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THE DIET FACTOR IN PELLAGRA.

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(With 22 Tables and 3 Charts.)

CONTENTS.

HISTORICAL SUMMARY.

THIS subject has been dealt with by so many investigators and, within recent years in the United States, in such minute detail that it would seem surprising that no definite conclusion has yet been reached as to the cause of the disease or the actual part played by the diet in bringing about the condition.

For an historical account of Pellagra and details of the various toxic and other theories of its etiology the text-books of A. Marie (1910), Roberts (1912) and Wood (1912) may be consulted; a brief epitome of work which has a bearing on the relation of pellagra to food deficiency must however be given.

As early as 1735 Casal of Oviedo in Spain who appears to have been the first to describe the disease connected it with poverty and bad nourishment.

Roberts quotes Townsend (1787) who visited Oviedo in 1787 as stating that "the people among whom the disease originates eat little flesh.... their diet is Indian corn, with beans, peas, chestnuts, apples, pears, melons and cucumbers."

Roussel (1866) found that pellagra can be cured by good food and that without this remedies were useless.

Since the year 1898 when Sandwith may be said to have brought pellagra to the notice of English clinicians and especially since 1907 at about which date, according to Wood (1909), the disease first appears to have been seen to any considerable extent in the United States, the nature of the dietetic defect and the possibility of infective or other causes have given rise to a very copious literature of which reference can only be made to a small part, in particular to those investigations bearing on a deficiency in the quantity or quality of the protein as the causative factor.

As to whether maize as such is the cause of the disease, a theory originally propounded by Strambio in the eighteenth century (1786) and revived in Italy by Lombroso, is ably and fully discussed by Sambon (1910) who shows conclusively that pellagra may occur in persons who have never consumed any maize.

An experiment carried out at the State Asylum at Peoria, Illinois (1912), is of interest. Sixty patients were fed on a liberal maize dietary for twelve months, during that time four certain and one doubtful case occurred; sixty other patients received a diet containing no maize, five certain cases and five doubtful developed among them.

Note. A work (*Pellagra*, by H. V. Harris, M.D., Atalanta, U.S., Macmillan, New York, August, 1919) has come into the writer's hands since the completion of this paper. The author gives a valuable historical summary of existing knowledge in all branches of the subject up to the year 1919. In regard to etiology, the maize theory in a slightly modified form is strongly supported. It is suggested that the disease is due to: (*a*) an intoxication with "certain phenol poisons" produced by the action of moulds on the cereal; (*b*) that the intoxication is inherited and that possibly all pellagrins have this hereditary taint. The hypothesis is given in full on p. 120 of the book. Eleven reasons are advanced (p. 118) in support of the assumption, but no facts are adduced which are not open to considerable doubt or do not admit of a different interpretation. Zein is described as a tox-albumin. Numerous reported cases, where maize was known not to have been consumed, are explained as being either not true pellagra but a condition resembling it described by the author as "para-pellagra"; or on the supposition that the patients had an ancestral taint. It is also suggested that rarely the moulds producing the toxin may grow on other cereals.

F. M. Sandwith (1913), who had for many years supported this theory of pellagra, suggested that the deficiency in maize might be explained by the lack of tryptophane in its chief protein zein,

The disease is traced by Casimir Funk (1913, 1914) to a deficiency similar to that to which he attributes beri-beri, an insufficiency of vitamines in the food.

Voegtlin (1914) draws attention to the importance of investigating: (*a*) the possible connection with a deficiency of certain accessory food substances (vitamines); (*b*) the toxic effects of aluminium salts; (*c*) the deficiency of appropriate amino-acids.

The essential curative character of high value protein in the treatment of pellagra is illustrated by the experience of Lorenz (1914) in advanced

mental cases, Ridlon (1916) and in particular by the orphanage experiments of Goldberger, Waring and Willets (1915); (see also Goldberger (1916)). The results obtained were so striking that they may with advantage be quoted. In two orphanages, M.J. and B.J., there had been frequent recurrences of pellagra: the number of cases between January and September 1914 was at M.J. 79, at B.J. 130. The diet appears to have consisted largely of cereals, partly maize, with very little animal food; from September 1914 onwards oatmeal replaced grits, a considerable increase in the meat was made, leguminous food which had before been absent was introduced and milk and eggs were given.

Not only, in fact, was the diet improved in quantity but it is clear that a large amount of protein of high biological value was added. The result in 1915 was that at M.J. no case occurred, at B.J. one recurrence.

In similar orphanages at which the old diet was continued recurrences occurred to the extent of from 58 to 75 %.

A like result was seen at the Georgia State Asylum. A ward was set apart for pellagrins, the patients in this ward received an extra half-pound of meat in addition to milk and leguminous food. No recurrences took place, while in the control wards, in which the improved diet was not given, recurrences were among the white patients 53 %, among the coloured 40 %.

In neither of these cases are the components of the diets given in sufficient detail to allow of an estimate being made of the quantitative composition in proximate principles.

Goldberger (1914) advises that in pellagrous families, who cannot afford to buy sufficient animal food, leguminous food products, in view of the richness in protein, should be used.

A direct attempt to discover whether pellagra could be produced in healthy men by diminishing the protein intake was made by Goldberger and Wheeler (1915, 1916) in the Rankin Farm experiment. These authors have recently (1920) published a complete account of the composition of the diet and of the clinical symptoms which resulted. From this it appears that from April to the end of October 1915 eleven volunteers in this convict establishment were fed on a diet the average gross protein content of which was no more than 44 grammes. The writer has given a description of this diet (Diet 10, Table IX) in this paper, it will be seen that the biological value of the protein estimated on the basis of K. Thomas' (1909) investigations was 14·5, the minimum normal requirement being 30.

Control squads receiving a diet the gross protein content of which varied from 88 to 110 including 18 to 35 grammes of animal protein but being under otherwise similar conditions were observed.

The fats were large in amount, averaging 108 g. daily. After four months six if not seven of the eleven volunteers had developed cutaneous and general symptoms characteristic of pellagra; none appeared in any other occupant of the locality. McNeal (1916) casts doubts on the correctness of the diagnosis;

no one however with some experience of the disease can fail to be convinced, after reading Goldberger's recent paper (1920), that these men suffered from pellagra; the writer from recent experience in Egypt would be inclined to believe, from the peculiar lingual and intestinal symptoms described, that four others might well have been included as pellagrous, leaving one only out of the eleven who does not appear to have become affected.

McCollum (1919) believes, in view of the experiments of himself, Simmonds and Parsons (1917 and 1918) on animals, that the Rankin Farm dietary was probably deficient in three factors, namely the amino-acids, the inorganic salts and the fat-soluble accessory substance. Goldberger (1920) admits that in view of Sherman's (1918) observations, the low calcium content of ·2 g. daily may have had an influence, Sherman considering that ·45 g. is the human minimum requirement. The complete absence of xerophthalmia, shewn by McCollum to be connected with a lack of the fat-soluble accessory substance in the food, or of any symptoms of beri-beri or scurvy among the subjects of the experiment make it improbable that an absence of vitamines was the effective factor.

Experiments by Sullivan (1920) using hens fed on a diet of the same composition as the Rankin Farm dietary indicated a deficiency of the anti-neuritic vitamine B. The same observer (1920) with rats failed to get this result.

An observation which has a considerable bearing upon the points just discussed may be mentioned here.

Owing to the frequency of pellagra recurrences among the inmates of Abassia Asylum for the Insane at Cairo and the occurrence of occasional new intra-mural cases, the writer (1919) was asked to report as to whether the diet of the institution, which appeared to be adequate for normal persons, was in any way defective. The protein of the diet (No. 17, Table XVIII, this paper) will be seen to have a biological value of 46·4 (possibly 49).

The rations, in addition to other articles, contained 100 g. of meat, 50 g. of milk, and 300 g. of fresh vegetables. The calorie value was sufficient. It was thought however that as the minimum protein requirement of a pellagrous and insane community was likely to be higher, possibly considerably higher, than the normal (which the writer regards as equivalent to 40 grammes of animal protein) it would be well to increase the protein. This was done by the addition of 45 g. of meat and 50 of milk raising the biological value to about 60. During the following year the death rate from pellagra was diminished by nearly 50 %.

There was no other change dietetic or administrative. It is impossible to avoid the conclusion that the protein of the diet was raised from below the average minimum requirement of the community to something above it.

Note. The number of deaths ascribed to pellagra among the inmates of the Abbassia and Khanka Asylums, was, in 1918, 127; in 1919, 64. The death rate from all causes was in 1918, 13·4 % of the resident population, 1919, 8·2 %. The death rate from general paralysis remained unchanged.

This experience differs from others of a similar kind, such as the orphanage and other experiments described above, in that there was no change from a diet very deficient in high value protein to one very rich in such material, where it might be said that the large additions of animal food-stuffs had introduced other accessory substances previously lacking; in this case in view of the original composition of the diet it is difficult to suppose that it was lacking in either vitamines, using the term generally, or in salts of lime, or that the additions made could have added anything of great importance in these respects: there remains only the increase in the protein as the effective factor.

Chittenden and Underhill (1917) fed dogs for eight months on food consisting of biscuits, peas and cotton-seed oil: symptoms which they considered resembled those of pellagra were produced. They regard the result as due to a dietetic deficiency of unknown nature.

McCollum (1919) did not obtain any such symptoms in rats and regards Chittenden's results as due to an infection supervening on lowered vitality resulting from a faulty diet.

H. Chick and E. M. Hume (1920) carried out a series of experiments on monkeys in which all the accessory food factors (fat-soluble A, anti-neuritic and anti-scorbutic factor) were added in more than sufficient amount to the food, which was so constituted as to be deficient in the two amino-acids tryptophane and lysin, the protein consisting to the extent of 70 % of zein. Definite cutaneous symptoms were produced after periods varying from 58 to 117 days.

The addition of tryptophane to the food gave a definite beneficial effect but did not bring about a cure, the addition of a mixture of lysin, arginin and histidin gave little additional benefit in one case in which it was tried. A supplement of 5 to 10 grammes of caseinogen given with the food in the case showing the worst cutaneous lesions was followed by a rapid cure. The authors point out that the rapidity of the cure excludes the possibility of an infective agent having played a part in the condition. This important experiment seems to connect the pellagrous condition with a deficiency in the biological value of the protein and no other.

Enright (1920) in the belief that the diet of the German prisoners of war in Egypt was of high protein and calorie value finds that the epidemic (65 cases out of 7000 prisoners) among these men disproves the view that pellagra is a deficiency disease.

Goldberger (1920) and Lelean (1920) in replies to Enright's article, show that the food actually consumed by the prisoners was of very low calorie value and that the protein content was little if at all above the minimum requirement. The writer (1920) can endorse, from personal investigation of this epidemic, the opinions expressed by the two latter observers. It may be pointed out in addition that none of the 65 patients could be considered normal, all of them having suffered from malaria, dysentery or chronic diarrhoea, 62 of the 65 being affected by the two latter maladies. It may be taken

as certain that the combined effect of chronic disease of the intestine and the increased call on the protein of the food made by the insufficient energy intake, raised the level of protein requirement in these men to a point considerably above the normal.

The outbreak of pellagra among the Armenian refugees at Port Said in 1916 is of especial interest. White (1919) who has reported on this epidemic, examined with great care the epidemiology; he finds that there was no evidence of any infective origin either by insect carriers or other means.

In regard to case to case infection the epidemic is instructive in view of the statements of Siler, Garrison and McNeal (1914, 1917).

Pellagra is very rare at Port Said, the camp was a few miles from the town and was located in the desert on the Syrian side of the Suez Canal. The tent distribution of cases was carefully recorded and the results gave no evidence of the disease being either infective or contagious (*l.c.* p. 18).

[A similar conclusion was arrived at from the investigation of the outbreak among Turkish prisoners of war referred to below. A careful survey of the tent distribution of cases at the Kantara camp was made and the results submitted to Mr T. L. Bennet (Director of the Statistical Dept., Egypt); mathematically no probability was found that the occurrence of any one case influenced the appearance of any other (*l.c. infra*, p. 13).]

The writer (1916) examining the diet (Diet 7, Table III, this paper) in force at the time of the outbreak by the method first adopted in regard to the Egyptian Prison Dietaries (1914), namely on the basis of K. Thomas' observations, the validity of which method will be discussed below, was led to conclude that the low biological value of the protein showed the most obvious deficiency. This for the whole camp was equal to about 21 and for adults to 23 grammes of caseinogen daily. The rations contained a preparation of the whole wheat grain and a fair proportion of fresh vegetables, this was thought to exclude a vitamine deficiency. The view adopted as to the protein deficiency was confirmed by the beneficial results of improvements in the food, the biological value of the protein content being raised from 23, first to 37·7 (Diet 7*a*) later to 41·7 (Diet 8, Table VII) and for previously pellagrous persons to 59 (Diet 9, Table VIII), pellagra almost completely disappearing from the camp where, in the previous year, 20 % of the inmates had been affected.

The light thrown by the investigation of this epidemic led the writer to examine a series of other diets known to be pellagrous or the reverse; the results obtained, which form the basis of this paper, were given to the Commission which considered the outbreak of pellagra among the Turkish prisoners of war (1918) and have been published in brief in their Report by Boyd and Lelean (1918, 1920).

SUMMARY OF THE WRITER'S CONCLUSIONS.

The results the writer has arrived at, evidence of which will be given in this paper, may be summarised as follows: (*a*) The chief etiological factor is a deficiency of protein in the food, this is best determined by an estimation

of the biological value from K. Thomas' figures. (*b*) The minimum safe value of this factor is 40 below which pellagra is likely to appear in the affected community. (*c*) Large individual variations occur in the minimum requirement but the lower the biological value of the food protein the larger is the proportion of persons attacked. (*d*) The level of protein requirement is raised by labour if the energy intake is deficient, by a previous attack of pellagra and by illness especially chronic disease of the alimentary tract.

Thus while many healthy individuals may escape whose food protein has a biological value of no more than 20, the minimum safe value for a community would be 40, for hard labour probably 50 and for a community of persons with chronic intestinal disease or previously affected with pellagra as much as 60. Applying these conclusions it is thought that an explanation may be found for many of the obscure cases reported in the literature of pellagra.

Note. In a recent publication, received since the completion of this paper, Goldberger, Wheeler and Sydenstricker (1920) give an account of a valuable epidemiological survey of the relation of diet to pellagra incidence. These authors conclude that a restriction of animal proteins, meat and milk products, in the food is of definite etiological significance. They believe also that their data indicate the possibility of a vitamine deficiency, particularly in the fat-soluble A substance, being in part responsible for the disease.

In the course of an investigation carried out in Egypt during the present year (printed as a Report to the D.M.S. Egypt) Hammond Searle and Stevenson state that advanced cases of pellagra can be restored, at least temporarily, to health if placed on a dietary the biological value of the protein of which has been greatly augmented by the addition of milk proteins in a concentrated form = "Plasmon" or freshly prepared curds from which the whey has been expressed).

INTRODUCTION.

From a consideration of the literature of the subject, in part referred to above, the following statements will receive general acceptance:

(*a*) That pellagra is a disease of poverty.

(*b*) That the disease is found chiefly among communities whose food is mainly vegetarian.

(*c*) That it affects largely communities whose staple article of cereal food is maize.

(*d*) That unless the disease has reached a certain point it can be cured and recurrence prevented by a suitable dietary.

(*e*) That pellagra can undoubtedly occur in persons whose food contains no maize products.

(*f*) That it is almost unknown in some countries, *e.g.* Mexico where much maize is eaten. And is apparently very rare among rice-eating communities such as the Japanese and the inhabitants of a large part of India, as also in northern European regions where animal products form a staple article of diet.

(*g*) That the disease appears to have almost disappeared from those parts of the south of France where it was formerly common and

has greatly diminished in northern Italy, in both cases the event accompanying a general increase of prosperity. While it is increasing in the southern states of America and apparently also in Egypt, in the former case at any rate this increase has accompanied a greatly increased cost of food without a corresponding increase of purchasing power.

(*h*) That pellagra has been known to occur among children or adults whose power of obtaining sufficient and suitable food is not open to doubt. It is, however, a medical curiosity.

These seem to be the most salient general facts. Nevertheless in the literature which has been available I have nowhere been able to find any record of the composition in proximate principles of dietaries thought to have been responsible for pellagra or which appeared to have a curative effect.

(Since this was written Goldberger and Wheeler's paper (1920) on the Rankin Farm dietary has appeared.)

It is therefore of interest to put on record the constitution of a number of diets known to have been connected with pellagra and to compare this with that of others of known value in curing or preventing the disease.

The writer's object is not to discuss the various hypotheses which have been proposed regarding the etiology of the disease, but to examine the question as to whether the theory of protein deficiency does not provide a sufficient explanation.

