	73.6	1.4	1.2
60–69	8.8	103.6	11.2	112.8	1.3	1.1
70–79	16.7	140.5	14.4	162.2	0.9	1.2
80+	14.8	126.7	11.8	256.0	0.8	2.0

[a]Represents death rates from states in the death registration system.

enrichment law was enacted. A state law affects only the population within the state. Thus, to estimate the annual fortification score for the 13 states, we weighted the state score by the percentage of the population exposed to the enrichment—that is, by the population of the state that enacted an enrichment law as a percentage of the total population of the 13 states. For example, an annual fortification score of 1 was assigned to 1938 for the voluntary bread enrichment that year. An annual score of 0 was assigned to each year between 1939 and 1941 because there were no qualified national, federal, or state enrichment activities during these years. In 1942, a federal regulation for enriched flour and farina became effective, and thus an annual fortification score of 1 was assigned to 1942 for this federal enrichment regulation. In the same year, Louisiana and South Carolina enacted a mandatory enrichment law for bread and flour. The population of Louisiana accounted for 7% of the total population of the 13 southern states, and that of South Carolina accounted for 5%. Therefore, the fortification score for Louisiana was weighted by 0.07 and that for South Carolina by 0.05. The total annual fortification score for the 13 states for 1942 equals 1.12, which is the sum of 1 for the federal regulation, 0.07 for the Louisiana law, and 0.05 for the South Carolina law. Cumulative fortification scores were then calculated by summing annual fortification scores for the years studied. For example, the cumulative fortification score is 1 for each year from 1938 to 1941. The cumulative fortification score for 1942 for the 13 states equals 2.12, which is the sum of 1 for the cumulative score in 1941 and 1.12 for the new federal and state enrichment activities in 1942. These cumulative fortification scores were used to examine the relationship between food fortification and the pellagra rate.

Results

Pellagra Mortality Rates in the United States

Between 1900 and 1907, there were 0 to 2 reported cases of deaths from pellagra each year. By the mid-1910s, the annual number of deaths surpassed 1000. The number of deaths from pellagra peaked at about 7000 in 1928 and then began to decline. There were 2 distinct periods of rapid decline, one between 1928 and 1932 and the other beginning in 1939 (Figure 1). The pattern of pellagra mortality was the same whether the deaths were plotted in terms of total number of deaths per year or in terms of the age-adjusted yearly rate per 100 000. The pattern of pellagra mortality for the 13 southern states during the years critical for the evaluation of food fortification overlapped that of the United States (Figure 1). This is not surprising, because pellagra was primarily a disease of southern states, and deaths in these states represented about 90% of the total deaths from pellagra in the United States.

The relationships of age, sex, and race/ethnicity with pellagra mortality for selected years are presented in Tables 1 and 2. Age-adjusted rates were much higher for non-Whites than for Whites and for females than for males (Table 1). Between 1928 and 1940, the rates were about 6 to 15 times higher for non-Whites than for Whites. The ratio decreased with time for women, but after 1928 it was relatively stable for men. For both races, about twice as many females died from pellagra as did males. Analysis of sex- and race-specific death rates for various age groups in the peak year of the pellagra epidemic (Table 2) also showed that (1) the death rate increased with age for both sexes and races, (2) females of childbearing age were at a greater risk than males in the same age category, and (3) the higher death rate for females shown in Table 1 was primarily due to a higher rate of death for women, especially non-White women, during childbearing years. Clearly, pellagra was a much more serious health problem for non-Whites than for Whites and for females than for males. These demographic characteristics probably reflect differences in economic status, dietary habits, availability of medical treatment, and perhaps the increased nutrient requirements of pregnancy and lactation.

Economic Growth and Pellagra Deaths

Economic factors as measured by national per capita disposable personal income and pellagra deaths between 1929 and 1955 are compared in Figure 2. The sharp decline in the income curve from 1929 to 1932 indicates the effects of the economic depression. This decline was followed by an increase in income in subsequent years, with the exception of a transient fall in the late 1930s and a decline during the mid-1940s, with subsequent peak levels of income achieved in the the early 1950s. During the periods of economic depression and subsequent economic growth, the death rate from pellagra showed a steady decline.

Food Availability and Pellagra Deaths

Figure 3 shows changes in the availability of animal-derived foods that would be expected to have the most impact on niacin nutrition for the period 1925 to 1955. Availability of these foods showed a slight decrease during the first rapid decline in pellagra deaths from 1928 to 1932 and then increased above the baseline level beginning in 1939. Although plant-derived foods were not included in the availability data, there was no consistent or meaningful change in the availability of plant-derived foods high in niacin and/or tryptophan, such as nuts—particularly peanuts—and legumes, during the same period.

