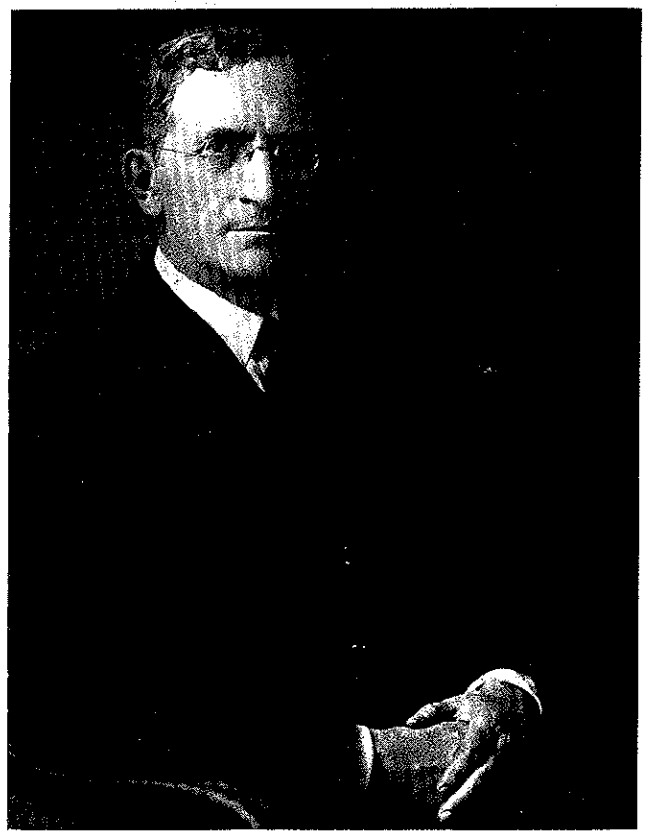

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Goldberger on Pellagra

Edited, with an Introduction by

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Louisiana State University Press : Baton Rouge

5. *The Experimental Production of Pellagra in Human Subjects by Means of Diet*[1]

JOSEPH GOLDBERGER
G. A. WHEELER

Introduction

The experiment presented in this report is part of an investigation of pellagra begun in the spring of 1914 and still in progress. Brief reports, in part preliminary, of some of the more important phases of this investigation have already been published.[2]

In the course of some preliminary surveys relating to the prevalence of pellagra, especially at such institutions as asylums for insane and orphanages, a very high incidence of pellagra in certain groups of inmates was found associated with a diet which differed from the diet of the exempt groups, so far as was then apparent, only in that it included but minimal quantities of the animal protein foods. In the light of certain broad, previously well-recognized, epidemiological features of the disease and with the then recent advances in our knowledge of beriberi in mind it was tentatively inferred that this very striking association had etiologic significance. At the beginning of 1915 an opportunity presented itself to put this inference to the test of experiment in the human subject. Through the kind offices of Dr. E. H. Galloway, then secretary of the Mississippi State Board of Health, the interest of Gov. Earl Brewer was enlisted, who, on the offer of a pardon, secured 12 convicts for this purpose. Advantage was immediately taken of this opportunity and the experiment carried out between February 4 and October 31, 1915, a preliminary report of which was published November 12, 1915 (Goldberger and Wheeler, 1915).

In the following pages we give the details of this experiment, presentation of which has been unavoidably delayed by the pressure of continuing field investigations.

1 *Hygienic Laboratory Bulletin*, No. 120 (February, 1920), 7–116.
2 Goldberger, 1914; Goldberger, 1916; Goldberger, Waring, and Willets, 1915; Goldberger, Wheeler, and Sydenstricker, 1918; Sydenstricker, 1915.

Purpose

The purpose of the experiment was to test the possibility of producing pellagra in previously healthy men by feeding a one-sided, monotonous, principally cereal diet of the type found in previous studies to be associated with a high incidence of pellagra.

Plan of Experiment

The experiment was carried out at the Rankin farm of the Mississippi State Penitentiary. The subjects were white male convicts who volunteered in consideration of a pardon which was to be and was granted them by the governor on completion of the study. In order to make the test as rigorous as possible white male adults were chosen, for, judging by the available data with respect to incidence, this race, sex, and age group would seem to be least susceptible to the disease.

The volunteers were segregated and kept under special guard primarily for the purpose of preventing access to food other than the prescribed diet. Incidentally, this served also to minimize access of any hypothetical infection. As a check on the latter, we had under observation as controls the remaining population of the farm, both convict and free.

In planning the experiment it was believed that its value and significance would be enhanced if, in the event of success in producing pellagra, the attack or attacks developed at a season when the incidence and the prevalence of the disease were normally on the decline, say in August or September. Accordingly, having estimated that it would take some three or four months to develop the disease, it was proposed to begin with the experimental diet early in May. As the organization of the volunteer squad was completed on February 4 this plan provided a period of three months for preliminary observation. The growing impatience of the volunteers to begin and to get through with their ordeal obliged us, however, to begin the feeding experiment about two weeks earlier than planned, that is, on April 19, 1915.

During the first or preliminary period the men were kept under observation with no change in the regular prison fare. This period afforded a desirable opportunity for a close scrutiny of the men for any evidence of pellagra that might conceivably already have existed. It also afforded time for the men to become habituated to the routine of work and discipline. One or two of the squad had previously been "trusties," doing clerical work; for these this period served

as a period of training, accustoming them to work in the field.

As a condition of their volunteering it was agreed that the men would not be kept on the experimental diet for a period longer than six months, at the end of which time they were to be pardoned and freed. It was agreed also that in the event that symptoms of pellagra were late in appearing that this period might be extended somewhat. Events proved this stipulation to have been wise, but, unfortunately, we were permitted an extension of but two weeks, the men being freed on November 1, 1915. The second period of the study, the feeding experiment strictly speaking, extended therefore from April 19 to and including October 31, 1915, a period of approximately six and a half months.

Controls and Subjects

The population of the prison farm consists ordinarily of the prison officials, a warden, two assistant wardens, and a night watchman, and their families, and a fluctuating number of white male convicts. All of the work of the farm was done by the latter under the supervision of the officials.

About one-half of the prisoners serve as clerks, cooks, guards, teamsters, etc. These are the "trusties"; they are selected from among the more dependable prisoners and have the freedom of the farm, and, on occasion, even beyond. The others are at all times under armed guard and are therefore spoken of as "under the gun," or "gunmen." Dereliction of duty on the part of a "trusty" may be punished by return "under the gun." Depending on the needs of the prison and good conduct, such convict may again be detailed to special work and again become a trusty. A prisoner may, therefore, alternate as gunman and trusty. The gunmen when not at work in the field were confined within the limits of a stockade, later to be described.

Controls.—All persons other than the volunteers resident on the farm during the study were under observation as controls. At the beginning of the study this included 65 prisoners; before the end a number of these were transferred, released, or escaped, while others, 43 in all, were admitted and remained for varying periods. There were therefore under observation for varying periods as controls a total of 108 convicts. Of these 108 convict controls 30 were present at the beginning and remained under observation to the end of the study. The other 78 were under observation for periods which varied between two or three weeks and eight to nine months. [Tabulation of this material deleted. ED.]

Of the 8 men who were under observation between eight and nine months, 4 were present at the beginning of the study and continued under observation to October 5, 12, 14, and 26, respectively, while 4 were admitted in February, early during the preliminary observation period, and remained to the end. Of the former group, 1, at least, may be considered to have been under observation practically to the end, while all 4 of the latter group were clearly under observation throughout the most significant period, both with respect to the pellagra season in general and the experimental feeding period in particular. For practical purposes, then, it may be stated that we had under observation a group of, in all, 35 convicts for a period comparable to the period of observation of the subjects of the experiment; these are our full-time convict controls.[3]

While all of the controls were under satisfactory observation, it was not practicable to examine all of them as regularly and systematically as was done with the volunteers. In this respect only 20 are fully comparable to the volunteers and will be referred to as our special full time convict controls.

In age the convict controls varied between 19 and 64 years, the full-time convict controls varying between 19 and 61 years, and the special group between 19 and 51 years (See Table 2).

The convict controls all denied having had pellagra, but 6 gave histories of the disease in members of the family or near relatives. Of these 6, 1 was under observation through the entire period of study, 1 from May to the end, 1 from April 19 to August 24, 1 from February 4 to June 12, and the remaining 2 for the briefer, less significant periods of 1 and 3 months, respectively.

In addition to the convict population there were resident at the farm a varying number of free individuals (officers and their families) of whom 12 were present throughout the study, our full-time free controls. These, though not regularly or systematically examined, were nevertheless under such observation as would have permitted us to detect the occurrence of pellagra, and, therefore, may properly be considered as controls. Included in this group were

3 The official pellagra morbidity reports for Mississippi show that in 1915 approximately 80 per cent of the cases were incident between Apr. 1 and Oct. 1. It is of interest therefore to note that of the control group under observation for less than the whole period of study 9 were under observation from not later than Apr. 1 to at least Oct. 1. Taken with the 30 who were under observation throughout the entire period of study we have in all a control group of 39 men who were under observation throughout that season when 80 per cent of the pellagra in the state developed.

6 adult males, 4 adult females, and 2 children, 1 a boy of 12 and the other a girl of 2 years (See Table 2). This group is of special interest because of the supposedly greater susceptibility of women and children. In this connection it may be of interest to note that this group was increased by one, a young married woman, who took up her residence at the home of the warden on May 7 and who remained under observation throughout the remainder of the period of study.

None of this group of "free controls" gave a history of pellagra.

TABLE 2—*Age distribution of volunteer subjects and full-time controls.*

Age periods.	2	12	19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50	51	52	54	57	61	78	Total
Volunteers.....	0	0	0	1*	1	0	4+	0	5	1	0	0	0	0	0	0	12
Full-time controls:																	
Convict--																	
All.....	0	0	2	8	5	5	3	4	4	0	2	0	1	0	1	0	35
Special.....	0	0	1	8	3	2	2	2	1	0	1	0	0	0	0	0	20
Free--																	
Male.....	0	1	0	0	0	3	0	0	0	0	1	1	0	1	0	0	7
Female.....	1	0	0	0	0	1	0	0	1	0	0	0	0	1	0	1	5

*This man was 24 years old. +One of these dropped out July 1.

Subjects.—The squad of 12 volunteers, or "Pellagra Squad" as it came to be called, was organized between February 1 and February 4, segregated and placed under a special guard of men employed for that purpose and under our control. On April 9, while still under preliminary observation, one of these men attempted to escape. He was promptly recaptured and turned back to the general (or control) group of prisoners, his place in the squad being taken by another volunteer (G. R.) until then under observation among the general group (controls).