In order to do this it is necessary to find some measure by which the protein from different sources may be reduced to a common level. The biological value of protein will be taken as this measure.

Rubner (1912, 1913) was the first to introduce K. Thomas' conception of the differing biological value of proteins into the current literature of dietetics; but, unless this observer's original description (1909) of his experiments be consulted, the impression is gained that the numerical expression of the relative value of proteins is more to be relied upon than is actually justified.

Karl Thomas' work was based on the dictum of v. Leyden (1897) which, put briefly, is that the minimum requirement of protein varies with the variety of protein. The whole of Thomas' numerous observations were carried out on himself and in each experimental period protein from only one source was present in the food, both these facts add much to the value of the conclusions. The method used is however open to question and the results, particularly in regard to maize, must be accepted with considerable doubt.

The validity of Thomas' results is disputed by some recent authors. Sherman, Wheeler and Yates (1918) state as a result of experiments carried out on a man and two female subjects that the proteins of oats, wheat and maize have the same value in human nutrition as the average protein of the usual mixed diet, and need only to be supplemented with a small amount of milk protein to be efficient in maintaining nitrogen equilibrium. The amount

of milk protein added by these observers was however as much as from 10 to 20 % of the total protein. Sherman (1920) gives details of an experiment in which a woman weighing 55 kilos maintained nitrogen equilibrium on a diet 88 % of the protein of which was from maize, the remainder from milk, the total protein corresponding to 37 g. for a weight of 70 kilos. It is to be noted that the minimum requirement of animal protein upon which these subjects could maintain nitrogen equilibrium was not known; for purposes of comparison as between different proteins this is a point of considerable importance in view of the great individual variations in this respect; the results tabulated by Sherman (*l.c.*) of 109 determinations made by different observers showing that on a mixed diet the minimum protein requirement varies from as little as 21 g. to as much as 65 g. daily with an average of 44 g.

The introduction of milk protein in addition to the single protein vitiates to some extent Sherman's conclusion as to the value of the latter. Osborne and Mendel (1918) find that if cereal proteins be supplemented by the proteins of meat, milk and eggs, less total protein is required for maintenance and growth than with the cereal protein alone. These authors (1920) also find that the rate of growth in rats for each gramme of cereal protein in the food is only half that for each gramme of milk protein.

McCollum, Simmonds and Parsons (1917) state that the value of the protein mixtures present in all the more important seeds is without exception much lower than that of milk protein. Their values differ considerably from those given by K. Thomas, protein from wheat, maize and rice they find to have 50 %, from beans 25 %, of the milk protein value. The same authors (1918) show that maize, rye and barley proteins produce growth in rats at only half the normal rate; the low value of maize protein is particularly apparent from Chart VI (Lot 722) in the paper referred to.

It seems clear from the results of these different observers, that, while Sherman's experiments do not in fact demonstrate the true relative value of different proteins, the results of Osborne and Mendel, McCollum and his co-workers prove that vegetable proteins have a much lower value than those from animal sources. It will be found actually that if the various diets considered in this paper be dealt with on the basis of McCollum's figures (1917, *loc. cit. supra*), the comparative value of the protein in these diets would not in most cases differ much from the estimates which have been formed on the basis of K. Thomas' values.

Under the circumstances and particularly in view of the fact that, whatever may be the true explanation, the biological value of protein, estimated as it has been, forms a reasonably accurate criterion of the pellagrous or non-pellagrous character of a diet, the writer has adhered to the method which had been adopted before the appearance of the papers discussed above.

The "biological value" of proteins from different sources was found by K. Thomas (*l.c.* p. 266) to be as follows, for the more common food-stuffs:

Beef 104, milk 100, rice 88, potato 79, pulse 55, wheat 39, maize 29.

For approximately estimating the comparative value of a given amount of protein from different sources the total quantity of each protein may be divided by the following factors: animal protein 1, rice protein 1·12, potato 1·27, pulse 1·82, wheat-flour, 2·55, maize 3·4.

The minimum protein intake which is therefore necessary for a man of 70 kilos weight under the most favourable conditions would be from animal sources 30 grammes daily, rice 34, potato 38, pulse 54, wheat-flour products 76, maize 102.

It is clear that, accepting these figures as a basis of calculation, a diet in which the gross protein content might appear to be sufficient, as for example one in which maize-flour bread formed the main component (as no doubt often happens among the poorer classes of countries in which maize is the chief cereal) might be physiologically deficient.

It must also be noted that the minimum values given are only possible if the diet in other respects than protein has a high energy value, and that the lower the total energy value the higher must be the protein intake. It will thus be seen that a subsistence diet in which a certain amount of animal protein is given may be sufficient to maintain health with a low calorie value, while a subsistence diet of the same calorie value, derived entirely or very largely from vegetable sources, might be quite unable to do so. That nitrogen equilibrium may be maintained upon an amount of protein corresponding to 30 g. of protein from animal sources is probably only possible under the favourable conditions such as it is possible to establish in an experiment and that therefore under the ordinary conditions of life protein deficiency might easily arise unless a considerable margin above the absolute minimum were allowed.

It seems also to be the case that the minimum intake of protein, as determined by experiment, is that which is sufficient under normal conditions of health and that any deviation from the normal, such as diminished absorption from gastro-intestinal disturbance even of short duration, conditions constantly occurring in ordinary life, will upset the equilibrium which can only be re-established by a considerable excess of the intake over the minimum. A safe margin is necessary for this reason.

As stated above, the figures given are for the man of a certain weight, for individuals of lower weights the requirements would be less, probably in proportion to the surface and height of the body.

Using the above facts regarding the biological value of protein in gauging the sufficiency of the protein ration in the largely vegetarian Egyptian prison dietaries, the writer (1914–1917) has adopted as a minimum, except for short periods of detention, a biological value of 40 for "light labour" and of 45 for the rations of "hard labour" convicts.

There can be little doubt that the cause of the discrepancy in the biological value of proteins from different sources is the well-known difference in the proportion of the various amino-acids which compose the protein molecule,

some of which appear to be more essential than others in the maintenance of health and growth.

The feeding experiments of Hopkins and Willcock (1907) using zein with the addition of tryptophane, and of Kauffman, Aberhalden and Bloch and others (*vide* Cathcart, *l.c.*); also the work of Hopkins and Aekroyd (1916) with arginin and histidin, are sufficient proof that, at any rate in the human being and the carnivore, nitrogenous equilibrium and eventually life cannot be maintained on a diet devoid of the more complex amino-acids, and incidentally that these cannot be synthesised in the organism and must therefore be obtained in sufficient quantity from the food and ultimately from vegetable sources.

It is clear that the more nearly a protein approaches in constitution the body protein, the less of it should be required to provide the necessary building material; it is this fact which explains the higher biological value of animal protein as human food. An examination of tables showing the constitution of proteins (see Aders-Plimmer, pp. 20–25) provides an explanation in some cases, particularly in that of zein, for the low value of the protein. In the case of zein not only are tryptophane and lysin completely lacking but two other important amino-acids, arginin and histidin, are present in unusually small proportion.

It may be possible in the future to evaluate the protein for dietetic purposes by chemical analysis, hitherto, even assuming that the whole of the amino-acids composing the protein molecule were known, their percentage proportion in different proteins has been only partially determined, a large proportion of the total nitrogen being unaccounted for in all analyses. Under these circumstances Thomas' results form an extremely useful basis for the determination of the protein food value of any given diet.

Apart from the fact that protein deficiency may, in diets of low protein content, be due to the food material yielding protein of low value, there is little doubt that in a mixed community there exist many individuals who require a larger protein intake for the maintenance of the nitrogen equilibrium than do others. There are in fact various and in some cases very large differences in the individual requirements in protein. In considering the incidence of a disease probably due to protein deficiency these individual differences are of considerable importance among a community whose food contains little more than the minimum amount of nitrogen required by the average individual.

It is of interest in this connection to examine the results of the experiment carried out by Chittenden (1905) and his four co-workers upon themselves, the purpose of which was to determine the minimum protein intake required to maintain nitrogen equilibrium with a mixed diet in some cases mainly vegetarian in nature.

Accurate details are given of the composition of the diets, the amount of nitrogen intake from each of the food materials taken daily, the total nitrogen intake and output and the nitrogen balance in each of the five observers. These

were Chittenden himself, Mendel, Underhill, Beers and Dean. The food was analysed for a period of days, varying from four to seven in different cases, in which the protein intake was insufficient to maintain nitrogen equilibrium, there being a negative nitrogen balance; and during a second period of a similar number of days during which the protein intake was slightly greater, when a positive nitrogen balance was attained. In Dean's case the second experimental period was omitted.

In order to find the comparative value of the protein intake in the different cases, an attempt has been made to estimate the biological value. The following table gives the results in the five subjects.

Table I.

Estimate of individual protein requirement from Chittenden's figures.

("Physiological Economy" in *Nutrition*, 1905, pp. 34–108.)

Subject	I		II		III		IV		V
Body weight in kilos	57		70		61·5		65		64
	March	June	Febr.	May	Febr.	May	Febr.	June	Febr.
Dates of experiments	20–25	23–27	9–14	18–24	9–14	6–12	10–14	1–4	9–14
Absorbed protein in grammes	40	36·6	48·9	51·2	55·5	68·7	55·2	42	55·2
Biological value of protein	24·4	22·6	22·4	29·7	29	38·1	34	28	25·2
$\frac{\text{B.V.} \times 70}{\text{body weight}}$	29·9	27·7	22·4	29·7	33	43·3	36·7	30·1	27·5
Nitrogen balance	+·165	−·07	−1·19	+·38	−·953	+·346	+·158	−·442	−1·555
Calorie value of food	1613	1549	1975	2440	2168	2152	2068	1785	2529
Raised to value of 70 kil. man	1980	1901	1975	2440	2470	2450	2216	1921	2764

The nature of the diet in the five cases was as follows:

I. Chittenden. Diet mixed, with meat and other animal protein.
II. Mendel. Mainly vegetarian. With milk, cheese and eggs.
III. Beers. Mainly vegetarian. With a good deal of milk and milk products.
IV. Underhill. Mixed diet with meat and fish daily.
V. Dean. Vegetarian with no milk and little milk products.

The method adopted in making the calculations from Chittenden's data was the following. Taking the nitrogen values given for the components of the daily diets, the nitrogen from all animal sources, rice and potatoes, is summed and multiplied by the factor 6·25, giving a certain figure; the nitrogen from all other sources (excluding tea and coffee) is similarly converted to protein, giving a second figure which, added to the first, would represent the gross protein of the diet (not shown in the Table). To obtain the absorbed (nett) protein (line 4, Table I) 5 % is deducted from the first figure, 20 % from the second and the results added. The biological value (line 5, Table I) is estimated from the absorbed protein; the first figure (protein from animal sources, rice and potato) being given the unit value of meat protein, the second figure (protein from other sources) being reduced to the value of wheat protein by dividing by the factor 2·5, the two results being added together.

It is obvious that the figures cannot be more than perhaps a close approximation, for example some of the articles of diet contain mixtures of animal and vegetable protein, for example chocolate pudding; in such cases an estimate has been made on the basis of the known composition of such mixtures and the protein entered under the two heads. While in some cases the value of the protein on the basis of Thomas' figures is unknown.

The figures from all the five cases having been treated in an identical manner the figures are comparable and demonstrate clearly enough that after reducing the whole protein to the value of meat protein the quantity necessary to maintain nitrogen equilibrium differs very considerably in different individuals living under otherwise similar conditions.

To obtain a more exact expression for comparison of the five cases the figures tabulated above have been treated thus.

To the biological value of the protein in the five cases in which there was a negative nitrogen balance has been added the value of the body protein metabolised in each case respectively as estimated from the excess of the nitrogen output over the intake, the figures so obtained are assumed to give the total amount of protein metabolised. The following table gives the results:

Table II.

Subject	I	II	IV	V	III
Body weight in kilos	57	70	65	64	61·5
B.V. of assimilated protein A (grammes)	22·6	22·4	28	25·2	29
Nitrogen balance	−·07	−1·19	−·442	−1·355	−·952
Body protein metabolised B... ...	·437	7·4	2·7	9·4	5·95
A + B total as animal protein ...	23·3	29·8	30·7	34·6	34·9
Ditto per kilo body weight	·4	·42	·47	·52	·57

The last line gives the grammes of animal protein metabolised per kilo of body-weight and shows a minimum of protein consumption daily ·4 g. per kilo in the case of Chittenden and of ·57 g. in the case of Beers which would correspond for a man of 70 kilos to 28 grammes in the first case and 39·9 grammes of protein in the second, this being the minimum requirement in the two cases.

Accepting the above figures as approximately expressing the true value of these diets in animal protein, they show very well that taking a community of persons receiving a certain diet as for example in a camp or institution, the diet which might be sufficient in protein for the majority of the inmates might be actually deficient for some.

A hypothetical case may be suggested.

A diet containing about a 100 g. gross protein equal to 80 g. available protein. If this should consist to the extent of 40 g. maize protein, 10 g. wheat protein, 20 g. leguminous protein, 6 g. animal protein and 4 g. rice protein, it would have a biological value of 37·7 g. Such a diet while being sufficient to maintain nitrogenous equilibrium in the majority of individuals

of ordinary weight might lead to gradual protein starvation in a certain number, although the protein intake is by no means small.

In institutional diets, at any rate in countries such as Egypt where vegetable foods are bound to supply the greater part of the nutriment, the apparent value of a diet is apt to be deceptive; in such cases it is particularly necessary to adopt some method, such as has been used above, for the purpose of gauging the value of protein. Even then it is difficult to avoid approaching the boundary line beyond which a few exceptional individuals will be found who are likely to suffer; it is for this reason that the writer (1917, *l.c. supra*) suggested that in a vegetarian diet the protein should have a biological value equal to not less than 40 grammes of animal protein.

In considering such institutional diets where the rations are based upon the absolute requirements in essential components a deficiency of protein may arise from defects in the mode of preparation owing to which the absorption of protein from the alimentary tract is insufficient, the protein thus not being available for nutrition to the normal extent.

Part I.

ANALYSIS OF VARIOUS DIETS WITH THE INCIDENCE OF PELLAGRA AMONG THE AFFECTED COMMUNITIES.

With this introduction as to method, the writer proposes to examine certain diets, some of which are thought to have had a causal relationship to pellagra, others which are known to have been curative in the disease. Apparently such a comparison has not hitherto been made, nor is there in the literature at the writer's disposal any detailed analytical treatment of pellagrous or anti-pellagrous diets.

1. ARMENIAN REFUGEE EPIDEMIC.

The first diet is that of the Armenian Refugees' Camp at Port Said. These persons to the number of nearly 4000, after undergoing great hardships in the mountainous coast region between northern Syria and southern Asia Minor, were rescued and carried to Port Said where they were received in September 1915. After an organisation for their relief had been established, they were put on the diet[1] described below. In May 1916 pellagra[2] was found to exist among the refugees, and owing to the large amount of sickness in the camp apparently due to this cause, Dr R. G. White of the Public Health Department (Egypt) was sent to investigate the epidemic; about 380 cases of the disease were found, almost exactly 10 % of the population being affected.

[1] This diet was introduced in April but was preceded by two very similar diets of almost identical value.

[2] For some months previously, diarrhoea and digestive troubles had been very prevalent.

Diet 7[1].

At the beginning of June the Diet Sheet was submitted to the writer for examination. The mean daily ration and nutritive value of the same was as follows:

Table III.

Armenian Refugees' Diet. Port Said, 1916.

(Diet 7)

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Gross fat	Available carbo-hydrates	Salts
Bread*	750	—	37·5	15	7·5	356	9·7
Bourghoul†	5·5	—	·5	·2	·11	3·5	—
Cheese	17·1	—	2	2	2·7	—	1·7
Meat	8·6	—	1·6	1·6	·34	—	·1
Oil	5·3	—	—	—	5·3	—	—
Lentils	11	—	2·1	1·17	·22	6	·25
Beans	7·1	—	1·3	·7	·14	3·8	·2
Rice	8·6	—	·56	·5	·03	6·5	·03
Sugar	18·8	—	—	—	—	18·8	—
Vegetables ...	53·4	—	·53	·25	—	1·6	·5
Onions	2·5	—	·03	·01	·05	·07	·8
Olives	14·3	—	·11	·05	2·8	·7	·7
		57	46·2	21·4	19·2	397	14·1
Value of diet for adults (over 14 years)		64	51·5	23	21·6	430	——

* Wheaten with 25 % maize flour. 750 g. to persons over 14 years of age. 4–14, 375 g. 0–4, 125 g.

† Crushed wheat, boiled in water and afterwards dried for storage—a sort of porridge being made from it.