Fortification of Grain Products and Other Nutritional Factors

From the mid-1910s to the mid-1920s, Goldberger and his associates, conducting several human experimental studies, demonstrated that pellagra is a noninfectious disease that can be prevented by adding to the diet liberal amounts of high-protein foods such as milk, eggs, meat, and yeast.[16,17] Several additional significant nutritional events occurred during the period 1932 to 1939. In the early 1930s, both riboflavin and pyridoxine were mistakenly thought to be antipellagra vitamins. In 1936, however, human pellagra was successfully treated with a liver filtrate factor free of these vitamins.[18] In 1937, nicotinic acid was finally identified as the antipellagra vitamin.[14,15]

Around this time, a movement that favored the fortification of grain products began. In a meeting held on March 12, 1936, the Council on Foods and Nutrition (CFN; then known as the Committee on Foods) of the American Medical Association (AMA) announced its general policy on fortification.[19] On March 18, 1939, the CFN issued a statement encouraging the restorative addition of nutrients to foods on the basis of the report submitted by a joint committee of the CFN and the Council on Pharmacy and Chemistry of the AMA.[20] In an effort to improve the nutritional quality of bread, bakers in 1938 voluntarily began to enrich bread with high-vitamin yeast,[21] known at the time to prevent pellagra and a good source of protein as well as niacin and other B vitamins. During the years when synthetic vitamins were very expensive, most bread was enriched by this type of yeast.[21] In 1939, some bakers also began to use synthetic vitamins and produced 12 million pounds of bread per month with added vitamin B complex and nonfat dry milk.[22]

During the 1940s, the Food and Drug Administration (FDA) began to formulate standards-of-identity regulations for enriched grain products, and various states implemented mandatory enrichment laws (hereafter referred to as laws or enrichment laws). By the end of the decade, 26 states had enacted enrichment laws for flour and/or bread. In addition, 5 states had enrichment laws for cornmeal and corn grits. More detailed information on the fortification of grain products has been reported elsewhere.[23,24] With these intense fortification activities, pellagra deaths steadily decreased (Figure 1).

Influenza and Pneumonia and Pellagra Deaths

The relationship between age-adjusted pellagra death rate per 100 000 and age-adjusted death rate for IP is presented in Figure 4. An IP epidemic occurred in 1918 through 1920 and the pellagra death rate increased during the same period, although the upward trend in pellagra mortality preceded the IP pandemic. The pattern of the pellagra curve did not resemble that of the IP curve between 1920 and the late 1930s, after which both curves showed a similar downward trend.

