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EXPERIMENTAL PELLAGRA IN WHITE MALE CONVICTS *

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Four years ago we published a brief note¹ on a feeding experiment, carried out at the Mississippi State Penitentiary, in which we reported the successful production of pellagra in some white male convicts. Preparation of the detailed report of this experiment was unavoidably delayed by the pressure of continuing field investigations, but has now been completed and is in course of publication.² Because of the importance of some new points relating to the etiology of the disease that certain observations in connection with the experiment suggest, it has seemed worth while to present on this occasion a somewhat condensed report of this experiment and of the indications that it affords.

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 observed by us in other previous studies to be associated with a high incidence of the disease.

PLAN OF EXPERIMENT

The experiment was carried out at the Rankin farm of the Mississippi penitentiary. The subjects were white male convicts who volunteered for the purpose. White adult males were chosen in order to make the test as rigorous as possible, for, judging by the then available incidence data, this race, sex and age group seemed least susceptible to the disease.

Believing that the significance of the experiment would be enhanced if, in the event of success in producing pellagra, the attack or attacks

* From field investigations of Pellagra, U. S. Public Health Service.

* Read in the Section on Pathology and Physiology at the annual meeting of the American Medical Association, New Orleans, April 26-30, 1920.

1. Experimental Pellagra in the Human Subject Brought About by a Restricted Diet, Public Health Rep. **30**:3336 (Nov. 12) 1915; also: Pellagra; Causation and a Method of Prevention, J. A. M. A. **66**:471 (Feb. 12) 1916.

2. Bull. Hygienic Laboratory, No. 121.

developed at a season when the incidence and prevalence of the disease were normally on the decline, say in August or September, and having estimated that it would take about three or four months to develop the disease, it was planned to begin with the experimental diet early in May. As the organization of the volunteer squad was completed February 4, this 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 about two weeks earlier than planned, namely, April 19, 1915.

During the preliminary period (February 4-April 19) the volunteers were provided the regular prison fare and were closely scrutinized for any evidence of pellagra that might already have existed. It also afforded time for them to become habituated to the desired routine of work and discipline.

As a condition of volunteering, it was agreed that the men would not be kept on the experimental diet longer than six months. They were freed and, with one exception, passed from observation Nov. 1, 1915. The period of the feeding experiment extended, therefore, from April 19 to and including Oct. 31, 1915, approximately six and one-half months.

CONTROLS AND SUBJECTS

The population of the farm is made up of the prison officials and their families and a fluctuating number of white male convicts.

Controls.—All persons other than the volunteers resident on the farm during the study were under observation as controls. This included a total of 108 convicts. Of these, thirty were present and under observation from the beginning to the end of the study; of five others, one was present at the beginning and continued under observation to October 26, while four were admitted in February, early during the preliminary observation period, and remained to the end. Practically, therefore, we had under observation a control group of thirty-five convicts for a period comparable to the period of observation of the subjects of the experiment. In age, the members of this control group varied between 19 and 51 years. All denied having had pellagra.

There were resident at the farm a varying number of free individuals (officers and their families) of whom twelve were present throughout the study. Included in this group were six adult males, four adult females and two children, one a boy 12 years of age, and the other a girl 2 years of age. This group is of special interest because of the supposed greater susceptibility of women and children. None of this group of free controls gave a history of pellagra.

Subjects.—The squad of twelve 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 employed for that purpose and under our control. The ages of these men varied between 24 and 50 years. None gave a history of having had pellagra, or of the occurrence of the disease in any member of the family or a near relative.

July 1, one of this group was released because of the development of a condition thought to be a prostatitis. This left eleven men who remained in the test to its close.

GENERAL ENVIRONMENT

Farm.—The prison farm is located in Rankin County, about eight miles east of the City of Jackson, Mississippi. It is roughly a square of about 3,200 acres. The country surrounding the farm is sparsely settled.

Camp.—A little to the north of the center of this farm is located the group of prison, official residence and farm buildings locally designated as the "camp." Near the center of this camp is a fence-enclosed quadrangular area within which are the structures, "cage" etc., in which the general convict population was housed. The volunteers were lodged in the so-called new hospital, a small, one-story cottage, of recent construction, about 500 feet southeast of the "cage" and outside of the 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 trustees and one of the assistant wardens. By reason of this, the cottage was, by comparison with the quarters of the other convicts, exceptionally clean. In addition it was given a general overhauling and thorough cleaning before the volunteers were lodged therein.

