XVIII. THE PRODUCTION IN MONKEYS OF SYMPTOMS CLOSELY RESEMBLING THOSE OF PELLAGRA, BY PROLONGED FEEDING ON A DIET OF LOW PROTEIN CONTENT.

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(With Plate V.)

The dietary interpretation of the etiology of pellagra has been growing in favour and the disease seems to stand in much the same relationship with the eating of maize as beriberi stands with the eating of rice.

More than 50 years ago, Roussel [1866] pointed out that pellagra can be cured by good food and that without dietetic improvement all remedies fail.

The various theories of its causation which have been advanced are discussed by Funk (1913) who is of opinion that the facts can be best explained by that one which attributes the disease to partial starvation of some important dietary constituent.

Voegtlin [1914], although inclining to the view that pellagra is a chronic intoxication, points out that in the U.S.A. it is endemic only upon a population whose diet is mainly vegetarian and that the possibility of its causation by a vitamine deficiency, or by the defective supply of certain amino-acids in the protein ingested, must be seriously considered.

Lorentz [1914] and Willets [1915] treated advanced cases with mental symptoms by a generous diet with favourable results.

Goldberger [1916] investigated the conditions at two orphanages in Jackson, Missouri, in which cases of pellagra occurred. Some of the children had been admitted pellagrous but others became ill after prolonged residence in the orphanages. Milk and meat were sparingly used in the institutions. By greatly increasing the quantity of meat, milk and milk products, but without disturbing the other conditions, the disease disappeared and failed to recur next spring.

Goldberger, also, made observations upon eleven criminals who volunteered for the following dietetic experiment. The pellagra squad was fed upon a diet consisting of white flour, corn grits, corn meal, corn starch, polished rice, sugar, sweet potatoes, pork-fat, cabbage and turnip-tops. The only animal protein was 4 oz. of meat once a week. The calorific value of the daily diet was 2950 and the prisoners performed only light work. Nevertheless, loss of weight occurred early. After 7½ months cutaneous manifestations were noticed which, in the opinion of experts who were asked to see the cases,
justified a diagnosis of pellagra. These symptoms cleared up on the resumption of a normal diet. Goldberger concludes that the evidence strongly suggests that pellagra will be proved to be a deficiency disease closely related to beriberi but, whatever its nature, it is capable of correction or prevention by including in the diet suitable proportions of fresh animal protein.

Wilson [1916, 1918] had an exceptionally favourable opportunity to study the relation of diet to pellagra in the case of an outbreak of the disease amongst the population of a camp of Armenian refugees at Port Said during 1915, 1916 and 1917. The diet at first supplied was inadequate. It contained only 2200 calories and 92 % of its protein was derived from vegetable sources, of which about $\frac{3}{4}$ was from wheat and $\frac{1}{4}$ from maize. Wilson (using Thomas’ [1909] data) calculates that the biological value of the total protein only equalled 22 g. of caseinogen.

Nearly 10 % of the inhabitants of the camp developed pellagra within a year. When, however, the diet was enriched so as to contain 3000 calories and proteins of a total biological value equal to 41 g. of caseinogen, fresh cases soon ceased to occur and the camp remained thereafter free from the disease.

Wilson concludes, from the above observations and from extensive studies of Egyptian and other dietaries, that the cause of pellagra is to be found in an inadequate supply of some one or more of the essential amino-acids and is generally occasioned by relying too exclusively upon cereals, and especially maize, for a supply of protein.

Wilson considers the danger line to be crossed when the total protein intake has a biological value of less than that of 40 g. of caseinogen.

Chittenden and Underhill [1917] produced in dogs a condition which they regard as suggestive of pellagra, by feeding for eight months upon a diet of biscuits, peas and cotton-seed oil. They referred the symptoms to a deficiency of some essential dietary constituent of unknown character. McCollum and his colleagues [1917 to 1919] made a biological analysis of pellagra-producing diets by experiments on rats. They obtained merely evidence of malnutrition and conclude therefore that pellagra is caused by an infection supervening upon lowered vitality due to faulty diet.

A further study of the relation between the incidence of pellagra and dietary was made by Goldberger, Wheeler and Sydenstricker [1918], who have compared the diets partaken of by households in South Carolina villages, in which pellagra occurred, with those of similar households free from the disease. The food consumed by the latter contained more milk, fresh meat, eggs, butter and cheese, and depended less upon cereals for proteins.

