PELLAGRA IN AFRICAN CHILDREN

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Definition

Pellagra in African children and infants displays certain unusual features. It is an endemic disease which has been described in certain African tribes both on the East and West Coast and also in Central Africa. It is characterized by an acute course progressing usually towards a fatal termination in the second and third month. It displays itself by oedema which is often severe, a rash which in some respects is unlike the classical description of that in pellagrous adults, diarrhoea, dysentery and perhaps fatty stools. Only a few cases develop obvious neurological signs. Differing thus from the more common but slow and remittent type of the disease as seen in adults no clinical observer who has recorded cases in Africa has been able to agree that it is pellagra. Its interest for English clinicians lies in the points in which it resembles and yet differs from pink disease. It is known variously in Africa as 'Gillan's oedema,' 'Williams's disease,' 'mal-nutritional oedema,' and is believed to be a new clinical entity.

General considerations

It is not suggested in this article that the disease is anything but pellagra. Nevertheless until this opinion has proved acceptable it may be as well to designate it 'infantile pellagra' since slow and remittent pellagra which conforms with the usual descriptions has been described in children (Goldberger and Wheeler¹²). The addition of any terminology to a subject as large as pellagra is regrettable, but this variety displays certain unusual features, notably oedema, which is sometimes extensive, pallor of the negroid skin, and fatty stools which cannot easily in the present state of knowledge be related to the usual clinical findings in pellagra.

Further support for a possible variation of the clinical picture of pellagra when found in African children may be gained from a consideration of the fact that other known deficiency states display a different clinical picture in children and adults. Scurvy was first known in adults; then Barlow gave his classical description of the disease in infants. Beri-beri was first known in adults; more recently Bray² has given a description of the infantile variety. Rickets and osteo-malacia stand largely to one another as the same deficiency in children and adults. If pellagra occurs in infants it would be surprising if it reproduced exactly the same clinical condition as found in adults.

Historical

Infantile pellagra has been described by various observers in East and West Africa who believed that they were dealing with a new clinical entity, and rejected the idea that the disease was a manifestation of pellagra.

Sequeira²⁷ has recently drawn attention to the fact that the first brief clinical description was given by Procter²³ while working in the Kikuyu reserve of Kenya Colony:—

‘The other disease occurs only in quite young children, the child is nearly always an extraordinary light colour and is usually brought up on account of swelling of the feet. The only history obtainable appears to be that in a number of cases there had been slimy motions for some time. As the disease progresses the child becomes paler in colour and the pigment seems to be concentrated into a curious black desquamation which is most often seen at the bends of the elbows and knees, and there may be a general oedema. The child, so far as my information goes, nearly always dies.’

Williams³⁵ then recorded her observations in the Gold Coast, reporting some twenty cases, with three post-mortem examinations. She gave a good description of the skin changes and the oedema. The gastro-intestinal signs were also noted, but the stools, which were not analyzed, did not appear fatty. No neurological changes apart from irritability were noted by her. A nutritional deficiency was postulated and in her opinion the distribution of the rash precluded the possibility of pellagra.

Gillan¹⁰ unaware of these articles described twelve cases of a mysterious form of fatal oedema attacking infants in the Kikuyu country near Nairobi, Kenya Colony. He noted the skin changes and proved the high fatty content of the stool in one case. Bacilluria was present in two cases. Two post-mortem examinations were performed, but apart from a fatty liver nothing else was noted. The blood changes were described by him and were recorded in six patients, three of whom had a hypochromic anaemia and three a hyperchromic anaemia. In his opinion the disease was a new clinical entity and he considered its relationship to coeliac disease, sprue and pancreatic disease and also saw close clinical analogies to pink disease.