The writer (1916) presented a report in reference to this diet, the conclusions arrived at being that the cause of the epidemic of pellagra was to be found in:

1. The low biological value ot the protein content of the food.
2. The low total energy value.
3. The low fat value.

Conclusions 1 and 2, in so far as the calorie value has a bearing on the maintenance of nitrogen equilibrium, appear to be confirmed by the subsequent investigations recorded below. The more in fact that this epidemic is considered, the more strikingly it stands out as an example of the production of pellagra by the use of a diet of low protein value.

Since this report was written, by the courtesy of Dr White, Dr Devletian and others it has been possible to obtain some information as to facts concerning this diet.

It would seem that the rations were not originally introduced as forming a complete diet, it being expected:

(*a*) That a sufficiency of other food would be forthcoming as the result of help in money or in kind from charitable sources.

[1] The numbers given to diets, *e.g.*, Diet 7, refer to their order in the "General Table of Diets," Table XX.

(*b*) That the refugees, at any rate the men, would be able to obtain work at a wage which would enable them to provide sufficient food for their families.

(*c*) That failing the above the fact that a full diet was issued for each individual in the camp irrespective of age would lead to the deficiency in the case of the adults being balanced by the excess in the case of the children.

The writer is informed that as regards (*a*) the general population of the camp were little benefited, pregnant women, nursing mothers and young children, as was natural and right, receiving chief attention.

As regards (*b*) it appears that work was irregular and that although some families benefited many did not, while in many cases the men were inclined to save what money they received rather than spend it for the support of their families.

There can in fact be no doubt that the bulk of the population lived solely on the food provided in the diet sheet given above.

The third point (*c*) is capable of analytical investigation.

Unfortunately the only part of the full ration issued without regard to age was the food material other than bread.

The bread was issued thus: 750 g. to persons over 14 years, 375 g. to persons over 4 to 14 years, 125 g. to children up to 4 years.

The age distribution in the camp was in June 1916 as follows:

Table IV

(Figures kindly given by Dr White)

	0–5	6–14	15–20	21–30	31–40	41 upwards
Males ...	265	470	371	199	137	315
Females ...	253	480	372	338	236	404

From these figures the following estimates have been made:

Total population	3840
Children 0–4 years	468
„ 4–14 „	1000
Males 15 years upwards	1022
Females „ „	1350

The mean food requirements at the different ages are as follows estimated from Rubner's tables and the tables of *American Household Requirements* (from Russell-Wells, 1915):

First 4 years of life	32 % of adult male requirement
5 to 14	60 % „ „ „
Over 15 (women)	80 % „ „ „
Over 15 (men)	100 % „ „ „

Taking the age distribution in the camp and distributing the available food in the above proportion according to age, the following table gives

the calorie value and protein (calculated as animal protein) which each group would have received:

Table V.

Age	Calories	Protein. B.V.	Fat	Carbohydrate
Males 15 upwards ...	2160 (gross 2280)	23 (gross 64)	21·6	430
Females 15 upwards ...	1728	18·4		
Children 5–14	1290	13·8		
,, 0–4	690	7·3		

The above table shows that for the different ages the diet, as far as the calorie value is concerned, provided a bare subsistence for the first age group and is deficient even in this respect for the others as compared with any known figures.

The protein is more strikingly deficient.

The proportionate age requirements given above are not applicable to the protein, the daily amount needed to maintain health and growth being relatively greater.

A child of eight months naturally fed receives about 16 grammes of animal protein daily; this may be taken as the physiological need at that age. The requirement gradually increases with age; it has been suggested above that 40 g. should be the minimum biological value of protein for the adult, the estimated minimum protein requirements (estimated as animal protein) for the different age groups would be thus in the order of the above table, 40 g., 32 g., 25 g., and 20 g. daily; with lower figures than these it is doubtful whether health and growth could be maintained over any considerable period of time.

Comparing these figures with those given in the table (V) showing the value of the food actually distributed, the general condition of protein starvation becomes obvious.

No doubt some food was available from other sources, to this reference has been made above. There is however every reason to suppose that the married women with families, tended in this camp as happens in ordinary life under conditions of poverty to sacrifice part of their food to the feeding of their children and husbands; persons familiar with the Armenian peasants, from whom the population of the camp was drawn, state that this is particularly likely to have been the case with the women of that race. When we correlate three factors, poverty (or a restricted food supply), the maternal instinct and the care of a household with a disease due to deficient nutrition, that disease might be expected to attack the married women to a greater extent than other classes.

The distribution of the cases occurred very strikingly in the camp and is equally marked in the case records given of the Spartenburg epidemic by Siler and Garrison (1914) and elsewhere in the United States by Grimm (1916).

A table constructed from case records obtained from Dr Devletian is of interest in this connection.

Total population of camp 1916 (June), 3790.

Total cases of pellagra 1916, 643.

Table VI.

	Number	Pellagra cases	% affected
Males 0–14	735	54	7·4
Females „	683	66	9·8
Males over 14	1022	77	7·6
Females „	1350	445	33
Males 15–50	812	34	4·2
Females „	1071	329	31

The figures for adult males between 15 and 45 are affected to some extent as the majority of these men left the camp for work elsewhere in September 1916; as however the bulk of the cases occurred before this, the effect on the estimate is not great.

The age distribution of the cases, compiled from Dr Devletian's statistics, and a similar record of the Spartenburg cases is shown in Chart I. The similarity in the two curves is striking.

Diet 7a.

In view of the great deficiency in the diet, various recommendations were made in collaboration with Dr White and in November the following diet was introduced:

Bread 770, meat 10, oil 18·7, rice 31·2, lentils 50, beans 75, fresh vegetables 100, onions 12·5, cheese 7·1, wheat 14·8, sugar 20, salt 15, tea 20.

The figures represent the mean daily amount in grammes.

The nutritive value of the diet was as follows:

Protein (av.) 60·2, B.V. 37·7, fat 35·2, carbo-hydrates 498.

Calories (av.) 2676, salts of food 13·45.

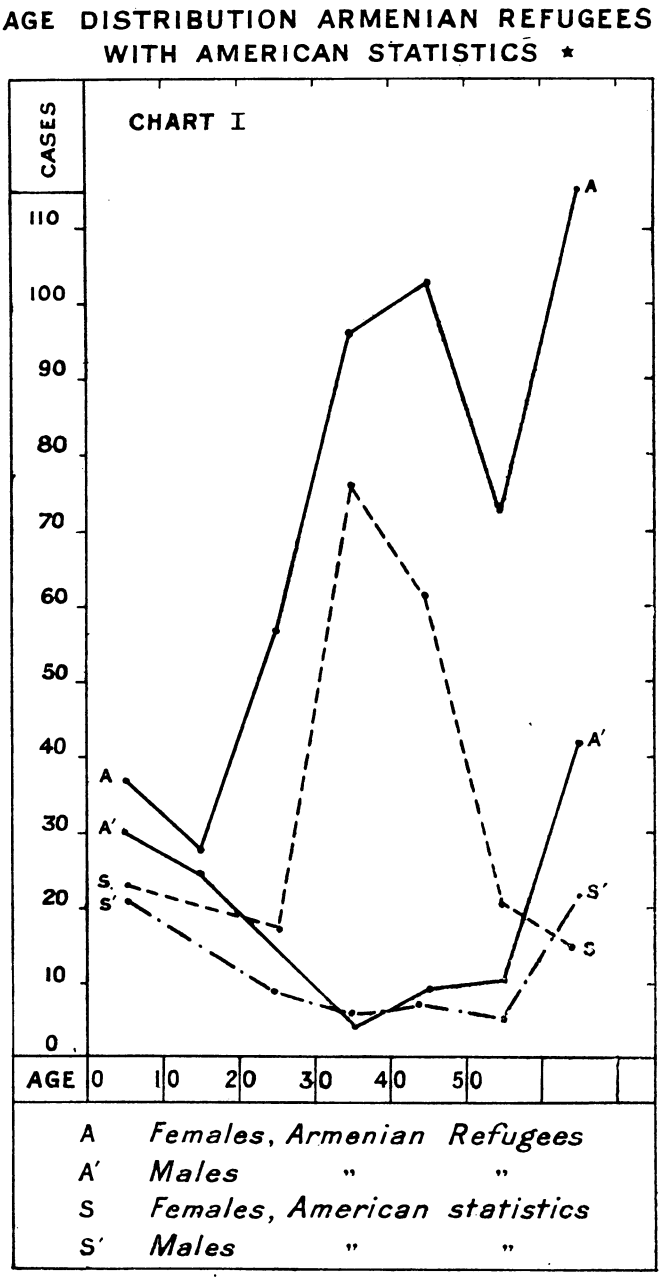
Considering that more than half of the protein value is derived from other sources than bread compared with only 25 % in the old diet, the age-distribution of the protein would have been sufficient.

This diet was in force for two months. Unfortunately, owing to national or other prejudices, the bean ration was disliked and the following diets (8 and 9) were introduced in February 1917.

The two diets were eminently successful.

Diet 8 was general for all adults in good health and not having suffered from pellagra. It is not perhaps surprising that no cases of pellagra occurred on this diet if it be considered that the persons receiving it had escaped the disease in the previous year when consuming the much lower diet then in force.

Diet 9 was introduced as an anti-pellagrous diet and was given to all persons who had suffered from pellagra in the previous year or who showed symptoms which might in any way have been connected with the disease. It is a striking testimony to the curative effect of a diet of high protein value that the last case of pellagra left hospital in June and although some rare relapses occurred in 1917 and 1918, the disease practically ceased to exist in the camp. This diet may in fact be said to be a true anti-pellagrous diet



* *1st Progress Report, Thompson McFadden Commission, p.32.*

Chart 1. Age and sex distribution of pellagra. Armenian refugee epidemic with comparative figures of the Spartenburg cases recorded in the Thompson McFadden Commission Report.

Diet 8.

Table VII.

Armenian Refugees' Camp. Port Said.

Diet for healthy adults. February 1917.

Articles of diet	Daily amount in grammes	Gross protein	Available (nett) protein	Biological value of protein	Gross fat	Carbo-hydrates
Bread (wheaten)... ...	675	45	34	13·6	6·7	310
Meat (– bone)	42	8·4	8	8	2·1	—
Tripe or fish	60	10·5	9·6	9·6	3	—
Lentils	50	12	9·6	5·2	1	27·2
Rice	50	3·7	3·7	3	·2	38
Bourghoul	50	6	4·7	1·9	·9	34
Vegetables	150	2	1·5	·8	—	4·5
Oil...	20	—	—	—	20	—
Suet	10	—	—	—	7·5	—
Onions	15	·2	·18	·09	·03	·42
Cheese (skim-milk) ...	12	1·8	1·5	1·5	—	—
Olives	7	·08	·06	·03	1·4	·35
Halwa	7	·1	·07	·03	1·8	4·6
Sugar	20	—	—	—	—	20
Salt	15	—	—	—	—	—
		90·6	72·5	43·7	46·1	439

CALORIES: gross, 2693; available, 2513.

Diet 9.

Table VIII.

Armenian Refugees' Camp. Port Said.

Anti-pellagrous diet for sick or ill-nourished.

Articles of diet	Daily amount in grammes	Gross protein	Available (nett) protein	Biological value of protein	Gross fat	Carbo-hydrates
Bread (wheaten) ...	600	40	30	12	6	287·5
Meat (– bone)	42	8·4	8	8	2·1	—
Tripe or fish	60	10·5	9·6	9·6	3	—
Eggs (1)	40	4·5	4·4	4·4	4	—
Lentils	33·3	8	6·4	3·5	·7	18·2
Rice	33·3	2·8	2·2	2	·1	25·3
Bourghoul	33·3	4	3·2	1·3	·6	22
Vegetables	100	1·2	1	·5	—	3
Onions	15	·2	·18	·09	·13	·42
Butter	30	—	—	—	27	—
Oil...	15	—	—	—	15	—
Milk (buffalo)	350	19	17·5	17·5	28	14
Olives	7	·08	·06	·03	1·4	·35
Halwa	7	·1	·06	·03	1·8	4·6
Sugar	60	—	—	—	—	60
Jam	14	·5	·4	·2	—	8·4
		99·3	83·0	59·15	89·8	443

CALORIES: gross, 3143; available, 3002.

in that it not only prevents the occurrence of primary cases but is also sufficient to prevent relapses.

The diet (9) is drawn up on lines very similar to those of the various diets which have been found to be anti-pellagrous in the numerous orphanage and other institutional experiments which have been carried out by Goldberger and his co-workers (1915) and by Ridlon (1916) in the United States. It was

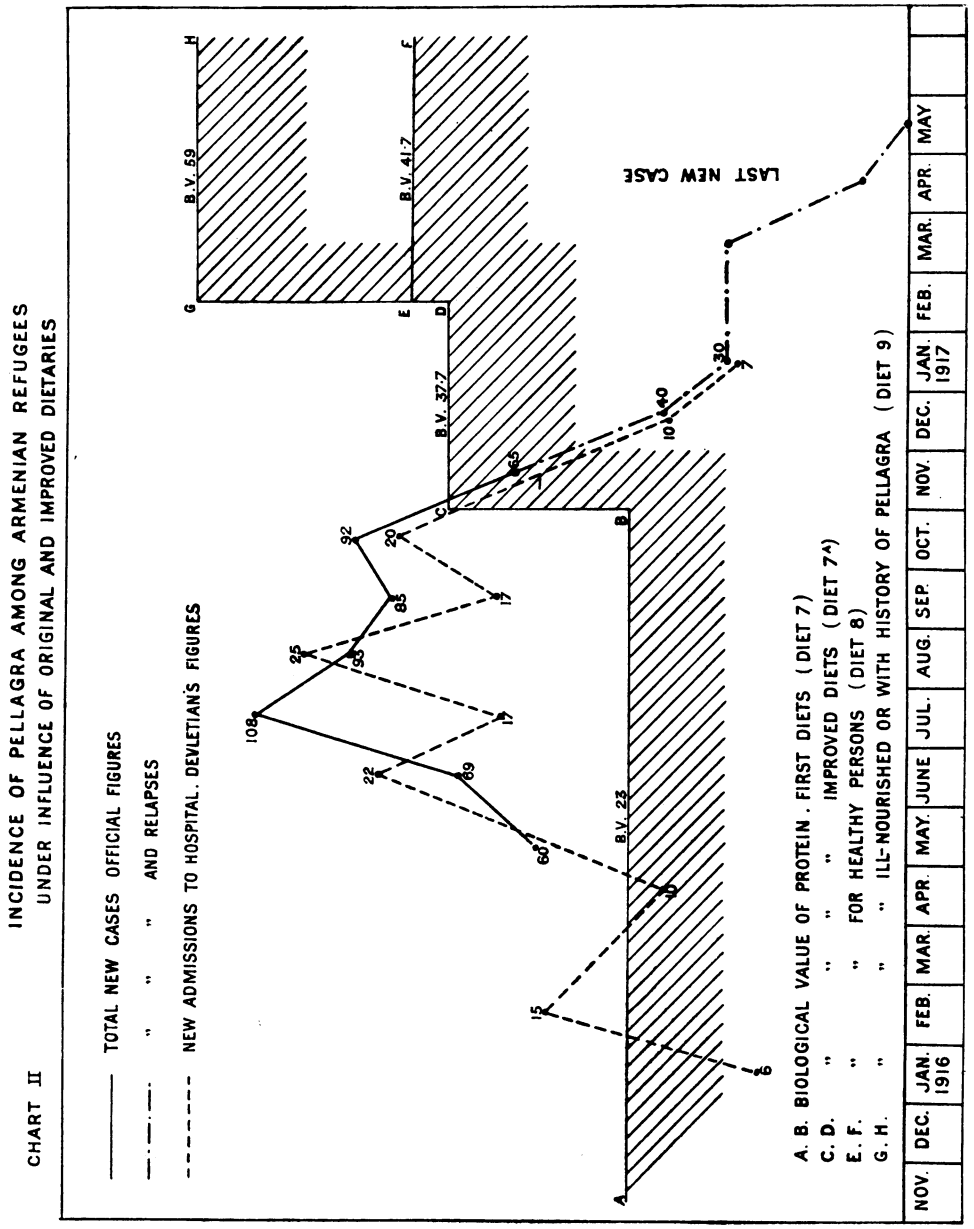


Chart 2. Relation of the biological value of the protein in diets 7, 7a, 8 and 9 to the monthly pellagra incidence in the Armenian refugee epidemic.

as successful as these latter, for although a few cases were seen during four months after its introduction, no cases of pellagra occurred after June 1917. It will no doubt always be found that a generous diet rich in readily assimilated proteins and in fats allowing therefore a large margin for the defective digestive powers of the pellagrous or persons susceptible to that disease, will prevent its appearance; it is however also probable that such cases would again relapse if placed on an ordinary diet which would be amply sufficient for normal individuals. Whether a diet as rich as this in proteins but containing only a small proportion of fats would be equally good there is no direct evidence to prove, all the anti-pellagrous diets employed being characterised not only by their richness in readily assimilated protein but also in animal fats. There is however evidence to show that diets in which the proteins are of fair biological value but the fats very small in amount are not pellagrous. Certain diets (Nos. 19, 21, Table XX) are given later as evidence of this.