The effect of the absence of tryptophan from the protein zein, which forms nearly 50 % of the proteins of the maize endosperm, was demonstrated by Willcock and Hopkins [1907] in the case of young mice, and that of the absence of lysine from the same protein was studied by Osborne and Mendel [1914, 2; 1915]. These two obvious deficiencies, particularly that in trypto-
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phan, have frequently been suggested as the cause of pellagra in human beings, the protein of whose diet has been too exclusively derived from maize endosperm. Were such an explanation correct, i.e. that pellagra is a lysine or tryptophan deficiency, it would also cover those cases of the disease which are reported in persons who have never touched maize, for doubtless a diet deficient in tryptophan or lysine can be attained by other means than by eating too exclusively of maize endosperm.

The present paper gives, very tentatively, an account of preliminary experiments which were planned in order to make a close study of the symptoms which might develop in monkeys fed on a diet of which the protein was deficient in tryptophan and lysine. The results obtained seemed sufficiently promising to warrant publication.

EXPERIMENTAL.

The diet selected had to satisfy a number of requirements. It had to be adequate from the point of view of fat and of calorific value; it had to contain enough of all the known accessory food factors and it had to be sufficiently palatable for the animals to eat it. It had also to be composed of materials which could be prepared on a large scale, as the experiments were likely to last over many months. The use of purified foodstuffs was thus excluded and the diets had to be so planned as to consist of ordinary foodstuffs or of products of manufacturing processes.

The accessory food factors were supplied throughout as follows:

- **Fat-soluble A.** Butter. 10–20 g. per head daily.
- **Water-soluble B.** Marmite. 2 g. per head daily.
- **Anti-scorbutic factor.** Orange juice. 10 cc. per head daily.

The fat-soluble A ration also provided the fat ration. The orange juice and the marmite were always consumed separately but the butter was mixed with the other food and was not therefore always all consumed. As regards the adequacy of these rations previous experience had shown that 200 cc. daily of milk (about 7 g. of butter fat) would keep a monkey in health over long periods (six months and over) when it was the almost exclusive source of fat-soluble A [Barnes and Hume, 1919]. The same amount of fat derived from the same milk ration and about 5 g. of fat derived from wheat germ, of which by no means all was eaten, has been found adequate throughout our scurvy experiments on monkeys.

The antiscorbutic ration was far in excess of that needed to maintain a monkey in health; 2.5 cc. of lemon juice has been found adequate [Chick, Hume and Skelton, 1918], and lemon juice and orange juice, by experiments on guinea-pigs, have been found to have approximately equivalent values (unpublished experiments to which reference is kindly permitted by Miss A. J. Davey).

As regards the water-soluble B ration, the amount needed to protect a monkey is quite unknown, but it was judged that 2 g. daily of marmite should
amply suffice, as it evidently did, for the onset and control of any symptoms which occurred were entirely independent of the supply of this factor. The value of the commercial yeast preparation “marmite,” for preventing the onset of polyneuritis in pigeons fed on a polished rice diet, had already been demonstrated by us [Chick and Hume, 1917].

The rest of the diet was composed of sugar, cornflour (maize starch, almost protein-free, supplied by the kindness of Messrs Brown and Polson), salt, and corn gluten; a small daily ration of apple or banana was given as a relish. The corn gluten which was almost the sole source of protein in the diet was a product of the manufacture of corn starch; it was similar to that described by Osborne and Mendel [1914, 2, p. 5] for which the following composition is given:

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zein</td>
<td>31.25</td>
</tr>
<tr>
<td>Maize glutelin</td>
<td>13.75</td>
</tr>
<tr>
<td>Total protein</td>
<td>45.00</td>
</tr>
</tbody>
</table>

The remaining 55% of the corn gluten is oil and carbohydrate.

The product was supplied as a dry cake by the kindness of Messrs W. Mackean of Paisley, and served the purpose well as it was not too unpalatable. No special analysis of it has been attempted, for the figures would have had no value in the interpretation of the results since it has not been attempted within wide limits to determine how much the monkeys consumed.

Table I.

Daily ration offered but not always consumed.

Items common to Diets I, II and III.