Meanwhile Stannus³⁰ reviewed at length the cases described by Williams, and to him belongs the credit of stressing the fact that the skin eruption was certainly typical of pellagra in native children.* Williams³⁶ published a second article which drew from Stannus³¹ even more stringent criticisms. Stones³⁷ and Carman³ recorded cases in Uganda and Kenya of ‘Gillan’s oedema’ for they were unable to accept the attention drawn by Loewenthal¹⁷ to the opinion of Stannus³⁰. Dyce Sharp²⁸ recorded another case on the West Coast. Much confusion has therefore arisen in the tropics where ‘Gillan’s oedema’ and ‘malnutritional oedema’ are described on the East Coast and finally ‘Williams’s disease’ and ‘Kwashiorkor’ in West Africa.

Finally, a long review was published by Stannus³² of these cases. He was then of the opinion that Gillan’s cases ‘would appear to be more closely allied to child beri-beri.’ The writer has visited the hospital where Gillan worked; it is close to the place where these observations were made and it is certain that the disease is the same at both places.

* After seeing the photographs published with this article, Stannus is further confirmed in this opinion.

The present series of observations

1. Locality, distribution, age and sex.—Observations were made on twenty-six patients who were admitted to Nairobi Hospital, Kenya Colony, during 1934 and 1935. In addition, in neighbouring hospitals of Kikuyu country some twenty other cases have been observed by the writer but are not included in this series. All were African children. Such children come to Nairobi Hospital largely from the surrounding Kikuyu reserve and to less extent from the less numerous and more scattered Masai and Kamba tribes. Immigrant labour in Nairobi township, mainly Luo, is also the source of nearly half of the routine admissions to the children's ward, and resident Swahili families in the native locations of Nairobi normally contribute a few in-patients. Nevertheless, the disease shows a definite selection of the Kikuyu tribe (24 cases); there was only one case from both the Luo and Swahili tribes. This is consistent with a disease due to a dietetic deficiency.

Infantile pellagra occurred only in children from six months to four years of age. The age incidence was as follows:—6 months—1 case, about 1 year—3 cases, about 2 years—12 cases, about 3 years—5 cases, about 4 years—5 cases. Two typical cases of the usual type of pellagra were seen by the writer in older Kikuyu children aged 9 and 12 years respectively. Both had scaly dermatitis on the lower arms and legs, relapsing diarrhoea and signs of involvement of the pyramidal tract. One had slight oedema of the ankles and proceeded to dementia and death. Pellagra, however, is at present almost unknown in the native adult community and Dr. H. L. Gordon, Visiting Physician to Mathari Mental Hospital, Nairobi, in a private verbal communication, stated he had never seen a case of dementia due to pellagra.

Stannus³² has reviewed at length the published reports on pellagra on the East and West Coast. Briefly, apart from pellagra in institutions, such as jails, few cases have been reported, but it is suggested in this review that this disease may be much more common than might be expected, since it may easily be overlooked by those who are unacquainted with the protean manifestations of the disease. The writer, however, has not yet seen pellagra in an adult of Kenya or Uganda. The series comprised 14 males and 12 females.

2. Seasonal distribution.—The first signs of illness appeared with equal distribution during all months of the year with the exception of July and August, when no cases occurred. These months have the least amount of sunshine, for the sky is usually completely clouded over. Other months have several hours of sunshine each day. The hottest season is from January to March. During the rains which occur mainly in November, April and May there is much sunshine between the heavy showers. It has been stated that in temperate regions pellagra is found more during the spring months. In the tropics there appears to be no seasonal variation and in a series as small as this the absence of new cases in the cloudy months of July and August may be only fortuitous.

3. The clinical picture.—(a) **THE ONSET.** Patients presented themselves on an average about a month after the alleged onset of the complaint, but careful questioning revealed the fact that the child had been ailing for some time before the occurrence of definite illness had been recognized. During this preliminary period the child had appeared wretched, had shown irritability, photophobia, a desire to sit down rather than to run and play, some anorexia and perhaps some puffiness of the face, hands and feet. These preliminary signs may simulate pink disease, a point which is discussed later.

After this preliminary period the occurrence of any one or all of the main signs of the disease; oedema, the rash or gastro-intestinal symptoms ushered in unmistakable signs of illness. Of these oedema was usually the first to appear but any one of these three conditions may precede by a week or two, but seldom longer, the appearance of one or both of the other signs.