Screening.—All of the residence buildings and quarters were supposed to be screened. The screening of the general convict quarters was incomplete and defective; that of the cottage occupied by the volunteers was carefully scrutinized and all defects repaired before beginning the study and kept so throughout.

Water Supply and Sewerage.—This was essentially the same for all sections of the population of the farm.

Disease Prevalence.—Pellagra is fairly prevalent throughout the county, but, so far as we could learn, no case of this disease had been observed on the farm.

External Communication.—Although an isolated community, the camp was in frequent communication with the outside world through visitors to the families of the officials and through visiting friends or relatives of the prisoners other than the volunteers. The needs of

the camp made it necessary also for officers or trustees to visit Jackson and other points beyond the farm. While no pellagrin is known to have visited the camp during the study, some of the free individuals or trustees may have come into direct contact with pellagra on the occasion of their visits beyond the farm. The volunteers, however, were segregated and under special guard, and 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.

TABLE 1.—APPROXIMATE COMPOSITION OF THE FOOD CONSUMED BY A GROUP OF CONVICT CONTROLS (THIRTY-FOUR MEN) DURING WEEK ENDING JULY 26, 1915

Food	Quantity Consumed, Pounds	Protein, Pounds	Fat, Pounds	Carbohydrate, Pounds
Biscuit.....	197.62	17.19	5.14	109.28
Biscuit pudding.....	57.00	4.96	1.08	20.58
Flour cakes (fritters).....	13.25	1.15	0.34	1.31
Corn bread.....	73.44	3.78	2.35	30.33
Grits.....	16.25	0.27	0.08	2.45
Rice.....	23.19	0.41	0.02	5.66
Butter.....	6.19	0.06	5.26	
Milk, skimmed.....	264.94	9.00	0.69	13.51
Eggs.....	2.37	0.31	0.22	
Brown gravy.....	8.19	0.11	0.08	0.09
Beef gravy.....	5.31	0.23	0.02	0.06
Beef hash.....	27.56	5.90	14.25	
Beef liver.....	1.75	0.36	0.08	0.08
Beef roast.....	13.12	2.92	3.75	
Salt pork.....	47.12	3.96	34.26	
Vegetable soup.....	50.62	1.47	0.10	0.25
Potatoes, Irish.....	127.12	3.17	0.13	26.57
Cabbage.....	15.00	0.15	0.05	0.84
Corn on cob.....	12.75	0.39	0.05	0.98
Cucumbers.....	6.52	0.07	0.01	0.17
Okra.....	22.12	0.15	0.24	0.71
Onions, raw.....	2.86	0.05	0.01	0.23
Peppers, sweet green.....	4.94	0.36	0.21	1.32
Tomatoes.....	17.62	0.21	0.07	0.69
Apple pie.....	17.50	0.54	1.72	7.49
Apples, baked.....	0.37	0.04
Apples, stewed.....	21.75	0.07	0.07	2.35
Sugar.....	34.75	34.75
Sirup, cane.....	48.75	0.23	26.85
Total.....		57.47	70.13	296.79
Per man per day (gm.).....		110	134	566

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 and free of vermin.

Each volunteer was required to wash hands and face before each meal and to take a full bath at least three times a week.

Work.—The volunteers continued to do a share of the work of the farm. At first the hours of the volunteers were those of the other prisoners, but after beginning the experimental diet the hours were shortened, and when in the field they were allowed a rest period of ten minutes in every hour. 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.—While it varied somewhat from week to week, the character of the diet of the convict controls during the second period of the study is fairly well illustrated in Table 1, for the week ended July 26, 1915. Weighings were made of the food consumed by a group of this class of controls during four sample periods of a week each. Chemical analyses were impracticable, and as in the case of some of the cooked dishes an estimate had to be made of the quantity in place of actual weighings of the individual ingredients; the composition shown in this table (computed by means of the Atwater and Bryant Tables³) is an approximation which, while probably fairly close, cannot be regarded as exact. Judged by the indications afforded by the four sample-week periods, summarized in Table 2, the diet of the controls, although tending to be rather high in fat, conformed fairly well to recognized standards. The potential energy varied between 3,500 and 4,000 calories. The intake of protein varied between approximately 90 and 118 gm., that of fat between 95 and 135 gm., and that of carbohydrate between 540 and 580 gm. Approximately, from 20 to 35 gm., or about 20 to 35 per cent. of the protein was from animal food.