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>Total quantity</th>
<th>Protein</th>
<th>Carbohydrates</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butter ...</td>
<td>...</td>
<td>10-20 g.</td>
<td>0-1-0.2 g.</td>
<td>8.4-16.8 g.</td>
</tr>
<tr>
<td>Banana ...</td>
<td>25 g.</td>
<td>0.3 g.</td>
<td>5.5 g.</td>
<td>0.15 g.</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>Apple ...</td>
<td>25 g.</td>
<td>0.1 g.</td>
<td>3.5 g.</td>
<td>0.1 g.</td>
</tr>
<tr>
<td>Sugar ...</td>
<td>26 g.</td>
<td>—</td>
<td>26 g.</td>
<td>—</td>
</tr>
<tr>
<td>Orange juice ...</td>
<td>10 cc.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cornflour biscuit ...</td>
<td>34 g.</td>
<td>—</td>
<td>34 g.</td>
<td>—</td>
</tr>
<tr>
<td>Marmite ...</td>
<td>2 g.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Totals</td>
<td>...</td>
<td>0.2-0.5 g.</td>
<td>63.5-65.5 g.</td>
<td>8.5-17.0 g.</td>
</tr>
</tbody>
</table>

Table II.

Variable constituents of Diets I, II and III.

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>Total quantity</th>
<th>Protein</th>
<th>Carbohydrate and fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zein</td>
<td>Other protein</td>
<td>Total protein</td>
</tr>
<tr>
<td>Diet I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn gluten</td>
<td>50 g.</td>
<td>15-6 g.</td>
<td>6-8 g.</td>
</tr>
<tr>
<td>Corn starch</td>
<td>30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diet II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn gluten</td>
<td>32</td>
<td>10-0</td>
<td>4.4</td>
</tr>
<tr>
<td>Corn starch</td>
<td>45</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diet III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn gluten</td>
<td>17</td>
<td>5-3</td>
<td>2.3</td>
</tr>
<tr>
<td>Corn starch</td>
<td>62</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
The corn gluten was fed in three different proportions, Diets I, II and III as set out in Table II. Table I shows the food common to Diets I, II and III, Table II shows the starch and protein values (calculated from the above percentage composition for corn gluten) in which Diets I, II and III differ from one another. For the total value of any of the three diets the values in Table I must be added to it and it must be remembered that these figures represent, approximately only, the amount offered to the animals; it is not to be supposed that the total ration offered was consumed for it never was. In experiments such as these the difficulty of getting the animals to consume the monotonous and rather tasteless food for a period of many months is very great; it is a difficulty which it would seem can never be completely overcome, for even if the animal eats the diet well when in health it usually begins to lose appetite when it begins to sicken. The partial starvation which results, with the consequent general lowering of the metabolism, seems to have the effect of moderating the development of the typical and florid symptoms of any deficiency disease. The distaste of a sick animal for the diet also makes it impossible to obtain that rise in weight, following a cure of the symptoms, which is desirable in order satisfactorily to clinch the cure.

Every effort in the present experiments was made to render the food palatable; part of the cornflour was cooked up with the corn gluten into a sort of blancmange and the rest of the cornflour was made into a biscuit through the kindness of Messrs Huntley and Palmer. These efforts were however only moderately successful as partial starvation certainly hastened the decline in weight, particularly in the case of two out of the three monkeys. After symptoms had been alleviated by a modification in the diet it was also found that it was not possible to do more than arrest the fall in weight; the animals did not begin to regain weight until they were put on to a normal diet; on that however they regained weight rapidly, showing that the whole of their trouble was dietary.

The experiments concern three monkeys only, Lazarus, Diana and Jonathan. They all belonged to the species *Macacus rhesus*; this species was chosen because it is one which has an almost hairless, flesh-coloured face, upon which it was hoped that any skin lesion or erythema would show up clearly; much of the rest of the body is dark bluish in colour.

Attempts were made to study the effect of direct sunlight in producing or in increasing any skin lesions that might appear; some results were obtained during the summer but the most important part of the experiment, *i.e.* that in which Diana was upon Diet III, fell in the winter months when sunshine was not available.

Of the three animals, two, Lazarus and Jonathan, lost weight on Diet I (total protein content 23 g.; total protein other than zein 7·3 g.); they were therefore retained on it throughout (Lazarus 92 days, Jonathan 195 days). The third, Diana, liked the corn gluten feed much better and almost maintained weight for 90 days on Diet I and for 26 days on Diet II (total protein...

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15 g.; total protein other than zein 5 g.). It was not until she received Diet III (total protein 8.2 g.; total protein other than zein 2.9 g.) with its very much lower protein value that she also began seriously to lose weight. The three diets did not differ to any extent in palatability and there seems no doubt that the only reason, at any rate at the commencement of Diet III, for the loss in weight in this case, when at last it did begin, was the lower level of protein intake on Diet III.