The relations of the incidence of pellagra to the biological value of the protein in the above diets (7–9) is shown in Chart II constructed from the official figures of the total cases of pellagra known to have occurred in the camp from May 1916 when the disease was diagnosed until April 1917, when the last case entered hospital. For these figures the writer is indebted to Lt-Col. Lelean and Dr Devletian. In the Chart the monthly incidence is plotted against the biological value in protein of the diets consumed by the refugees during the period January 1916 to June 1917.

2. RANKIN FARM EXPERIMENT.

Diet 10.

The second diet which is known to have had a direct causative relation to pellagra is that administered in the experiment on eleven convicts by Goldberger and Wheeler (1915) at the farm of the Mississippi State Penitentiary, Jackson, Miss.

Goldberger gives the total quantities of cooked food consumed during one week (ending August 8th, 1915) by the experimental squad; from his figures an estimate has been made of the composition and the nutritive value of the mean daily diet as set out in the following table. Leguminous food and meat (except 4 oz. on one day in the week) were excluded.

It is not until the protein of this diet has been estimated on the basis of the biological value that the extreme deficiency of the protein is brought out quantitatively. The biological value is seen to be no more than 14·6 grammes daily. The body weights of the men varied from 56·4 to 86·4 kilos—average 67·7. The biological value of the protein absorbed daily appears to have averaged only ·215 gramme per kilo with a minimum in one man of ·17. The lowest of the five cases recorded by Chittenden (see p. 10) was ·4 in a man of 70 kilos. The energy value was probably sufficient for the type of

labour; the result cannot therefore be ascribed to deficiency in that respect as might have been suggested from an examination of the Refugee diet (7).

Table IX.

Mean composition of Diet 10. *Rankin Farm experiment.*

Articles of diet (1)	Daily amount in grammes	Gross protein	Available protein (2)	Biological value of protein (3)	Gross fat	Carbo-hydrate
Butter-milk	10·2	·306	·306	·306	·05	·49
Corn-meal	212	19·5	15·6	4·6	4	160
Grits	35·3	3·3	2·7	·8	·25	28
Corn-starch	19·7	—	—	—	—	17·7
Wheat-flour	134·2	14·5	11·5	4·6	1·47	100
Rice	22·9	1·83	1·5	1·4	·06	18
Cane syrup	37·3	·18	·17	·8	—	28·2
Cane sugar	62·4	—	—	—	—	62·4
Sweet potatoes	97·3	1·75	1·4	1·1	·68	26·6
Turnip	6·3	·08	·06	·03	·01	·51
Turnip-greens	22·3	·94	·7	·35	·13	1·4
Cabbage	34·3	·54	·4	·2	·1	1·9
Collards	17·8	·8	·6	·3	·1	1·1
Pork fat	101·4	·09	·09	·09	101·2	—
	813·4	43·82	35·0	14·6	108·0	446·3

Gross calorie value, 3014; available calorie value (fats and carbohydrates -5%), 2836.

(1) The mean daily amounts are estimated from Tables XVIII–XXIV given in the detailed account of the Rankin Farm Experiment, Goldberger and Wheeler (1920), the estimate of gross nutritive value from Table of Constitution (Appendix C, p. 92). The figures agree closely with those given in Goldberger and Wheeler's Table XXV (p. 29).

(2) Estimated from Rubner's (1912) figures of absorbability of similar foodstuffs.

(3) From K. Thomas' figures: corn products protein, $\frac{1}{3{\cdot}4}$; wheat, $\frac{1}{2{\cdot}5}$; rice, $\frac{1}{1{\cdot}1}$; potato, $\frac{1}{1{\cdot}26}$; animal protein, $\frac{1}{1}$; other proteins assumed, $\frac{1}{2}$.

In this paper as originally compiled the writer made an estimate of the probable value of the Rankin Farm diet from a brief description of the food given by Goldberger and Wheeler in an earlier publication (1915). This estimate in which the gross protein appeared to be 65 and biological value 25·5 has been corrected on the basis of Goldberger's recent paper (1920), the gross protein being 43·8 and the biological value being no more than 14·5. (Sullivan's estimate (1920) from analysis of the food gives a somewhat lower value for the gross protein.)

3. INCIDENCE AMONG ITALIAN PEASANTS.

Diet 11.

A. Marie (*l.c.* pp. 316–319) gives details regarding the food of Italian peasants in pellagrous districts. The only one of these diets of which the details are sufficiently precise for analysis is that on page 318, the average daily diet of a hired peasant of the province of Ferrara; it is as follows: A. being the average for eight months of the year when labour is said to be light. B. for four months when labour is more arduous.

Table X.

Average daily food (Diet 11), hired peasant, Ferrara district, Italy.

Estimated from details by A. Marie. Lavinder's Translation, pp. 317–18.

A. Eight months of year Article of food	Amount in grammes	Gross protein	Available (nett) protein	Biological value of protein	Gross fat	Carbo-hydrates
Polenta (from maize meal)	1000	24	20	5·8	4·3	260
Egg (2 each week) ...	12	1·5	1·5	1·5	1·2	—
Onion	30	·5	·4	·2	·5	1·2
Wheat-bread	50	3·6	2·8	1·12	·5	23·5
Maccaroni	50	6·7	5·4	2·16	·4	37
Meat (pork)	10	1·8	1·7	1·7	2	—
Cheese	5	1·8	1·8	1·8	·9	—
Beans	150	34	23·5	13·1	3	81
Fish	20	3	3	3	1	—
		76·9	60·1	30·4	13·8	402·7

CALORIES: gross, 2174; available (nett), 2020.

Table XI.

Average daily food, hired peasant, Ferrara district, Italy.

B. Four months of year. Article of food.	Amount in grammes	Gross protein	Available (nett) protein	Biological value of protein	Gross fat	Carbo-hydrates
Polenta	160	3·8	3·2	·9	·6	40
Egg	30	3·9	3·9	3·9	3	—
Onions	60	1	·8	·4	1	3
Wheat-bread	400	27	20	8	4	190
Maccaroni	200	26·8	21·5	8·6	1·8	148
Meat (pork)	60	10·8	10·3	10·3	12	—
Cheese	20	7·4	7·2	7·2	2·8	—
Beans	40	9	6·4	3·5	·8	22
		89·7	73·2	43	24·4	403

CALORIES: gross, 2333; available, 2164.

Note. Polenta is a form of thick gruel or porridge made by mixing maize meal with about twice its weight of boiling water the meal being scattered into the water while boiling. The mixture contains about one-third its weight of maize-meal. The beans are assumed to be the ordinary variety (*Vicia faba*) with which the writer is familiar as a food material in Egypt, having a somewhat higher protein content than many other leguminous foods.

It is also assumed that the weight given is that of the dry uncooked beans. If as is possible the weight represents that of a dish of cooked beans the nutritive value would be $\frac{1}{3}$ of that given.

It is probable that the protein of the pork is over-estimated and the fat under-estimated. The value therefore given for the protein of the diet is likely to be a maximum.

The protein value of the diet is low, the fat content exceptionally small and the energy value considerably below that for persons doing even light labour.

In diet B the protein value is probably sufficient; the energy and fat values are still low. The comparatively high protein value of diet B would not prevent the deleterious effect of the deficiency of diet A, extending as

it does continuously over eight months of the year. The low energy value in A would accentuate the ill-effect of the deficient protein.

It will be remarked that the biological value of the protein in the Ferrara peasant diet (diet 11) is considerably greater than in the case of diets 7 and 10, the incidence of pellagra was however much less. According to the census of pellagrins 1905 (Marie, *l.c.* p. 60) there were in the Compartment of Emilia of which Ferrara is a province 3357 known cases. The population of the whole Compartment was in 1901, 2,477,697 (Ashby, 1911), giving an incidence rate of about ·14 % for the whole population, it may be safely assumed that the peasants in the province of Ferrara were not affected to the extent of more than 3 %, while the population subjected to diet 7 (Armenian refugees) were affected to the extent of approximately 20 % and in the case of diet 10 (American convicts) at least 54, possibly 91 %.

4. INDIVIDUAL CASES AMONG EGYPTIAN FELLAHIN.

Diets 1–6.

Three cases of pellagra have recently come under the writer's notice whose diet it was possible to verify, from villages near his house in the neighbourhood of Cairo.

(*a*) A boy of 11 employed on light work in the garden, receiving monthly wages, and getting his food from his home.

The family is very poor, the father making a precarious living as a fisherman. Early in March 1917, the boy complained of pain in the abdomen, he was treated with a small dose of calomel and castor oil, the appearance was that of ill-health, but no special significance was attached to the condition. On the 24th of March a distinct pellagrous rash was noticed in the usual situations, neck, forehead, wrists, hands and legs (from half-way between knee and ankles), the parts uncovered by clothing. From the 31st March onwards, the boy was given daily 240 c.c. of milk mixed with one egg (40 g.) giving a total addition to the diet of 14·5 grammes of animal protein.

It is perhaps interesting to note that there was no instinctive liking for this nutritious mixture; the boy had in fact to be watched while drinking it, otherwise he gave it to one of the dogs and on one occasion was caught pouring it away and covering up the traces with sand although the mixture was slightly sweetened by the addition of about 5 g. of sugar. The patient was told that the mixture was only milk and egg with no medicine in it but he was probably suspicious[1]. He was purposely not told why he was being fed or that he had any malady, as it was feared that this might lead to his altering his food in some other direction.

No other change was made in the habits of work or food, he continued to lead exactly the same life as before.

The diet of this boy consisted of five loaves of dura (maize) bread daily

[1] Dr Dudgeon states that pellagrins generally dislike liquid nourishment and do not do well on it, this is of interest in connection with the defective gastric secretion.

with an occasional onion and some salt at midday, some raw or boiled green vegetables at supper and about twice a week some boiled beans, probably about 60 g. of beans on each occasion (60 g. being taken as the amount as this is about the quantity in an ordinary portion of "ful mademmis").

The five loaves together weighed 450 g. The loaves vary considerably in weight, they are roughly circular and about 10 inches in diameter, and of the thickness of stiff cardboard.

The bread is made from very soft unleavened dough, after baking it is crisp and biscuit-like in consistence.

A specimen of the bread was analysed, it contained 21 % of water, the dry residue containing 7·8 % of protein estimated from the total nitrogen. The bread therefore contained 6·24 % of protein; assuming that 80 % of this would be absorbed and be available for nutrition the available protein was 5 % = 22·5 g. daily, having a biological value of 6·7. Adding the protein from beans and vegetables, the total available protein was 29 g., having a biological value of 10·4 g. daily. The milk and egg raised the available protein to 29 + 14·5 = 43·5 and the biological value to 24·9 g. daily, an amount sufficient for a boy of eleven.

The rash continued to increase slightly for two weeks, it then began rapidly to improve, disappearing first from the face and neck; traces could still be seen on the wrists as late as the 7th of May.

The boy's general condition and appearance improved coincidently.

This case has been recorded because it seemed to be of interest to observe whether the mere raising of the protein value to a point just above the minimum by the addition of a fairly accurately known daily quantity without the variation of any other factor would be curative. In most patients who come under treatment not only is the addition to the protein much more considerable than in this case, but the patient gets rest from work and is usually removed from the direct action of sunlight.

(*b*) The second case is that of a boy aged 12 living in great poverty, the father having died and the mother married again. The boy lives in the house of an uncle. His food consists of five loaves daily, similar to the type mentioned above, with a certain amount of green vegetables and about 25 g. of native cheese daily. The total available protein was approximately 30 g. daily, having a biological value of 11·7 g. The rash was very marked on the exposed regions, the "Casal collar" being particularly well seen. There was some enteritis. The boy was sent to hospital where he was treated, being put on the ordinary diet (diet 18) of the hospital. He was found to be suffering from ankylostomiasis for which he was treated in the usual manner with eucalyptus oil. On May the 25th the rash had greatly improved, the general condition was obviously better.

(*c*) Youth aged 15 to 16 years. A very severe case, the rash being unusually intense. Considerable mental hebetude. Stated that he had not been able

to work for some time. His food consisted of six dura loaves daily with some green vegetables in the evening.

The estimated available protein 31 g. having a biological value of 10 g.

This case was admitted to Kaar-el-Aini Hospital on the same date as case (*b*) under the care of Dr S. Asmi. This patient was also treated for ankylostomiasis.

The urine in cases (*b*) and (*c*) contained a trace of albumin, but in neither of the three was indican present.

(*Note.*—There is some doubt as to the last point.)

The last two cases are probably examples of a not uncommon condition of poverty, among the poorest class of the fellahin, namely those not in constant employ on some landowner's estate but working for a precarious daily wage. The exceptionally high price of dura and the almost prohibitive price of wheat (to the poor) no doubt make the conditions particularly hard this year (1917).

An adult fellah would eat 18 or more of the loaves mentioned daily, approximate weight 1600 g. containing 80 g. available protein, having a biological value of 25 g.; in addition he would eat various vegetables, some cheese or olives, occasionally beans or lentils, possibly raising the biological value of the protein to 35 g.; it will be seen therefore that even under normal conditions a large part of the peasant population of Egypt must be living on the border-line of protein deficiency.

5. INCIDENCE AMONG TURKISH PRISONERS OF WAR IN EGYPT.

Diets 12 and 13.

These diets (Tables XII and XIII), under the influence of which a large number of cases of pellagra occurred, are of considerable interest. Diet 12 was provided for a large group (A) of men on no labour. Diet 13 for a similar group (B) with moderate labour.

H. E. Roaf and the writer investigated the metabolism on this diet in a group of five men during a period of five days with the result that it was found that the percentage loss of protein in the alimentary tract was 33 %, and of fat, 19·5 %, the available nutritive value being thus reduced to the following:

Available protein, 60. B.V., 33·5. Fat, 21·8. Calories, 2545.

This was ascribed to the coarse nature of the bread and the fact that the beans were insufficiently cooked, hard and indigestible.

With reference to a diet originally supplied to these prisoners, almost identical with this, the writer reported as follows to the D.M.S. Egyptian Expeditionary Force in April 1917:

"This diet is sufficient in calorie value for men doing very light labour. The biological value of the protein is however rather low. The minimum allowable for this factor is said to be 30, but it is wise to allow a fair margin for individual idiosyncrasies and it would probably be advisable to take 40 as the minimum.

Table XII.

Turkish Prisoners of War Diets. Egypt, 1918.

Group A. Non-labour.

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates
Bread, wheaten (10 % millet)... ...	785	52·5	39·2	15·6	7·8	370
Meat (with bone) ...	31·2	4·8	4·5	4·5	1·2	—
Oil...	15·4	—	—	—	15·4	—
Cheese (skim-milk) ...	27	5·9	5·6	5·6	·3	—
Sugar	15·4	—	—	—	—	15·4
Rice	94	7·2	6·1	5·6	·3	72
Lentils or beans	62·5	17	11·8	6·3	1·2	34
Fresh vegetables... ...	140	1·7	1·4	·7	—	4·2
Onions	15·4	·2	·14	·07	·27	·75
Dates	27	·45	·4	2	·5	15·5
Salt	15·4	—	—	—	—	—
TOTAL (normal factor of protein availability)		89·7	69	38·6	27	511·8
	CALORIES: gross, 2825; available, 2629.					
TOTAL (protein loss* 33 %, fat 19·5 %):			60	33·5	21·8	511·8
	CALORIES: available, 2545.					

* From estimates of faecal N and fat, by H. E. Roaf and W. H. Wilson (1918).

Diet 13. Moderate labour. Group B.

Table XIII.

Turkish Prisoners of War diets. Egypt, 1918.

Group B. Labour.

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates
Bread (wheaten, 10 % millet)... ...	906	60·5	45·3	18·1	9	430
Meat + bone	114	18	17·1	17·1	4·5	—
Oil...	14·2	—	—	—	14·2	—
Sugar	28·4	—	—	—	—	28·4
Rice	85	6·6	5·6	5·2	·3	65
Lentils or beans	65	17·5	12·3	6·8	1·2	35·5
Fresh vegetables... ...	114	1·3	1·1	·5	—	3·4
Onions	14·2	·17	·13	·06	·25	·7
Dates	56·7	·9	·8	·4	1	31
Salt	14·2	—	—	—	—	—
TOTAL (normal factor of protein availability)		105	82·3	48·2	30·5	594
	CALORIES: gross, 3265; available, 2954.					
TOTAL (protein loss, 33 %; fat, 19·5):			70	40·9	24·5	
	CALORIES: available, 2849.					
Reduced value*	—	95·5	63	36·8	22·5	535
	CALORIES: gross, 2903; available, 2650.					