TABLE 2.—SUMMARY OF APPROXIMATE AVERAGE COMPOSITION OF THE FOOD CONSUMED BY SOME OF THE CONVICT CONTROLS PER MAN PER DAY DURING THE SPECIFIED SAMPLE PERIODS

Sample Period, Week Ended	Protein			Fat, Gm.	Carbohydrate, Gm.	Calories	Percentage of Total Calories Derived from Protein
	Total, Gm.	From Animal Food					
		Gm.	Percentage of Total				
June 6	88	29	33	97	568	3,500	10
June 29	97	35	35	117	539	3,685	11
July 26	110	32	29	134	566	4,020	11
Oct. 21	92	18	20	96	579	3,645	10

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 Oct. 31, 1915.

3. Bull. U. S. Department of Agriculture, No. 28.

The ingredients of the diet were white wheat flour, corn (maize) meal, hominy grits, cornstarch, white rice, granulated cane sugar, cane syrup, sweet potatoes, pork fat, cabbage, collards, turnips, turnip greens and coffee. In the preparation of biscuits and cornbread "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 sirup was home-produced, from "ribbon" sugar cane raised on the farm.

All ingredients appeared to be of excellent quality and, with one or two exceptions, were 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 might be 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 significance that had for so long attached to the quality of the maize, we provided the best quality of both meal and grits obtainable on the local market. In order that we might have a biologic check on the quality of these maize products, we arranged to secure our supply from part of that being used at one of the orphanages at which a study of the preventability of pellagra by diet was being made at the time and at which, it may be recalled, no pellagra occurred during 1915. For purposes of additional check, we arranged also that the controls should share with the volunteers the hominy grits thus provided.

The diet served was not absolutely uniform throughout the experimental period, as we felt it necessary by various devices to counteract, from time to time, the tendency of the volunteers to minimize the consumption of maize. There were also individual variations in the diet consumed resulting from individual variations in preference for different foods leading to a certain amount of trading of favorite dishes. Compared with the average diet we have in more recent studies⁴ in cotton mill villages found associated with pellagra our experimental diet differed most notably from this in that it was very much more restricted, included no dried legumes, practically no animal

4. Goldberger, Wheeler and Sydenstricker: *J. A. M. A.* **71**:944 (Sept. 21) 1918; also, *Public Health Rep.* **35**:648 (March 19) 1920.

protein, and included relatively considerable quantities of green vegetables. So far 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 one week each. Chemical analyses were impracticable so that the general composition of the diet was computed by means of the well-known Atwater and Bryant tables and the mineral constituents by means of the factors published by Sherman.⁵ The results obtained for the week selected as fairly representative are shown in Table 3, and a summary for each of the weighing periods is shown in Tables 4 and 5. Reference to these shows a variation in energy intake of between about 2,500 and 3,500 calories, or a variation of between about 40 and 54 calories per kilo 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."⁶ About 6 per cent. of the calories were contributed by the protein.

TABLE 3.—APPROXIMATE COMPOSITION OF THE FOOD CONSUMED BY THE VOLUNTEERS DURING THE WEEK ENDING AUGUST 9, 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
Cornmeal.....	178.4	16.23	3.35	133.01	0.032	0.148	0.376	0.069	0.335	0.258	0.196	0.0016
Grits.....	35.1	3.30	0.25	27.59	0.004	0.020	0.061	0.007	0.051	0.016	0.048	0.0003
Wheat flour....	166.9	18.03	1.84	124.84	0.033	0.030	0.192	0.100	0.154	0.124	0.295	0.0017
Rice.....	30.0	2.40	0.09	23.70	0.003	0.010	0.021	0.008	0.029	0.016	0.035	0.0003
Cane sirup.....	35.1	0.16	0.00	26.53
Cane sugar.....	72.5	0.00	0.00	72.50
Sweet potatoes.	163.1	2.94	1.14	44.60	0.031	0.046	0.648	0.064	0.073	0.153	0.030	0.0008
Cabbage.....	15.6	0.25	0.05	6.87	0.007	0.002	0.039	0.004	0.005	0.004	0.010	0.0002
Collards.....	58.9	2.65	0.35	3.71	0.062	0.018	0.302	0.015	0.058	0.040	0.102	0.0011
Pork fat.....	105.9	0.10	105.65	0.00
**Total	859.0	46.00	113.00	457.00	0.170	0.270	1.640	0.270	0.710	0.610	0.730	0.0060

* Not including table salt or baking powder. **Total calories, 3,115.

