

ENDEMIC PELLAGRA IN NORTHERN PORTUGAL

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In Portugal endemic pellagra has been known for many years. Since 1896 about twenty-five papers have dealt with the subject, the most valuable being those of Pereira da Silva (1905) and Manuel Ferreira (1927). No country-wide statistics of the prevalence are available, but all authors agree that pellagra is widespread in all the maize-growing districts of Portugal. The purpose of the present work was to study the disease, using some of the recent methods for the appraisal of nutritional status.

The county of Celorico de Basto (Minho), where pellagra is frequent, was selected for the study, which was made in the summer of 1942. It included a clinical record of a group of patients, with special emphasis on possible symptoms of dietary deficiency, a series of laboratory tests, a dietary survey and a therapeutic test with nicotinamide. The examinations were carried out as thoroughly as the primitive conditions of our field work permitted.

The patients all belonged to the rural class and the majority worked in the fields. In their food habits, their primitive housing conditions and their clothing and sanitation, these patients and their families formed a very homogeneous social group. The predominantly vegetarian diet of this section of the country is characterized by its simplicity and monotony. The bulk of the food is furnished by a short list of articles, mainly white maize, dried beans, olive oil and cabbage greens. Maize is by far the most important food. Each week the quantity required is sent to the local water-mill, the grinding stones of which are of granite. A sort of whole grain flour is obtained, which is made into a bread called *broa*, different from the Italian 'polenta' and from the bread rolls of the southern U.S.A. As maize proteins have few of the glutinous qualities so desirable in bread making, a more palatable loaf is obtained by adding about 10% of rye to the maize flour. Cabbage greens are the most popular vegetable among the poor in Portugal. The leaves, which are similar to those of kale, are consumed as soup. Soup is also the vehicle for the beans, the olive oil and much of the bread.

The meals, usually four, conform with slight variation to the following composition and schedule:

Breakfast, at sunrise: bread, sometimes milk or salt cod. Dinner, at noon: soup, bread, sometimes potatoes or rice. Afternoon meal, at 6 p.m.: bread, onion or fruit. Supper, at sunset: soup, bread.

Black tongue in dogs could not be investigated because the pellagrins are too poor to possess dogs.

MATERIAL AND METHODS

Population. From 15 June to 15 July 1942, we observed about 100 pellagrins from a few villages with a population totalling about 3000. Of them, twenty-two women and eight men, all with skin symptoms, were selected for the clinical and therapeutic study, but only eighteen, with their families, were included in the dietary survey. Owing to lack of time and shortage of nicotinamide we could not extend these examinations to possible cases of deficiency without erythema. The ages of the thirty persons included in the clinical and therapeutic study varied from 11 to 67 years. Four were below 20, four between 20 and 30, six between 30 and 40, six between 40 and 50, six between 50 and 60 and the remaining four 60 or over. Most of them worked on the land, but there were a few in other trades. There was, for example, one maidservant, one blacksmith, one embroideress and one beggar. In five instances the disease had lasted over 10 years and in one case 48 years. The remainder had had signs or symptoms for less than 10 years, but only one for a single year.

Of the members of the eighteen families included in the dietary survey twenty were adult males (seven pellagrous), twenty-one adult females (seventeen pellagrous), seven children between 15 and 19 (five pellagrous), twelve children aged 10-14 (two pellagrous), seventeen children aged 5-9 (two pellagrous), and nine were younger children, all apparently normal.

Clinical investigation

As a rule each patient was seen three times at 5-day intervals. In the first interview a detailed questionnaire about history and objective symptoms was answered. The diet was also inquired into and samples of blood and urine were collected. A

supply of nicotinamide sufficient for 5 days was then distributed. 0.10 g. of nicotinamide was given five times a day by mouth to nearly all patients. Three suffering from diarrhoea received 0.10 g. subcutaneously daily. Co-operation was almost perfect. In the second interview the early effects of treatment were investigated and the rest of the nicotinamide distributed. In the third all previously collected data, particularly those about the diet, were checked, and each patient was once again thoroughly examined.