FIG. 1.—Infantile pellagra, showing large areas of the exanthem.

(b) **OEDEMA.** The oedema was stated to have begun abruptly in the majority of cases and to have proceeded to its greatest extent in a few days. It might be slight and in two cases it was absent throughout the entire illness. In the majority it soon became moderate, in a minority it became extreme. When slight it was limited to the face, hands and feet. When severe it was generalized; the face resembled that of a patient with acute nephritis and the eyes were often completely closed. Serous sacs were also involved. The severe oedema was usually more in the dependent parts so that on waking in the morning a child who had slept on one side might have the lower eye completely occluded. In rapidly progressive cases death intervened in the oedematous stage, in less rapid cases the oedema showed a tendency to abate or even to disappear before death, recovery, or an intermediate state of partial recovery ended the period of observation in the hospital. As the oedema disappeared great emaciation was noted in un-

favourable cases and it was as emaciated infants but showing little or no oedema that bodies came most frequently to post-mortem.

(c) **THE EXANTHEM.** This was present in all except one early case, which presented only oedema and gastro-intestinal signs. Many cases, however, occur of children who have oedema and some gastro-intestinal upset but in the present state of knowledge it would be unwise to include them. Doubtless some are cases of infantile pellagra, but until more is known of this condition, there would be a tendency to include other diseases such as errors of feeding, cachectic oedemas, nutritional oedemas, anaemic

FIG. 2.—Showing oedema, 'crazy pavement' black patches and pale areas, and generalized pallor of the skin except at the black patches.

oedemas, among those who certainly have all the stigmata of infantile pellagra. The skin changes were extremely complex but they may be discussed under the various heads, and indeed in many cases there appears to be a definite sequence of evolution. This cannot be demonstrated in the majority of cases.

(i) Black patches occurred as jet-black areas of hyperkeratosis. They were slightly raised above the surface of the surrounding skin, but this was never obvious except to the closest inspection. They never resembled the

raised kerato-follicular lesions of Majocchi which are a classical variety of the pellagrous rash, nor the enlarged sebaceous glands of Nicholls²², nor the pilo-sebaceous folliculitis of Loewenthal¹⁶, all of which are in the opinion of Stannus³² probably identical, and are manifestations of pellagra. Black patches were the commonest early characteristic lesion. They varied in size from an eighth of an inch to that of one continuous plaque covering most of the abdominal wall. The patches often extended in area until they became confluent and it is assumed that the large plaques arose in this

FIG. 3.—Showing alopecia, pale hair, pale areas, septic skin lesions.

manner. The patches showed a tendency to exfoliate disclosing underneath areas of pink or pale skin. They had usually a smooth shining flat surface as if black varnish had been painted on to the skin and had subsequently cracked. They thus resemble the pellagrous exanthem as described by Stannus²⁹ in Nyasaland.

(ii) Pale areas varied in shade and colour being dead white, coffee-coloured, pink or copper-coloured. In many cases they were found where it could be presumed that black patches had peeled, or septic skin lesions had occurred, but it was not by any means certain that all pale areas had arisen in this manner. Pale areas were commonest where a discharge had favoured early exfoliation of the black patch, that is around the mouth, nose, anus and penis and also in the moistened groins and armpits.

(iii) Sodden areas of heaped-up white skin or of raw excoriated skin were seen at the lateral corners of the mouth, around the nostrils and canthi of the eyes, and around the anus. The prepuce was frequently ulcerated either at its free surface or on its inner surface. The labia majora were often completely raw and sodden. The scrotum showed raw excoriated areas.

(iv) Fissures occurred at the natural flexures of the skin but only in the later stages of severe cases. Deep linear fissures, invading the subcutaneous layer and showing no surrounding inflammatory reaction or discharge were seen in the groin, in front of the elbow, above and around the anus, at the lateral corners of the mouth, at any part of the lips, at the corner of the nostrils and above and below the pinna.