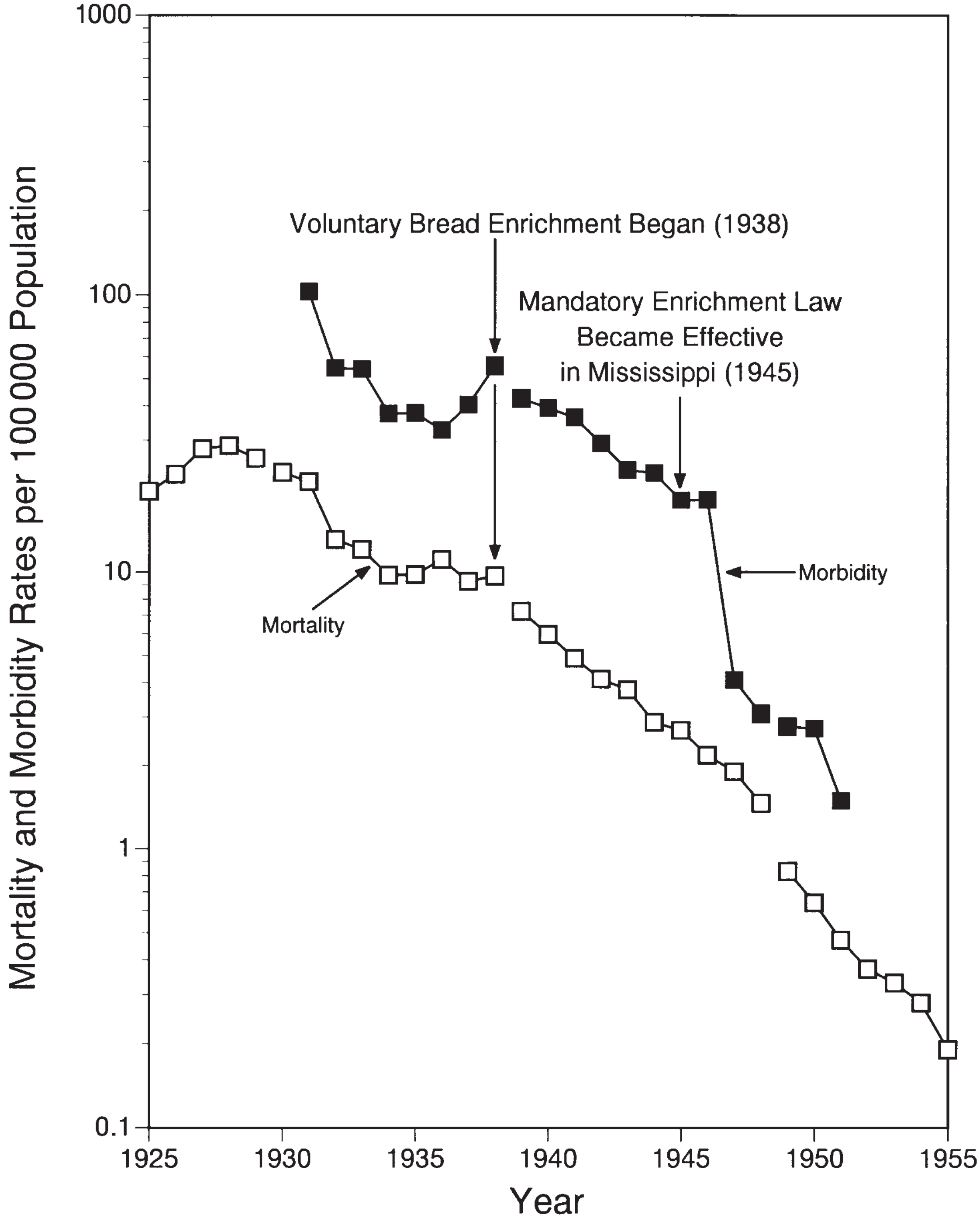
Morbidity and Mortality From Pellagra

Figure 5 presents crude morbidity and mortality rates for pellagra for 5 of the 13 southern states. Since cases of pellagra were not required to be reported in most states, morbidity data are not available for the United States; nonetheless, we were able to obtain the reported cases of pellagra from Alabama, Arkansas, Mississippi, Tennessee, and Texas (L. Gedel, P.C. White Jr, D. Blakey, J. Hard, and N. Robinett-Weiss, written communications, 1977–1983). Morbidity and mortality rates from pellagra sharply decreased starting with the year following the initiation of voluntary enrichment of bread. There was another sudden and precipitous decrease in the morbidity rate between 1946 and 1947 (Figures 5 and 6) following the enactment of the mandatory enrichment law for bread, flour, cornmeal, and corn grits in Mississippi in 1944; the law became effective in 1945. The sudden decrease in morbidity in the 5 states (Figure 5) was a reflection of the precipitous decrease in Mississippi; there was no sudden decline in pellagra morbidity in the other 4 states.

Statistical Analysis

Because the pattern of the pellagra mortality and morbidity rates differed for the years before and after the voluntary enrichment of bread, a separate simple correlation analysis was done for the 2 periods 1933 to 1938 and 1938 to 1950. Between 1933 and 1938, knowledge about the cause of pellagra was significantly associated with the decline in the pellagra mortality rate for the 13 southern states combined (r=–0.86, P=.03), but not for Mississippi. Income, availability of animal-derived food, and IP rate were not associated with the decline. The morbidity rate in Mississippi was not associated with any of the contributing factors. Following the initiation of voluntary bread enrichment, the decline in the mortality rate for both the 13 southern states and Mississippi showed a highly significant association with food fortification (r=–0.90 for the 13 states and r=–0.91 for Mississippi, P<.001 for both), IP rate (r=0.95, P<.001 for both the 13 states and Mississippi), and income (r=–0.85, P<.001 for the 13 states; r=–0.86, P<.001 for Mississippi). The availability of animal-derived food was also significantly associated with the mortality rate in the 13 states (r=–0.60, P=.03) and in Mississippi (r=–0.66, P=.02). The decline in the morbidity rate in Mississippi showed a strong association with food fortification (r=–0.74, P=.004) and IP rate (r=0.78, P=.002) and a weaker association with income (r=–0.63, P=.02), but it had no significant association with the availability of animal-derived food.

Multiple regression analysis showed that after knowledge, availability of animal-derived food, and IP rate were adjusted for, the decline in both the mortality and the morbidity rates in Mississippi and the decline in the mortality rate for the 13 states were strongly associated with food fortification (β=–0.49 to –1.64, $P \leq$ .0001).