* For some months this diet was reduced by approximately 10 %.

"I am inclined to think that the capacity of a diet for maintaining health, particularly in regard to pellagra, is measured by this factor. If this view be correct, it would be well to raise the protein value by the addition of some extra beans or lentils. It has to be remembered that many of these men arrived in this country after a period of semi-starvation in the Hedjaz, and that to build up the body protein under such circumstances requires a diet considerably richer in protein than would suffice under ordinary circumstances; it is also to be noted that some of these men have previously suffered from pellagra, and that for such persons a diet richer in protein is probably required than would be the case for normal individuals."

The inference drawn appears to have been justified by the occurrence of a considerable outbreak among the men receiving the diet described above.

The total nitrogen elimination was examined in the urine of five men on this diet during a period of five days; the results showed that the waste of protein in the intestine was even more marked than in the first case; the absolute percentage loss could however not be determined. Assuming that this was the same as in the first case the available nutritive value of the diet was:

Available protein, 70; B.V., 40·9; fat, 24·5; cal., 2849.

During some months previous to the severest incidence of the disease, the value was still further reduced by 10 % owing to deficiencies in the supply. The nutritive value being during this time:

Protein (gr.), 95; protein (av.), 63; B.V., 36·8; fat, 22·5.
Carbohydrate, 535; calories (gr.), 2903; calories (av.), 2650.

The fact of special interest in regard to these two groups is that whereas both were rather heavily affected by pellagra there is no doubt that in the labour group the incidence was considerably greater than in group (A).

These diets are examples of ones having a protein value on the border line of sufficiency which were rendered absolutely deficient owing to the defective absorption brought about by faulty methods of preparation. (Diets 15 and 14, Tables XIV, XV.)

Note. An account of this epidemic has since been published by Boyd and Lelean (1918, 1920).

6. INCIDENCE OF PELLAGRA AMONG CONVICTS IN EGYPT.

Diets 14–15.

The following two diets have been in use for some years in the Egyptian convict prisons for long term prisoners:

(A) For hard labour (chiefly work in the stone quarries).
(B) For light and moderate labour (stone-breaking, building, gardening and industrial labour).

Neither (A) nor (B) contain any dura (maize) or maize product; there can be no doubt about this as the millet from which the bread is made is milled and the flour made into bread within the prison precincts.

These two diets are of interest as illustrating in the case of (A) a diet with a protein value considerably above the minimum requirement and a calorie

value below the energy requirements, the higher incidence of pellagra in (A) being due apparently to the secondary effect on the protein metabolism of heavy work on a deficient energy supply, bearing out the conclusion arrived at as regards the group of men on diet 13.

The hard labour diet (15) has the following composition:

Table XIV.

Prison dietaries. Tura.

No. III. Diet for hard labour. (Group A.)

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates	Salts
Millet bread	936	60	31·8	9·3	14	421	11·2
Meat (– bone)... ...	118·5	23·7	22·5	22·5	4·7	—	1·5
Lentils	56·2	35·5	24·8	13·7	2·6	71·2	4
Beans	75						
Rice	37·4	2·87	2·4	2·2	·1	28·4	·1
Onions	12·5	·2	·2	·1	·2	·6	·1
Fresh vegetables ...	100	1·2	1	·5	—	3	1
Oil	25	—	—	—	25	—	—
Salt	12·5	—	—	—	—	—	12·5
		123·5	82·7	48·3	46·6	524	30·5

CALORIES: gross, 3195; available, 2920.

The light labour diet (14) is as follows:

Table XV.

Prison dietaries. Tura.

No. II. Diet for light labour. (Group B.)

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates	Salts
Millet bread	936	60	31·8	9·3	14	421	11·2
Meat (– bone)... ...	31·2	6·3	6	6	1·2	—	·3
Lentils	75	40·5	28·5	15·7	4	81·6	4·5
Beans	75						
Rice	31·2	2·4	2	1·9	·1	22·6	·1
Onions	12·5	·2	·2	·1	·2	·6	·1
Fresh vegetables ...	100	1·2	1	·5	—	3	1
Oil	25	—	—	—	25	—	—
Salt	12·5	—	—	—	—	—	12·5
		110·6	69·5	33·5	43·5	528·8	29·8

CALORIES: gross, 3062; available, 2854.

STATISTICS OF PELLAGRA AT TURA.

In regard to this question the pellagra statistics for the year 1917 of the Egyptian Government convict establishment at Tura are particularly instructive.

The number of prisoners varies annually, being usually rather over 2000. For purposes of labour, the convicts are divided into three classes: (Class I) light labour, (Class II) moderate labour, (Class III) hard labour, the energy value in kilogramme metres being in the three classes respectively approximately 60,000, 80,000 and 140,000. A description of the types of labour and the basis upon which the above estimate has been made will be found in the report of a committee appointed in 1914 to consider prison diets. (Interim Report of the Prisons Diets Committee, 1917, Appendix VI, pp. 29 to 39.) Prisoners on hard labour, receive diet 15 (Table XIV), on moderate and light labour diet 14 (Table XV).

The prisoners when first incarcerated are in Class III with hard labour, passing in course of years first to Class II, eventually to Class I. Men, however, who are not thought to be medically fit for hard labour may be placed at once or at any time on moderate or light labour. It would therefore have been expected that pellagra would have been least prevalent among the most healthy group. The reverse is the case.

The convicts properly belonging to Class III form 60 % of the inmates, 40 % belonging to Class II and I. After the transfer of unfit men from Class III to the lighter forms of labour, the hard labour group form only 35 % of the whole. The following table gives the distribution of labour and the incidence of pellagra:

Table XVI.

Class of labour	III	II	I	Total
Number of men	720	870	470	2060
Per cent. of total number ...	35	42	23	
Number of cases...	44	33	15	92
Per cent. of total cases	48	35·5	16·5	
Per cent. of men (incidence) ...	6·4	3·8	3·2	
Per cent. incidence after deducting relapses from 1916 (estimated)	4·4	2·8	1·5	

Of the cases among convicts in Classes II and I, 18 out of 33 had been transferred from Class III, as medically unfit, in the former, 10 out of the 15 in the latter, it results therefore that of men on moderate labour, who might be considered physically fit, only 15 contracted pellagra, while of physically fit men on light labour only 5 were affected.

It will be seen that convicts on hard labour receiving a diet having the available calorie value of 2920 (gross 3195) and a protein biological value of 48·5 were affected to the extent of 4·4 %; men on moderate labour on a diet having an available calorie value of 2854 (gross 3062) and protein biological value of 33·5, to the extent of 2·8 %; and men on light labour with the same diet as the last group, to the extent of only 1·5 %.

The figures are perhaps more surprising if it is remembered that the convicts of Class III may be regarded as selected for physical fitness, nearly two-thirds of Class II and a smaller proportion of Class I consisting of men found to be unfit for hard labour.

The incidence of pellagra among these three groups seems thus to be definitely associated with the relation between the energy requirement and the energy intake[1].

Diet 16.

This diet is given to pellagrous cases occurring among the convicts of all classes, the men *being taken off labour* and retained under supervision in a prison ward set apart for such cases; the seriously ill only being admitted to hospital.

The composition of the diet is as follows:

Table XVII.

Prison dietaries. Tura.

Hospital diet: with extra half-loaf of bread. Diet for pellagrous cases.

Article of diet	Daily amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates	Salts
Bread (wheaten) two loaves	624	47·2	35·2	14	7	334·5	8·4
Mutton (– bone) ...	94	16·9	16·1	16·1	5·6	—	1·8
Milk (Buffalo)	337	13·5	13·3	13·3	26	18	2·7
Lentils	62·5	17·2	12	6·7	1·2	34	1·7
Rice	62·5	4·8	4·1	3·7	·2	47	·2
Onions	7·5	·45	·34	·17	·67	1·8	·2
Fresh vegetables ...	156	1·8	1·6	·8	—	4·6	1·5
Oil	18·5	—	—	—	18·5	—	—
Salt	12·5	—	—	—	—	—	12·5
		101·8	82·7	54·7	59·3	440	29

CALORIES: gross, 2871; available, 2695.

On this diet the patients in most cases recover rapidly.

It will be noted that the biological value of the protein is relatively high, 54·7 as compared to 33·5 for the light labour and 48·5 for the hard labour diet; and that the protein is also in a more digestible form, mainly owing to the bread being of wheaten flour in the place of millet. The calorie value is 160 below that of (B) but is amply sufficient for men on no labour.

[1] I have to thank Dr Kirton, P.M.O., Prisons Department, and Ali Bey, P.M.O., Tura Prisons, for the list of cases, and Randall Bey, Governor of Tura, for the figures upon which the above estimates are based.

Diet 15 for hard labour is deficient to the extent of not less than 200 calories (*vide* Prisons Diets Report on the estimated energy requirement).

7. OCCURRENCE OF INTRA-MURAL CASES OF PELLAGRA AMONG AN ASYLUM COMMUNITY ON A DIET OF MEDIUM VALUE NORMALLY CURATIVE OF THE DISEASE.

Diet 17.

The following is the ordinary diet provided at the Egyptian Government Asylum for the Insane at Abassia:

Table XVIII.

Mean daily ordinary diet, Abassia Asylum.

Article of diet	Amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates	Salts
Bread (wheaten) ...	562	37·6	28	11·2 (?8·2)	5·6	270	5·6
Meat with bone ...	150	21	20	20	5·2	—	1·3
Vegetables and salad ...	250	3	2·5	1·2	—	7·5	3
Onions	50	·6	·4	·2	·9	2·5	·5
Rice	50	3·8	3·2	3	·2	38	·2
Lentils or beans ...	100	27	19	10·5	2	54	3
Flour	17	1·4	1·1	·5	·3	11·4	·2
Wheat	21	2·5	1·9	·8	·35	13·8	·25
Milk (Buffalo)	50	2·1	2	2	4	2·4	·4
Sugar	29	—	—	—	—	29	—
Treacle	21	—	—	—	—	14	·6
Margarine (veg. fats) ...	25	—	—	—	45	—	—
Oil	20						
Salt	18	—	—	—	—	—	18
Pepper	·25	—	—	—	—	—	—
		99	78·1	49·4 (?46·4)	63·5	442·6	31·8

CALORIES: gross, 2910; available, 2720.

Dr John Warnock, C.M.G. (Director of the Lunacy Division, Egypt), informs me that of the large number of cases of pellagrous insanity which are admitted annually to the asylum, the majority of cases of recent origin rapidly recover. Until lately this diet appeared to be definitely anti-pellagrous in the sense that although annual relapses were not uncommonly seen among inmates admitted with the disease, intra-mural cases were only seen with great rarity.

During the past eight months (1916–1917) however twelve inmates have become affected in whom no previous symptoms have been noted and none of whom have been less than four years in the asylum. These cases were admitted with insanity not of the pellagrous type. Dr Warnock was good enough to allow the writer to see these patients. The cutaneous symptoms were in some cases exceptionally well marked; there was little wasting, some individuals being particularly well nourished. No other symptoms were observed.

The only known change in the dietary during the past year (1917) is that whereas formerly the bread was baked in the asylum from tested wheat flour,

about a year ago the bread was put out to contract and it is highly probable that owing to the present high price of wheat, the bread may have been made from flour adulterated with maize flour. The writer examined a specimen of the bread, two loaves were found to be 8 % below the contract weight, to contain an excess of water (42 %) and to be poor in protein, the content being 5·8 % gross = 4·4 % available (nett) protein. The bread had the appearance and smell of a sample of bread made from a mixture of wheat and maize flour in equal parts. It is probable therefore that the bread contained maize flour possibly to the extent of 50 %. A mixture in this proportion is very commonly used for making bread, especially among the labouring classes in towns. Taking the various deficiencies into account and assuming the presence of 50 % maize flour, the biological value of the protein of the whole diet would be reduced to 46·4 in place of 49.

As mentioneda bove, intra-mural cases of this kind have occurred occasionally in former years, when the dietary is known to have contained no dura flour or other maize product.

It is difficult at first sight on the basis of the composition of the diet to explain these cases. It is true that the biological value is not much above the border line, it seems however unlikely that the protein was insufficient to maintain N equilibrium in normal individuals provided these patients, who were all of them women, consumed the diet as laid down in the diet sheet.

The diet is obviously sufficient in calorie value for persons doing no work as at Abassia, it is fairly well balanced, both the protein value and fat are not too low and yet a seemingly primary pellagra occurs.

Unfortunately, as both Dr Warnock and Dr Dudgeon (Director of Khanka Asylum) point out, it is difficult to draw any conclusion from a knowledge of the ration scale laid down in an asylum; it is impossible, especially in the melancholic type of insanity common among the pellagrous, to be sure that the patients eat the food provided, in many cases almost certainly they do not, they may suffer from a lack of appetite or the food may be stolen by another patient.

It is not difficult to imagine that where, as happens in many of the insane, an apathetic condition or a distaste for food leads to a considerable part of the food being left unconsumed, a disease due to dietetic deficiency might arise just as it would in persons, who, through poverty, were unable to provide themselves with sufficient food.

In regard to such cases, Goldberger (1914, Reprint 203) quotes Motley (Georgia State Sanatorium) as having seen pellagra in inmates who had been for ten years in the institution, also Herrington (State Hospital for the Insane, Miss.) as recording cases, one after 15, another after 20 years' residence. Both these observers state that no case has ever been seen in an attendant, although in most cases they receive exactly the same rations as the patients, many of them sleeping and living in the same wards as the patients, the only difference being that they are able to purchase additional food if they wish to do so.

Dr Dudgeon (Director of Khanka Asylum), who has a large experience of pellagrous insanity, states that in his opinion, such cases of apparently intra-mural origin are in reality relapses, and that pellagra does not arise "*de novo*" in properly fed persons. He believes that "once a pellagrin always a pellagrin" and that a relapse may occur after years of freedom from the disease. As shown however by Goldberger and his co-workers, referred to above, the seasonal reappearance of pellagra in institutional cases is almost entirely prevented by a suitable diet.

There seems to be little doubt that in persons who have suffered for long or repeatedly from pellagra some permanent damage to the digestive functions results which renders necessary a higher level of protein intake than is the case in normal individuals; to this cause must be ascribed the apparent deficiency of the Abassia ordinary diet.

The possibility of the existence of three etiological types of pellagra will be referred to later.

8. A DIET OF MEDIUM VALUE USED SUCCESSFULLY IN THE TREATMENT OF PELLAGRA.

Diet 18.

The following may be recorded as an example of a diet of relatively low calorie and gross protein value which is known to be curative of the disease.

In the year 1898 F. M. Sandwith and the writer drew up a diet which has been in use since that date as the ordinary diet at Kasr-el-Aini Hospital, Cairo. It is as follows:

Table XIX.

Egyptian Government Hospital, Kasr-el-Aini. Ordinary diet.

Article of diet	Amount in grammes	Gross protein	Available protein	Biological value of protein	Fat	Carbo-hydrates	Salts
Bread (wheaten) ...	600	40·2	30	12	6	292·5	7·2
Meat without bone ...	105	21	20	20	5·2	—	1·2
Milk (buffalo)	200	8·3	8	8	15·8	9·6	1·6
Fresh vegetables ...	120	1·5	1·2	·6	—	3·6	1·2
Onion	30	·4	·3	·15	·6	1·2	·3
Melted butter (Semn)	20	—	—	—	19	—	—
Ground lentils... ...	50	13·5	9·7	5·3	1	27	1
Rice	75	5·8	4·8	4·5	·3	57	·3
Sugar	30	—	—	—	—	30	—
Salt	20	—	—	—	—	—	20
Pepper...	·25	—	—	—	—	—	—
		90·7	74	50·6	48	421	33

CALORIES: gross, 2631; available, 2475.

Pellagrous patients recover satisfactorily on this diet with no other special treatment[1], and if it be remembered that mild cases do not enter hospital,

[1] Those familiar with pellagra will be aware that advanced cases are seen in which no treatment, dietetic or other, is of avail.

this fact would appear to be sufficient evidence that a diet not very greatly in excess of the physiological minimum requirements supplies the material to the deficiency of which the disease is due. The comparatively high biological value of the protein, considerably greater than that of the almost entirely vegetarian food of the bulk of the population, is noteworthy as bearing on the effect of this diet in pellagra.

9. NON-PELLAGROUS DIETS.

The following are some selected diets for comparison with the pellagrous diets discussed above. Some are of low calorie or fat value but all are above the minimum safe value (40) in protein if raised to the scale of a man of 70 kilogrammes body weight. (Diets 19 to 28, Table XX.)

Diet 19–20.