(v) Generalized hypo-pigmentation of the skin occurred in most cases in addition to the localized hypo-pigmentation of the pale areas. In the majority, but by no means in all, the whole of the body became pale, so much so that the children might be a pale coffee-colour and could be diagnosed correctly even when seen a long way off. On entering a ward full of black babies these coffee-coloured patients attracted so much attention that from this alone it was possible to diagnose infantile pellagra. It is quite true as Williams³³ has stated that all African patients who suffer from any cachexia show generalized loss of skin pigment, but this change is seldom a marked one. In infantile pellagra the loss of pigment is usually more marked than in any other disease, and is therefore in the opinion of the writer probably a specific change and not merely a manifestation of cachexia. In patients who are recovering the pigment re-appears.

(vi) The hair and nails showed changes. In the former they were so marked that they must be considered specific; in the latter the changes are found in other conditions of cachexia. There was a marked loss of hair. In some cases almost complete alopecia was found and the remaining hair was all shades of chocolate, coffee, or even grey and white; it was also thin, brittle and straight. Normal African hair is coarse, tough, extremely curly and jet black. In conditions of cachexia the African hair tends to become straighter and paler but the changes are not as marked as in infantile pellagra. The nails were often as thin and soft as paper and exhibited longitudinal ridging. The hair changes have been noted in pellagra and have been produced in experimental animals suffering from a deficiency of vitamin B₂ by Goldberger and Lillie¹¹.

(vii) Septic skin rashes of all varieties such as impetigo, bullous impetigo, pustules, and boils were common.

The character of the rash was modified by the oedema for the black patches, especially if large, did not allow distension to occur. The normal furrows of the skin appeared as pale shallow cracks leaving the black patch as 'crazy pavement,' an excellent description of Williams³⁵. In early cases the skin all over the body appeared slightly rough and branny desquamation occurred. The skin had an atrophic shining appearance. These early changes have been described in pellagra, but by themselves are not in the opinion of the writer sufficiently distinctive to be included under the specific changes seen in African infants. The distribution of the rash, as Stannus³⁰ has pointed out, must be regarded as suggestive of pellagra although it does not conform to the usual description as given in text-books, and for this reason neither Procter, Williams or Gillan considered it pellagrous. In adults pellagra usually appears as an insidious disease and the rash appears as successive crops of dermatitis on the exposed surfaces of the nape of the neck, the bridge of the nose and the backs of the hands. These are the parts irritated by trauma, wind, dust and sunlight and Stannus³² has drawn attention to the fact that it cannot be adequately explained in terms of solar irradiation. Undue attention has been paid to this in the usual text-book descriptions, but it cannot be stressed too much that the rash appears in areas subject to all forms of irritation. In any case the pellagrous rash in semi-naked African children might be expected to differ from that in clothed Europeans, whose skins are not protected from sun trauma by the deep pigment present in the native skin.

The rash occurred principally on the areas exposed to the irritation of pressure or of some discharge and bore no relationship to the parts exposed to solar irritation. Pressure produced the rash over the buttocks, back of the thighs, and the calves of a sitting child, and in addition over the back of the trunk, the great trochanter, the back of the shoulders and arms especially at the elbows of a recumbent child. The scrotum was commonly affected and appeared to itch for scratching was frequent. Clothing was variable in nature and extent so that its rubbing had usually produced changes over the napkin area, outer sides of the thighs and knees. The irritation of discharges had produced the rash in the perineum (due to diarrhoea) and around the mouth (from increased salivation) and nostrils (from the nasal discharges). This was the essential distribution of the rash in most cases. Severe cases may show the rash in all parts of the body, but in every case the changes were maximal over the buttocks and perineum. Solar irritation had in a few cases produced the typical pellagrous scaly dermatitis on the backs of the forearm and the dorsum of the foot and the crown of the head. In one case this rash ended dramatically where a short sleeved shirt finished in the upper arm. In most cases the skin appeared extremely irritable and scratching was excessive. This may explain the frequent occurrence of septic skin rashes which complicated the clinical picture.