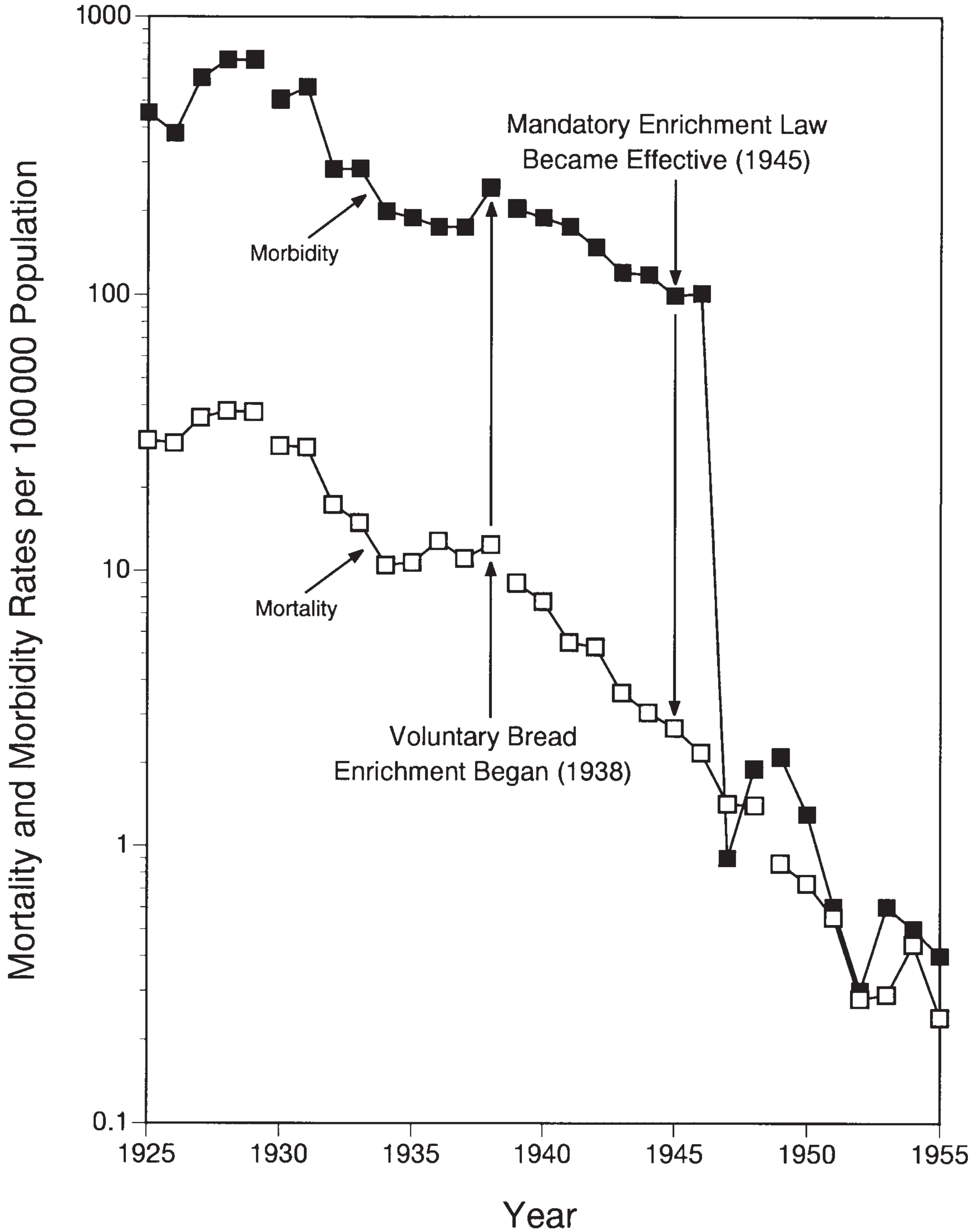
Note. The 5 states are Alabama, Arkansas, Mississippi, Tennessee, and Texas. Morbidity rates before 1937 do not include data from Texas. The broken line between 1936 and 1937 in the morbidity curve indicates the difference in the number of states included. Other broken lines in the morbidity or mortality curves indicate changes in the coding system for the *International Classification of Diseases.* Mississippi's mandatory law included flour, bread, cornmeal, and corn grits.

FIGURE 5—Morbidity and mortality rates for pellagra in 5 southern states.

Discussion

Pellagra is still a public health problem in areas of the world such as Africa, India, and China.[25] In the United States, it was virtually eradicated by 1960. Pellagra is now seen only occasionally in this country, mostly in association with alcoholism and much less frequently in association with other disorders in which the intake of a balanced diet is compromised over prolonged periods.[26–28]

There were 2 periods of large, consistent decline in pellagra mortality, one between 1928 and 1932 and the other beginning in



Note. The broken lines indicate changes in the coding system for the *International Classification of Diseases.* Mississippi's mandatory law included flour, bread, cornmeal, and corn grits.

FIGURE 6—Morbidity and mortality rates for pellagra in Mississippi.

1939. The first large decline does not appear to have been related to improvements in per capita income or per capita dietary availability of niacin- and/or tryptophan-rich foods, since these factors were declining as the country entered the Great Depression. The most likely explanation for the dramatic decline in pellagra mortality between 1928 and 1932 is probably related to the fact that by the mid-1920s, several antipellagra foods, such as milk, eggs, meat, and yeast, had been identified, although the cause of pellagra (i.e., deficiency of niacin) was still unknown.[14,15] The most successful preventive or treatment measure at that time would have been supplementation of the diet with these high-protein foods. Indeed, the American Red Cross extensively distributed yeast, which is rich in protein, niacin, and other B vitamins.[3] The program began in 4 states in 1927 following flooding of the Mississippi River, and it gradually spread to adjoining states and throughout the South. However, since there was not enough yeast for all, it was given only to those who needed it most.[3] Thus, the decline in pellagra mortality from 1928 through 1932 was likely due to use of the identified curative agents by informed physicians and to distribution of yeast and possibly other high-protein foods to people in the areas with pellagra. As the economic depression continued and less money was available for the purchase of yeast, distribution was curtailed.[3] The plateau in pellagra mortality during the mid-1930s may have been due to the curtailment of antipellagra food distribution. It may also represent the segment of the population with pellagra that was not reached by informed physicians and/or public health officials and possibly also those who were re luctant to change their dietary habits.