This diet is given by Greig (1912) as being the type of diet responsible for a disease of nutrition (epidemic dropsy). It is quoted as an example of low fat and calorie value:

Nutritive value (70 kilos scale): gross protein, 59; available protein, 50; B.V. 42·5; fat, 3·7; carbohydrate, 380; calories (gr.), 2371; calories (av.), 2240.

This is a common diet among the class of Bengali affected by epidemic dropsy. The average weight of the persons concerned is 55 kilos. The diet is remarkable for the extremely low fat value. It consists largely of rice, which accounts for the high value of the protein and in part for the poorness in fats; it is of interest to note that recently in Germany and elsewhere (Starling, 1918) dropsy has been recognised as resulting from a deficiency of fats in the food. Had pellagra been common among the population affected by this diet it seems improbable that it would not have been noted. Among the large number of cases of epidemic dropsy analysed by Greig (*l.c.*) cutaneous symptoms are mentioned in some cases, but the description of these in no way resembles that of the well-known symptoms of pellagra. The absence of pellagra is in this case probably related to the sufficient value of the protein in spite of the deficiency of the diet in other respects.

Diet 21–22.

Diet of Japanese prisoners (from Atwater and Milner, 1911). The composition is not given, but from the values in proximate principles this diet must have consisted to the extent of more than 90 % of rice with probably some leguminous food-stuff or possibly fish and a little added fat.

Protein (gr.), 43; fat, 6; carbohydrate, 444; calories (gr.), 2056.

(The value given in the table referred to is 2110.)

Assuming the above composition and the body-weight as 60 kilos, the value of the food for a man of 70 kilos would be:

Protein (gr.), 51·5; protein (av.), 46; B.V. 43·5(?); fat, 7; carbohydrate, 510; calories (gr.), 2361; calories (av.), 2118.

This diet is recorded chiefly as an example of one very poor in fat with a protein value above the minimum safe value. Beri-beri is known to occur among persons subject to such diets, but pellagra has not been recorded.

Diet 23.

Diet 23 shows the mean composition of six Indian gaol dietaries estimated from figures given by McKay (1908). The values are as follows:

Protein (gr.), 99·3; protein (av.), 76; B.V. 50; fat, 34; carbohydrate, 684; calories (gr.), 3523; calories (av.), 3270.

The diet is for industrial labour. It is given as an example of a dietary containing no animal protein or fat. The protein value is fairly high. The calorie value above the energy requirement. Pellagra has not been known to occur in these institutions.

Diet 24–25. English sewing girl.

The composition in proximate principles is given by Hutchison (1916) as an example of a subsistence diet common among the poorer working women of East London[1]. The actual value given is:

Protein (gr.), 52; fat, 33; carbohydrate, 316; calories, 1820.

A diet of almost exactly this composition would be obtained from the following quantities of ordinary cheap English foodstuffs:

Bread, $1\frac{1}{4}$ lb.; cheese, $\frac{3}{4}$ oz.; sugar, 1 oz.; milk, $3\frac{1}{2}$ oz.; dripping, $\frac{1}{2}$ oz.; smoked herring, 2 oz.

Nutritive value:

Protein (gr.), 53·8; protein (av.), 47; B.V. 34; fat, 33; carbohydrate, 316·5; calories (gr.), 1824; calories (av.), 1731.

Raised to adult male scale:

Protein (gr.), 72; protein (av.), 62; B.V. 45; fat, 44; carbohydrate, 422; calories (gr.), 2563; calories (av.), 2440.

The diet is quoted to show that in European countries, especially in England, owing to the considerable amount of cheap animal food eaten even by the poorest classes, the wages of this class were at the date when the statistics were compiled no more than 3*s*. 9*d*. weekly, the food has a sufficiently high protein value to make the occurrence of pellagra improbable.

Diets 26 and 27.

These are Scotch prison dietaries (1895) No. IV Rate for industrial labour, and No. VII Rate for hard labour. (Dunlop, 1899.)

Diet 26 is given for comparison with diet 14 with which it has a close resemblance in purpose and calorie value, the fat value however being not much more than half that of the Egyptian prison diet but the protein value considerably higher.

[1] The original statistics from which Hutchison's information is derived are not given.

Nutritive value of 26:

Protein (gr.), 117·7; protein (av.), 98; B.V. 55; fat, 24·3; carbohydrate, 517; calories (gr.), 3029; calories (av.), 2750.

Nutritive value of 27:

Protein (gr.), 124; protein (av.), 105; B.V. 66; fat, 54·6; carbohydrate, 654; calories (gr.), 3709; calories (av.), 3510.

The latter is given for comparison with diet 15 as an example of a hard labour diet of sufficient protein and calorie value.

Diet 28.

This diet shows the mean daily value of the writer's food for one week. It is given to illustrate the average composition of the food of an Englishman not restricted in his choice of food and leading a more or less sedentary life, in order to show, for comparison with the other diets given, what the biological value of the protein is in such a case.

Nutritive value:

Protein (gr.), 103; protein (av.), 91·6; B.V. 80; fat, 104; carbohydrate 300; calories (gr.), 2681; calories (av.), 2593.

RÉSUMÉ OF DEDUCTIONS FROM TABLE XX

The figure 40 for biological value of the protein has been taken as the dividing line between diets which are primarily pellagrous and those which may be pellagrous relative to other causes than deficiency in the intake. Diets 1, 2, 3 (4), 7, 10, 11, 12, 13 and 14 belong to this group.

In diet 15 the protein value is above 40, the deficiency in this case being secondary; many of the recipients being unable to maintain N equilibrium under conditions of hard labour with a deficient energy intake. The effect of diet 13 appears to have been aggravated by the same condition.

Diet 17. The Asylum Diet. The deficiency may probably be traced to the existence of chronic digestive disturbances common in pellagrous subjects (of which probably achlorhydria, leading to defective utilisation and bacterial destruction, is the most important), the deficiency being secondary to the alimentary defect. Such persons clearly require a higher protein intake than the normal.

12 and 13 are examples of border-line diets as regards protein intake rendered absolutely deficient by the indigestible nature of the food due chiefly to defective preparation.

In 14 and 15, the gross protein is fairly high. The deficiency being secondary to (*a*) the defective utilisation of millet protein, (*b*) the low biological value of protein of this type.

6, 8, 9, 16 and 18 are curative diets. 6 being the diet on which case (*a*) recovered without any change in other conditions or work: the energy value of this diet is high.

8 is a non-pellagrous diet for normal men. 16 curative for groups on diets 14 and 15 with rest from labour.

Diet 9 may be regarded as certainly anti-pellagrous in the sense that it was not only sufficient to cure pellagra but was sufficient to prevent the occurrence of the disease in susceptible persons of the group on diet 7.

DESCRIPTION OF CHART III.

Chart III is drawn from the figures given in Table XX, the diets being given a reference number to their order in that table.

The diets are arranged from left to right in the order of their gradually decreasing protein value.

It is desired to show by this chart in a graphic manner: (*a*) that the only diet factor which correlates closely with the incidence of pellagra is the biological value of the protein; (*b*) that the

Table XX. *General Table of Diets described in Part I.*

Communities receiving pellagrous or non-pellagrous diets	Incidence of pellagra	Gross protein	Available protein	Biological value of protein	Protein from animal sources	Fat	Fat from animal sources	Carbo-hydrate	Available calories	Gross calories
1. Case *c*, boy of 14	+ +	35	29	8·5	0	10·5	0	350	1570	1667
2. „ *b*, boy of 13	+	37	30	11·7	0	12	0	305	1488	1584
3. „ *a*, boy of 11–12	+	37	29	10·4	0	10	0	390	1813	1926
4. „ ÷ 0·6 to adult male scale	+	61·6	48·3	16·7	0	17	0	650	3021	3210
5. „ + milk and eggs (actual)		52	43	24·8	14·5	28	18	402	2091	2291
6. „ ÷ 0·6 to adult scale		86·6	71·6	41·3	24	46·6	30	670	3485	3735
7. Refugees' Camp at Port Said, May 1916	+ + +	64	51·5	23	4	21·6	3·4	430	2160	2280
8. „ „ „ adults, healthy, February 1917 ...		90·6	72·5	43·7	19	46·1	11	439	2513	2693
9. „ „ „ „ anti-pellagrous, Febr. 1917		99·3	83	59·1	39·5	89·1	64	443	3002	3143
10. Rankin Farm, Experiment	+ + +	43·8	35	14·6	·4	108	101·2	446	2836	3014
11. Italian peasant (Ferrara Province)	+	76·9	59·6	30·4	7	13·3	5·1	408·7	2047	2194
12. Pellagrous group A non-labour (Turkish prisoners, Egypt, 1918)...	+	89·7	60	33·5	10	21·8	1·4	511·8	2545	2825
13. „ „ B hard, moderate, and light labour (Turkish prisoners, Egypt, 1918)	+ + +	95·5	63	36·8	13·7	22·5	4	535	2650	2903
14. Egyptian convicts light and moderate labour	+	110·6	69·5	33·5	·6	43·5	1·5	528·8	2854	3062
15. „ „ hard labour	+ +	123·5	82·7	48·3	22·8	46·6	6	524	2920	3195
16. „ „ curative diet + rest		101·8	82·7	54·7	29·4	59·3	31·6	440	2695	2871
17. Ordinary diet, 'Abâssia Asylum	+	99	78	46·4	22	63·5	9·2	443·6	2720	2910
18. „ „ Kasr el 'Aini Hospital		90·7	74	50·6	29·3	48	40	421	2475	2631
Non-pellagrous diets										
19. Bengali diet (actual)		46	39	33·5	0	3·7	0	380	1757	1863
20. „ „ × 70/55 to adult scale		59	—	42·5	0	4·8	0	483	2240	2371
21. Japanese prisoners		43	39	37	—	6	—	444	2000	2110
22. „ „ × 70/60 to adult scale		51·5	46	43·5	—	7	—	510	2118	2361
23. Mean of six Indian gaol diets		99·3	76	50	0	34	0	684	3290	3523
24. English sewing girl (actual)		53·8	47	34	21·5	33	29	316·5	1731	1824
25. „ „ „ ÷ 0·75 to adult scale		72	62	45	—	44	—	422	2440	2563
26. Industrial labour, Scottish prisons		117·7	98	55	13·7	24·3	12·5	517	2750	3029
27. Hard labour, Scottish prisons		124	105	66	32·5	54·6	32	654	3510	3709
28. W.H.W. To show comparative values of better class English diet		103	91·6	80	45	104	—	300	2593	2681

7–9. R. G. White (*l.c.* 17).
10. Goldberger and Wheeler (*l.c.* 1916, pp. 10–14).
11. A. Marie (*l.c.* p. 318).
12–13. Boyd and Lelean (*l.c.* 1918, App. VIII. 61).
19–29. Greig (*l.c.* 33).
21–22. Ref. *Encycl. Brit.*, 1911 edition, article "Dietetics."
23. Estimates from McKay's figures (*l.c.* 39).
24–25. Estimates based on case tabulated by Hutchison (*l.c.* p. 32).
22–27. Dunlop (*l.c.* 1899, pp. 15–17, 34, 84–86).

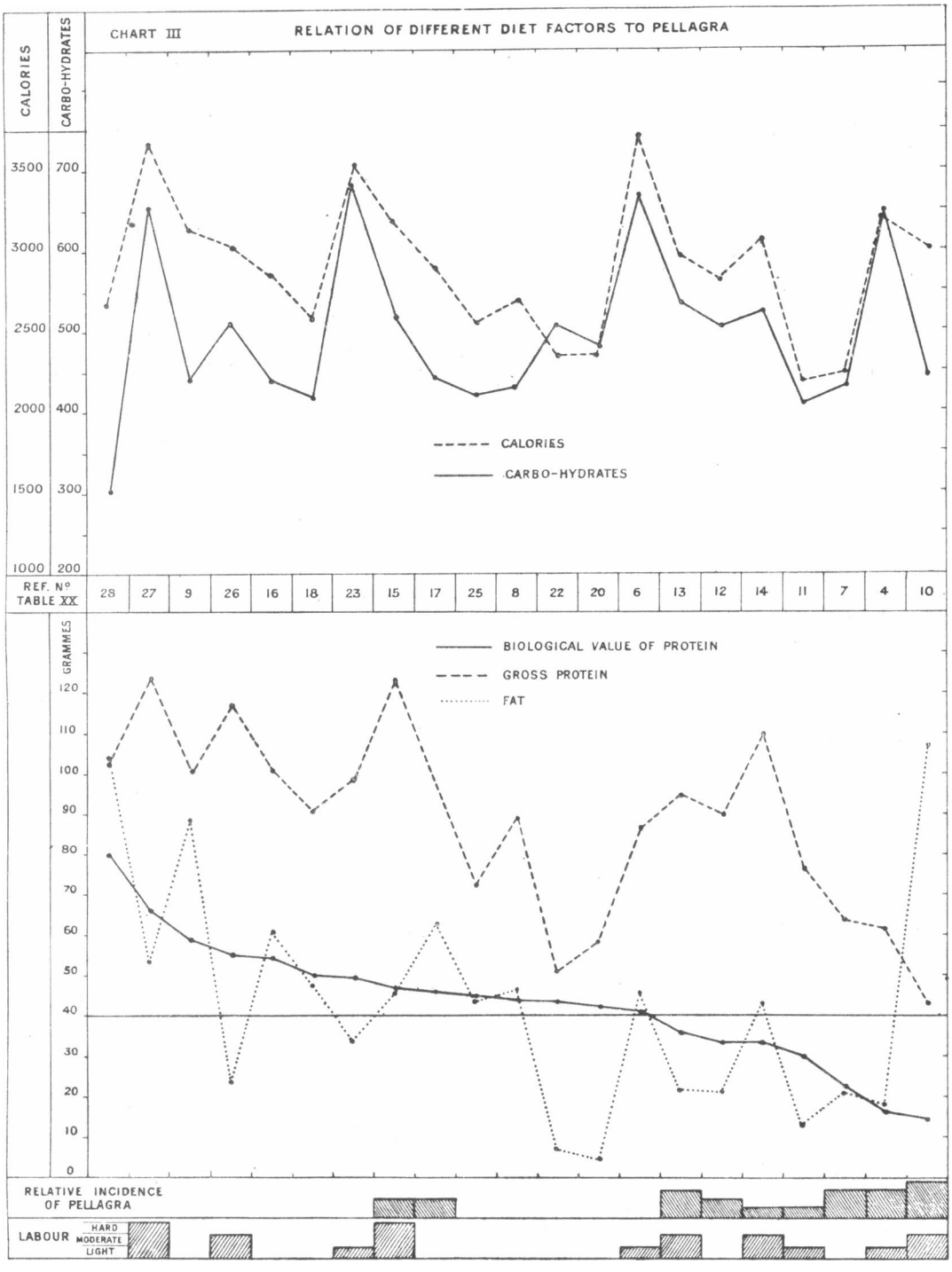


Chart 3. Relation of the different factors in the dietaries considered to the incidence of pellagra in the affected communities.

gross protein value gives little information as to the pellagrous character of a diet; (*c*) that labour augments the effect of deficient protein and raises the minimum protein value required to prevent pellagra.

The height of the columns showing the relative incidence of pellagra has no numerical relationship to the percentage of persons affected, but merely shows that one community was more or less severely affected than another.

Diet 4 is that of one individual, the pellagra incidence that of the class to which he belonged.

Diet 17 is that of an asylum population thought to have a high level of minimum protein requirement for reasons given in the text.

Part II.

DISCUSSION OF VARIOUS FACTORS HAVING A POSSIBLE RELATIONSHIP TO THE ETIOLOGY OF PELLAGRA.

In the series of diets recorded in Part I there are a number of factors which either singly or in combination may be responsible for the disease.

It is well to point out here that pellagra and starvation are not convertible terms; it is possible to conceive of chronic starvation on a diet containing, for example, a sufficiency of protein without the occurrence of pellagra and it is undoubtedly the case that pellagra may occur in persons who are otherwise well-nourished.

Although the tables of pellagrous diets show almost without doubt that a deficiency in the protein value is a chief etiological factor in pellagra, there are certain aspects of this question and the possible importance of deficiencies in other directions, in some cases not apparent from the known constitution of the diets, to which some consideration must be given.

These questions are as follows:

1. Deficiency in accessory food substances.
2. ,, of fats and lipoids.
3. ,, of protein[1].
   - (*a*) Absolute deficiency of intake below the normal requirements.
   - (*b*) Deficiency relative to individual or energy requirements.
   - (*c*) Deficiency due to low availability of protein resulting from the nature of the food or defective preparation.
   - (*d*) Secondary deficiency due to excessive bacterial destruction of protein in the intestine or defective powers of digestion or assimilation.

ACCESSORY FOOD SUBSTANCES.