The average intake of protein varied between approximately 41 and 54 gm., that of fat between 91 and 134 gm., and of carbohydrate between 387 and 513 gm. From 80 to 97 per cent. of the protein was from cereal sources; practically none was derived from animal food.

Comparison shows the experimental diet and the diet of the controls 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 contrasting groups, also with respect to energy.

5. Sherman, H. C.: Chemistry of Food and Nutrition, 1918, 2d Ed.

6. Lusk, Graham: The Elements of the Science of Nutrition, 1917, p. 345.

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

TABLE 4.—SUMMARY OF AVERAGE COMPOSITION OF THE DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Protein, Gm.	Fat, Gm.	Carbo- hydrate, Gm.	Total Calories	Calories per Kg.	Percentage 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
Aug. 9.....	46	113	457	3,115	49	6
Aug. 29.....	46	117	479	3,240	51	6
Sept. 13.....	47	119	481	3,305	52	6
Sept. 20.....	44	114	459	3,125	50	6
Oct. 6.....	44	105	479	3,120	51	6

TABLE 5.—SOURCES OF PROTEIN IN DIET OF THE VOLUNTEERS DURING SPECIFIED SAMPLE PERIODS (PER DAY)

Sample Period Week Ended	Total, Gm.	From Animal		From Cereal		From Other Foods	
		Gm.	Percentage of Total	Gm.	Percentage of Total	Gm.	Percentage 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	0.9	2.0	37.0	90.0	3.0	8
Aug. 9.....	46	0.1	0.3	40.0	87.0	5.8	13
Aug. 29.....	46	0.1	0.3	42.5	92.0	3.4	8
Sept. 13.....	47	0.1	0.3	43.8	93.0	3.3	7
Sept. 20.....	44	0.1	0.3	40.5	92.0	3.0	7
Oct. 6.....	44	0.1	0.3	40.0	91.0	3.8	9

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

RESULTS

Aside from a number of more or less ill-defined ailments and minor injuries, there were observed among our controls a number of rather sharp attacks of malaria, one of appendicitis with appendectomy, one of hemorrhoids with surgical operation, one of probable ureteral cal-

culus, and one of cerebral tumor, but in none was there any evidence justifying even a suspicion of pellagra. It was quite otherwise with the volunteers as may be seen from the following analysis of the manifestations observed among them. The detailed clinical record of each individual cannot, of course, be presented within the limits of the present paper, but will be found in our full report.

ANALYSIS OF SYMPTOMS

First Symptoms.—After instituting the test diet, no complaints to which we would attach any significance were recorded until May 2, when we have a complaint by "A. E. S." of weakness and dizziness. Six days later another of the volunteers, "A. W.," brother of the first, made his first complaint, that of epigastric pain. By June 20, all eleven men had begun to complain in one way or another. Eight of the eleven men made their first complaint between May 18 and June 20, that is, during the second month of the test diet. Of the symptoms first complained of, weakness, alone or accompanied by some other symptom or symptoms, was mentioned by five. Of the other six men, four mentioned abdominal discomfort or pain (epigastric or right iliac) and two mentioned headache (with nausea in one and "indigestion" in the other) as the first, or among the first, symptoms.

Weight.—All of the volunteers lost weight, the loss varying between 6 and 22.6 per cent. Comparison of the weight curves of the volunteers with those of a comparable group of controls discloses a very marked difference. The weights of all the volunteers show a general downward trend which is particularly marked during the last four weeks of the experiment. In the control group the weights tend to be stationary or a slight early downward trend is followed by an upward tendency; in none is there any significant loss during the last four weeks.

Weakness.—In all of the volunteers there developed clear indications of some diminution in strength and vigor. In some this loss was very conspicuous, being shown by an unsteady gait and, when standing, by a tendency to seek for the support of the back of a chair, a table, or a wall. Subjectively, all the men complained of a general weakness. In some there was the additional special complaint of weakness in the legs, and one complained of stiffness in the legs, of which, however, there was no evidence apparent to the observers. At the close of the experiment, all of the volunteers looked worn. In several the objective and subjective indications of weakness and exhaustion were very great, quite out of proportion to the actual loss in weight.