Biochemical study

Blood collected by vein puncture was divided in two portions. One was allowed to clot, the other mixed with Heller & Paul's (1934) potassium-ammonium oxalate mixture. The erythrocyte picture was worked out according to Wintrobe (1933). The other estimations were performed by the colorimetric methods described by the following authors: serum proteins (Robinson, 1940); calcium (Loureiro & Janz, 1944); phosphorus (Fiske & Subarow, 1925); carotene and vitamin A (Clausen & McCoord, 1938). Urine was collected and preserved with sulphuric acid for the estimation of nicotinic acid (Melnick & Field, 1940) and porphyrins (Beek, Ellinger & Spies, quoted by Spies, 1938). Evelyn's photoelectric colorimeter was used in all estimations.

Dietary survey

The particular conditions under which we worked, amidst an illiterate population, and without the help of a nurse or dietician, led us to deviate from the standard types of dietary inquiry. The consumption of non-perishable staple foods was obtained by studying the family records over a period of months or years; the consumption of fresh foods, such as milk and cabbage, was assessed by direct measurement during the week. Working on such data the daily family consumption was calculated, disregarding table or kitchen residues which are practically non-existent. Since almost the whole of the family income went into food, the people had a keen sense of the quantities eaten, at least of those of the staple foods with a cash value. This prevented any gross errors in our estimates.

The individual consumptions were computed using Bigwood's (1939) coefficients for calories, calcium and phosphorus and a per capita distribution for iron and vitamins. These seemed the best methods, since the children were accorded no dietary priorities.

The following tables of the composition of foods were utilized: Chatfield & Adams (1942), Sherman (1939), Atwater & Bryant (1906), McVicar & Berryman (1942), Grande (1942) and those used by the European Health Commission of the Rockefeller

Foundation. In a few instances we judged it necessary to analyse the local products.

RESULTS

Clinical examinations

History. With one exception the disease had lasted for 2 or more years. Each year the symptoms had tended to become more conspicuous and more numerous. The first attacks as a rule had been mild and short and confined to the hot season. Later the attacks had lasted longer and relapses had occurred. In the most chronic cases the patients were never entirely free of symptoms, even in the winter months.

The disease had not prevented the women becoming pregnant, but the age of *ménarche* varied from 13 to 20 with a mean of 15.8 years, which is higher than the average of 14 years for normal girls in Oporto (Paulo, 1936). Many women referred to periods of amenorrhoea lasting from 2 to 10 months.

General symptoms. Asthenia was the outstanding subjective complaint, and the chief concern of the patients, on account of the relative incapacity produced by it. The sense of weakness had been very variable, but in four cases it had made the sufferers into total invalids. The onset of symptoms had been accompanied by loss of weight in about half the cases.

Cutaneous symptoms and signs. All the patients had lesions of the skin; the hands were invariably affected and generally the feet and legs. The faces and necks had usually escaped, only eight out of the thirty being affected. Most patients complained of aching in the affected regions, less often of itching or of a feeling of heat, burning or swelling worsened by exposure to sun or heat. The lesions consisted typically of erythema, excessive pigmentation and desquamation. Fissuring of the skin was rare and limited to the dorsum of the feet; vesiculation and oedema were exceptional. Only one case, which had lasted for 48 years, presented the characteristic signs of true skin atrophy. At the time of observation, most of the lesions were in the regressive stage. Desquamation was usually scaly, less often larger pieces of skin were flaking off. All the lesions were limited to the exposed parts and followed the usual distribution of sun-tan. In contrast with the classical descriptions, however, we often found a transitional zone between normal and affected skin.

Tongue lesions. Five cases were noted to have a moderate subacute glossitis, with redness and swelling of the papillae, but the typical finding was an atrophic glossitis, present in twenty-one patients, usually limited to the tip and edges of the tongue and often associated with fissuring. Four, all adults, had normal tongues, although one of them had had the disease for 10 years.

Dental lesions. Pyorrhoea, usually fairly severe, was found in twenty-eight cases, carious teeth and roots in twenty-seven. Dental abrasion, i.e. wearing of the chewing surface of the teeth, was found in all the patients over 15 years old and its intensity increased with age. When moderate it was limited to the tubercles of the molars, when intense all teeth were involved. The affected teeth did not give rise to pain.