The second large decline in pellagra mortality started in 1939 (Figure 1). Several factors that would be expected to reduce pellagra deaths occurred around this time. These factors included fortification of grain products, increased availability of animal-derived foods, improved treatment, availability of vitamin supplements, and a recovering economy. In 1938, bakers voluntarily began to enrich bread with high-vitamin yeast; a large decline in pellagra deaths occurred in the following year. (Note that voluntary enrichment of grain products actually began several years before the promulgation of federal fortification regulations or state enrichment laws.) The availability of animal-derived foods also increased beginning in 1939; that year, the per capita availability of these foods increased by 16.5 g/d over the 1938 value, representing an increase of 0.3 mg of niacin per day and 22 mg of tryptophan per day, or a total of 0.7 mg of niacin equivalents per day.

This increase in niacin equivalents from the increased availability of animal-derived food most likely had a relatively smaller effect on pellagra mortality than did fortification. For example, on the basis of the per capita intake of white bread of 260 g/d in the mid-1930s[29] and the first enrichment standard for niacin of 2.2 to 3.3 mg/100 g (equivalent to 10.0–15.0 mg/lb [enrichment standards are defined in milligrams per pound]),[30] we estimate that the enrichment of bread would have increased per capita niacin intake by 2.9 to 5.7 mg/d. This is about 4 to 8 times more than would be attributable to the increase in the availability of animal-derived foods.

Since information is not available on a state or regional basis, the food availability data here represent national averages, not the food availability to the population most severely affected by pellagra. In light of the below-average economic growth in the southern states,[31] the increase in consumption of the high-priced animal-derived foods in these states would likely have been smaller than the national average. Consequently, the increase in intake of niacin equivalents from these foods would be expected to be smaller than the national average of 0.7 mg/d. On the other hand, because the diet of southerners was higher in grain products than was the diet of people in other parts of the country,[22,32] it is likely that the impact of enrichment on the niacin intake of these people was more significant than suggested by the above per capita estimates.

Many studies have reported the effectiveness of fortification in alleviating the incidence of nutritional deficiency diseases and/or improving the general nutritional status of people here and abroad. Notable examples include a paucity of B vitamin deficiency diseases among 16 000 alcoholic inmates of the Chicago House of Correction surveyed in 1948 and 1949, compared with an occurrence of these diseases during the preenrichment years;[33] a large decrease in the incidence of B vitamin deficiencies in New York following bread enrichment in the early 1940s;[21] an absence of pellagra among 10 000 patients admitted to the Hillman General Hospital in Birmingham, Ala, in the early 1950s;[34] considerable improvement in the general nutritional status of the people in Norris Point, Newfoundland, following the enrichment of flour;[35,36] and a remarkable remission in signs of riboflavin and niacin deficiencies among troops of the Chinese National Army following the introduction of enriched rice.[37,38]

The improved treatment of pellagra could have accounted for the decrease in pellagra mortality after 1938. Synthetic niacin became available to physicians in the latter half of 1938.[3] Therefore, its use in the treatment of pellagra likely contributed to the decrease in pellagra deaths observed in 1939 and later. However, it is not possible to quantify the respective contributory effects of enrichment and treatment on prevention. Statistics on the incidence of pellagra, rather than the number of deaths, would eliminate the effects of treatment, because treatment affects the number of deaths but not the incidence. It is not known whether the pellagra morbidity data received from the 5 southern states (Figure 5) represent incidence data (new cases) or prevalence data (all existing cases, new and old). Mississippi had the most extensive data on cases, and the cases-to-deaths ratios agree with the ratios reported in the literature for a limited number of years.[39] However, it is also not clear whether the cases reported in the literature are incidence or prevalence data. To be on the conservative side—that is, to avoid overinterpreting our findings—we assumed the Mississippi data to be prevalence data. In any event, the pellagra morbidity rate began to show a steep decline beginning in 1939, the year following the voluntary enrichment of bread (Figures 5 and 6; note that the vertical axis is a log scale). Age-specific morbidity data are not available; thus, the morbidity rate data presented here are crude rates, not age-adjusted rates. However, we do not believe that age adjustment of the crude rate would change the pattern of the morbidity rate, since the pattern of the age-adjusted pellagra death rates for the United States was parallel to the pattern of the total number of deaths from pellagra, which was not adjusted for population size or age (Figure 1).

The effectiveness of the mandatory enrichment program is clearly seen in Mississippi (Figure 6). Following the initiation of mandatory enrichment of bread, flour, cornmeal, and corn grits in that state, the pellagra morbidity rate dropped precipitously, from 101 per 100 000 in 1946 to fewer than 1 per 100 000 in 1947; it remained low thereafter, although the consumption of animal-derived foods decreased considerably during this period (Figure 3).

There was a lag of 3 years between the enactment of Mississippi's mandatory law and the large decrease in pellagra cases; however, this is not unusual. Mississippi enacted the law in 1944, but the law did not become effective until February 1945. It often takes a few years from the time such a law is enacted for unfortified products to be cleared from the marketplace and for compliance by all the mills to be enforced, especially mills serving small communities.

There was no large decrease in pellagra mortality corresponding to the precipitous decline in pellagra morbidity following mandatory enrichment. This sudden decline in morbidity is probably not attributable to a possible change in treatment because (1) there is no evidence of a sudden improvement in the treatment of pellagra in 1947 and (2) if there were a sudden improvement in treatment, there would have been a corresponding decline in pellagra mortality, because such an improvement in treatment would have resulted in a large reduction in pellagra deaths. The absence of a sudden decrease in pellagra deaths in 1947 suggests that the precipitous decline in pellagra morbidity that year was primarily due to prevention of pellagra by mandatory enrichment of grain products.