Headache.—Headache variously localized and of varying degree, both as to intensity and frequency, was complained of by seven of the volunteers.

Pain.—Painful sensations of one kind or another, other than headache, occurred in all eleven men. Pain in the small of the back and abdominal pain or discomfort were of about equal frequency, the former occurring in five and the latter in six of the men. Pain in the side was the next in order of frequency, being recorded in four of the volunteers. In three of these four subjects the pain was in the left side. In all four it was referred to the region of the costal border near the corresponding nipple, or mid-axillary, line.

Pain in the right iliac region⁷ occurred in three cases, in the epigastric region (probably dyspeptic) in two, and in the hips in one case. Cramps in the legs and darting pains starting at the ankles and passing upward were complained of by one of the men.

Nervousness of varying degree was one of the most nearly constant of the manifestations recorded. It occurred in ten of the volunteers. *Vertigo* occurred in five cases. *Wakefulness* of varying degrees and for varying periods was complained of by five of the volunteers. In some of these, and at times in the others, it appeared to be brought about by some painful sensation (headache, etc.) in others, or at other times, there appeared to be no reason for it other than "nervousness" or restlessness.

Paresthesias.—Vague nervous manifestations that may be grouped as paresthesias were also noted. Burning in the "stomach" occurred in two cases, and burning in the feet and legs in one. A complaint of a feeling of heat was noted in one of the men. A sensation described as if an acorn had lodged in the chest was spoken of by one, and as if a "knot of something in the stomach" by another.

Mental Depression.—Apprehension and moroseness of a degree to be decidedly noticeable was recorded in one man.

The *knee jerk* became exaggerated in five of the eleven men. In one it appeared to be reduced and in five no change was recognized. Of the five that were exaggerated the change was noted October 17 in one, and October 24 in four; in all the change was first noted at or shortly after the close of the sixth month of the test diet.

Digestive Tract.—Reddening of the tongue at tips and margins was noticed in five of the men. In two of these there was also some reddening of the mouth. In all instances the reddening of the tongue was slight to quite moderate in degree. Burning of the mouth was reported

7. This pain is very suggestive of appendicitis and we have some reason to believe has occasionally led to operation. The surgeon will do well to keep in mind that pain in the right iliac region may be associated with pellagra.

by one of the men, and in another there was noted a slight increase in the salivary flow. Although complaints of diminished appetite were made at one time or another by nearly all of the volunteers and was fairly marked in at least three of the men, they all, nevertheless, ate fairly well.

Dyspeptic symptoms, including gaseous or acid eructations, were noted in at least five of the men. Vomiting occurred in four and nausea without vomiting was noted in two of the subjects. Gastric analyses were not practicable.

A mild diarrhea, up to three or four watery evacuations a day, occurred in three and a tendency to constipation was noted in one of the men. In seven no change from the normal was noted.

Skin.—A reddening of the oral commissures with tendency to fissuring was noted in one, and in a second, besides the reddening, there was noted an actual fissuring with a somewhat linear erosion extending for about one centimeter downward and backward on the cutaneous surface.

A well marked dermatitis varying somewhat in extent but bilaterally symmetrical, sharply margined and more or less scaly developed on the ventral or ventrocaudal surface of the scrotum of each of six of the volunteers. The skin of the median raphé retained a normal appearance in all instances. A fairly definite bilateral erythema affecting the scrotum was noted in a seventh and a doubtful erythema on the scrotum of an eighth man. The earliest date of the beginning of this eruption was September 12, or at about the end of the fifth month of the diet. The evolution of these lesions (scrotal) was at first rather slow, so that it was not until very near to the end of the experimental period that they became sufficiently well-defined to permit of more than a suspicion of their significance. In some of the cases this dermatitis was accompanied by slight itching and burning. In one man there were no subjective local sensations, and the lesion on the scrotum might have escaped observation had we not made our examinations after completely stripping each man.

In three of the cases with lesions on the scrotum the erythema or dermatitis extended in some degree to the under surface of the penis, and in two of these there was also some involvement of the prepuce.