The theory that pellagra is due to a deficiency in vitamines normally contained in the germ and surface-layers of maize and other cereals was first propounded by Casimir Funk (1913, 1914), the deficiency being due to the removal of these layers by modern methods of milling.

[1] The question has been already briefly discussed in the historical summary at the commencement of this paper.

This view is supported by Nightingale (1914) on the evidence of an epidemic of pellagra among convicts in South Africa who were fed on maize milled to 75 %, the epidemic disappearing when native ground millet was substituted for machine-milled maize flour. The evidence would have been more convincing if the fine maize flour had been replaced by an equal amount of hand-ground maize.

Voegtlin, Sullivan and Myers (1916) also bring forward evidence in favour of the avitamine theory (see also Voegtlin, Lake and Myers (1918)).

In none of the communities receiving the diets tabulated above was either beri-beri or scurvy (with the exception of pellagrous groups A and B, diets 12 and 13, among whom scurvy was frequent) noticed, and although, as Miss Chick (1918) has shown, the occurrence of the anti-neuritic vitamine in a particular foodstuff is no measure of its anti-scorbutic properties and *vice versa*, the fact that neither of these vitamines was deficient makes the absence of a hypothetical anti-pellagrous vitamine at least improbable.

The maize flour used in Egypt for bread-making by the fellahin is coarsely ground, little more than 7 % of the grain being removed in milling.

In diet 7 (Armenian refugees) a considerable amount of a substance, eaten largely in Asia Minor, called "Bourghoul" was used. This consists of the whole wheat grain, crushed and made into a sort of porridge, the grain being sometimes crushed, then boiled, dried and stored for use, sometimes crushed and at once made into the material as eaten. In addition these people received a fair amount of fresh vegetables including onions and tomatoes.

In the experiment on 11 American convicts (Goldberger, *l.c.*) the food contained a considerable ration of "grits" composed largely of the maize germ and in addition a quantity of fresh green vegetables.

To make the assumption probable it would be necessary to prove that there did not exist some definite deficiency in the known components of the dietary which could be correlated with the occurrence of pellagra before ascribing the disease to the deficiency of an unknown component.

FATS.

I am not aware that any author has suggested a deficiency of fats as a factor in the causation of pellagra; if however the tabulated series of diets be examined, it at once becomes apparent that the pellagrous character of these diets is, roughly, inversely proportional to the amount of fat present (with the exception of diet 10).

A deficiency of fats does not appear to have been noticed elsewhere in pro-pellagrous diets. Thus Ridlon (1916) states that in the study of dietaries consumed by his cases previous to their coming under treatment "the vegetable and fat components were notably conspicuous and the animal protein foods were relatively inconspicuous."

Lard and fat pork were used very largely by the class from which the patients came; it was owing to this peculiarity of their previous dietaries that

in the diet used for treatment of the condition, Ridlon did not allow any salt fat pork (*l.c.* p. 9).

Similarly Sydenstricker (1915, p. 29) concludes that the rise in the price of foodstuffs has restricted the supply of protein among the southern poor families to a much greater extent than it has the supply of carbohydrates and fats, and that "the proportion of proteins in the diet of the southern families is considerably less and of carbohydrate and hydrocarbons considerably more than in the diet of northern families"; it is in the former region that pellagra has become so prevalent.

The following diets from a table given by Atwater and Milner (*l.c.*) have been selected as being of very low fat value while in none of the communities or groups of men affected has pellagra been recorded, the protein value of all these diets being noticeably above the minimum value adopted as sufficient for nutrition.

Table XXI.

	Protein	Fat	Carbo-hydrates	Calories
Japanese jinricksha runner (heavy labour) ...	137	22	1010	5050
„ rice cleaner (moderate labour)	103	11	917	4415
Bavarian mechanic (light labour)	112	32	553	3060
Japanese prisoners (no work)	43	6	444	2110
Prussian prisoners „	90	27	427	2400

The percentage of calories from fat to total calories is as follows: (1) 4 %, (2) 2·5 %, (3) 9·2 %, (4) 2·7 %, (5) 10·5 %.

In all diets which have been used for the treatment of pellagra it has been found advantageous to employ a large ration of milk and sometimes eggs (see Goldberger, Waring and Willet (1914); see also anti-pellagrous diet 9, Table VIII). These diets contain a large amount of animal fats, an unavoidable concomitant of the increase of animal protein caused by the addition of milk and eggs.

It appeared of interest in this connection to determine whether the beneficial effect of such diets was to be ascribed solely to the high biological value of the protein or whether in addition the fat itself exerted some useful influence. With this end in view, at the writer's suggestion, Col. Boyd, R.A.M.C. (1918, p. 21–22) then in charge of numerous pellagrous patients at No. 2, P.O.W. Hospital Abassia (Egypt), was good enough to carry out the following experiment.

Three groups of patients: *A*, 37 men; *B*, 10 and *C*, 10 men were fed on different diets for a period of three weeks, their weights being recorded.

A received the ordinary hospital ration containing 200 g. milk.

B received the same diet + 20 g. butter.

C received the same diet as *A* with no milk but an addition of 62 g. beans or lentils.

The calorie value of *B* and *C* was the same. The result was as follows:

Average increase in weight of *A* = 1 lb.
„ „ „ *B* = 2·2 lb.
„ „ „ *C* = 7 lb.

It may be concluded from the above that a deficiency of fat is not directly related to the production of pellagra and that the apparent connection shown in Table XX and Chart III is accidental.

THE LIPOIDS.

The absolute quantity of fat in the diet from an estimate of the proximate principles gives no information as to the content in these essential components.

The phosphatid content of various food materials is given by Maclean (1918). The percentage of lecithin in the most important foodstuffs is as follows:

Muscle (rabbit)	0·6
Milk (cow)	0·06–0·116
Beans	0·81
Wheat	0·65

In view of these figures it is unlikely that the pellagrous character of vegetable diets has any relation to this factor.

With regard to cholesterol, J. A. Gardner and his co-workers (Gardner, Dorée, Ellis and Lander, 1907, 1909, 1912, 1914) and Lander (1915) show that this is an essential element of the food which cannot be manufactured at any rate by the mammalian organism and that it must therefore be obtained from outside either as such from animal sources or from plants in the form of phytosterol.

There is some evidence that a deficiency of cholesterol occurs in pellagra. M. L. Koch and C. Voegtlin (1916) have shown that certain chemical changes are noticeable both in the brains of advanced cases of pellagra and of monkeys which have been fed for a considerable time on an insufficient and ill-balanced diet. These consist chiefly in a disturbance of the normal ratio between the various lipoids of the cerebrum, the cerebellum and the spinal cord, there being a marked deficiency in the cholesterol and sulphatid content of the hemispheres, in some cases a deficiency, in others an apparent increase in the cholesterol of the cord. The degeneration of the nerve fibres of certain tracts of the cord commonly seen in pellagra, is shown by these authors to be almost exactly reproduced in the experimental animals.

The fats of the sebaceous secretion are composed largely of cholesterol fats and the absence of this secretion in sufficient amount accounts very largely for the characteristic dryness and perhaps other cutaneous symptoms in pellagra.

The writer has not been able to find any statement as to the cholesterol content of the various vegetable foodstuffs. It is however improbable that the cholesterol content of the diets known to have been pellagrous (Table XX) can be less than that of diets 19 and 21, consisting mainly of rice, in which the fats are reduced to a minimum.

The above facts are brought forward not with the intention of suggesting that a deficiency of lipoids (or in particular cholesterol) is the cause of the

disease but that it may be a contributory factor at any rate in the production of some of the nervous and other lesions.

PROTEIN.

That a deficiency in the amount and quality of the food is of primary importance in producing the disease, has been pointed out by the majority of observers from Casal onwards; as also the reciprocal fact that a generous diet will cure the disease.

The evidence of the diets given in the table as well as that of the orphanage and asylum experiments recorded by Goldberger and his co-workers and Ridlon in America, prove this latter point. The fact that the disease affects especially the very poor is well recognised. Siler and Garrison (1914) show that of the cases reported 83 % were in a state of poverty, 15 % comfortably off, 2 % in affluent circumstances; with reference to the latter it is remarked that the presence of abundant food is no proof that it is eaten. Sandwith (1905) states that in some villages of lower Egypt which he visited in the year 1902, 62 % of the population appeared to be pellagrous; these villages were occupied by fellahin employed upon the State Domains Administration lands at a daily wage amounting to about three piasters ($7\frac{1}{2}d.$) daily, an amount that, even at that date, was not sufficient to supply a small family with sufficient food. He contrasts these villages with others in the same region occupied by more prosperous peasants in which only 15 % of the men appeared to be affected.

Sydenstricker (1915) states as an explanation of the increase of pellagra in the United States, that in those regions most affected, while wages had increased between the years 1900 and 1913 by 25 %, the cost of foodstuffs had risen 60 %, also (*l.c.* p. 19) that the increase in the price of the protein of the food had risen to an extent which was 60 % greater than in the case of carbohydrates and fats. In the Spartenburg Report (p. 7) it is stated that "the most striking defect is the absence of fresh meat, animal protein being supplied largely in the form of salt pork, especially bacon."

These few references are sufficient to show that while insufficient food has been generally recognised as the cause of pellagra, particular attention has been directed to a deficiency in the protein.

The series of diets shown in Table XX has been collected and the nutritive value estimated for the purpose of elucidating this relationship of protein deficiency to pellagra. That such a relationship actually exists and is probably the essential element in the etiology of the disease, appears to be clearly demonstrated by the figures in column 4 (giving the biological value of the protein in the different dietaries). It will be seen that these diets having a biological value in protein of 30 or less are all primarily pellagrous, while those with a biological value of above 37 are relatively non-pellagrous in cases in which the diet is fully sufficient to meet the energy requirements but apparently not so, as in 13 and 15, where the energy value is below the amount

required by the work (non-pellagrous, that is in regard to normal persons who have not previously shown symptoms of the disease).

None of these diets with the exception of 9 are such as to prevent the re-appearance of the disease in persons previously affected.

(*Note.* Since writing the above an experimental investigation has been carried out on a group of healthy men selected from among those receiving diet 12, in collaboration (1918) with Capt. H. E. Roaf. It was found that owing to the character of the bread and the mode of preparation of the rest of the rations the loss of protein in the intestine from non-absorption was 33 % in place of 25 % as estimated from the absorbability of food-stuffs composing the diet as given in the literature on the subject. The defective absorption of protein reduces the biological value to 33 and accounts for the considerable incidence of pellagra among these men. This diet is a good example of a diet on the border-line of protein sufficiency in which an insufficiency arose from the defective digestibility of the food as issued for consumption. It is not improbable that, if it were possible to examine certain other diets which appear to have been pellagrous but in which the protein value does not appear to be sufficiently low to explain this, a similar result might be obtained.)

ANIMAL PROTEIN.

With regard to the nature of the protein, it will be noted that animal protein is completely absent in diets 1, 2, 3 and 10 and small in amount in 7, 11, 12 and 14, animal protein is however completely absent in 19, 21 and 23 which, as far as any record to the contrary shows, are non-pellagrous.

Although it has been found to be impossible to rear growing animals—mammals—on a purely vegetarian diet (McCollum, *l.c.*) it is doubtful if this applies to the maintainance of full-grown animals. There is in fact no doubt that the majority of the poorer inhabitants of far eastern countries (especially where rice is the chief cereal) live on a purely vegetarian diet.

THE VALUE OF MAIZE.

The question as to the part played by maize in the causation of pellagra seems to be answered in the main by the low biological value of maize protein, one-third that of animal protein as found by Thomas. This is largely accounted for by the fact that 50 % of the protein of the endosperm is in the form of zein (Osborne and Mendel, 1914).

That pellagra is not due to maize as such is demonstrated by the fact that some of the diets (12, 13, 14 and 15) contain no maize product of any kind. The occurrence of 10 recorded cases in different asylums in Great Britain (Sambon, 1913) where maize products were not used, is evidence of this; as also the 15 cases among a rice-eating community in the Straits Settlements recorded by Sidney Sheppard (1912).

That it is impossible to maintain animals in a state of health on a diet in which zein forms the only protein was shown by Osborne and Mendel (1911). Sandwith (1913) appears to have been the first to suggest that the absence of tryptophane in zein is related to the pro-pellagrous character of maize. Further evidence in regard to the question of the bearing of the tryptophane deficiency on pellagra will be discussed below.

The low value of maize as a source of protein is however not entirely

due to the presence of a large percentage of zein (it must be remembered that other proteins are present, which contain at any rate a small percentage of tryptophane), but also to the fact that maize is more variable in its protein content than probably any other cereal. Mayrhoff (1912) gives the range of variation as from 5·5 to 14·8 % and the writer has himself analysed a sample of bread consisting chiefly of maize flour which contained nitrogen equivalent to only 4·8 % of protein having a biological value of no more than 1·4. It is clear that on the lowest computation it would be necessary for a man to eat daily no less than 2140 g. (4½ lb.) of such bread to obtain protein having a biological value of 30.

The better milled the maize flour, the less will be the protein content and the higher the proportion of zein to total protein. Osborne and Mendel (*l.c. supra*) find that zein forms 41·4 % of the protein of the whole kernel. This may explain the improvement in the prisoners referred to by Nightingale (*l.c.*) when their diet was changed from the highly milled maize to the roughly ground millet.

The comparative rarity of pellagra in rice-eating communities must be ascribed to the high ratio 1/1·1 of the protein as compared to that of other cereals, especially maize, the ratio of rice to maize being in this respect 3 : 1.

Sheppard (*l.c.*) describing 15 cases of pellagra in the Straits Settlements, rice being the chief food of these patients, remarks: "the patients are of the poorest class and further observation leads one to think that even rice, the cheapest food, was not always within their reach."

The value of the protein in diets 19 and 21, in which rice probably formed 90 % of the food, it will be seen, in spite of the low calorie value of 2240 and 2110 respectively, is higher than that of any of the pellagrous diets given. It is almost certain that although the first and probably the second of these two diets may have given rise to beri-beri, cases of pellagra did not occur; in regard to this point Greig (*l.c.*) gives a careful analysis of the symptoms seen in some hundreds of cases of epidemic dropsy traced to diets similar to 19, and in no case is any symptom described which might possibly have been the cutaneous manifestation of pellagra.

Sufficient has been said to support the view that pellagra is more closely related to a deficiency or inadequacy of the protein value of the diet than to any other dietetic cause.

SIGNIFICANCE OF INDICANURIA.

There are certain facts which seem to suggest that tryptophane may be the essential component of protein, the deficiency of which may be responsible for the disease. A deficiency of lysin may be of equal importance. Both these amino-acids are absent from zein and both are essential in an adequate protein. Osborne and Mendel (1916) show that a minimum amount of tryptophane and lysin are required for growth and nutritive equilibrium. (See also Chick and Hume, *l.c. supra.*)

The question of the proteins of maize has been already dealt with. Milk, the caseinogen of which contains 1·5 % of tryptophane and 5·8 % of lysin (Plimmer), appears to be generally regarded as the most efficient addition to the diet as an anti-pellagrous measure.

The gliadin of wheat, forming a little less than half the total protein, contains as much as 1 % of tryptophane but no lysin; other important amino-acids, phenylalanine, tryosine and histidin, are however deficient in the proteins of wheat as compared to those of milk. Such differences no doubt account for the differences in biological value.

Tryptophane has been shown by Hopkins and others previously referred to (*a*) to be an essential element in the food for maintenance and growth; (*b*) not to be built up in the animal organism, in this last respect resembling others of the higher amino-acids, at any rate those united to an aromatic or hetero-cyclic nucleus.

Tryptophane (indol-amino-propionic acid) is peculiar in that the protein molecule appears to contain no other amino-acid in which occurs the indol ring; it must therefore be present in sufficient amount as such in the protein of the food, whereas in the case of others, as for example arginin and histidin, the structure is sufficiently similar to allow of their mutually replacing each other in the food (Hopkins and Ackroyd, 1916).

The fact that trytophane cannot be formed in the body but must be obtained from the products of the intestinal digestion of the proteins taken in the food, implies that the skatol and indol frequently found in the faeces and the derivative of indol "indican" found in the urine, must be formed at the expense of the tryptophane of the food protein.

That indol has its origin in the large intestine was shown by Ellinger and Gentzen (1904). Ellinger (quoted by Mackenzie Wallis, 1911) also shows that the injection of indol into the caecum is rapidly followed by the appearance of indican in the urine, and Assayama (1916) has demonstrated that alkaline solutions of tryptophane given by the mouth or injected into the large intestine greatly increase the indican of the urine, subcutaneous introduction of such solutions giving no result.

The importance of tryptophane in nutrition renders the loss from intestinal putrefaction a matter of considerable importance when the amount in the proteins ingested is minimal. Some amount of intestinal disturbance is commonly associated with pellagra and it has been frequently observed that pellagrins excrete excess of indican.