Still another factor that could have influenced pellagra morbidity and mortality is voluntary use of vitamin supplements. According to the representatives of vitamin/mineral supplement manufacturers, over-the-counter vitamin pills became available in the early 1940s (R.L. Raycroft and D. Webb, personal communications, 1983); however, self-administration of vitamin pills was not prevalent at that time. During the early years, promotional efforts for over-the-counter vitamin pills were directed toward physicians, not the public. The sale of over-the-counter vitamin pills increased significantly for the first time in 1957 (D. Webb, personal communication, 1983). In the early 1940s, the production of synthetic vitamins was too low to meet even the demands of fortification, and the cost was so high that many bakers preferred to enrich their bread with high-vitamin yeast.[21] Even in the late 1940s, vitamin supplements were used primarily by people who had enough money to afford the supplements or by those who were ordered to take such supplements by their physicians.[33] Screening of patients admitted to large medical facilities (e.g., general hospitals) revealed that use of vitamin pills was very rare in the late 1940s.[33,40] It is highly doubtful whether a segment of the population too poor to afford nutritious meals would have had the desire or the money to buy vitamin pills. The decreases observed in pellagra deaths and cases in the 1930s and 1940s are thus probably not attributable to self-administration of vitamin supplements.

The *International Classification of Diseases,* used for the classification of morbidity and mortality, was revised 3 times between 1925 and 1955: in 1930, 1939, and 1949. The fifth revision, adopted in 1939, had a separate code for alcoholic pellagra; thus, beginning in 1939, death data for pellagra excluded pellagra deaths due to alcoholism.[41] Data on deaths from alcoholic pellagra are available for 1939 to 1945, after which no deaths from alcoholic pellagra were recorded in the mortality statistics. From 1939 to 1945, there were fewer than 15 alcoholic pellagra deaths in any given year, which is insignificant compared with the total number of annual pellagra deaths during those years. Thus, exclusion or inclusion of alcoholic pellagra deaths in the total number of pellagra deaths would not have any significant impact on the trend in pellagra deaths shown in Figures 1 through 6.

Comparability ratios are used to determine whether differences in mortality data based on 2 revisions of the *International Classification of Diseases* are attributable to differences in coding procedures. Such ratios are calculated by dividing the number of deaths assigned to a given disease under the new revision by the number of deaths assigned to that disease under the old revision. Comparability ratios are available only for comparisons between the fourth and fifth revisions and between the fifth and sixth revisions.[42,43] The comparability ratio for pellagra for the fourth revision (years before 1939) and the fifth revision (years beginning with 1939) was 0.996. Thus, the second large drop in pellagra deaths observed in 1939 was not affected by the changes in the coding procedures adopted that year. The comparability ratio for the fifth revision (years before 1949) and the sixth revision (years beginning with 1949) was only 0.6. Therefore, the break in the death curve between 1948 and 1949 partially reflects the lack of comparability in the coding procedures of the 2 revisions. However, this discontinuity is not of concern, since pellagra was already under control by 1948 and the extent of the decrease in deaths is no longer critical to the discussion in relation to food fortification.

Mortality data before 1933 are for states in the death registration system. With the exception of Texas, which entered the registration system in 1933, all southern states had entered the death registration system by 1929. Thus, participation in the system would not have influenced the 2 major periods of decline in pellagra death rates, although the first peak would have been higher had Texas entered the death registration system earlier. The increase in the number of deaths from pellagra between 1925 and 1928 (Figures 1–4) may have been influenced by the entry of Arkansas (1927) and Oklahoma (1928) into the system during that period. However, the late entry of these 3 states into the system did not influence the interpretation of the effect of fortification, since all 13 southern states had entered the system by 1933 and fortification of grain products did not begin until the late 1930s.

Examination of mortality from IP suggests that the smaller peak in pellagra deaths in 1918 to 1919 (Figure 4) reflects the likelihood of increased deaths of individuals with pellagra from complications due to IP infection. The IP curve also suggests that the aforementioned distribution of yeast and, possibly, of other high-protein foods and enrichment of grain products improved people's general nutritional status, which in turn may have protected them from infections. During the period of active food distribution in the early 1930s, IP death rates were consistently lower than in previous years, and the curtailment of food distribution in the mid-1930s was followed by a slight transitory increase in IP death rates in 1936 and 1937. After 1938, when voluntary bread enrichment was begun, IP death rates showed a consistent downward trend (Figure 4).

The relative importance of improved economic status vs food fortification in the eventual elimination of pellagra in the United States has been debated for years. Proponents of the economic theory have suggested that economic growth would bring about changes in dietary patterns, leading to better nutrition, and that pellagra was already decreasing before the federal and state fortification movement began in the early 1940s. However, the data presented here are not consistent with this hypothesis. As mentioned previously, the first major decline in pellagra mortality occurred concomitantly with the economic depression of the late 1920s and early 1930s, contrary to what the economic theory would predict. Pellagra mortality showed another steep fall beginning in 1939; however, there was no sudden change in the economy that year to account for this decrease. Rapid growth in the economy occurred 2 years later. Thus, economic growth per se did not account either for the first large decline in pellagra mortality between 1928 and 1932 or for the early stages of the second large decline that started in 1939, although its role in the disease's eventual elimination cannot be discounted.