The age distribution of the men in the squad thus constituted is shown in Table 2. As may be noted, the ages varied between 24 and 50 years.

As may be seen by reference to the individual records none gave a history of ever having had pellagra or of the occurrence of this disease in any member of the family or a near relative.

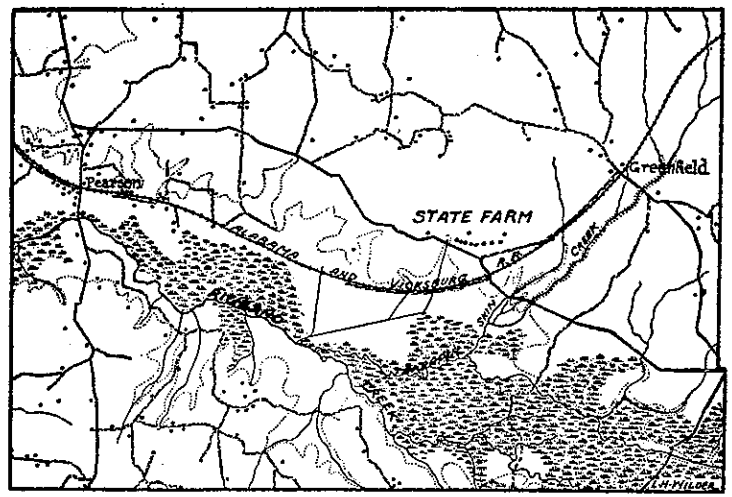
On July 1 one of this group of men was released because of the development of a condition that later was thought to be a prostatitis. This left 11 men, who remained in the test to its termination.

General Environment

Farm.—Rankin farm is located in Rankin County, about 8 miles east of the city of Jackson, Miss., on the Alabama & Vicksburg Railway. It is roughly a square of about 3,200 acres. The country surrounding the farm is sparsely settled, the nearest hamlets, hardly villages, being Greenfield, about 1½ miles to the east, and Pearson, about 3½ miles to the west (See map below).

Camp.—A little to the north of the center of the farm is located the group of prison, official residence, and farm buildings, locally designated as the "camp" (See map p. 60).

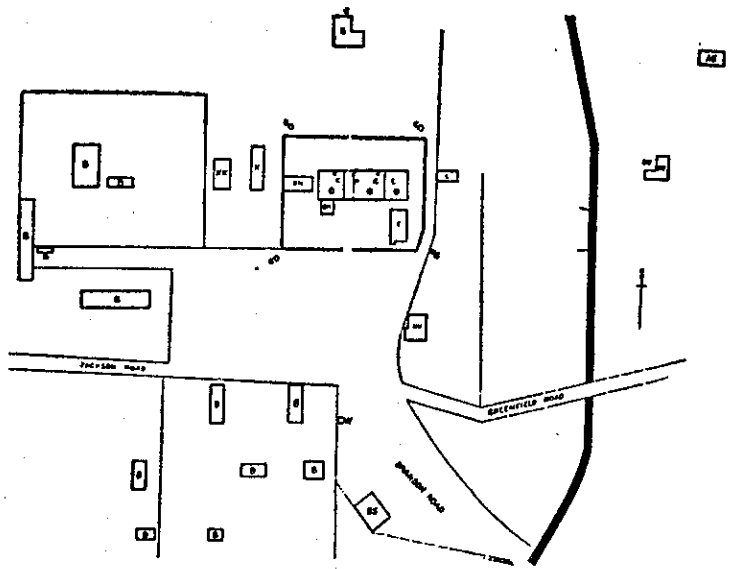
Near the center of the camp is a quadrangular area inclosed by a board fence, at each corner of which is a small guardhouse. Within this stockade are four frame structures, namely, the "cage," "old hospital," dining hall, and church. In the cage and old hospital are the dormitories in which the general convict population is lodged. All were quartered in these buildings during the period of the study, with the exception of the volunteers. The latter were lodged in the "new hospital," a small, one-story cottage, of recent construction, about 500 feet southeast of the cage and outside the



Location of Rankin State Prison Farm and sparsely settled surrounding country. (Modified from U.S. Geological Survey quadrants.)

stockade. Originally intended for use as the camp hospital, this cottage had served instead as a tailor shop and as quarters for one of the trusties and one of the assistant wardens. By reason of these facts, this cottage was, by comparison with the quarters of the other convicts, exceptionally clean. It was given a general overhauling and thorough cleaning before the volunteers were lodged therein. One of the rooms continued to be used by the assistant warden, but the trusty convict was moved April 18, the day before the beginning of the second period of the study.

A little to the north of the cage was a one-story cottage which served as the residence of the warden and his family. Another cottage about 300 yards northeast of the cage designed for use by one of the assistant wardens served, during the study, to lodge the special



Location of buildings constituting the camp at the Rankin Prison Farm. (Diagrammatic.) AS, assistant warden's cottage; B, farm buildings; BS, blacksmith shop; C, church; DH, dining hall for gunmen; G, convict guard; K, convict kitchen; KK, commissary; L, laundry; MP, sawmill and water pump; NH, new hospital, volunteers' quarters; OH, old hospital adjoining cage, convicts' dormitories; S, warden's cottage; W, water tank; H, surface privy.

guard of the volunteers. The second assistant warden and his family resided in a cottage about a quarter of a mile to the west of the cage.

Other buildings included in the group were the general kitchen, including the dining room for the trusties, commissary, blacksmith shop, mill and pump house, and barns.

Screening.—All of the residence buildings and quarters were more or less completely screened against flies.

The screening of the cage and old hospital was incomplete and defective, so that flies and mosquitoes had easy access to these quarters, the quarters of the convict controls.

The cottage occupied by the volunteers was carefully screened at all doors and windows. This screening was carefully scrutinized before the beginning of the study and all defects repaired and kept so throughout the study. Its efficiency, while not perfect, was superior to that of any in the camp and notably so to that of the quarters occupied by the other convicts.

In this connection it may be noted that the cage and old hospital were infested with fleas and bedbugs, whereas the cottage lodging the volunteers was kept entirely free of this vermin throughout the study.

Water supply.—The water supply of the camp was from two shallow wells, located close to the mill and pump house. The water was pumped to an elevated tank from which it was piped to various points in the camp.

Sewerage.—One water-carriage sewer served the cage, old hospital, and warden's cottage, and a second the new hospital. Both discharged into an open ditch, which traversed the camp and emptied into a creek. In addition, there were four surface privies. One of these was back of the warden's cottage, one at each assistant warden's cottage, and the fourth was over a drainage ditch near the mill.

Disease prevalence.—Information with respect to disease prevalence for any period prior to 1909 was not available. Since that year Dr. A. G. McLaurin, of Brandon, has been prison physician, and to him we are indebted for the information that some cases of typhoid and a considerable number of cases of malaria have occurred, and that measles, pneumonia, "influenza," and colds have been observed. But although pellagra is fairly prevalent in the county, no case of this disease had been observed on the farm.

External communication.—Although an isolated community the camp was not without communication with the outside world. Visitors to the families of the officials were not infrequent, and from time to time friends or relatives visited the prisoners other than the

volunteers. The officers and members of their families not infrequently visited the city of Jackson or more distant points, and the needs of the camp made it necessary for a trusty to call at the post office at Greenfield practically every day; occasionally also some teamsters (trusties) would drive to Jackson for supplies.

While no pellagrin is known to have visited the camp during the study, some of the free individuals or trusties may have come into direct contact with pellagra on the occasion of their visits to points beyond the farm. It was quite different, however, with the volunteers. From the beginning, as already stated, these were segregated and under special guard. No communication was permitted them with the outside except through one of us (G. A. W.) who resided at the camp throughout the study. While, therefore, some of the controls may have come into direct contact with pellagra, such contact was, we believe, absolutely excluded for the volunteers. In other words, while direct exposure of some of the controls to a hypothetical infection was possible and may have occurred, we believe that this possibility was excluded and did not occur in the case of the subjects of the experiment.

Hygiene.—The quarters of the convict controls were inadequately looked after and were for the most part dirty and vermin infested. The practice of personal cleanliness was left to the individual and therefore varied within wide limits. In contrast, the quarters of the volunteers were regularly and thoroughly cleaned. Once each week beds and bedding, personal effects, and furniture were taken out, aired, and sunned, and the dormitory well scrubbed. Each volunteer was required to wash hands and face before each meal and to take a full bath at least three times a week. Fresh clean underclothing and bedding were supplied each week and each man was required to make a change regularly.

Work.—The volunteers were required to do a share of the work of the farm. The character and amount of labor performed by them may be judged by the sample periods on the top of page 63.

The character and amount of work of the convict controls is indicated by the periods on the bottom of page 63.

For a proper estimate of the relative amount of work performed by the two groups, certain facts in addition to the foregoing must also be considered. The hours of the volunteers at first were those of the other prisoners, but after beginning the experimental diet they were shortened. After June 3 the volunteers were allowed to sleep 1 hour later in the morning than were the other prisoners, and when in the field were allowed a rest period of 10 minutes in every hour.

	Days
Week ended July 11, 1915:	
Hoeing corn	2.0
Shelling peas	2.5
Rest	2.5
Week ended Aug. 8, 1915:	
Whitewashing fences and buildings	2.5
Sawing lumber (ram sawmill)	2.0
Rest	2.5
Week ended Sept. 12, 1915:	
Cutting weeds and grass	0.5
Chopping cordwood	5.0
Rest	1.5
Week ended Oct. 10, 1915:	
Baling hay	4.75
Resting	2.25
Week ended Oct. 31, 1915:	
Walking	3.5
Resting	3.5

During the last 6 weeks of the study, although maintaining this routine, the amount of work performed was very little, and during the final week no work at all was done, walking being their only exercise. In brief, when compared with the convict controls the volunteers were at no time pushed, had shorter hours of work, had

	Days
Week ended July 11, 1915:	
Plowing	0.5
Cutting and hauling wood	1.0
Thrashing oats	3.0
Resting	2.5
Week ended Aug. 8, 1915:	
Cutting and hauling wood	3.0
Cutting grass and weeds	1.5
Resting	2.5
Week ended Sept. 12, 1915:	
Squad of 15 men—	
Cutting and hauling wood	2.5
Harvesting hay	3.0
Resting	1.5
Others—	
Working road	5.5
Resting	1.5
Week ended Oct. 10, 1915:	
Working road	1.75
Harvesting corn	4.0
Resting	1.25
Week ended Oct. 31, 1915:	
Plowing	6.0
Resting	1.0

regular rest periods when in the field, did less actual work, and toward the close of the study did practically no work at all. The work of the convict controls is rated by us as requiring moderate to hard, that of the volunteers as requiring moderate to light muscular exertion.