In addition to the lesions on the genitalia, three of the men presented lesions on other parts. One presented a slight erythema over the knuckles of the middle and ring fingers of both hands, to which our attention was first called by Professor Haase, one of our dermatologic consultants, one presented a very well marked, indeed, a classical, pigmented, keratosed, bilaterally symmetrical dermatitis of the backs of the hands, and the third a well marked erythema of the dorso-

lateral areas of the deeply tanned skin of the neck.⁸ The volunteer presenting the lesions at the oral commissures presented no other cutaneous lesions. The classically marked dermatitis on the back of the hand, though later in appearing, was of much more rapid evolution than that on the scrotum. This and the case with the erythema on the sides of the neck confirmed our interpretation of the nature of the genital (scrotal) lesion in these and the other cases.

With respect to *temperature* and *pulse* our data are in such form as to permit only of the general statement that these showed no notable deviation from the normal.

Palpitation was complained of by two of the men; this should probably be considered a manifestation of indigestion.

Urine.—The conditions under which we worked made it impracticable to regularly secure twenty-four-hour specimens, so that with but few exceptions the urine sample represented that first passed in the morning. The results of the examinations of these specimens can, therefore, be interpreted only in a very general way. In all instances there was a more or less marked trend to a reduced acidity. A tendency to reduced specific gravity was also suggested, but this was not clear. We found indican in the urine of at least seven of the volunteers during the period of the test diet. In six of these it had also been present before that period; whether this was also the case in the seventh we cannot say, as no examination was made in this instance prior to the beginning of the experimental diet. In four of the volunteers indican was detected in the urine before beginning the diet, but none during the course of the experimental period; in two of these indican reappeared in the specimen passed about eighteen hours after return to a high animal protein diet. In one albumen present during the preliminary period disappeared after about two months of the test diet.

Diagnosis.—The volunteers were seen with us on three occasions and a diagnosis of pellagra concurred in, in six 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.

8. In this connection the following from a letter from Professor Haase, referring to one of the volunteers seen by him in Memphis shortly after the latter's release, is of interest: "He had not only a sharply marginated pigmented lesion on the left side of neck, but two pigmented lesions on right hand over the articulations." Unfortunately, Professor Haase was unable to furnish the name of this man so that he cannot be identified definitely. We think it probable, however, that this refers to volunteer "E. W. H.," in which event the lesion on the right hand had escaped our observation or had developed after his release.

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 Engman, professor of dermatology in the Washington University Medical School, St. Louis, Mo., were utilized in consultation. 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 of the U. S. Public Health Service, all of whom concurred in the diagnosis. In this connection it may be stated that in response to an inquiry (August, 1918) addressed to our dermatologic consultants as to whether they were still of the opinion that the known dermatoses other than pellagra could be excluded in our experimental cases, Professor 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 Professor Haase, under date of Aug. 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 dermatologic condition, except pellagra, that would produce lesions seen, and on my return home looked for early lesions occurring on scrotum and observed two such cases." We may add that in the four years since the close of the experiment we have seen many hundreds of cases of pellagra (over a thousand cases were seen by us in a cotton mill village study in South Carolina in 1917 alone) and this exceptionally large experience with all types of cases has afforded ample additional confirmation of the soundness of our diagnosis in our experimental cases.

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, so that it would appear to follow that, having recognized the six cases presenting the skin lesions as pellagra, this diagnosis may properly be extended to apply to the five without the distinctive cutaneous lesions, but presenting the other manifestations. In other words, we are of the opinion that every one of the volunteers developed pellagra, at least six with skin lesions and four or five without ("pellagra sin pellagra").

Discussion.—The fact of 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 manifesta-

tion than had theretofore been believed. The literature on this point, at the time of the publication of our preliminary note was, and still is, extremely meager. There existed, so far as we are aware, only two first hand reports of this lesion, a paper by Deiacco⁹ and a report by Stannus.¹⁰ In the one case reported by Deiacco the scrotal eruption was not the initial one, but was preceded by lesions in other locations. Although Merk, by implication, clearly suggests¹¹ that the scrotal lesion may be the first to appear, Stannus seems to have been the first to actually record such cases. In his report of pellagra in Nyasaland, Stannus records nineteen cases (out of 100 with eruption) that presented the scrotal lesion, and of these nineteen, 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 Crosby¹² from South Carolina, and by Wood¹³ 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 twenty-three 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 twenty-three cases examined, eight were claimed to be first and fifteen recurrent attacks, so that we had one of eight first attack cases with the initial site of the dermatitis on the genitals and three of fifteen 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 unusual one. Its appearance in all our cases with eruption as the initial lesion is therefore of exceptional interest. It is extremely difficult if not impossible to interpret 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