The two monkeys, Jonathan and Lazarus, which lost weight on Diet I form one group and the third monkey, Diana, which only began to lose weight when put on to Diet III stands apart. The two first showed only incipient symptoms, the third developed skin lesions of a striking type; the inconclusive skin symptoms of the first two were however identical with the incipient symptoms of the third. It seems probable that Jonathan and Lazarus were suffering from partial starvation, Diana on the other hand was not, at any rate in the earlier stages of the experiment.

A description of the symptoms, together with an account of attempts which were made to perform cures with tryptophan, lysine and caseinogen, will be found described in detail in the protocols; the cures were only partially successful except in the case of Diana, whose cure with caseinogen was of a startling and dramatic nature.

Protocols.

Lazarus. Diet I, Male. Initial weight 2540 g. (see weight curve, Fig. 1). This animal at once began to lose weight on Diet I and on the 51st day showed a faint erythema on the face, particularly on the bridge of the nose, after spending an hour on the roof in direct sunlight (May 15th).

The mouth at this time was rather unclean and the gums inclined to bleed; the animal was subdued and there was some intestinal upset, the abdomen being often distended with gas. It should be noted that this animal was one always rather subject to digestive disorders. The stools were loose, sometimes amounting to diarrhoea.

The erythema, which was of a papillo-macular type, continued intermittently but progressively for the whole of the rest of the experiment. It was never very marked; it left patches which remained faintly pigmented for a few days and sometimes scaled off; it was most marked on the brows, retreating back into the hair, but it was also apparent on the cheeks and on the bridge of the nose and sometimes on the neck, down to the chest and trunk and even on the inner sides of the thighs.

The appetite was bad and the meals were only partially consumed. About the 85th day the animal was becoming very weak, all the symptoms were aggravated and the mouth was somewhat sore inside and at one corner. The abdomen was very much distended with gas.

On the 89th day the condition seemed very precarious and 0.2 g. tryptophan, i.e. the tryptophan from about 13.3 g. of caseinogen, taking the value 1.5 %
tryptophan in caseinogen, as given by Mathews [1916], was given by the mouth.

On the 90th day the animal was much weaker, the lips sore and the diarrhoea bad; 0.2 g. tryptophan was again given and later in the day 3–4 g. of caseinogen with brandy. No improvement took place; the animal was however probably in any case too far gone before a cure was attempted; the next day it was moribund and was chloroformed.

The post mortem showed nothing remarkable; the body was much emaciated and the caecum and colon greatly distended with gas and soft faeces, but the walls of the intestine showed no special alteration.

There was no sign of tuberculosis or other intercurrent disease.

Jonathan. Diet I, male. Initial weight 2170 g. (see weight curve, Fig. 1). This animal also began to lose weight from the first. On the 33rd day a dull
reddish patch began to appear about the centre of the lower lip, where the
skin and mucous membrane meet, and there were also patches on the scrotum.
These were at the time attributed to some skin disease, but they cleared up
on a good diet and the patch on the lip closely resembled the patch on the
lips developed in the case of Diana.

On the 49th day slight erythema below one eye was noticed but it did
not appear to be much enhanced by exposure to sun.

The stools were generally well formed, sometimes rather soft and of a
greenish brown colour; diarrhoea was never observed.

The erythema progressed and appeared on the brows and face; on the
71st day it was observed faintly on the chest and on the inside of the thighs.
The appetite became bad and the intake of food much diminished, even the
ration of banana was often refused. The coat became very scanty, the skin
scurfy and chaffy, the gums receded from the teeth but the tongue and inside
of the mouth were not sore. The legs were tremulous. The animal had now
lost about 20% of its initial weight and seemed in a very dangerous condition;
a daily ration of 0·2 g. of tryptophan was therefore initiated on the 92nd day
and continued without any change or addition for 61 days. The loss in weight
ceased and the animal seemed brighter and better but no gain in weight took
place. Erythema was still recorded from time to time and the animal continued
in very poor condition; when the treatment started however there seemed
no possible likelihood of life being prolonged for another 61 days if no treat-
ment were given.

On the 153rd day of the experiment 0·4 g. of the unseparated di-amino-
acids lysine, arginine and histidine (prepared from caseinogen) was adminis-
tered by the mouth together with the 0·2 g. of tryptophan already being
given; this treatment was persisted with for 29 days up to the 181st day of
experiment but no marked change was observed. Addition of further butter
and more cornflour failed to make the animal put on weight; probably it
liked the diet insufficiently well to eat enough to make it put on weight in
any case.