Diet of Controls

The diet of the controls varied somewhat with the different groups in respect, principally, to liberality of supply of certain foods. As might be anticipated, the diet of the free controls (officials) included a more generous supply of milk, butter, lean meat, and eggs than that of the convict groups. As there were no notable differences in availability in other respects, we shall confine ourselves to a consideration of the character of the more restricted diet provided the convict controls. During the first period of the study this was also the diet of the volunteers. A general idea of the character of this diet may be formed by reference to Table 3, which shows how frequently the articles enumerated appeared at meals during the 74⅓ days (223 meals) of the first period of the study. It was evidently quite a restricted diet, although it included a fairly liberal amount of meat. Table 4 shows in a similar way the general diet of the convict controls during the second period of the study. This was somewhat more varied than that during the first period. The influence of season is clearly indicated; there is noticeable a marked

TABLE 3—*Food* served convict controls and volunteers during period February 4 to April 19, 1915.*
(Days, 74⅓; meals, 223)

Food.	Times served.+	Food.	Times served.+
Biscuit	195	Pork, cured"	201
Corn bread	74	Brown gravy	109
Rice	78	Potatoes, Irish	8
Oatmeal	4	Rutabagas	7
Butter	1	Tomatoes, canned	2
Buttermilk	5	Tomato gravy	8
Eggs#	23	Navy beans	37
Beef, fresh	14	Cowpeas, dried	14
Kid, fresh	3	Sugar	166
Pork, fresh	14	Sirup, cane	223

*Not including coffee and condiments.
+Maximum possible 223.
#Served to volunteers.
"Includes salt pork, "backs" and "sides."

reduction in lean meat, an increase in milk and in fresh vegetables, particularly greens. An idea of the more intimate make-up of this diet is afforded by Table 5, which shows the approximate composition and energy value of the convicts' diet for a period of one week. [Tabulation of three other sample weeks deleted. ED.] This table was computed with the aid of the Atwater and Bryant tables (U. S. Dept. Agr. Bull. 28); chemical analyses on the ground being impracticable, and as in the case of some of the cooked dishes we were unavoidably obliged to content ourselves with an estimate of the quantity in lieu of an actual weighing of the individual ingredients, the composition shown is an approximation and is not to be interpreted too closely.

TABLE 4—*Food* served convict controls during period April 19 to October 31, 1915.*
(Meals, 586)

Food.	Times served.+	Food.	Times served.+
Bakers' bread	3	Ice cream	1
Biscuit	559	Vegetable soup	21
Biscuit pudding	21	Beets	1
Cake	1	Cucumbers	35
Crackers, sweet	4	Potatoes, Irish	83
Fritters	2	Potato soup	1
Corn, fresh	6	Sweet potatoes	11
Corn bread	190	Sweet potatoes, canned	5
Grits, hominy	25	Cabbage	35
Oatmeal	14	Lettuce	14
Rice	114	Mustard greens	2
Rice pudding	2	Okra	25
Rice with tomatoes	3	Peppers, green	79
Butter	58	Tomatoes, fresh	33
Buttermilk	36	Tomatoes, canned	4
Skimmed milk	122	Tomato soup	12
Cheese, cream	2	Tomato gravy	1
Eggs	4	Turnips	4
Beef, fresh	40	Turnip greens	27
Beef hash	6	Onions	50
Beef liver	2	Apples, stewed	16
Beef soup	9	Apple pie	9
Beef gravy	13	Bananas	1
Beef dressing	1	String beans	34
Kid, fresh	5	Navy beans	86
Kid soup	1	Bean soup	1
Pork, fresh	5	Peas, English, fresh	2
Salt pork	547	Cowpeas, fresh	19
Salt pork dumpling	3	Cowpeas, dried	11
Brown gravy	15	Sugar	390
Fish, fresh	1	Sirup, cane	585
Sardines, French	2	Pickle, mixed	5

*Not including coffee and condiments. +Maximum possible 586.

TABLE 5—*Approximate composition of diet of convict controls (33 men) during week ended June 6, 1915.*

Food.	Quantity consumed.	Protein.	Fat.	Carbohydrate.
	Pounds.	Pounds.	Pounds.	Pounds.
Biscuit	234.12	20.36	6.09	129.47
Corn bread	76.13	3.92	2.44	31.44
Oatmeal	55.13	1.20	.28	6.34
Rice	23.12	.41	.02	5.64
Butter	3.05	.03	2.99	.00
Buttermilk	206.10	6.18	.62	10.51
Eggs, fried	6.06	.79	.55	.00
Beef gravy	2.07	.09	.01	.02
Beef roast	19.15	4.27	5.48	.00
Beef soup	4.05	.18	.02	.04
Salmon, canned	1.14	.16	.09	.00
Salt pork	42.03	3.47	30.56	.00
Vegetable soup	34.12	.99	.07	.17
Beets	18.00	.41	.02	1.33
Potatoes, Irish	58.60	1.45	.06	12.25
Cabbage	12.10	.12	.04	.68
Onions, raw	13.90	.20	.04	1.38
Tomatoes, fresh	6.09	.10	.02	.24
Turnips	16.10	.13	.14	.92
Turnip greens	19.00	.17	.04	.78
Sugar	33.50	.00	.00	33.50
Sirup, cane	72.00	.34	.00	54.42
Total		44.97	49.58	289.13

Grams per man per day were: Protein, 88; fat, 97; carbohydrate, 568.
Calories per man per day were 3,500.
Protein from animal food was 29 grams per man per day.
Per cent of total calories derived from protein, 10.

TABLE 6—*Summary of approximate average composition of the diet of convict controls for the specified sample periods per man, per day.*

Sample period, week ended—	Protein.			Fat (grams).	Carbohydrate (grams).	Total calories.	Per cent of total calories derived from protein.
	Total grams.	From animal food. Grams.	From animal food. Per cent of total.				
June 6	88	29	33	97	568	3,590	10
June 29	97	35	35	117	539	3,695	11
July 26	110	32	29	134	566	4,020	11
October 21	92	18	20	96	579	3,645	10

Judging by the indications afforded by the four sample-week periods summarized in Table 6, the diet of the controls, although tending to be rather high in fat, conformed fairly well to recognized standards. The energy value varied between about 3,500 and 4,000 calories of which 10 to 11 per cent was derived from protein. The protein intake varied between approximately 90 and 110 grams, fat between 95 and 135 grams, and carbohydrate between 540 and 580 grams. Most of the protein was derived from cereals and peas and beans; about 20 to 35 per cent was from animal food.

Experimental Diet

The volunteers began the experimental diet with the midday meal of April 19, 1915, and continued it up to and including the midday meal of October 31, 1915. This is the second period of our study.

In planning the diet to be tested we followed, as closely as we could, the rather crude indications afforded by the institutional surveys previously referred to, and by other miscellaneous observations.

The ingredients of the diet were white wheat flour, corn (maize) meal, hominy grits, cornstarch, white rice, granulated cane sugar, cane sirup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, and coffee. In the preparation of biscuits and corn bread Royal baking powder was used. Table salt and pepper were freely allowed for seasoning. Up to July 28 buttermilk was used in making the wheat biscuit, this being the same biscuit as that provided the controls. During the week ending June 27, 3 pounds of beefsteak were served at one of the meals, thus giving each man approximately 4 ounces of lean beef on this occasion.

No fats other than those occurring naturally in the foods specified were used; the pork fat was extracted from salt pork by frying or boiling. The pork crackling or connective tissue remaining was not served. The sirup was home produced, made from "ribbon" sugar cane raised on the farm.

All ingredients appeared to be of excellent quality and, with one or two exceptions, part of the general camp supply. The principal exception was the maize meal. That of the camp was home ground from corn raised on the farm and was unbolted. As it was desired to keep the antineuritic vitamin content of the diet low, and as it was believed that the milling was a factor of importance in this and possibly other respects, we preferred to use a bolted meal and accordingly provided the volunteers with such.

Having in mind the great etiologic importance that had for so long attached to the quality of the corn, we provided the best

quality of both meal and hominy grits obtainable on the local market. In order that we might have a biological check on the quality of these products we arranged to secure our supply from part of that being used at one of the orphanages (M. J.) at which a study of the preventability of pellagra by diet was being made at the time. (No pellagra occurred at this institution during 1915. See Goldberger, Waring, and Willets, 1915.) For purposes of additional check, we arranged also that the controls should share with the volunteers the hominy grits thus provided.

The diet was not absolutely uniform throughout the experimental period. Thus, as already mentioned, the biscuit included buttermilk up to July 28, after which date the milk was entirely excluded. Having the idea that corn bread was the cause of pellagra, the volunteers tended to minimize its consumption with a corresponding increase in the consumption of biscuit and vegetables. In order to counteract this tendency, the biscuit was sophisticated in the manner mentioned below and the quantity of vegetables provided gradually reduced.

Beginning about August 1, corn meal replaced part of the flour in the biscuit. The meal was objected to so that after August 14 it was replaced by cornstarch which was added in the proportion of 1 of cornstarch to 8 of flour. On August 29 an increase was made in the proportion of starch entering the biscuit so that after this date the biscuit included 1 of starch to 5 of flour. A further increase was made on September 29, the proportion becoming 1 of starch to 4 of flour.

In order to further counteract the tendency of the volunteers to minimize the consumption of maize, corn meal was added to the flour in making the gravy.

Besides these variations in the diet as served there were also individual variations in the diet consumed resulting from individual variations in preference for different dishes. Some would eat freely of one dish and some of another with, in addition, occasional trading of favorite dishes, a moderate amount of which was permitted.

The menu was varied so far as circumstances permitted, but this was very little. A typical weekly specimen is on page 69.

Our field studies (Goldberger, Wheeler, and Sydenstricker, 1918) of the past three years show that this diet differs most notably from the average diet associated with pellagra, at least in cotton-mill villages in South Carolina, in that it is very much more restricted, includes practically no animal protein, no dried legumes, and does include relatively considerable quantities of green vegetables. So far

Bill of Fare, Week Ended August 8, 1915.

AUGUST 2
Breakfast: Biscuits, fried mush, grits and brown gravy, sirup, coffee with sugar.
Dinner: Corn bread, cabbage, sweet potatoes, grits, sirup.
Supper: Fried mush, biscuits, rice, gravy, cane sirup, coffee, sugar.