After the influences of other contributing factors—such as improved knowledge about the cause of pellagra, the availability of animal-derived food, and IP rate—were adjusted for, statistical analysis of the relationship between food fortification and the decline in the pellagra mortality rate showed a highly significant association between the 2 factors. The data were not adjusted for a possible continuing improvement of treatment because of lack of data. However, the morbidity rate, which is not as sensitive to treatment as the mortality rate, also showed a highly significant association with food fortification. In the absence of state-specific data on the availability of animal-derived foods, we used national per capita availability as a surrogate. In light of the below-average economic growth in the southern states,[31] the availability of high-priced animal-derived foods has been lower than the national average. Using national averages in place of state-specific data would have given the appearance that the changing availability of animal-derived foods had a greater effect than it actually did. This, in turn, would have weakened the estimated relationship between food fortification and the pellagra rate after other influencing factors were adjusted for. Thus, we have probably underestimated the relationship between fortification and the pellagra rate.

Because of the absence of data on annual estimates of the percentage of enriched grain products, we used a fortification scoring system to estimate the exposure to enrichment. This system assumes that a national- or federal-level fortification activity affected the whole US population and that a state-level activity affected only the population in the state that enacted the enrichment law. Available information shows that by the spring of 1941, about 30% of the white bread and flour produced in the United States was voluntarily enriched.[21] By the end of 1942, following promulgation of the federal enrichment regulation and enactment of mandatory enrichment laws by 2 southern states, 75% to 80% of all family flour and baker's white bread produced in the United States was enriched.[21,22] The results of the statistical analysis, which showed a strong correlation of food fortification with the decline in the pellagra mortality and morbidity rates after other influencing factors were adjusted for, strengthen our belief that food fortification played a significant role in the elimination of pellagra in the United States.

Conclusion

A chronological examination of trends in pellagra morbidity and mortality and of the development of state, federal, and other nationwide fortification laws, policies, and trends supports the conclusion that food fortification played a significant role in eliminating this nutritional deficiency disease, which was prevalent in the southern part of the United States in the first half of the 20th century. The findings presented in this report demonstrate that food fortification designed to restore amounts of nutrients lost through grain milling can be an effective tool in preventing or treating nutritional deficiency diseases in the United States when the relationship between a disease and a nutrient deficiency is clearly demonstrated, the risk group is identified, and the vehicle for the fortification is appropriate for targeting the risk group without undue harm to nonrisk groups. □

Contributors

Y. K. Park planned, designed, and conducted the study, analyzed and interpreted the data, and wrote the paper. C. T. Sempos provided epidemiologic analysis and expertise and contributed to the writing of the paper. C. N. Barton performed statistical analysis and interpretation. J. E. Vanderveen and E. A. Yetley provided guidance on the content of the paper and the interpretation of data.