9. Deiacco, Pius: Ueber lokalisation und natur der pellagrösen hautsymptome, Wien. klin. Wchnschr. **20**:967, 1907.

10. Stannus, Hugh S.: Pellagra in Nyasaland, Tr. Soc. Trop. Med. and Hyg. **7**:32, 1913.

11. Merk, Ludwig: Die Hauterscheinungen der Pellagra, Innsbruck, 1909, p. 20.

12. Crosby, C. E.: Pellagra with Erythema of Scrotum as Initial Skin Manifestation, J. A. M. A. **68**:1403 (May 12) 1917.

13. Wood, E. J.: The Diagnosis of Pellagra, Arch. Diagnosis, **10**:139 (April) 1917.

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. It seems to us that we have here, at least, one element in the explanation of some of the reported differences in the manifestations of pellagra in different localities and in the same locality in different years.

CONCLUSIONS

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

In considering its significance in relation to the etiology of the disease this experiment should be regarded as evidence not apart from but in conjunction with other evidence bearing on this problem. When so considered it is our judgment that this evidence clearly and consistently points to diet as the controlling factor in the causation as well as in the prevention of the disease. We have elsewhere considered at some length the more important evidence in favor of an essential infective etiological factor in this disease.¹⁴ We shall, therefore, confine ourselves here to a consideration of only one of the arguments frequently advanced in its favor. This most commonly 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, 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 be or 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 infec-

14. Goldberger and Wheeler: *Bull. Hygienic Laboratory*, No. 121; also, Goldberger, Wheeler and Sydenstricker: *Public Health Rep.* **35**:648 (March 19) 1920.

tion, as is so commonly suggested, then either (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 hypothetical 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 no 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 in favor 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 cooler northern mountainous section, and that the disease has long been highly endemic in such relatively rigorous climates as those of Bukowina, Transylvania, Roumania and Bessarabia.

In view of these facts, it seems to us that the assumption that "poor nutrition" of a general character favors invasion with the hypothetical "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.

As in beriberi and scurvy, however, no unequivocal evidence in support of the existence of an essential infective factor in pellagra has yet been adduced. Nevertheless, if in spite of this fact and in spite of the evidence demonstrating the vital rôle of diet in these diseases, one still considers it logical to hold that there is also a second essential extrinsic factor, an infection, in beriberi and likewise one in scurvy, we recognize that it is equally logical to hold a similar view with respect

to pellagra. Clearly, however, even in such event diet is necessarily recognized as the primary controlling element.

DIETARY FACTORS

Having evaluated the controlling etiologic influence of diet, we may next seek to determine the factor or factors in the diet which are to be charged with bringing about the pellagra syndrome or syndromes. We have already seen that as relates to 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 characters of the diet would seem therefore not to be of primary importance, an interpretation which is supported by the results of our studies of the food supply of pellagrous households in cotton mill villages.¹⁵ 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 much increased by the low plane of protein intake. This interpretation is strengthened by the indications afforded by the results of some feeding experiments in rats carried out by Sullivan (Hygienic Laboratory Bulletin No. 121) at the U. S. Pellagra Hospital at Spartanburg, S. C., pointing to the protein as one of the limiting factors of the diet for this species.

The antineuritic vitamin content of the diet was planned to be low and feeding experiments by Sullivan show that the diet 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 anti-scorbutic 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 any eye symptoms currently considered suggestive of a deficiency in this food essential.

15. Goldberger, Wheeler and Sydenstricker: *J. A. M. A.* **71**:944 (Sept. 21) 1918; also, *Public Health Rep.* **35**:648 (March 19) 1920.