AUGUST 3
Breakfast: Biscuits, mush, rice, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

AUGUST 4
Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, rice, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

AUGUST 5
Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, rice, gravy, sirup, coffee, sugar.

AUGUST 6
Breakfast: Biscuits, mush, rice, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

AUGUST 7
Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, rice, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

AUGUST 8
Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, rice, gravy, sirup, coffee, sugar.

as may be judged by such (surface) indications, our experimental diet was probably not altogether a typical or average one.

Weighings of food consumed were made for eight periods of a week each; the results for the first-week period, in terms of cooked food and raw ingredients, are shown in Table 7, having been computed by means of ratios previously determined. [Tabulations of quantities consumed in seven other weekly periods deleted. ED.] A chemical analysis of the diet on the ground was not practicable. (See, however, Sullivan and Jones, *Hyg. Lab. Bull.*, Feb., 1920.) The composition of the diet of these sample-week periods has been computed and the results are summarized in Tables 9 and 10. (Table 8 shows the composition of the diet for the first-week period.) Reference to these tables shows a variation in energy intake of between about 2,500 and 3,500 calories, or a variation of between about 40 and 54

TABLE 7—*Quantities, in pounds, of different articles of food consumed by twelve volunteers during the week ended May 27, 1915.*

Cooked food.		Raw ingredients.											
Article.	Quantity.	Buttermilk.	Cabbage.	Corn meal.	Flour.	Grits.	Pork fat.	Rice.	Sugar.	Sweet potatoes.	Sirup.	Turnips.	Turnip greens.
Biscuit	37.75	8.30*	.....	.....	24.54*	.....	2.34*	.....	.....	.....	.....	.....	.....
Cabbage	27.63	.....	17.13	.....	.....	.....	.83*	.....	.....	.....	.....	.....	.....
Corn bread	33.19	.....	.....	19.25	.....	.....	.....	.....	.....	.....	.....	.....	.....
Fried mush	62.63	.....	.....	26.93	.....	.....	8.77	.....	.....	.....	.....	.....	.....
Grits	39.37	.....	.....	.....	.....	8.66	.....	.....	.....	.....	.....	.....	.....
Gravy	38.00	.....	.....	.....	1.10	.....	5.32	.....	.....	.....	.....	.....	.....
Rice	19.25	.....	.....	.....	.....	.....	.....	4.04	.....	.....	.....	.....	.....
Sugar	10.12	.....	.....	.....	.....	.....	.....	.....	10.12	.....	.....	.....	.....
Sweet potatoes	26.12	.....	.....	.....	.....	.....	4.96	.....	3.92	30.56	.....	.....	.....
Sirup	7.81	.....	.....	.....	.....	.....	.....	.....	.....	.....	7.81	.....	.....
Turnips	11.56	.....	.....	.....	.....	.....	.35*	.....	.....	.....	.....	7.17	.....
Turnip greens	30.63	.....	.....	.....	.....	.....	.92	.....	.....	.....	.....	.....	12.86
Total	344.06	8.30	17.13	46.18	25.64	8.66	23.49	4.04	14.04	30.56	7.81	7.17	12.86

*Estimated.

calories per kilogram of the average weight of the volunteers. This it will be recognized compares favorably with the requirement by the organism of "35 calories per kilogram of body weight in the average man doing light work on a mixed diet" (Lusk, 1917, p. 345). About 6 per cent of the calories were contributed by the protein.

The average protein intake varied between 41 and 54 grams, the fat between 91 and 134 grams, and the carbohydrate between 387 and 513 grams. The protein was predominantly (between 80 and 97 per cent of the total) from cereal sources (wheat flour, maize, and rice).

Comparison shows the experimental diet and the diet of the controls during the corresponding period to be much alike with respect to intake of fat and carbohydrate and, when due allowance is made for the difference in the amount of work done by the two groups, also with respect to energy.

In relation to protein, however, there are some rather outstanding differences between the two. The intake of protein by the convict controls was approximately twice that of the volunteers and while at least 20 to 35 per cent of the protein in the diet of the former group was from animal sources practically none at all of the protein in the diet of the latter was derived from this class of foods.

With respect to the mineral constituents and vitamins differences can be indicated in very general terms only. The inclusion of milk, butter, peas, and beans in the diet of the controls and their complete

TABLE 8—*Approximate average composition* of the diet of the volunteers during the week ended May 27, 1915.†*

(Average per man per day.)

Article.	Quantity (gm.).	Protein (gm.).	Fat (gm.).	Carbohydrate (gm.).	Minerals (in grams). Ca.	Mg.	K.	Na.	P.	Cl.	S.	Fe.	Calories.
Buttermilk	44.8	1.34	0.22	2.15	0.047	0.007	0.068	0.029	0.043	0.044	0.012	0.0001	.....
Cornmeal	249.4	22.94	4.74	188.05	.045	.209	.531	.097	.474	.364	.277	.0022	.....
Grits	46.8	4.40	.33	36.78	.005	.027	.081	.009	.067	.022	.064	.0004	.....
Wheat flour	138.5	14.96	1.52	103.60	.028	.025	.159	.083	.127	.102	.245	.0014	.....
Rice	21.8	1.74	.07	17.22	.002	.007	.015	.005	.021	.012	.026	.0002	.....
Cane sirup	42.1	.20	.....	31.82	.....	.....	.....	.....	.....	.....	.....	.....	.....
Cane sugar	75.8	.....	.....	75.80	.....	.....	.....	.....	.....	.....	.....	.....	.....
Sweet potatoes	165.0	2.97	.12	45.21	.031	.046	.655	.064	.074	.155	.040	.0008	.....
Turnips	38.7	.50	.08	3.13	.025	.007	.131	.022	.018	.016	.025	.0002	.....
Turnip greens	69.4	2.91	.42	4.37	.241	.019	.213	.057	.034	.117	.048	.0012	.....
Cabbage	92.5	1.48	.28	5.18	.042	.014	.228	.025	.027	.022	.061	.0010	.....
Pork fat	126.8	.11	126.50	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Total	1,112.0	54.00	134.00	513.00	.470	.360	2.080	.390	.890	.850	.800	.0075	3,570

*Not including table salt or baking powder.
†Tabulation of average composition of the diet of volunteers for seven other weekly periods deleted. ED.

TABLE 9—*Summary of average composition of diet of the volunteers during specified sample periods.*

Sample period, week ended--	Protein (grams).	Fat (grams).	Carbohydrate (grams).	Total calories.	Calories per kilo.	Per cent of total calories derived from protein.
May 27.....	54	134	513	3,570	54	6
June 21.....	41	99	426	2,835	45	6
July 12.....	41	91	387	2,600	40	6
August 9.....	46	113	457	3,115	49	6
August 29.....	46	117	479	3,240	51	6
September 13..	47	119	481	3,265	52	6
September 20..	44	114	459	3,125	50	6
October 6.....	44	105	479	3,120	51	6

absence (milk, after July 28) from the diet of the volunteers would suggest that the former had a more satisfactory mineral composition because of the milk, at least, and was richer in both the fat soluble and the antineuritic vitamin.

Results

During the period of study various minor ailments and a number of rather sharp attacks of malaria were observed among the controls, but in none was there observed any evidence justifying even a suspicion of pellagra. On the other hand, of the 11 volunteers who remained in the test to the end, not less than 6 developed evidence

TABLE 10—*Sources of protein in diet of the volunteers during specified sample periods.*

Sample period, week ended--	Total grams.	From animal.		From cereal.		From other foods.	
		Grams.	Per cent of total.	Grams.	Per cent of total.	Grams.	Per cent of total.
May 27.....	54	1.5	3.0	44.0	81.0	8.0	16
June 21.....	41	1.4	3.4	33.0	80.5	6.6	16
July 12.....	41	.9	2.0	37.0	90.0	3.0	8
August 9.....	46	.1	.3	40.0	87.0	5.8	13
August 29.....	46	.1	.3	42.5	92.0	3.4	8
September 13....	47	.1	.3	43.8	93.0	3.3	7
September 20....	44	.1	.3	40.5	92.0	3.0	7
October 6.....	44	.1	.3	40.0	91.0	3.8	9

which experienced observers joined with us in recognizing as that of pellagra.

The volunteers were seen with us on three occasions, and a diagnosis of pellagra concurred in, in 6 of the men, by Dr. E. H. Galloway, then secretary of the Mississippi State Board of Health, and by Dr. Nolan Stewart, one time superintendent of the Mississippi Asylum for the Insane, at Jackson, and among the first to recognize pellagra in Mississippi. In excluding the known dermatoses other than pellagra the special knowledge of Dr. Marcus Haase, professor of dermatology in the Medical College of the University of Tennessee, Memphis, Tenn., and that of Dr. Martin F. Engman, professor of dermatology in the Washington University Medical School, St. Louis, Mo., was utilized in consultation. Dr. Haase saw these men on October 27, and Prof. Engman on October 29. In addition to the foregoing who were formally called into consultation, the subjects were also seen by Drs. C. R. Stingily and F. L. Watkins, of the state board of health, and by Dr. C. H. Waring, assistant surgeon, United States Public Health Service, all of whom concurred in the diagnosis.[4]

4 So far as we are aware the diagnosis of pellagra in these cases has not been questioned by any of our fellow workers except MacNeal (1916). By reason of the tone and personal character of MacNeal's criticism we have not felt that it required any special notice, preferring to let the record of our work speak for itself. Some reference seems, however, to be called for by reason of the fact that McCollum, in a paper appearing (*J. Biol. Chem.*, May, 1919) after this manuscript had been submitted for publication, seems to have been led to attach importance to MacNeal's criticism. McCollum states that "Goldberger seems to have safeguarded his experimental men against infection and it is unfortunate that a sufficient number of undisputed authorities were not called into consultation to forestall the possibility of a question arising concerning the accuracy of the diagnosis of pellagra, such as MacNeal has raised." The question as raised by MacNeal is as follows: "The National Association for the Study of Pellagra held its third triennial meeting at Columbia, S. C., October 21 and 22, 1915, or approximately one month after the appearance of the dermatitis in these cases. Dr. Goldberger attended this meeting. It may be pertinent to inquire why no mention of this alleged important discovery was made at this meeting and why recognized authorities on the diagnosis of pellagra, such, for example, as Dr. C. H. Lavinder, surgeon, Public Health Service, then president of the National Association for the Study of Pellagra, or Dr. J. F. Siler, captain, Medical Corps, United States Army, then vice president and now president of this association, were not invited to see such alleged important cases."