(d) GASTRO-INTESTINAL SIGNS. Loss of appetite was frequently severe. The children often refused everything but the nipple, which was continuously sucked by day and by night. Other children sucked fingers or clothes and made continuous champing movements with the jaws. Vomiting was not common except at the outset. In a few cases the tongue was furred and raw at the edges but usually it was smooth, denuded and contained no fur at all. Aphthous stomatitis was present in a few cases. Salivation appeared excessive. It is impossible to state if soreness of the mouth, so suggestive of pellagra, was present, but it may be presumed from the difficulty in feeding the child with anything but liquid food. All except four cases gave a history of loose stools and subsequently developed these while in hospital. There were spontaneous remissions and exacerbations of this intestinal upset. During the exacerbations blood was frequently seen in the stool, in two cases blood and mucus were passed, but as subsequently stated no cause was found for this dysentery. During less severe exacerbations diarrhoeic stools of all varieties of consistency and colour were seen. Fatal cases often had persistent diarrhoea.

When the gastro-intestinal symptoms were not severe the majority of patients passed a stool which has been accurately described by Gillan¹⁰. It was pale, soapy, soft and bulky and had a peculiar offensive odour. Undigested food could frequently be recognized by the naked-eye. As discussed later it was found by analysis that fat was present in this stool in large amounts. This type of stool improved under treatment in favourable cases.

(e) NEUROLOGICAL SYMPTOMS AND SIGNS. The onset was marked by wretchedness and irritability. The children refused to play and sat sadly, then took to bed. In bed they lay curled up and covered by bed-clothes. Photophobia and red eyes were often present. Children were petulant, were continually crying, were suckled continuously by indulgent mothers, hanging almost by the hour from the nipple. Others sucked fingers or a thumb. Some indulged in excessive scratching which was unexplained by any known cause. They presented a constant picture of misery. In these mild cases the only neurological sign found in the majority, but by no means all, was marked hypotonia of the muscles. The fingers could commonly be bent backwards until they lay parallel to the forearm and the whole foot could be dorsiflexed to an angle of forty-five degrees with the lower leg. Limbs could be twisted into unnatural positions. In these cases no alteration was detected in power, sensibility to pain or in the tendon reflexes. The majority died in this condition with no other sign of nerve involvement and the majority who recovered showed nothing else.

In eight patients, however, the picture of hypotonia and the absence of other neurological signs gave place to the picture of hypertonia, increased tendon reflexes and an extensor plantar response. The first indication of this change was an increase of tone most marked in the legs which were adducted and flexed at the hips. Later the arms were held rigidly in general flexion. Tremors were noted in a few of these cases in the arms and the

legs, but never in the tongue. The tendon reflexes became unduly brisk but ankle-clonus was never definite. In three cases both plantar responses became definitely extensor at an age when the normal response should be flexor. The abdominal reflexes were never lost. No cranial nerve involvement was detected, but the optic disc was seldom examined. Muscular cramps were common in the legs of these advanced cases.

Changes in the special senses were limited to the eyes where conjunctival injection and increased lachrymation were common. Mild conjunctivitis and blepharitis were common. As a food deficiency had been postulated every case was examined for xerophthalmia but this was only found in one case as a terminal condition.

Drowsiness, so typical of pellagra, was frequently seen in the last few days of life. Dementia was never seen but its recognition in young native children is extremely difficult and would not be expected in these acute cases.

(f) URINARY SIGNS. A faint trace of albumin was detected by the boiling test in eight cases. This could be explained by urinary infection, fever, toxæmia and cachexia; and albuminuria is seen in pellagra. Williams^{3.5} and Gillan¹⁰ detected no albumin in their cases so that in their opinion this formed the main distinction from nephritic oedema. In the opinion of the writer nephritis is excluded by the absence of other signs of nephritis and the presence of other signs of infantile pellagra, notably the rash. Maclean's urea concentration test was performed in these eight cases of albuminuria and gave normal concentrations except in one infant who could not be separated from the mother. She suckled it continuously and diuresis may thus explain the low concentration of 0.9 per cent. urea in the urine. Nephritis was not detected at post-mortem examination. Bacilluria was common and *B. coli* were cultured in large numbers from the catheter specimens of five cases. Pyuria was detected in three of these specimens.