Marie (*l.c.* p. 218) states that he has almost constantly found indican in the urine. Ormsby and Slinger (1911) found a marked indican reaction in the urine of all cases examined. Myers and Fine (1914) found indican present in all the 13 cases examined, the daily excretion of this substance varying from a minimum of 21 mg. in one case to a maximum of 240 mg. in another. In April 1917 the writer examined 38 cases at the Tura Convict Prison, 3 of the men were in hospital, the remainder under supervision; the pellagrous

symptoms were no longer visible in a number of these. Of these men 3 showed indican in large amount, 21 in smaller quantities. Of 64 Egyptian medical students, said to be in good health, 7 only showed indican in the urine; 4 traces, 2 well marked, and 1 in large amount; the latter stated that he had recently suffered much from dyspepsia and diarrhoea. This examination was made in the hot weather of May. An examination made in the cold weather of the previous January gave a similar result. Hunter, Givens and Lewis (1916) find indican very generally present in considerable quantities in pellagrins and make the interesting observation that indol-acetic acid is present in large quantities inversely with the indican (see their tables, pp. 48, 49).

The following results (in percentages) were obtained recently in the examination of 152 apparently healthy Egyptian medical students made by the writer and Dr A. M. Mahmoud Bey (assistant in the Physiological Dept.):

None, 73·8; trace, 11·8; below $\frac{1}{15}$, 7·2; below $\frac{1}{4}$, 5·9; below 1, 1·3; above 1, 0.

My friend, Capt. H. E. Roaf, R.A.M.C. (T.), with whom I have been recently collaborating in the investigation of certain aspects of the pellagra question, gives me permission to quote the following figures:

Table XXII.

Amount of Indican in the Urine of Turkish Prisoners on Diet 12.

	None	Trace	Below $\frac{1}{15}$	Below $\frac{1}{4}$	Below 1	Above 1
Healthy						
%	64·4	24	9·6	2	0	0
Quiescent pellagra						
%	34·3	19	21·9	13·3	11·4	0
Active pellagra						
%	7	5·6	28·2	31	22·5	5·6

The fractions refer to dilutions of Fehling solution with distilled water. A solution of indigo-carmine may be used in place of the Fehling, one part of indigo-carmine in 5000 parts of water being almost exactly equal in tint to undiluted Fehling. From this it is possible to estimate roughly the amount of indican present in the urine, 200 mg. per litre of indigo-carmine corresponding to 238 mg. of indican (ratio of molecular weights).

Taking this figure as a basis of calculation, the amount of indican excreted daily by active pellagrins would be: 33·8 %, 15 mg. or less; 31 %, 15–60 mg.; 22·5 %, 60–238 mg.; and 5·6 %, more than 238 mg. per litre of urine. Jaffé gives 5 to 20 mg. as the daily excretion of indican in healthy men.

Borden (1907) finds the average output to be 12 milligrammes, 40 being rare in health. Hunter, Givens and Lewis (1916) place the normal upper limit of indican in the urine at 25 mg.

Stanford (1911) draws attention to the frequent presence of indican in the urine in melancholic and akinetic forms of insanity. Such types of insanity commonly result from pellagra. Mackenzie Wallis (1911) in the same journal finds an increase in indican in many forms of insanity, combined with which they find a marked diminution and abnormal variability in the creatinin as well as in the neutral sulphur of the urine. It is interesting to note that Myers and Fine find the same conditions in pellagra. Mackenzie Wallis considers these abnormalities as evidence of an altered state of cell-metabolism regarding the indican, on what grounds is not stated, as being of endogenous origin

and not as arising from intestinal fermentation. This author refers to the low physical condition of the peasants of Northern Italy as being possibly connected with the absence of tryptophane in the zein of the maize largely consumed in that region, without however mentioning pellagra.

It is difficult to avoid the impression that many of the cases of insanity investigated by these two authors in English Asylums, may have been pellagrous.

Myers and Fine (*l.c.*) show that in addition to indican, the other ethereal sulphates are increased to a corresponding extent. This indicates that the aromatic amino-acids are destroyed to a like extent with tryptophane and hence it may fairly be assumed that the indican of the urine represents the destruction of the whole protein molecule as far at any rate as many of its most essential components are concerned and that the indican may therefore be taken as a measure of the loss of a corresponding amount of protein to the body.

The molecular weight of tryptophane is 204; of indican, the potassium salt of indoxyl sulphonic acid, 251.

240 mg. of indican, the maximum[1] amount found by Myers and Fine (*vide supra*), would be derived from 195 mg. of tryptophane, an amount contained in 13 g. of caseinogen or 20 g. of the gliadin of wheat, representing about 400 g. of milk in the first case, or about 500 g. of wheaten bread in the second and very much more than this amount of maize bread. It is true that the glutelins and other proteins of bread contain some tryptophane; at the same time it will be readily seen that the indican of the urine may be an evidence of a very large loss of protein to the body through its bacterial destruction in the digestive tract.

Myers and Fine state that there is a great increase of indol and skatol in the faeces of pellagrins while the faeces of normal individuals contain neither of these substances.

The urinary indican represents therefore only a part of the loss of protein to the body.

A-CHLORHYDRIA.

Niles (1912) found in 64 cases of pellagra that the gastric HCl was absent in 18, diminished in 31, normal in 3, increased in 12; Myers and Fine find it absent or greatly diminished in all cases; related to this they form the conclusion that "the presence of much indican with high ethereal sulphate elimination and much indol and skatol in the faeces indicate peculiar bacterial conditions, probably high up in the intestine."

Hunter, Givens and Lewis (*l.c.*) find HCl absent in 52 %, deficient in 10 %. They state that a-chlorhydria, once present, is not recovered from in pellagrins, even when the other symptoms of the disease disappear. This fact, if true, has an important bearing on the appearance of the relapses so common in

[1] In 5·6 % of the cases examined by Roaf this amount was exceeded.

this disease and on the impossibility of curing cases of pellagra after they have passed beyond a certain stage.

The absence or diminution of HCl in the gastric juice has been noted by Moore and Roaf in many debilitating diseases, especially cancer, whether in such cases it was accompanied by indicanuria was not observed.

That such a condition would lead to the invasion of the intestine by an excessive number of micro-organisms is doubtless true; it would also lead to other effects tending to produce defective absorption of proteins in the small intestine thereby favouring their destruction by bacteria.

The absence of the HCl of the gastric juice or even its considerable diminution, would result almost certainly in a diminution of the pancreatic secretion[1] by the removal of the normal stimulus to the production of secretin. This would no doubt lead to incomplete digestion of protein and its passage onwards into the large intestine, the partially digested or undigested protein undergoing putrefaction either in the small intestine or after its passage into the large intestine with the production of useless waste products, manifested by the appearance of indican in the urine and a more or less important loss to the organism.

Myers and Fine (*l.c.*) examined the excreta of their patients and concluded that the nitrogen absorption in pellagrins was not markedly different from that of normal individuals; this may be true and yet the nitrogen may be absorbed in a useless form to the organism as pointed out above. Such substances as for example indol would be excreted in the urine, their nitrogen would not appear in the analyses of the faecal output but would be included in the presumed metabolised nitrogen of the urine. It is clear therefore that the determination of the total nitrogen excretion by the urine and faeces respectively gives in pellagrins a false picture of the assimilation of proteins.

(*Note.* In the experimental investigation of the nitrogen assimilation from diet 12 (see p. 28) a group of 5 pellagrins was examined, the conditions being the same as those for a similar group of healthy men. The loss of protein by the intestine was 33 % in the healthy, 35 % in the pellagrous group, a comparatively small difference.

The urine of the pellagrins contained however in all cases some indican, this substance being absent in the case of the healthy men.

If the loss of protein, which a given amount of indican represent, be considered, it will be obvious that in some cases, at any rate among the men examined, the total loss of protein must have been much in excess of the 35 % actually shown by the estimation of the faecal nitrogen.)

The writer has attempted to show that, measured by the indican of the urine, the protein destroyed in the intestine by bacterial action may amount to a considerable part of the total nitrogenous intake.

If this be so it will be easily understood that (*a*) persons in the general community suffering from indicanuria would, if reduced to a protein intake near the minimum requirement for normal people, be actually living under

[1] Evidence is given of this by the assimilation experiment referred to on p. 28. It was found that in the pellagrous group examined, 28 % of the fat intake was un-absorbed (Soxhlet extract of faeces) as compared with 19 % in the healthy group.

conditions of protein starvation, and that they would be necessarily more liable to develop a disease due to protein deficiency than other persons. Thus even on what might be considered a quite adequate dietary for normal individuals, persons with the very marked indicanuria not unfrequently seen in apparent health might suffer from protein deficiency. It is in fact not an improbable supposition that the indicanuria so generally present in pellagra is not entirely a resultant symptom of the disease but that those members of the population who suffer from indicanuria and the conditions leading to it are unable to maintain their nitrogen equilibrium on a protein intake fully sufficient for quite normal people and are therefore predisposed to pellagra.

(*b*) If there existed a chronic condition of deficient gastric HCl or defective pancreatic digestion accompanied by excessive bacterial fermentation apart from, or acquired as the result of an attack of pellagra, that persons so affected would be in a condition in which they would require more protein, possibly much more, to provide them with their minimum requirements.

It would not be difficult under such circumstances to understand the fact that recovered pellagrins tend constantly to relapse if living under similar conditions to the poorer population generally, or even occasionally when provided with what would ordinarily be considered a very liberal diet.

At the Abassia Asylum, where relapses are not uncommon, an example of such a case is seen. A few relapses occurred at the Refugee Camp even after the antipellagrous diet was introduced in February 1917.

The question of indicanuria has been discussed at some length as it appears to have a bearing on the part played by protein deficiency in the causation of the disease, the significance of which has not been sufficiently appreciated.

INDIVIDUAL VARIATIONS.

It is not intended to suggest that only persons with indicanuria or digestive disturbances develop pellagra; this is certainly not the case. Among the poorer classes of a community living on barely sufficient food, there must be many individuals whose normal protein requirements, apart from the above causes, exceed the average, and probably others who can maintain health on a minimum of protein considerably below the average.

Earlier in this paper (p. 13) the writer has attempted to illustrate this normal variability by an approximate estimate of the differences in the minimum protein value required by the five subjects of Chittenden's experiment, the requirement for the maintainance of nitrogen equilibrium varied from rather below 30 to about 40 g. (See also Sherman, *l.c. supra.*)

If a population be imagined of this character living on a diet having a value in protein of 37, it is obvious that while the majority would be obtaining sufficient for their normal requirements, a certain percentage would be suffering from chronic protein deficiency. Border-line diets such as this will be found among those presented and it will be seen that the incidence of pellagra on the communities affected accords well with the explanation offered.

INFLUENCE OF WORK.

That the calorie value of the diet has no direct relationship to pellagra appears from an inspection of the table of diets (Table XX and Chart III).

It will be seen that certain diets (*e.g.* No. 10) of a relatively high calorie value, are pellagrous, while others (No. 22 and 25) have calorie values of bare subsistence values but are not known to have been pellagrous.

There are however in the table three diets in which the indirect effect of a deficient energy intake appears, namely 13, 14 and 15. (For statistical details upon which the conclusion as to the influence of these three diets is based, see Part I, pp. 28–33.) The explanation of this indirect effect of labour must be sought in the well-established fact that to maintain the nitrogen equilibrium on a diet which is below the energy requirements, an increased supply of protein is necessary (ref. Argutinsky and Krummacker, 1890; also Cathcart, *l.c.* p. 111); and also that work, especially if severe, raises the protein requirements apart from the use of protein in the body as a source of energy (ref. Zuntz and Schumberg, Wolpert and Broden, 1901; Dunlop, Noël Paton, Stockman and Maccadam, 1897; Melville with J. S. Haldane, M. S. Pembery and others, 1913).

It is clear, if the nitrogen metabolism is influenced by labour or by work carried out under unfavourable conditions, that on such diets as those discussed with a narrow margin of sufficiency in protein, an increased incidence of pellagra will accompany an increase in the energy requirements if these are not fully met by the energy intake.

GENERAL REMARKS.

A considerable number of cases of pellagra are recorded in the medical literature of the British Isles an explanation of which, on the lines suggested in this paper, appears difficult; all such cases will remain obscure until, in addition to the observation of clinical details as regards symptoms, some attempt is made to apply modern methods of bio-chemical investigation to their elucidation, especially in regard to the true protein intake and the coefficient of protein assimilation.

The most common type of such cases is that described by Hammond (1913) in which a long period of intestinal trouble preceded the appearance of the cutaneous symptoms; a number of similar cases are described.

It can scarcely be doubted that secondary protein deficiency must have existed resulting from defective powers of assimilation and destruction of protein in the intestine by bacterial action.

(*Note.* It has been pointed out to the writer as a matter for surprise that, supposing pellagra to be due to a deficiency of protein, symptoms of the disease should not have been noticed in sprue in which a very chronic form of enteritis not unlike that seen in pellagra occurs, often leading to great emaciation. If however Bahr's monograph (1915) on the subject be consulted, it will be seen that there are important bio-chemical differences between the two diseases. In sprue the coefficient of protein assimilation is high, indicanuria is not a marked feature and the

gastric HCl tends to be increased rather than diminished; it appears therefore that secondary protein deficiency such as may lead to pellagra, is unlikely to occur in this disease.)

The writer does not propose to discuss any of the non-nutritive theories of the disease from the alleged effects of the presence of an excess of alumina or silica in the drinking water to infective agents, bacterial, protozoal or other.

Anyone reading the extensive literature of the subject must be impressed by the contradictory nature of the evidence and the insufficiency of the explanation offered, and, with regard to the infective theories, the completely negative results. Reference may be made in this connection to the work of Goldberger and Anderson (1911), Lavinder, Francis, Grimm and Lorenz (1914), O. S. Hillman (1914), W. J. McNeal (1914), Francis (1917) and White (1919).

In bringing to an end this survey of the part played by protein deficiency in the production of pellagra, it is clear that much useful work remains to be done. This is especially true of the biochemical problems involved and of the minute anatomy of the various tissues of the body particularly of the digestive system. A great advance has been made in the latter region of investigation by Sundwall (1917) who has demonstrated the very important fact, by comparison of the tissues of pellagrins with those of underfed or improperly fed animals, that all those changes seen in pellagra in the nervous system and elsewhere can be ascribed mainly to malnutrition. Almost of necessity the material examined came from the bodies of persons dying of the disease in its cachectic state. It would be of the greatest interest to observe the conditions of the tissues of the digestive tract before the condition has reached the stage when actual destruction of tissues has concealed the earlier atrophic changes.

It appears to the writer that such investigations would throw light on the course of events induced by protein deficiency and might possibly increase the existing knowledge of protein metabolism in general.

CONCLUSIONS.

The following conclusions may be drawn from the study of the pellagrous and non-pellagrous diets brought together and the biochemical and clinical information collected.

1. Pellagra is the ultimate result of a deficient supply of protein.

2. The sufficiency or insufficiency must be judged of by the biological value of the protein, estimated on the amount available for assimilation and not on the gross protein: 40 may be taken as the minimum safe value for this factor. Below this cases are likely to occur in the affected community: owing however to the great normal variations in the minimum protein requirement, many individuals, the biological value of whose daily protein intake is as low as 20, will escape the disease, while it is possible that some, with a value above 40, may become affected.

3. The deficiency of protein may be:

(*a*) *Primary*, in which the supply is insufficient for the individual requirement or, when, owing to the indigestible character of the food, a somewhat restricted supply cannot be utilised to the normal extent.

(*b*) *Secondary*, in which owing to digestive disturbances, or other causes, the supply of protein cannot be assimilated.

4. In accordance with conclusion 3, three types of pellagra may be distinguished etiologically:

(*a*) The common type seen in poverty or deficient food from other causes.

(*b*) Relapse cases in which, owing to permanent defects—the result of a previous attack of pellagra—the protein supply is inefficiently utilised.

(*c*) Cases in which a disease of the digestive organs due to other causes than insufficient feeding, leads to defective utilisation of the protein intake.

5. That indicanuria is an important indication of the loss of protein in the intestine, the amount present being sometimes sufficient to account for the loss to the body of a large proportion of the protein intake.

6. Indicanuria is closely related to the deficiency of gastric hydrochloric acid. This is due to two causes:

(*a*) The resulting invasion of the intestine with bacteria.

(*b*) The absence of the normal stimulus to the secretion of pancreatic juice, whereby less protein is completely digested and more is lost in the large intestine.

7. Labour raises the level of protein requirement, an effect which is increased greatly by a deficient energy supply. Labour is therefore a factor in the causation of pellagra in a community whose protein supply is on the border-line between sufficiency and insufficiency.

8. There is evidence which seems to suggest that a deficiency of cholesterol may be related to some of the symptoms.

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