The following comments are submitted for the information of those who, like Professor McCollum, may be led to attach to MacNeal's criticism an importance which, when rightly considered, it totally lacks.

The announcement of the results of our experiment at the meeting of the

Discussion.—In formulating the diagnosis, we followed the conventional rule of not considering any case pellagra in the absence of definite skin lesions having the characters usually considered distinctive of the pellagrous dermatitis, namely bilateral symmetry, sharpness of delimitation, and, when sufficiently advanced, pigmentation, keratosis, and desquamation. As already stated, our consultants and ourselves agreed in a diagnosis of pellagra in six of the

National Association for the Study of Pellagra would have been premature, even though this meeting took place, as MacNeal states, "approximately one month after the appearance of the dermatitis in these cases," by reason of the fact that the dermatitis in these cases did not appear full-blown, as MacNeal seems to have assumed, but developed gradually and was not recognized by us as significant until after the date of this meeting.

It would have given us great satisfaction, had it been practicable, to have had Dr. Lavinder, Capt. Siler, and, indeed, Dr. MacNeal see our cases. As already stated, however, the evolution of the eruption on the genitalia was slow and that on the hands and neck very late in appearing, so that the evidence justifying a diagnosis of pellagra was not regarded by us as present until within a very few days of the close of the experimental period, which, as elsewhere stated, was abruptly terminated on November 1. We were obliged to limit our invitation, therefore, to such authorities on the diagnosis of pellagra as were quickly accessible. Fortunately Drs. E. H. Galloway and Nolan Stewart, to cite only those formally invited as clinical consultants, are well known to the medical profession of the state of Mississippi as careful clinical observers with large experience with pellagra. As for Profs. Haase and Engman, it would seem unnecessary to point out that their standing is in the front rank of American dermatologists with a large experience in pellagra; indeed, there are few, if any, larger pellagra clinics in the United States than that of Prof. Haase at the Memphis City Hospital. In this connection it may be stated that in response to a recent inquiry (August, 1918) addressed to these gentlemen as to whether they were still of the opinion that the known dermatoses other than pellagra could be excluded in our experimental cases Prof. Engman writes (Sept. 4, 1918): "Will say that I am at present even more confirmed in the opinion I gave you three years ago as to the nature of the eruption on the convicts in the experimental squad than I was at that time"; and Prof. Haase, under date of August 20, 1918, writes: "I have not changed my opinion in regard to cases seen with you and Wheeler at the prison farm near Jackson, Miss. As stated to you then, I knew of no dermatological condition except pellagra that would produce the lesions seen, and on my return home looked for early lesions occurring on scrotum and observed two such cases." It would seem to be unnecessary to comment further, particularly as the clinical notes of our cases are submitted as part of the present report. We may add that in the nearly four years since the close of the experiment we have seen many hundreds of cases of pellagra (over 1,000 cases were seen by us in the cotton-mill village study in South Carolina in 1917 alone), but have not only seen nothing that raises the slightest doubt as to the correctness of the diagnosis of pellagra in the convict volunteers but, indeed, our exceptionally large experience has throughout confirmed that diagnosis.

subjects. We believe, however, that a definite diagnosis of pellagra was justified in at least one other of the men (A–E. S.), but in deference to the opinion of our consultants who, in this case, did not regard the skin manifestations (a mild erythema of the scrotum) as sufficiently marked, this case was not included as such in our preliminary report.

It is a not infrequent observation that, in a family of several members, although only one may show the distinctive cutaneous lesions, some, if not all, of the others may present subjective and other manifestations which leave little room for doubt that they also are suffering from the same disease. Now it seems to us that our squad of volunteers is strictly comparable to a family group or unit; the members of this squad lived together, worked together, ate at the same table, and, within much narrower limits than obtained in any family, ate the same diet. It would appear to follow that, having recognized the six or seven cases presenting the skin lesions as pellagra, this diagnosis may properly be extended to apply to the four or five without the cutaneous lesions but presenting the other manifestations. In other words, we are of the opinion that every one of the volunteers developed pellagra, six or seven with skin lesions and four or five without ("pellagra sine pellagra").

In all the cases with distinctive skin lesions the eruption was first detected on the genitalia (scrotum). Although there was considerable individual variation with respect to the extent of the involved scrotal area and also with respect to the degree of involvement of the penis, nevertheless the genital lesions in these cases very clearly represent a single type, and by comparing our photographs with that of Deiaco's case and with the diagram from the report by Stannus of pellagra in Nyasaland it will at once be recognized that the genital lesion observed by us in our experimental cases is essentially identical with the lesion as observed in Europe and in Africa. [See *Hyg. Lab. Bull.*, Feb. 1920, pp. 32 ff., for photographic material which has been deleted. ED.]

The first appearance of the skin lesion on the scrotum in all our cases with definite eruption suggested to us that the scrotal lesion might be a much more common early skin manifestation than had theretofore been believed. The literature on this point at the time of the publication of our preliminary report was, and still is, extremely meager. There existed, as far as we are aware, only two first-hand reports of this lesion, a paper by Deiaco (1907), whose case was also seen by Merk (1909) who speaks of it in his monograph, and a report by Stannus (1913). In the one case reported by

Deiaco the scrotal eruption was not the initial one, but was preceded by lesions in other locations. Although Merk by implication clearly suggests (1909, p. 20) that the scrotal lesion may be the first to appear, Stannus seems to be the first to actually record such cases. In his report of pellagra in Nyasaland, Stannus records 19 (out of 100 with eruption) that presented the scrotal lesion, and of these 19 four presented the scrotal lesion alone; whether the scrotal lesion was the first to appear in any other of his cases is not clear from his report. Since the publication of our note a case of pellagra with the initial lesion on the scrotum has been reported by Crosby (1917) from South Carolina, and by Wood (1917) from North Carolina.

In the course of our study of pellagra in cotton-mill villages in South Carolina in 1916 notes were made (by G. A. W.) of 23 male cases examined for lesions on the genitals and of finding four with lesions on these parts as the initial site. Of these four cases one was a first and three were recurrent attacks. Of the 23 cases examined 8 were claimed to be first and 15 recurrent attacks, so that we had one of 8 first-attack cases with the initial site of the dermatitis on the genitals and three of 15 recurrent-attack cases with this lesion.

This experience would seem to bear out our suggestion that the pellagrous eruption occurs on the male genitalia as an initial lesion much more commonly than the literature might lead one to judge. It remains a fact, however, that the genital lesion, whether early or late, is a somewhat infrequent one. Its appearance in all our cases with skin lesions as the initial lesion is therefore of exceptional interest. It is difficult to accept this as merely a chance phenomenon or as an individual peculiarity. We are inclined to interpret it as a specific reaction, direct or indirect, to some special factor or combination of factors in the diet, and it suggests to us further that the site of at least the initial lesion in pellagra is bound up with a specific quality of the diet. Thus, we are inclined to believe that the dietary fault related to a case of pellagra with the initial lesion on the backs of the hands differs in some essential detail from that associated with a case in which the initial lesion appears on the backs of the feet, etc.

In this connection reference may be made to the opinion elsewhere expressed by us (Goldberger, Wheeler, and Sydenstricker, 1918) that pellagra, as conventionally defined, is probably not a single entity but probably includes at least two syndromes which are commonly associated but etiologically essentially distinct though closely related. One of these is the complex comprehended by the phrase "pellagra sine pellagra" and the other the dermal complex or pellagra without or with only slight other manifestations. These two

complexes were in a measure represented in our volunteers. Thus volunteer "A–W" lost markedly in weight, falling from 124 to 99.5 pounds, and showed other marked manifestations but without the slightest appreciable eruption; on the other hand, volunteer "J–G. R." lost but little weight, which fell from 126 to 118 pounds, but developed the most marked and most extensive eruption of any of the men. It might be objected that these were but individual variations, particularly as all the volunteers had the same diet. While the possibility of the differences referred to being but individual variations in reaction cannot be definitely excluded, it is perhaps worth pointing out that although it is true that the same diet was served to all individuals of the volunteer group there were nevertheless distinct differences in the relative proportion of the individual foods actually eaten. Some ate their meals as served, others traded dishes so that some had more than the average allowance, say, of greens and less, of sweet potatoes, or vice versa. The possibility that there were essential differences in diet corresponding to differences in some of the reactions observed is therefore distinctly present.

We incline to the view that seems to us the more probable one, namely, that there were such differences, as we do also to the opinion that there exist essential differences in the intimate make-up of the diet corresponding to observed differences in some, at least, of the clinical types of the disease. We may have in this the explanation of some at least of the reported differences in the manifestations of pellagra in different localities and in the same locality in different years.

We now turn to the question as to what factor or factors in the diet are to be charged with bringing about the pellagra syndrome or syndromes. It has already been pointed out that with respect to the quantitative intake of energy, fat, carbohydrate, and protein the experimental diet differed from the diet of the controls significantly only in that the intake of protein was low though within the limits of recognized standards. These features of the diet do not, therefore, come up for consideration in this connection. With respect to the more intimate make-up of the diet, it has previously been noted that the protein was almost exclusively from products of highly milled cereals (wheat, maize, rice). In the light of recent studies, notably those of Osborne and Mendel and of McCollum and associates, this would suggest the probability of a deficiency in intake of some one or more of the amino acids, a probability that would be increased by the relatively low protein intake. This interpretation is strengthened by the indications afforded by the results of some feed-

ing experiments in rats carried out by Sullivan at the United States Pellagra Hospital at Spartanburg, S. C., pointing to the protein as one of the limiting factors of the diet, at least for this species (See M. X. Sullivan, *Hyg. Lab. Bull.*, Feb., 1920).

The antineuritic vitamin content of the diet was planned to be low, and feeding experiments by Sullivan show that it was actually deficient in this factor for the common fowl and the pigeon. It is of great interest to note, however, that none of the subjects developed any distinctive clinical manifestations of beriberi; whether they would have done so eventually had they continued on the diet is an interesting speculation.

Judging by the fact that none of the men showed the slightest recognizable indications of scurvy, the content of the diet in the antiscorbutic factor would seem to have been adequate for the period of the experiment at least.

With regard to the adequacy of supply of the fat soluble vitamin, it is difficult to judge by reason of the meagerness of the available fundamental data; none of the men developed the eye symptoms currently considered indicative of a deficiency in this dietary essential.