Digestive symptoms. The most constant and characteristic symptoms were sensations of burning, heat or pricking of the tongue, which were stated to be accentuated by warm or acid foods. These symptoms were usually associated with a very dry mouth, less often with sialorrhoea. The most frequent gastric complaint was a dull or burning epigastric pain, which was described as starting in the morning or before meals, invariably disappearing after the ingestion of food. After meals there was often an exaggerated feeling of repletion or of sourness, nausea and vomiting. Appetite was said to be sometimes exaggerated, sometimes poor. Intestinal functions were strikingly normal, for only five patients had diarrhoea when the survey was carried out.

Neurological and mental manifestations. Many patients complained of painful tingling, pricking and sensations of heat in the distal parts of the limbs. There were no examples of true psychoses at the time of observation, and only two patients referred to such episodes in previous years. Yet, as a psychic counterpart to asthenia, the patients felt sad, depressed, and excessively worried about their future lives and the outcome of their sickness, which all feared might drag them into insanity. They had often become unsociable, irritable, and hyper-emotional with aggressive outbursts. There was without any doubt loss of memory for recent facts. Other intellectual functions were difficult to test owing to the rudimentary mental standards of the patients. The only neurological signs, all of which were rather inconstant and inconspicuous, consisted in exaggeration or sometimes absence of the deep reflexes of the limbs.

Other signs. An interesting circulatory finding was a moderately increased blood pressure in the majority of patients. Two were definitely hypertensive and a few only were hypotensive.

One patient complained of hemeralopia, presented conjunctival spotting, so discrete, however, that there was no suggestion of marked vitamin A deficiency or other deficiencies affecting the eye.

Therapeutic test with nicotinamide

The response was in general excellent, although some of the symptoms cleared up more completely and quickly than others. An improvement in the

asthenia was not noticeable for several days, even in the cases which were ultimately cured. The digestive, neurological and mental symptoms were greatly improved, and sometimes entirely cured. The subjective complaints originating in the skin and tongue began to go within 2 or 3 days and disappears completely with remarkable rapidity. So few of our cases had diarrhoea, which is so strikingly cured by nicotinic acid in acute pellagra, that our series was not particularly instructive in this respect. Cure or improvement of the skin lesions was secured in all except five cases. One of these had a gastric carcinoma, another hunger oedema and two others received insufficient doses. The effects upon reflexes were indefinite.

The most interesting objective change recorded, besides the improvement of skin lesions, was in the blood pressure. On the whole a hypotensive effect was exerted by nicotinamide, and falls of 20–40 mm. Hg in the systolic blood pressures were not unusual, with corresponding changes in the diastolic pressures. Two cases, one with normal and the other with very high blood pressure, showed no change, and moderate increases were found in four cases, three of whom had previously been hypotensive. Only in the case with steatorrhoea was a low blood pressure made lower by treatment. Kooser & Blankenhorn (1939) referred to the hypotensive action of free nicotinic acid, but we have found no mention in the literature of similar effects of nicotinamide.

Nutritional and biochemical findings

Nutritional status. A distribution into the categories good, fair, and bad was performed on the basis of the appearance, relation between height and weight, thickness of subcutaneous fat, colour of skin and mucosae, muscular development and bone formation. In ten of the cases the general picture was frankly bad, and only eleven of the thirty were classified as good.

Blood picture. There is no agreement in the literature about the haematological picture of pellagra. The majority of the American authors refer to a microcytic hypochromic anaemia, while Ruiz Gíjon (1941) found a macrocytic hyperchromic one.