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References

1. *Vital Statistics of the United States* [1900–1978]. Washington, DC: National Center for Health Statistics; 1906–1982. DHHS publication PHS 82-1102.
2. Food and Nutrition Board. *Recommended Dietary Allowances.* 10th ed. Washington, DC: National Academy Press; 1989:137–138.
3. Dekline W. Control of pellagra. *South Med J.* 1942;35:992–996.
4. Harris HF. *Pellagra.* New York, NY: Macmillan; 1919.
5. Sebrell WH Jr. History of pellagra. *Fed Proc.* 1981;40:1520–1522.
6. Miller DF. Pellagra deaths in the United States. *Am J Clin Nutr.* 1978;31:558–559.
7. Miller DF. Enrichment programs: helping mother nature along. *Food Prod Dev.* May 1978;12:30, 38.
8. Linder FE, Grove RD. *Vital Statistics Rates in the United States, 1900–1940.* Washington, DC: US Government Printing Office; 1943.
9. Grove RD, Hetzel AM. *Vital Statistics Rates in the United States, 1940–1960.* Washington, DC: US Government Printing Office; 1968. DHEW publication PHS 1677.
10. National Office of Vital Statistics. Death rates by age, race, and sex: United States, 1900–1953. Influenza and pneumonia, except pneumonia of the newborn. *Vital Stat Special Rep.* 1956;43(21):323–338.
11. *National Income and Product Accounts of the United States.* Vol 1. Washington, DC: US Dept of Commerce/Bureau of Economic Analysis; 1993:30–31.
12. Economic Research Service. *Food Consumption, Prices, Expenditures.* Washington, DC: US Dept of Agriculture; 1968:56–63. Agricultural Economic Report No. 138.
13. *SAS/STAT User's Guide, Version 6.* 4th ed. Vol 2. Cary, NC: SAS Institute Inc; 1989.
14. Elvehjem CA, Madden RJ, Strong FM, Wooley DW. Relation of nicotinic acid and nicotinic acid amide to canine black tongue. *J Am Chem Soc.* 1937;59:1767–1768.
15. Fouts PJ, Helmer OM, Lepkovsky S, Jukes TH. Treatment of human pellagra with nicotinic acid. *Proc Soc Exp Biol Med.* 1937;37:405–407.
16. Sydenstricker VP. The history of pellagra: its recognition as a disorder of nutrition and its conquest. *Am J Clin Nutr.* 1958;6:409–414.
17. Terris M. *Goldberger on Pellagra.* Baton Rouge: Louisiana State University Press; 1975.
18. Fouts PJ, Lepkovsky S, Helmer OM, Jukes TH. Successful treatment of human pellagra with the "filtrate factor." *Proc Soc Exp Biol Med.* 1937;35:245–247.
19. American Medical Association Committee on Foods. Fortification of foods other than fortification of milk with vitamin D. *JAMA.* 1936;107:39.
20. American Medical Association Council on Foods. Fortification of food with vitamins and minerals. *JAMA.* 1939;113:681.
21. Wilder RM, Williams RR. *Enrichment of Flour and Bread. A History of the Movement.* Washington, DC: National Academy of Sciences; 1944. National Research Council Bulletin 110.
22. Food and Nutrition Board Committee on Cereals. *Cereal Enrichment in Perspective, 1958.* Washington, DC: National Academy of Sciences; 1958.
23. Park YK, McDowell MA, Hanson EA, Yetley EA. History of cereal-grain products fortification in the United States. *Nutr Today.* In press.
24. Park YK, Miller DF, Vanderveen JE, Forbes AL. *Pellagra and Fortification of Cereal-Grain Products in the United States.* Springfield, Va: National Technical Information Service; 1984. NTIS publication PB84134410.
25. Statigos JD, Katsambas A. Pellagra: a still existing disease. *Br J Dermatol.* 1977;96:99–106.
26. Forbes AL. Pellagra. In: Conn HF, ed. *Current Therapy.* Philadelphia, Pa: WB Saunders; 1975: 406–407.
27. Spivak JL, Jackson DL. Pellagra: an analysis of 18 patients and a review of the literature. *Johns Hopkins Med J.* 1977;140:295–309.
28. Goldsmith GA. Curative nutrition: vitamins. In: Schneider HA, Anderson CE, Coursin DB, eds. *Nutrition Support of Medical Practice.* New York, NY: Harper & Row; 1977:101–123.
29. Chedrin VH, Williams RR. Studies of the average American diet. *J Nutr.* 1943;26:417–430.
30. US Dept of Health. Various kinds of bread. Definitions and standards of identity. *Federal Register.* 1943;8:10780–10788.
31. US Dept of Commerce/Bureau of Economic Analysis. *State Personal Income: 1929–87, Estimates and a Statement of Sources and Methods.* Washington, DC: US Dept of Commerce/Bureau of Economic Analysis; 1989.
32. Food and Nutrition Board. *Proposed Fortification Policy for Cereal-Grain Products.* Washington, DC: National Academy of Sciences; 1974.
33. Figueroa WG, Sargent F, Imperiale L, Morey GR, Paynter CR, Vorhaus LJ. Lack of avitaminosis among alcoholics; its relation to fortification of cereal products and the general nutritional status of population. *J Clin Nutr.* 1953;1: 179–199.
34. Sebrell WH. Enrichment: a public health approach to better nutrition. *Public Health Rep.* 1953;68:741–746.
35. Aykroyd WR, Jolliffe N, Lowry OH, et al. *Medical Resurvey of Nutrition in Newfoundland.* Toronto, Ontario: Murray Printing Co; 1949.
36. Goldsmith GA, Darby WJ, Steinkamp RC, Beam AS, McDevitt E. Resurvey of nutritional status in Norris Point, Newfoundland. *J Nutr.* 1950;40:41–69.
37. Pollack H. Studies on nutrition in the Far East, III: clinical indicator signs of nutritional insufficiencies before and after enrichment of rice with synthetic vitamins. *Metabolism.* 1956;5: 231–244.
38. Brockett JE, Crowley LV, Pollack H. Studies on nutrition in the Far East, IX: correlations between clinical signs and biochemical findings. *Metabolism.* 1956;5:283–286.
39. Sebrell WH. The nature of nutritional diseases occurring in the south. *Milbank Mem Fund Q.* 1939;17:358–366.
40. Bean WB, Vilter RW, Blankenhorn MA. Incidence of pellagra. *JAMA.* 1949;140:872–873.
41. *Manual of the International List of Causes of Death. Based on the Fifth-Decennial Revision by the International Commission, Paris, October 3–7, 1938.* Washington, DC: US Bureau of the Census; 1940.
42. Dunn HL, Shackley W. Comparison of cause-of-death assignments by the 1929 and 1938 revisions of the international list: deaths in the United States, 1940. *Vital Stat Special Rep.* 1944;19(14):153–278.
43. Faust MM, Dolman AB. Comparability ratios based on mortality statistics for the fifth and sixth revisions, United States, 1950. *Vital Stat Special Rep.* 1964;51(3):179–245.