Compared to the average intake afforded by various American dietaries as compiled by Sherman (1918, p. 271) the intake of some, at least, of the mineral ingredients in the diet of our volunteers would seem to have been decidedly low (See Table 8). Thus, for example, Sherman (1918, p. 264) considers that 0.45 gram of calcium approximates the minimum of actual daily need, while the average intake of the volunteers varied between about 0.13 and 0.20 gram during the period, after the buttermilk was excluded from the diet. With respect to phosphorus, the average daily requirement, according to Sherman (1918, p. 255) is 0.96 gram; the average intake by the volunteers varied between about 0.89 and 0.67 gram. As to the adequacy of sodium and chlorine little can be said, inasmuch as the quantities shown in the tables do not include the salt used in seasoning, which was freely allowed but not weighed; one is tempted to assume that the intake of these elements was sufficient. Whether the mineral intake as a whole was actually inadequate or improperly balanced for normal nutrition, it is perhaps impossible to state at the present time; that such may have been the case is rather strongly suggested, however.

It would seem from the foregoing considerations that our test diet was probably faulty in some degree with respect to the protein (amino acid or acids), antineuritic vitamin and mineral constituents. Judging by the results of our field observations with reference particularly to the inclusion of dried legumes in the diet of pellagrous families and individuals, it seems to us well-nigh certain, however, that a deficiency in the antineuritic vitamin is not an essential element in the pellagra-producing dietary fault. Consequently, of the now generally recognized essential dietary factors, there remain for consideration in this regard only the protein (amino acids) and the inorganic factor, and possibly also the fat-soluble vitamin, although our experiment affords no satisfactory basis for an opinion as to the latter. McCollum, in the light of his extensive studies in rats, believes that our diet is faulty in all three of these respects. Whether this interpretation can be directly applied to man is uncertain and must await further study for determination.

As to which or what combination (or combinations) of these, if any, or whether some deficiency in an as yet unknown dietary factor (vitamin?) alone or in combination with some one or more of the known factors constitutes the specific pellagra-producing dietary defect or (more probably) defects cannot be stated.

By reason of the etiological importance that has attached to corn (maize), particularly spoiled corn, it is worth noting that the quality of the maize included in the diet seemed to be excellent, judging (1) by appearance and taste, and (2) by the fact that none of the controls at the penitentiary or the large number using the same maize meal and grits at one of the orphanages under our observation, developed any evidence of pellagra. Spoiled maize would, therefore, not seem to be an essential factor in the production of the disease.

Conclusions

Having due regard for the conditions of the experiment, the conclusion would seem to us to be warranted that pellagra developed in at least 6 of our 11 volunteers as the result of the restricted diet on which they subsisted.

Discussion.—The significance of our experiment has been questioned on the ground that it was carried out in an "infected" state. It seems to us that those who advance this criticism have failed to take account of the controlled conditions under which it was performed and especially of the large number of the controls—over four times the number of the subjects of experiment.

In considering its significance in relation to the etiology of the disease the experiment should be regarded as evidence not apart from but in conjunction with other evidence bearing on this prob-

lem. The most immediately pertinent part of this other evidence may be summarized as follows:

1. In institutions for the treatment of pellagra ("pellagrosario" or hospital) employees (nurses and attendants) in constant contact with the disease practically never contract it while so employed. (Lavinder, 1911; Goldberger, 1914.)

2. It has been found that employees (nurses, attendants, etc.) resident in institutions in which pellagra is and has for long periods been endemic (occasionally also epidemic), and many of them in frequent or constant contact with cases of the disease, practically never contract it while so employed. This exemption has been found associated with a decided difference in diet and in no other significant respect. (Goldberger, 1914.)

3. Active cases of pellagra respond promptly and strikingly to an appropriate dietary. Exceptions are relatively rare and no more than might be expected when the experience in beriberi and scurvy are kept in mind. The natural tendency to recovery from the attack without change of environment and without therapeutic interference is associated with a significant seasonal change in diet. (Goldberger, 1916; Goldberger, Wheeler, Sydenstricker, and King, unpublished data.)

4. Pellagra may be prevented completely by a suitable diet without intervention of any other known factor, hygienic or sanitary. There is no sound evidence that the disease is controllable in any other way. (Goldberger, Waring, and Willets, 1915; Nesbitt, 1916; Goldberger and Tanner, unpublished data; Goldberger, Wheeler, and Sydenstricker, unpublished data.)

5. Attempts to transmit the disease to the human subject by inoculations of blood and of nasopharyngeal secretions and by feeding with dermal scales, urine and feces from cases of pellagra in various stages and of varying degrees of severity were without result. (Goldberger, 1916.) The report by Harris (1913) of a successful inoculation of a monkey with a filtrate from pellagrous lesions remains unconfirmed, although extensive attempts have been made to do so, notably by Lavinder and Francis (1914) and by Harris[5] himself.

6. Chittenden and Underhill (1917) have by feeding succeeded in producing pellagra-like symptoms in dogs.

When now we add to all this the results of our experiment and

5 Communicated at a meeting of Louisiana health officers, New Orleans, July, 1915.

consider this evidence as a whole, it is our judgment that it clearly and consistently points to diet as the controlling factor in the causation as well as in the prevention of the disease.

The possibility of the existence of an essential infective etiological factor must next be considered. When the evidence that has been advanced in support of the conception of pellagra as a communicable disease is critically analyzed, it is found that much of it is susceptible of an interpretation in harmony with, or at least as not inconsistent with, the view that pellagra is primarily of dietary origin. Further consideration of this portion of the evidence need not, therefore, detain us, but we may proceed at once to examine what is perhaps generally regarded as the most weighty part of the remainder of the evidence in favor of infection.

Much significance has been attached to the observation by some of our fellow students that there is to be found in a very large percentage of cases of pellagra, a previous association with other cases. In estimating the importance of such observations it has been overlooked, however, that they were admittedly made in endemic areas of high prevalence. In such localities contact with pellagra is so difficult to avoid that we doubt if many residents or visitors escape some degree of such association for more than a short period. Evidently, then, such a study is without the significance which has been attached to it, a view which has already been expressed by Vedder. (Vedder, 1916, p. 148.) In this connection reference may be made to the "domiciliary" study of the Thompson-McFadden Commission (Siler, Garrison, and MacNeal, 1914 and Aug., 1917).

This commission believes that this "domiciliary" study of theirs revealed relationships of such significance as seemed to them conclusive evidence of the correctness of their view that pellagra is an infectious disease (Siler, Garrison, and MacNeal, 1914, p. 370). In this study the population was divided into three domiciliary zones on the basis of proximity to the residence of a pellagrin or pellagrins, and the results seemed to indicate an incidence which was higher as proximity to a resident pellagrin increased. It must suffice for the present to point out that whether such relationship actually does or does not exist, this study is devoid of significance, because, among other reasons, the "arbitrary rules" adopted with regard to the exposed population were such that in practical effect the question was begged. Thus, as between their "Zone 1" and "Zone 2" on the one hand, and "Zone 3" on the other, the rules adopted required a minimum of two weeks' residence for the former zones, but of three months for the latter, the effect of which would be to credit incident

cases to "Zone 1" or "Zone 2" rather than to "Zone 3." Furthermore, under these rules, an incident case is not assigned to "Zone 2" if *"on account of previous residence in a house with a pellagrin (Zone 1) within a period of three months in summer or six months in winter, it has been possible to credit the case to Zone 1"* [italics ours].

In other words, under their "rules" if an incident case had resided 14 days in "Zone 1" and then, let us say, for as long as 2 months and 29 days in "Zone 2" before developing the disease, such case would be assigned to "Zone 1"; obviously the effect of the operation of such a rule is to favor "Zone 1" over "Zone 2" or, as we have said, it is begging the question. (See also Vedder, 1916, p. 150.)

Brief reference may also be made to another of the interesting studies of this commission. Having conceived that the methods of disposal of human wastes might prove to be a determining factor in the spread of pellagra,[6] the commission carried out an experiment, designed to test this hypothesis, at Spartan Mills, Spartanburg, S. C. (Siler, Garrison, and MacNeal, May, 1917). In this community, an endemic focus of pellagra, a water carriage system of sewage disposal was installed in 1913–14, replacing an insanitary system of surface privies. The commission reports (May, 1917) that subsequent to this change "the community has been transformed from a pellagra focus to a community in which pellagra no longer spreads." It so happens that in a study of factors influencing pellagra prevalence in cotton-mill communities in South Carolina during 1917 and 1918, Spartan Mill Village was one of the villages studied by us. We are, therefore, in a position to state that this commission seems again to have fallen into error, for we (Goldberger, Wheeler, and Sydenstricker, unpublished data) found pellagra quite as prevalent in this village as in a near-by village with sanitary conditions of the vilest character. Thus, in 1917 we recorded in Spartan Mill Village 37 first-attack cases, a rate of 26.2 per 1,000, while in the village without sewers and filthy in the extreme we recorded, on precisely the same basis, 17 first-attack cases, an incidence rate of 23.4 per 1,000, for the same year. Clearly, Spartan Mill Village has not only not ceased to be a pellagra focus, but the

6 This conception seems to have been developed, at least in part, as the result of the failure of their studies "to disclose any definite relation of the disease to any element of the dietary." This failure on their part seems to have been due to faulty and inadequate methods of study, as has elsewhere already been suggested by us (Goldberger, Waring, and Willets, 1915; Goldberger, Wheeler, and Sydenstricker, 1918) and by Vedder (1916).

disease was found by us during 1917 and 1918 at least as prevalent in this village as in some other near-by villages with but the crudest, most insanitary methods of sewage disposal.

This striking discrepancy between our results and those of the commission is probably due to a number of factors. At the outset the important question arises whether their data for newly incident cases occurring after the experiment was instituted are properly comparable to those for cases recorded before the beginning of the experiment. Doubt as to this point arises because of the fact that the field work of the commission is known to have been greatly restricted after October, 1914, so that, as they elsewhere implicitly suggest (Arch. Int. Med. 1916, vol. 18, p. 176) their data for 1915 and 1916 are probably not as complete as those for 1912, 1913, and 1914 when they were in the field for a large part of each year. The significance of this point would at first thought seem to be minimized by the apparently different course taken by pellagra in a control district immediately adjacent to Spartan Mill Village. In this district, with a population of approximately 300 or about one-sixth that of the mill village, pellagra, the commission states, continued to spread after 1913 (the year in which the installation of sewerage in Spartan village was begun) at about the same rate as it did before. In 1914, three new cases are reported to have appeared in the control district. "In 1915, after the general enforcement of the sanitary ordinance in regard to privies in Spartanburg City, *only* [italics ours] two new cases of pellagra appeared in this district." (Spartan village and the control district are included in the city of Spartanburg.) In 1916 four new cases are said to have occurred. A moment's consideration of these facts seems to us quite clearly to indicate, however, that this district cannot properly be considered a suitable control. Its population was actually and relatively so small, with so few cases of pellagra occurring from year to year, that it might readily be affected by circumstances of little or no general significance; these might manifest themselves in just such fluctuations as are indicated which, while relatively very great, are actually of no importance.