We found in twenty-one patients whose blood was examined mean values of 3,800,000 red blood cells/cu.mm., 14 g. haemoglobin/100 c.c. and 44.5% haematocrit. Thus the tendency in our patients was towards a macrocytic hypochromic type of anaemia distributed as follows:

Macrocytic hypochromic	12 (57%)
Macrocytic normochromic	8 (38%)
Normocytic hypochromic	1 (5%)

Serum proteins. With the exception of one person suffering from hunger oedema, all the cases had values for total proteins which were within the normal range, and the mean value for the group was 7.28 g./100 c.c. with a coefficient of variation of 21%. The figures for albumin were normal, which is in keeping with the significance attributed to their level by Youmans (1941) as an index of the protein nutrition of the individual. Hence, malnutrition did not affect seriously the blood-protein level. This observation agrees with the findings of Slatineanu, Balteanu, Potop & Franche (1937) in Roumania, but not with that of Ruíz Gíjon (1941), who found an average of 6.5% total serum protein.

Serum calcium and phosphorus. The calcium averaged 9.3 mg./100 c.c. and was uniformly normal, except in the case with gastric carcinoma in whom

found no references in the literature to vitamin A determinations in pellagrins, although some authors have described hemeralopia.

Nicotinic acid excretion. We were not able to carry out balance experiments with nicotinic acid. The rough picture given by the estimation of random samples of urine, which were found to contain an average of 2.3 mg./l., suggested that the excretion was on the low side. In twenty normal persons Cosin (1942) found a daily excretion of 10.7 mg. against one of 1.39 mg. in twenty-seven pellagrins. We examined only seven cases after treatment, five of whom showed an increased elimination.

Porphyria. We only tested for the ether-soluble porphyrins. These red pigments were found only in three old and fairly severe cases and disappeared after treatment.

Table 1. *Composition of the families and recorded daily consumption of food (g.)*

Family no.	Total no. in the family	No. of pellagrins in the family	Food consumption (g.)														
			Maize	Rye	Rice, noodles, manioc	Beans, chest-nuts	Potatoes	Onions	Cabbage greens	Olive oil	Olives	Eggs	Meat	Salt cod, sardines	Sugar	Wine	Milk
1	1	1	540	—	—	129	—	—	150	30	—	—	—	—	—	—	—
2	4	1	194	201	66	197	1230	—	248	62	18	—	—	59	66	—	—
3	4	1	1825	161	25	99	16	16	428	34	—	—	—	—	—	—	—
4 and 5	7	3	3701	407	11	294	1480	107	818	68	17	—	—	23	40	354	2000
8	9	3	4692	179	—	345	248	110	990	166	—	—	—	—	—	1380	3000
9	10	2	4817	—	—	245	986	216	1065	166	65	—	—	—	—	1145	497
11	5	4	1621	—	—	85	300	20	578	65	—	—	—	—	8	—	1000
13	5	1	1850	80	151	150	611	44	443	65	—	—	24	—	18	142	—
14	3	2	949	—	26	151	299	—	367	62	8	21	—	8	99	34	—
15	3	1	1342	40	18	71	109	57	315	36	—	11	—	17	6	38	—
18, 19 and 20	6	3	2098	167	49	494	984	110	548	87	15	30	194	—	15	1148	1000
21	6	1	1161	—	—	16	32	64	772	96	—	—	—	11	10	—	500
22	2	1	498	—	—	25	49	33	195	26	4	—	—	3	1	—	500
23	3	1	1069	—	39	65	—	22	248	24	—	26	—	—	7	36	250
24	2	2	1458	142	66	196	274	35	278	131	—	167	—	—	7	1533	—
25	4	2	2160	119	15	196	666	65	578	65	—	19	—	19	—	—	—
26	5	2	2880	223	68	198	1231	176	525	65	18	—	—	22	—	777	—
28	7	2	2591	377	36	214	816	107	758	97	—	50	—	31	—	765	250
Total	86	33															
Mean intake per consumption unit g.			354.4	20.5	5.7	31.7	93.3	11.8	93.0	13.4	1.4	3.2	2.9	1.9	2.7	73.5	89.9

the figure was 11.68 mg./100 c.c. The serum of the child with steatorrhoea, who also had tetany, was not examined for calcium. Gíjon often found hypocalcaemia, the Roumanian authors in severe cases hypercalcaemia.