On the 181st day the amino-acids were dropped and 5 g. caseinogen daily
were substituted and this treatment was continued for 14 days; still the
weight did not rise and on the 190th day it was put on to normal diet of
rice, wheat germ, autoclaved milk and cabbage. The weight rose at once by
leaps and bounds until it was far above that at the start of the experiment.
In 34 days on normal diet the monkey had regained its weight at the start
of the experiment and in another 40 days it had increased 500 g. beyond that.
Its coat now became thick and glossy; normal change of dentition set in,
all trace of skin lesions vanished and the animal, from being depressed and
sedentary, became happy and playful. There could be no possible doubt that
the whole of its disorder had been dietary.

Although the symptoms in this case were insufficiently marked to be able
to say whether a real cure took place or not, it is to be noted that in the
first 92 days of the experiment it lost 20 % of weight and was judged to have reached a precarious condition in which death could not be far off if no change in treatment were instituted. The additions to the diet which are detailed above were then made, starting when the animal's weight was 1750 g.; these additions were continued in all over a period of 103 days, yet no further loss in weight took place after they were instituted and when at the end of the 103 days the animal was put on to normal diet its weight was the same, i.e. 1750 g.

Diana. Diets I, II and III. Female. Initial weight 3130 g. (see weight curve, Fig. 1). This animal very nearly maintained weight for 90 days on Diet I, during which period she was occasionally exposed to the sun and very faint erythema of the face was sometimes observed.

On the 91st day the protein and starch were readjusted to the proportions of Diet II which was continued for 26 days; weight was still practically maintained and erythema was not observed but some scurfiness of the skin was present.

On the 117th day Diet III (total protein 8·2 g.; total protein other than zein 2·9 g.) was started and a marked loss of weight set in. Faint erythema with scurfiness of the skin was observed which was intermittent but also progressive.

Menstruation, which had been regular previous to the experiment, ceased and was never observed even on Diet I. The stools were fairly firm and greenish brown in colour.

On the 218th day, the face and brow ridges were distinctly marked with patchy erythema and there was oedema of the eyelids. The spots increased rapidly in brightness, particularly on the bridge of the nose, cheeks, brows and upper lip. A reddish patch of dermatitis began to develop at each angle of the mouth where skin and mucous membrane meet.

Local oedema continued to increase and appeared about the upper lip and face generally. The butter ration was increased and the oedema disappeared for a time, only to reappear later with much greater severity.

All the symptoms continued to progress; the whole skin became very scurfy; the face was often brilliantly red; the mouth showed rough red patches of dermatitis at the angles; these patches however only involved the very edge of the mucous membrane and the actual interior of the mouth appeared normal throughout. The skin of the face evidently itched for the monkey was seen to rub it and scabs were produced in this way. Strong illumination, even from an electric light, brought up the erythema and caused her to hide her face.

On the 253rd day of experiment (137th day of Diet III) the sketch (Plate V) for which we are indebted to Miss M. Rhodes was made.

On the 279th day of experiment (163rd day of Diet III) the animal's condition was deplorable; the oedema which was strictly confined to the area of erythema, i.e. on the face, was so severe that in the morning and evening when
the head was held down in sleep she could scarcely open her eyes; during the day, when the head was held up, the oedema tended to run down under the chin. The animal was very emaciated, having lost nearly 25% of weight; the face was erythematous all over; the patches of dermatitis at the corners of the mouth were large and very red, the skin was scurfy, the hair almost all gone, the tail was unhealthy looking with patches of dermatitis. On this day 0.2 g. of tryptophan was given by the mouth and by the next day the oedema was distinctly less. The next day 0.4 g. of tryptophan was given and the same dose continued daily for six days; the oedema continued somewhat less but it had always been intermittent; the erythema did not decrease and the animal's condition appeared to be very precarious. Fearing intercurrent disease, 5 g. caseinogen was given which was replaced after one day by the commercial preparation plasmon, this being simply caseinogen in a more palatable form, since much difficulty was experienced in administering the caseinogen.