In the newly sewered village, the commission states, "the number of new cases each year has shown a progressive diminution since 1913, being 18 in 1914, 8 in 1915, and 2 in 1916." This result the commission considers to be due to the installation of the sewerage. Disregarding the question already raised of the comparability of these figures with those for the period preceding the beginning of the experiment, and granting that some reduction in numbers actually

occurred, it seems to have escaped their notice that their own data show that in the year (1912) before the installation of sewerage was begun the number of new cases (8) was as low as in the year (1915) after the installation was completed (the number of new cases having fallen, according to the commission's figures, from 23 in 1911 to 8 in 1912). Clearly, before crediting the decline of pellagra after 1913 to the effect of improved sanitation, the factor or factors responsible for the marked drop in pellagra in 1912, whatever they may have been, should have been considered. This was not done, nor, what is still more important, has the commission presented any evidence to show that the behavior of pellagra in Spartan village during 1914, 1915, and 1916 differed essentially from that in other mill villages in South Carolina. Our own observations very clearly indicate that there was no such difference in 1917 and 1918, at all events.

It is but fair to say that these workers believe they have shown that certain factors of a general character, such as improved economic conditions were inadequate to explain the diminution in the number of newly incident cases. Thus, in discussing the possible influence of improved financial conditions, they say: "Granting, for the moment, that increased prosperity has caused a reduction in recurrent cases from 40 in 1914 and 40 in 1915 to 21 in 1916, it is evidently quite impossible to ascribe to it the decrease in newly incident cases from 30 in 1913 to 18 in 1914, when the recurrent cases increased from 26 to 40, or the further decrease to 8 incident cases in 1915, while the recurrent cases still remained at 40." This argument appears a weighty one until it is noted that numbers alone are stated without any indication of rates. Now, while such omission is of no significance with respect to newly incident cases in circumstances such as the present, where the population is reported as practically stationary, it is quite different when recurrences are considered, for where a distinction, such as the commission assumes, is drawn between the two classes of cases, the recurrence rate, unlike that for newly incident cases, must be based, not on the population but on the number of pellagrins included in that population. This basic point seems to have altogether escaped the commission. Fortunately, they publish the data (Arch. Int. Med. 1917, vol. 19, p. 688, Table 2) which enable one to compute the rate per cent of recurrences, and we find that the recurrence *rate* for 1913 and 1914, instead of increasing as the commission seems to have been led to believe by taking account of the number of cases alone, actually fell from 65 per cent to 61 per cent, and instead of being stationary for 1914 and 1915, as is suggested by a consideration of mere numbers, fell from 61 per

cent to 49 per cent. Thus it is evident that the recurrence rate fell as the newly incident cases fell, and, even though not to the same degree, it nevertheless clearly suggests the possibility of the operation of the same cause in both classes of cases, which in turn suggests what we believe to be a fact, namely, the essential etiological identity of newly incident and recurrent attacks.

Other sources of error might be suggested, but enough have been pointed out to show that the significance which the commission has been inclined to attribute to this experiment is entirely unwarranted.

In connection with the foregoing, consideration may be given to the findings of Jobling and Petersen (1916) which appear to show a relationship similar to that which the Thompson-McFadden commission believed they had observed between increased pellagra prevalence and insanitation. In comparing the incidence of pellagra in two sections of the city of Nashville, Tenn., Jobling and Petersen assumed that, because these included approximately equal numerical groups of Negroes in their population, this indicated approximately equal economic "standards" in the two divisions. They state that "apart from the evidence afforded by the apparently equal distribution of the Negroes, the two divisions are representative of equal economic and social conditions in other respects," but submit no evidence in support of the assertion. The Negro may conceivably serve as an index of economic conditions sufficiently well for some, perhaps many, purposes, but where equality of economic condition is, as here, a vital consideration, some evidence would seem to be called for to show that this really was a valid index in the circumstances under consideration. Furthermore, these gentlemen have evidently assumed that there exists no difference worth considering in economic condition among the Negroes themselves, and, as a considerable proportion of the pellagra in Nashville occurred in the Negro population, it is evident that these workers failed to give due consideration to the possible influence on diet of factors of an economic character, and, therefore, they have failed to show that the relationship, which they claim to have found, is anything other than a spurious correlation.

The results of our (Goldberger, Wheeler, and Sydenstricker, unpublished data) own extensive field studies in which this phase has been carefully considered have failed to reveal any necessary relation between sanitary conditions and pellagra prevalence, and we venture to suggest that in those instances where a relation appears to have been found inadequate or faulty methods of study have been applied or some point has been overlooked, or its im-

portance not sufficiently considered. This is well illustrated by the following: Jobling and Petersen (1917, pp. 122–123) in discussing the possible reasons for a rise in pellagra in 1915 and a decline in 1916 state that though "wages have either not advanced at all, or only in a limited measure during the fall of 1916," the cost of food products "increased at a most disproportionate rate" (in the fall of 1916), a fact which seemed to them inconsistent with the reduction of pellagra in 1916. Now, evidently what happened in the fall of 1916 could not much influence the pellagra incidence of that year, since the vast proportion of cases developed in the spring and early summer. If it had any effect this might be expected to show itself in 1917. As a matter of fact, this is just what did happen; there were more cases of pellagra in Nashville in 1917 than in 1916.[7] With respect to conditions in 1914–15 they say that "while unemployment was increased to some extent in 1914, the larger industries did not alter their forces, *nor did the applications for charity increase to our knowledge*" [italics ours]. Now, in discussing this phase of the subject in their first report (Jobling and Petersen, 1916, p. 528) they stated: "It appears then that there was a period of economic depression beginning about September, 1914, and lasting into the early summer of 1915. *This depression was made evident by the increase in the number of applicants for assistance at the charitable institutions*" [italics ours]. It would seem to us that this self-contradiction on a question of fundamental fact speaks for itself and renders further comment superfluous.

Finally, we desire very briefly to consider the views of McCollum (1917), whose brilliant studies in nutrition very justly give great weight to any opinions he may express. He states (1917, p. 110) that since "there seems to be good evidence that there sometimes occur cases of pellagra in individuals whose diets have included a certain amount of such articles as McCollum and his coworkers have designated as protective foods, viz., milk, eggs, and the leafy vegetables, the theory of infection is supported." No doubt pellagra does occur in individuals whose diets have included "a certain amount" of milk, eggs, and the leafy vegetables. Indeed, by reference to the account (p. 67 *et seq.*) of the diet of our convict volunteers it will be seen that this also included a "certain amount" of milk and leafy vegetables, but this, McCollum tells us (1917, p. 109), was not sufficient to make good the dietary deficiencies of the seed

7 Jobling (James W.): Personal communication. There was an increase also in other localities.

products which it included. And we would add that, so far as we are aware, there exists no good evidence of pellagra occurring in one whose diet was known (not simply assumed) to have included *enough* of the "protective foods." To be sure, pellagra in the nursing infant (an undoubted instance of a case in one exclusively breast fed we ourselves have never seen) might be cited as such an occurrence, but, when we recall reports of scurvy in nursing infants, such cases of pellagra may, with at least equal propriety, be interpreted as indicating that rarely the mother's milk may be faulty and pellagra-producing.

Continuing, McCollum states that "the prevalence of the disease in badly sewered districts supports this view" of an infection. We have already considered what may be regarded as the most important evidence on this point and have pointed out that there really exists no good reason for believing that this relation, when it occurs, is other than a spurious one.

Continuing further, this investigator says that the existence of a bacteriological factor in pellagra "is further supported in some degree by the fact that McCollum, Simonds, and Parsons observed only malnutrition without diarrhea or sore mouth in rats fed diets which, in the experience of Chittenden and Underhill, produce in dogs the gastrointestinal symptoms seen in pellagra in man. The sloughing of the mucous membrane of the mouth and the presence of ulcers in the intestine affords conclusive evidence of an infection in their dogs." These interpretations do not seem to us well founded. To us it seems quite as logical, if not more so, to interpret the difference in reactions observed in the rats on the Chittenden-Underhill diet as dependent on the difference in the species of the experimental animals as to attribute it, as McCollum does, to a chance infection in the dog. This view is strengthened by the fact that rats react to certain diets very differently from guinea pigs, for instance; the latter will develop scurvy on diets apparently entirely adequate for the former. Furthermore, to us the occurrence of the sloughing of the buccal mucous membranes and the intestinal ulcers affords no more conclusive evidence of an infection in the dogs so affected than the occurrence of inflammation of the eyes ("xerophthalmia") in rats on a diet too low in the fat soluble vitamin affords conclusive evidence that this is the result of an infection of the eye in the rat; or that the bleeding swollen gums, loosened teeth, painful, swollen muscles (calves) in man on a diet deficient in the antiscorbutic factor is conclusive evidence that scurvy is due to an infection.