The phosphorus level was normal (3.83 mg./100 c.c.). Slatineanu *et al.* (1937) recorded an average of 2.6 mg./100 c.c.

Serum carotene and vitamin A. These serum constituents presented fairly large variations, which are also found in normal individuals. The values for carotene were normal, and those for vitamin A at the low end of the normal range. Only four patients could have been regarded as having been on the border line of deficiency, but none of them had symptoms of avitaminosis A; the one suffering from hemeralopia had a high vitamin A level. We have

Dietetic inquiry

Table 1 contains data about the foods consumed and the distribution of normal and pellagrous individuals in the eighteen families investigated, and Table 2 the individual diets calculated in terms of 'consumption units' (calories, calcium and phosphorus) or on a per capita basis (iron and vitamins).

The calorie intake is fair and of the same order as that found by Widdowson (1936) for English men of the middle class, but the low quality of the diet is well shown by the predominance of carbohydrate, which supplies 69% of the calories, fat contributing only about 19%. The carbohydrate/protein ratio is 6.36:1. The poverty of the diet is characterized by the fact that only one-third of the daily 63 g. of fat is supplied by oil, i.e. by fat with any taste value as

such. The average of 81 g. protein seems fair, but 63% is in the form of maize proteins which are poor in lysine and tryptophane and only 10% is of animal origin, from milk and salt cod. Many individuals ate no animal food at all, others only occasionally at traditional festivities or if they were ill. The calcium intake was not low, for it averaged 870 mg./day. The Ca/P ratio was 1:2. There is no doubt, however, that much of the phosphorus in maize meal is present as phytic acid, so that the calcium and phosphorus available for absorption may be much lower than the figures would indicate (McCance & Widdowson, 1942).

An iron intake of 25 mg. daily seems well above the accepted requirement of 15 mg. daily, but, for the same reason, the amount available for absorption may be much below the daily intake because of

might expect in a community suffering from an endemic disease due to its deficiency. In all other avitaminoses the gap between the normal and the disease-producing diet is much wider, and the reason why such a slight deficiency in the supplies of nicotinic acid should lead to such manifest and widespread pellagra raises an interesting nutritional problem.

A partial explanation may be sought in the fact that the pellagra-preventing activity of the various foods does not follow exactly their total nicotinic acid contents. Justin-Bezançon & Lwoff (1942) attempted to define coefficients of availability of nicotinic acid, and stated that the normal daily requirement of the available nutrient is 7.0 mg., i.e. only slightly higher than the daily intake of the available nicotinic acid (6.23 mg.) in our group.

Table 2. *Calculated daily intake of nutrients per consumption unit (calories, calcium and phosphorus) or per head (iron and vitamins)*

Family no.	Calories	Carbo-hydrate (g.)	Fat (g.)	Protein		Minerals			Vitamins				
				Animal (g.)	Plant (g.)	Ca (mg.)	P (mg.)	Fe (mg.)	A (i.u.)	B ₁ (mg.)	B ₂ (mg.)	Nicotinic acid (mg.)	C (mg.)
1	2718	460	62	0	80	963	1753	34.2	3878	2.15	1.70	14.36	21.0
2	3234	596	54	8	82	863	1902	31.9	3670	2.30	1.56	16.31	53.0
3	2834	561	49	0	75	613	1459	22.8	2849	1.59	1.03	10.26	17.8
4 and 5	3651	649	67	15	88	1207	2295	30.5	3480	2.24	1.58	14.65	42.5
8	3564	585	83	15	82	1155	2020	25.6	3367	1.92	1.98	12.00	23.0
9	3101	533	66	2	74	717	1567	22.5	3086	1.62	1.14	11.09	28.8
11	2075	347	52	9	47	1049	1218	16.0	2853	1.24	1.09	7.96	25.9
13	3122	559	60	2	77	667	1628	27.7	2951	1.77	1.20	12.94	33.9
14	2246	385	50	4	55	695	981	19.9	2808	1.33	0.97	9.27	29.5
15	2840	508	54	8	72	699	1537	25.1	2851	1.51	1.01	10.17	21.9
18, 19 and 20	3844	619	86	22	95	1024	2283	34.5	3356	2.32	1.93	14.57	40.7
21	1088	175	30	5	25	744	629	10.3	2433	0.79	0.56	4.82	27.2
22	2011	314	59	15	42	951	1155	14.3	2481	0.99	0.98	6.10	20.6
23	2905	512	59	7	72	692	1425	19.2	2464	1.19	0.95	7.93	18.0
24	4957	740	127	12	110	1185	2822	75.4	5435	2.93	2.35	19.39	37.3
25	2713	489	50	5	70	906	1688	30.5	3949	2.27	1.55	14.29	41.0
26	4112	748	67	4	102	784	2116	32.5	3262	2.16	1.70	15.12	44.2
28	2777	485	53	8	69	754	1575	22.3	2773	1.56	1.07	9.85	19.7
Average	2988	515	63	8	73	870	1670	27.5	3219	1.77	1.31	11.73	30.5
S.D.	848	444	19.9	5.68	20.3	186.4	508.1	13.46	696.7	0.541	0.414	3.693	8.81
P.E.	±572	±299	±13.4	±3.83	±13.7	±125.7	±342.7	±9.08	±471.3	±0.364	±0.279	±2.491	±5.94