On the third day from the beginning of the caseinogen treatment, the oedema was almost completely gone, the erythema was reduced, with the nose and eyelids desquamating healthily. The backs of the fingers, parts of the feet and tail also desquamated extensively, showing that some superficial dermatitis must have been present though not easily observable on the dark skin of those parts. Some slight gain in weight took place and the angles of the mouth began to heal; these patches of dermatitis were so severe that, although they began to improve at once, 20 days of the plasmon treatment elapsed before they were fully healed. After 12 days the plasmon had been increased until sometimes as much as 10 g. were taken, but no marked increase in weight ensued. The lesions however completely healed; although the nose remained for long afterwards of a rather purplish red, the oedema had completely disappeared and the whole skin of the face, body, tail, hands and feet was clean. The appetite, however, continued very bad, the animal seemed weak, the weight dropped suddenly and it was decided on the 307th day of experiment (191st day of Diet III), 28 days after the attempts at cure started, to put her on to normal diet, as it was deemed impossible to secure a rise in weight while the same monotonous food was continued. The animal fell upon the food ravenously and a rise in weight at once commenced, strength began to come back and at the time of writing the animal bids fair to show the same return to condition as was shown by Jonathan in similar circumstances [see Postscriptum]. Considerable importance is attached to this return to form as it excludes all possibility of tubercular or other infection having played any part in the decline.
The foregoing experiments show that three monkeys fed on, or consuming, a low protein diet, whose proteins are at the same time of low biological value, lose weight rather slowly, two possibly from partial starvation through distaste for the diet and only showing mild skin lesions, while the third, which ate well of the diet, at first, showed florid skin lesions and co-extensive localised oedema. The development of these lesions took place after variable, rather lengthy periods.

Attempts to cure with tryptophan failed in one case which was probably too far gone when the cure was attempted, staved off death for many weeks in one case and slightly modified the severity of symptoms in one case.

An attempt to cure with a mixture of lysine, arginine and histidine seemed to have little added beneficial effect in the one case in which it was tried.

Addition of 5–10 g. caseinogen failed in the one very ill case, gave little added benefit in the second case but brought about a dramatic cure in the case where the skin lesions were most severe.

Owing to the small number of animals under consideration, it is not permissible to draw too definite a conclusion; the skin symptoms produced did however closely resemble those of pellagra and there can be no doubt that they were of dietary origin. The skin lesions were bilaterally symmetrical and appeared to be heightened by direct sunlight as in pellagra. They were the only symptom present in all three cases. Diarrhoea and flatulence only occurred in one case out of three, in an animal normally liable to digestive upset. In human pellagra diarrhoea is by no means universal. Nervous symptoms, such as occur in advanced cases of pellagra, were not observed.

As regards the localised oedema which developed in the case of the monkey Diana, which was co-extensive with the dermatitis, this is not uncommon in pellagrins when the dermatitis is acute. The association of general oedema and pellagra has been described by Bigland [1920] among Turkish prisoners of war in Egypt. General oedema has, however, been widespread amongst starving populations during and since the war, but whether it be occasioned by one or many dietetic deficiencies is at present uncertain. A single experiment by Harden and Zilva [1919], in which it followed prolonged feeding of a monkey upon a diet devoid of fat-soluble A but otherwise adequate, is an indication.

In the case of our experiments, the diet offered to the animals was deficient only in protein of good biological value but the exact amount of food consumed could not be determined, the quantity uneaten being often considerable, as their appetites became capricious. As to how far the pellagra-like symptoms and wasting were due to an inadequate supply of tryptophan, of lysine or of both, or of some other unappreciated constituent of the protein, the experiments do not supply an answer.

A portion of the expenses of the investigation was defrayed by a grant from the Medical Research Council, to whom our thanks are due.
Postscriptum.

On the 324th day, that is 17 days after the return to normal diet and at a time when the monkey appeared to be rapidly recovering weight and strength, it was found early one morning in convulsions. These recurred at frequent intervals during the day.

Three grains of chloral hydrate were administered and the animal slept, but on waking a further series of epileptic fits succeeded one another at shorter and shorter intervals.

The spasms were entirely bilateral, at first clonic and involving the flexors and terminating with tonic contractions in which the extensors overpowered. Next day the animal was very exhausted, refused food and the intervals between the fits became reduced to a few minutes.

As by evening there seemed little chance of it surviving the night, it was killed by chloroform. At the autopsy there was total absence of fat and the hair had to a large extent disappeared from the body, but the organs all appeared perfectly healthy. There was no abnormality discovered by the naked eye in the nervous system. Portions were taken of various parts for microscopical examination and will be reported upon later by Miss Tozer.

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