He states, finally, that "it seems logical in the light of all the data

available, to conclude that poor nutrition predisposes to infection and that there is an infectious agent involved in the production of pellagra." In this connection, a related argument not infrequently advanced in favor of pellagra as an infection is of interest chiefly, perhaps, because it seems directly to contradict the basic assumption just cited as favored by McCollum. The argument we have in mind most frequently takes the following form: "Inasmuch as bread lines and poor nutrition are of common occurrence in such large cities as New York, Chicago, etc., and as pellagra is of rare occurrence in these places, diet and poor nutrition can have nothing to do with pellagra." More recently this argument has at times been stated as follows: "Inasmuch as the people of Europe, particularly of the Central Powers, have been on starvation diets and necessarily badly nourished and we hear of no pellagra among them, diet and poor nutrition can have nothing to do with pellagra." Assuming the facts to be as stated by the advocates of this view, the fallacy in the argument at once becomes apparent when it is pointed out that beriberi, a disease well known to be dependent on a faulty diet, seems to have been no more prevalent than pellagra under the circumstances mentioned. Evidently, then, it does not necessarily follow that, because a disease is the result of a faulty diet, any faulty diet will bring it about. What this argument does suggest—and strongly—is that if poor nutrition favors infection as McCollum and others suggest, then (1) "poor nutrition" does not predispose to invasion with the hypothetical "infection" of pellagra, or (2) no such "infection" exists, or finally (3) that a specific kind of poor nutrition is necessary to permit the pellagrous "infection" to establish itself. In considering these possibilities it may be argued that "poor nutrition" does favor invasion with the specific pellagrous "infection" in localities where this "infection" is present in the environment. This would imply that in New York and Chicago and, incidentally, in our North as a whole the pellagrous infection is absent or held in restraint by some unknown factor. As a matter of fact, cases of pellagra, though relatively rare, are by no means of infrequent occurrence in our Northern states and in such cities as New York, Chicago, etc. The hypothetical infection of pellagra is present, therefore, and, it may be added, has been present in this environment at least since the notable epidemic of 1909 at the Peoria (Ill.) State Asylum. Consequently the important question presents itself, Why is the disease not more prevalent in these cities and in the North generally if poor nutrition favors its invasion? The restraint imposed by the cooler northern climate, the only explanation which

suggests itself and one frequently advanced as the explanation of the relative rarity of the disease in the North, fails as the explanation when it is recalled that in Italy pellagra has for generations been chiefly, if not entirely, prevalent in the colder northern mountainous section and that the disease has long been highly endemic in such relatively rigorous climates as those of Bukowina, Rumania, and Bessarabia. In view of this consideration and, still more, when the available evidence bearing on the question is considered as a whole, one must conclude that the view that "poor nutrition" of a general character favors invasion with the "infection" of pellagra, and that this is the explanation of the rôle of diet in pellagra, is untenable. This does not, however, in strict logic exclude the third of the above-stated possibilities, namely, that a poor nutrition of a specific kind is essential to enable this "infection" to establish itself. It will at once be recognized that this is identical with the view still held by some with reference to the etiology of such diseases as beriberi and scurvy, namely, that each is due to a specific infection which can arise only in one subsisting on a deficient diet of a specific character; in other words, an etiological conception calling for the concurrence of two specific factors for each of these diseases.

In pellagra, as in beriberi and scurvy, however, no unequivocal evidence in support of the existence of an essential infective factor has yet been adduced. Nevertheless, if in spite of this fact and in spite of the evidence demonstrating the vital relation of diet to these diseases, one still considers it logical to hold that there is also a second essential factor, an infection, in beriberi and likewise one in scurvy, we recognize that it is equally logical to hold a like view with respect to pellagra. It is clear, however, that even in this event diet is necessarily recognized as the primary controlling etiological factor. This is of considerable practical importance, for, whichever view may happen to appeal to the minds of those charged with the duty of preventing or controlling the disease, the fundamental guiding principle will not be affected.

Summary

1. An experiment was carried out to test the possibility of producing pellagra in previously healthy men by feeding a monotonous, principally cereal diet of the type found in other previous studies to be associated with a high incidence of pellagra.

2. The experiment was carried out at the Rankin farm of the Mississippi State Penitentiary, about 8 miles east of Jackson.

3. The subjects of the experiment were white adult male convicts

who volunteered for the purpose. They were segregated and kept under special guard. Of 12 volunteers who entered the experiment, 11 remained throughout, 1 had to be released because of the development of a physical infirmity. None of these men gave a history of having had pellagra or of the occurrence of this disease in any member of the family or a near relative.

4. All persons other than the volunteers resident on the farm were under observation as controls. This included 108 convicts, of whom 35 were under observation for a period comparable to the period of observation of the subjects of the experiment. In addition, there were 12 free persons who were present throughout the study; included in these were 4 adult females and 2 children.

5. The general sanitary environment was the same for subjects and controls. With respect to personal cleanliness, cleanliness of quarters, and freedom from insects and vermin, the volunteers were decidedly better off than the convict controls.

6. No direct communication with the outside was permitted the volunteers. There was no special restriction imposed on the controls, convicts or free. Direct exposure of some of the controls to a hypothetical infection was possible and may have occurred when beyond the limits of the farm; this possibility is believed to have been excluded in the case of the subjects of the experiment. There is no history of the previous occurrence of pellagra on this farm.

7. The volunteers were required to do a share of the work of the farm, but, when compared with the convict controls, they were at no time pushed, had shorter hours of work, had regular rest periods when in the field, and did less actual work. The work of the convict controls is rated as requiring moderate to hard, that of the volunteers as moderate to light muscular exertion.

8. The study falls into two periods, one extending from February 4 to April 19, during which the volunteers were kept under observation without any change in the regular prison fare. This afforded an opportunity for a close scrutiny of the men for evidence of any existing pellagra and also permitted them to become accustomed to the desired routine of work and discipline. The second period extended from April 19 to and including October 31, during which the volunteers subsisted on the experimental diet.

9. The diet of the convict controls provided an average of approximately 3,500 to 4,500 calories, about 90 to 110 grams of protein, 95 to 135 grams of fat, and 540 to 580 grams of carbohydrate. Approximately 20 to 35 grams or 20 to 35 per cent of the protein was from animal food. The diet was superior to the experimental diet with

respect to the protein, mineral constituents, and antineuritic and fat soluble vitamins.

10. The ingredients of the experimental diet were highly milled wheat flour, maize meal and grits, cornstarch, white rice, cane sugar, cane sirup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens, coffee, "Royal" baking powder, salt, and pepper. During the first three months some buttermilk was used in making wheat biscuits. All ingredients were believed to be of excellent quality and, with one or two exceptions, part of the general camp supply.

11. The average energy intake by the volunteers, as shown by eight periods of a week each during the experimental period, varied between approximately 2,500 and 3,500 calories. The average intake of protein varied between approximately 41 and 54 grams, of fat between approximately 91 and 134 grams, and of carbohydrate between approximately 387 and 513 grams. Eighty to ninety per cent of the total protein was from cereal sources (wheat, maize, rice). The antineuritic vitamin content was planned to be low, but in the absence of any distinctive clinical manifestations of beriberi in our volunteers it would seem to have been sufficient, at least not appreciably deficient, for their needs during the period of study. Similarly in the absence of recognizable indications of scurvy, the diet would seem to have included an adequate supply of the antiscorbutic factor. With regard to the adequacy of supply of the fat soluble vitamin, it is difficult to judge by reason of the meagerness of the available fundamental data; none of these men developed the eye symptoms currently considered indicative of a deficiency in this food element. The intake of some, at least, of the mineral ingredients of the diet was decidedly low. Whether the mineral intake was actually inadequate or improperly balanced for normal nutrition over a long period in man is uncertain.

12. The test diet was probably faulty in some degree with respect to the protein (amino acid deficiency), antineuritic vitamin, mineral constituents, and possibly also with respect to the fat soluble vitamin. In relation to the production of pellagra, this study suggests that the dietary factors to be considered as possibly essential are (1) an amino acid deficiency, (2) a deficient or faulty constitution of the mineral supply, possibly, but doubtfully, (3) a deficiency in the fat soluble vitamin intake and perhaps (4) an as yet unknown (vitamin?) factor. As to which or what combination (or combinations) of these constitutes the specific pellagra-producing dietary defect or defects remains to be determined.

13. Although both classes of controls (convict and free) were ex-

posed to the chance of direct contact with pellagra and although, as compared with the volunteers, the convict controls were at a disadvantage hygienically, and were required to work harder and further, although various minor ailments and a number of rather sharp attacks of malaria were observed among them, none of the convict (or other) controls developed any evidence of pellagra. On the other hand, although segregated and under special guard with the possibility of direct contact with pellagra excluded, and although under much more favorable hygienic conditions, not less than 6 of the 11 volunteers who remained in the test to the end developed evidence which experienced observers joined with us in recognizing as those of pellagra.

14. Having due regard for the conditions of the experiment, the conclusion seems warranted that pellagra developed in at least 6 of our 11 volunteers as the result of the diet on which they subsisted.

15. Significant subjective symptoms made their first appearance during the second month after beginning the test diet. These included weakness, abdominal discomfort or pain, and headache. All subjects lost weight, the loss becoming particularly marked during the last four weeks of the experiment. At least 6 of the 11 men developed a well-marked eruption. The earliest date of the beginning of this was September 12, or at about the end of the fifth month of the diet. The initial site in all of the cases was the scrotum; later classical lesions also developed on hands or neck of some of these. The knee jerk became exaggerated in five of the men, the earliest date being October 17, or at the close of the sixth month of the experiment.

16. The scrotal lesion is a much more common early skin manifestation of pellagra than has heretofore been realized, but is nevertheless a somewhat infrequent one.

17. It is suggested that the site of at least the initial dermatitis is bound up with a specific quality of the diet.

18. In its essential make-up the experimental diet was probably not entirely typical of the average pellagra-producing diet.

19. The view is advanced that there exist essential differences in the intimate make-up of the diet corresponding to observed differences in some at least of the clinical types of the disease. Pellagra, as conventionally defined, probably includes at least two commonly associated but etiologically essentially distinct syndromes.

20. Diet is at least the primary controlling etiological factor.

[Appendices deleted: A. Clinical record of volunteers; B. Analysis of symptoms; C. Tables of factors used in computing composition of experimental diet; D. Clinical record of full-time convict controls. ED.]

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6. *The Transmissibility of Pellagra. Experimental Attempts at Transmission to the Human Subject*[1]

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There is a very widely held belief, at least in the United States, that pellagra is a communicable disease. The evidence in support of this is almost wholly indirect and consists, in the main, of certain analogies to infectious diseases presented by some features of its epidemiology. When critically examined one finds that this evidence either completely falls or that it is susceptible of an entirely different interpretation.[2] The only direct evidence in favor of this view that calls for serious consideration is the report by Harris (1913), of New Orleans, of a successful inoculation of a monkey with a filtrate from pellagrous lesions.

The very extensive and comprehensive monkey inoculations by Lavinder and Francis (1914), like those of a number of other workers, including the later (unpublished) work[3] of Harris himself, have failed to confirm this report.

In order to throw further and, if possible, conclusive light on this subject the writer planned to test the question of the infectivity of the disease by experiment on an animal species known to be susceptible, namely, man himself.

This was made possible by the cooperation of a number of my colleagues and associates who, after being informed of the problem, freely volunteered to submit themselves to experiment. It was originally planned to carry out this test during 1915 concurrently with a test of the rôle of diet in the production of pellagra (Goldberger and Wheeler, 1915) to which a group of convicts were at that time being subjected. The pressure of other work, however, made it necessary to defer this phase of the investigation until the spring of the present year.

1 *Public Health Rep.*, Vol. 31, No. 46 (November 17, 1916), 3159–73.
2 A discussion of the literature is reserved for a later communication. In the meantime the reader will find the following of interest: Goldberger, 1915; Vedder, 1916; and Voegtlin, 1914.
3 Communicated at a meeting of Louisiana health officers, New Orleans, July, 1915.