the presence of the phytic acid (Widdowson & McCance, 1942). In regard to the vitamin supply, only that of thiamin is really satisfactory. The dietary coefficient of 0.73, calculated by the formula of Williams and Spies, is well above the minimum (0.30). The fat intake is very low, and vitamin A appears to have been supplied almost exclusively in the form of carotene. It is possible, therefore, that the supplies may have been a little short. Riboflavin intakes averaged 1.30 mg./day and ascorbic acid over 30 mg./day. Seven families had less than 25 mg. and only one reached the 50 mg. level. Since these estimates do not account for cooking losses the actual intake was probably lower.

The intake of nicotinic acid, which averaged 11.7 mg., was a little lower than the stated requirements of 15–20 mg./diem, but not as low as one

This shows that unless the estimated coefficient of availability for nicotinic acid is grossly wrong, which is improbable, the question as to why diets with minimal nicotinic acid deficiency should produce pellagra is still unsettled.

DISCUSSION

Our patients, as regards living conditions and food habits, are representative of a large section of the population of northern Portugal. They form a selected group showing the erythematous syndrome which may be defined clinically as pellagra. Besides this syndrome, the only significant pathological changes recorded were pyorrhoea, dental abrasion and a moderate degree of anaemia. The nutritional status of the patients was not good, for many of

them were slightly under weight, but the severe and general malnutrition so often recorded in pellagra outbreaks was conspicuous by its absence. Since, moreover, only a small proportion of the population was found to be affected, individual susceptibility must be at work on a common dietary background. One of the most characteristic features of pellagra in northern Portugal is its mildness and chronic character. One of the patients withstood recurrences for 48 years, and except in two cases with associated diseases, life did not seem to have been threatened by the yearly recurrences. The skin lesions, although extensive and typical in character, were not deep and not prone to cause skin atrophy.

The ominous symptoms of malignant pellagra, such as profuse diarrhoea, persistent vomiting, degeneration in posterior and lateral funiculi of the spinal cord, or mental changes were missing altogether. Associated deficiencies of other factors of the B complex, so often recorded by other observers (Grande Covian & Jimenez Garcia, 1940), were also absent.

Of the remaining symptoms usually associated with pellagra, the main ones found were fissuring of the tongue and atrophy usually limited to its tip and edges, which may have been primary, because there were practically no signs of acute glossitis, some gastric complaints, a slightly increased blood pressure, and a characteristic state of asthenia often associated with mental depression, sleep disturbances and paresthesia. All these symptoms, excluding atrophy of the tongue but including paresthesia, were cured or largely relieved by nicotinamide therapy.