Compared to the average intake afforded by various American dietaries as compiled by Sherman,¹⁶ the intake of some, at least, of the mineral ingredients in the diet of our volunteers was decidedly low. But whether the mineral intake as a whole or in any of its constituents 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. McCollum,¹⁷ as a result of his extensive studies in rats, believes that our diet was also deficient in the fat soluble vitamin. Judging by the results of our field and other observations with reference particularly to the inclusion of dried legumes in the diet of pellagrous households and of individuals, we are satisfied that a deficiency in the antineuritic vitamin is not an essential element in the pellagra producing dietary fault. Similarly the recent observation of the failure to prevent the disease in two individuals who for periods of four to five months before developing the eruption daily consumed the fat soluble vitamin contained in three ounces of creamery butter¹⁸ would seem to indicate that a deficiency in "fat soluble A" is not essential to the production of pellagra. The evidence that we have elsewhere adduced¹⁵ of the preventive value of a meat supplement, coupled with the seemingly small importance that attaches to this food as a source of minerals, would tend to indicate that the mineral factor is of no essential etiological importance. On the other hand, it may be pointed out that the sharp decline in seasonal incidence of the disease, in cotton mill villages of South Carolina, at least, is associated with a great increase in the food supply of green vegetables, a class of foods recognized as important sources of ash constituents in the diet. The facts at hand, therefore, do not warrant a definite judgment on this point. So that of the now generally recognized essential dietary factors, there remain for consideration as possibly essential in relation to the etiology of pellegra, the protein (amino-acids) and the inorganic factor. The determination of 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 some combination or combinations with one or both of these known factors constitutes the specific pellagra producing dietary defect or defects must await further study.

16. *Op. cit.*, p. 271.

17. McCollum and Simmonds: *J. Biol. Chem.* **32**:29, 1917.

18. Goldberger and Tanner, unpublished data. The amount of fat soluble vitamin derived from other sources during this period is believed to have been negligible.

SUMMARY

1. An experiment was carried out at the Rankin farm of the Mississippi penitentiary to test the possibility of producing pellagra in previously healthy men by feeding a monotonous, principally cereal, diet.

2. The subjects of the experiment were eleven white adult male convicts who volunteered for the purpose. They were segregated and kept under special guard. None gave a history of having had pellagra or of the occurrence of this disease in any member of the family or a near relative.

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

4. 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.

5. 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.

6. The volunteers continued to do a share of the work of the farm, but, when compared with the convict controls, they had shorter hours of work and had regular rest periods when in the field. The work of the convict controls is rated as requiring moderate to hard, that of the volunteers as moderate to light muscular exertion.

7. The study falls into two periods, one extended from February 4 to April 19, during which the volunteers were kept under observation without any change in the regular prison fare; the second period extended from April 19 to and including October 31, during which the volunteers subsisted on the experimental diet.

8. The average intake by the convict controls, as shown by four periods of a week, each varied between approximately from 3,500 and 4,500 calories, between 90 and 110 gm. of protein, 95 and 135 gm. of fat, and between approximately 540 and 580 gm. of carbohydrate. Approximately from 20 to 35 per cent. of the protein was from animal food.

9. 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, were part of the general camp supply. In its essential make-up the experimental diet was probably not entirely typical of the average pellagra producing diet.

10. The average intake by the volunteers, as shown by eight periods of a week each during the experimental period, varied between 2,500 and 3,500 calories, between 41 and 54 gm. of protein, between 91 and 134 gm. of fat, and between 387 and 513 gm. of carbohydrate.

11. Although both classes of controls (convict and free) were exposed 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 furthermore, 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 and the possibility of direct contact with pellagra excluded, and although under much more favorable hygienic conditions, not less than six of the eleven volunteers who remained in the test to the end developed evidence which experienced observers joined with us in recognizing as those of pellagra.

12. Significant subjective symptoms made their first appearance among the volunteers 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 six of the eleven 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 in one on the hands and in another on the neck. The knee jerk became exaggerated in five of the men, the earliest date being October 17, at the close of the sixth month of the experiment.

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

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

15. It is suggested that the site of at least the initial dermatitis accompanying an attack is bound up with a specific quality of the diet. 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.

16. In relation to the production of pellagra, the dietary factors to be considered as possibly essential are (1) an amino-acid deficiency, (2) faulty mineral supply or constitution and perhaps (3) 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.

The experiment herein described was made possible by the hearty cooperation of Governor Earl Brewer and Dr. E. H. Galloway, of the State Board of Health of Mississippi, to both of whom our grateful acknowledgments are due. We are indebted to Dr. Galloway also for his interest and aid as one of our consultants. Our thanks are due also to Dr. Nolan Stewart and Professors Haase and Engman for their valuable assistance as consultants. To Dr. A. G. McLaurin of Brandon, Miss., prison physician since 1909, we are indebted for information relative to disease prevalence at the prison farm and to Drs. Stingily, Watkins and Waring we are indebted for their interest and for many helpful courtesies.