The comparison of our therapeutic results with those of other authors is difficult because frequently no distinction has been made between symptoms and organic lesions. In our experience there was a striking contrast between the rapid disappearance of a given complaint, let us say skin burning, and the much slower or incomplete clearing of the erythema at the same site. The reverse was found by Kooser & Blankenhorn (1939), who claimed that the subjective complaints often persist after complete healing of the skin lesions. Paresthesiae are regarded by many authors as independent of pellagra, because they are refractory to nicotinic acid and curable by thiamin (Spies, Cooper & Blankenhorn, 1938; Mathews, 1938; Spies & Aring, 1938; Spies, Gelperin & Bean, 1938) or by other factors in yeast (Grande Covian & Jimenez Garcia, 1940). In our cases moderate paresthesiae were rapidly cured by nicotinamide, and seem to have been a part of the same general syndrome produced by very mild and almost pure nicotinic acid deficiency.

Dental lesions. A high incidence of dental caries is common in many areas of northern Portugal and

is probably to be correlated with local nutritional factors. Whether dental abrasion and pyorrhoea are equally common is uncertain. Our study has not enabled us to put forward any reason for the development of severe caries in our region. A high prevalence of pyorrhoea might have been tentatively explained by an association of a low intake of vitamin C with a fragility of the buccal mucosa analogous to pellagrous glossitis. The intakes of calcium were not, however, low.

The curious abrasion of the chewing surfaces, which attests an abnormal fragility of the enamel, may depend upon a shortage of vitamin A or D and calcium during growth. This condition is probably made worse by the fact that the bread is never free from siliceous particles derived from the granite mill stones.

Anaemia. There was in our group a definite tendency to a macrocytic type of anaemia, often associated with hypochromia, similar to the type described as 'dimorphic anaemia', and believed to express a double deficiency of iron and of the extrinsic factor. Both might be a consequence of the achylia known to be consistently associated with pellagra. It may also happen that anicotosis affects directly the mechanism of erythropoiesis, and in this case the anaemia would be a part of the primary pellagrous syndrome, like erythema or tongue atrophy. Our experiments were too short and incomplete to settle this question.

The pellagrous syndrome considered in relation to diet. Apart from the anaemia and the dental lesions which have already been discussed, the symptoms and signs of our subjects were well covered by the clinical concept of pellagra, and since all were improved by nicotinamide therapy, the immediate cause of the disease may be said to have been established. A new problem has, however, arisen, namely, why the diets did not provide enough nicotinic acid. Our dietary survey has shown that neither the total nor the 'available' nicotinic acid in the diets is in proportion as low as the levels which, in the case of other vitamins, produce just-discernible deficiency on clinical examination. Simple insufficiency in the diets, which would be the most obvious explanation and the one supported by most of the present-day American literature on the subject, does not, therefore, explain the incidence of pellagra in the maize-growing districts of northern Portugal. Grande Covian & Jimenez Garcia (1943) support our findings. They computed the amount of nicotinic acid in diets causing malignant pellagra in Madrid, and found it about normal (16 mg./day). They concluded, therefore, that the onset of pellagra must depend upon aetiological factors other than plain deficiency, among which may be the increased requirements of nicotinic acid when diets are low in protein.

The anti-vitamin theory has also found some supporters. Since typical endemic pellagra is nearly always associated with the consumption of maize, and since diets in which wheat or rye are the staple cereal may contain no more nicotinic acid than the maize diets, but not produce pellagra, it is reasonable to suggest that maize contains something which either binds or destroys nicotinic acid in the gut. If, however, maize contained much of a true anti-P.P. vitamin, it ought to 'poison' man, just as egg white poisons rats and raw fish poisons silver foxes. If it contained only a little of the anti-vitamin, the coefficient of availability of its nicotinic acid might be lowered below the level found for other cereals, but there is experimental evidence which seems to disprove this hypothesis. Finally, the observation that a rice diet precipitated a large outbreak of malignant pellagra in Madrid is evidence against the existence of a specific anti-vitamin in maize.

If a primary exogenous deficiency and a specific anti-vitamin effect are excluded, the nicotinic acid deficiency must depend upon effects produced by the rest of the diet. The value of a single nutrient may be affected by the rest of the diet in two ways: its absorption from the intestine may be lowered, or some phase of its metabolism may be upset. If the composition of all diets which are associated with pellagra be examined, one common factor stands out: their scarcity in animal protein.

Since protein promotes an easier absorption of certain minerals (McCance, Widdowson & Lehmann, 1942) and of certain organic nutrients of vegetable origin, it might favour also the absorption of nicotinic acid. However, here again, the role of an intestinal factor is ruled out by the fact that many other diets, not less strictly vegetarian, do not produce pellagra. If we consider that a plain vitamin deficiency may be ruled out, that the diets of groups like ours are on the whole satisfactory as regards calories, nitrogen and mineral salts, and that all starches behave in the same way from the point of view of nutrition, it is hard to escape the conclusion that the fault must be attributed to the protein. If so, attention is at once drawn to the fact that maize proteins are of notoriously lower biological value than those of other cereals. A maize diet, therefore, even if it seems quantitatively adequate, must place a constant strain upon protein synthesis. It has not yet been ascertained whether nicotinic acid has a role in this synthesis, or whether it can itself be synthesized by the human body. It may be that if a minimum is supplied with the food, the synthesis can be effected, just as unsaturated fatty acids can be built up if the same condition is fulfilled. At any rate, apart from the question of the underlying physiological mechanism, the existence of some correlation between the nature of the dietary protein and nicotinic acid balance seems

proved by a series of facts, some of which have already been discussed, but which when brought together, form an impressive bulk of evidence:

(1) Diets which produce pellagra are low in high-grade proteins and nearly normal in their nicotinic acid contents.

(2) On normal calorie and protein intakes pellagra is often associated with the consumption of maize proteins which are of low biological value.

(3) On low calorie and low protein intakes any vegetarian diet may produce pellagra, and the severity of the syndrome is related to the degree of the accompanying malnutrition.

(4) A diet rich in meat was the old and effective method of treating pellagra.

(5) The doses of nicotinamide required to obtain a cure of pellagra when no change is made in the diet are out of all proportion to the small amounts supplied by an effective meat diet. This indicates that meat provides some accessory factors (probably essential amino-acids) which, acting on a relatively small dose of nicotinic acid, enhance its effect or increase its efficiency.

(6) The disease is much more frequent in women than in men, which may depend upon the fact that menstruation, pregnancy and lactation place a strain upon the nitrogen anabolism. Menstrual disorders are common, and delay in *ménarche* may precede any other symptoms by a long time.

(7) The normality of the level of the plasma proteins of our patients does not seem to be an objection to this hypothesis because the finding of low levels is a late rather than an early sign of protein deficiency.

Little is actually known about the long-continued effects of deficiencies of specific amino-acids. It is not impossible that chronic shortage of one amino-acid, let us say tryptophane or lysine, will produce effects quite different from those produced by a deficiency of another, e.g. cystine or methionine. In the second year of the siege of Madrid the staple food was changed from rice to lentils. The lentils contained little more nicotinic acid than the rice, but the expected spring outbreak of pellagra was replaced by an outbreak of hunger oedema which was, however, cured by cystine. This historic observation shows the different ways in which a protein shortage can affect the balance of other nutrients, according to the dominant amino-acid deficiency.

SUMMARY

1. A clinical and biochemical study of a group of thirty patients from northern Portugal shows that they were suffering from a mild form of pellagra with no signs of severe malnutrition or of associated deficiencies except dental abrasion caries and pyorrhoea.

2. The diet of these patients in most respects was chemically satisfactory. Apart from a very low consumption of animal protein the gross intake of calories, total protein minerals and vitamins, including nicotinic acid, was satisfactory.

3. Since the syndrome was completely cured by nicotinic acid, it is suggested that the main characteristic of a diet on which pellagra is likely to develop is not a shortage of nicotinic acid; but a lack of high-grade protein.

4. A maize diet, satisfactory so far as calories and total protein are concerned, may produce pellagra because maize proteins are short of certain essential amino-acids. Other cereal diets may also produce pellagra if the general level of nutrition is very low.

5. The syndrome may be cured either by very large doses of nicotinic acid without change of diet or by moderate doses accompanied by abundant animal protein.

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