(g) RESPIRATORY SIGNS. A persistent purulent nasal discharge was often present. A few cases showed signs of bronchitis and a terminal but silent bronchopneumonia was one of the commonest causes of death, being found in half of the cases.

(h) CARDIO-VASCULAR SIGNS. In most severe cases the extremities were unduly cold and clammy, but apart from this no increase of sweating was noted. The pulse-rate was usually quickened but could adequately be accounted for by fever or cachexia. Apart from a terminal heart failure from the same causes, no signs of heart failure were found to explain the oedema or to suggest that the disease was a manifestation of beri-beri.

(i) GENERAL SIGNS. Severe emaciation disclosed itself in unfavourable cases as soon as the oedema disappeared. In less severe cases no increase of weight, that is no growth occurred, until all the other signs of the illness had disappeared. Fever of an irregular type was present in most severe cases, during some period or other of the complaint. In mild cases or those

undergoing recovery the fever was mild or absent, in fatal cases the temperature rose higher. In most cases adequate cause of the fever could be detected in septic skin affections, pyuria, enteritis, bronchitis or bronchopneumonia. Pallor of the mucous membranes was present in severe cases of anaemia.

Investigations

1. Investigations yielding negative or inconclusive results.—Blood films were examined in every case and revealed sub-tertian parasites in four cases due to a superimposed malarial infection. The Kahn test was performed on all infants and their mothers; all the former gave negative results, five of the mothers gave a feeble positive reaction, presumably due to old yaws which was formerly common among the Kikuyu, among whom syphilis is rare. There is thus no evidence that the disease is a manifestation of congenital syphilis as some have suggested and for which the majority have in the past been treated.

The stool was examined twice for ova and cysts and a culture (when possible employing the faecal mucus) was performed on every case. Culture revealed only *B. coli* except in one case in which Morgan's No. 1 bacillus was found. Stools were examined for ova and cysts after spinning with saline and examining the deposit. The following ova and cysts were seen:—*Taenia saginata* two cases, *Ankylostoma duodenale* four cases, *Ascaris lumbricoides* three cases, *Trichuris trichiura* one case, *Giardia intestinalis* four cases, *Chilomastix mesnili* one case, *Strongyloides stercoralis* two cases, *Entamoeba coli* five cases, *Oxyuris vermicularis* one case. No known cause of dysentery or enteritis was found and the oedema cannot be explained by ankylostomiasis.

X-ray films were taken in one case and revealed no evidence of rickets nor were any signs of this disease obtained clinically. Dentition was normal.

2. Investigations yielding positive results.—TOTAL AND DIFFERENTIAL BLOOD COUNTS. These were performed on twenty-cases. Practically no case gave a normal blood picture. Comparison had to be effected with European normals, since these figures for African children resident at Nairobi, a height of 5,000 feet, are not known. Seventeen cases showed varying degrees of microcytic anaemia. The haemoglobin estimated in fifteen cases by Sahli's method averaged 77 per cent. and ranged from 50 to 98 per cent. The red cell count averaged 3,900,000 and ranged from 2,740,000 to 5,290,000 per c.mm. The colour index averaged 0.78 and ranged from 0.57 to 0.98. The mean diameter of the red cells estimated by Eve's halometer averaged 7.64μ . In a few cases polychromasia and stippling were noted in the red cells; apart from this no other abnormality was seen.

Three cases showed a moderate macrocytic anaemia:—

Case 1: haemoglobin 70 per cent., R.B.C. 2,540,000, colour index 1.4, diameter of red cells 8.89μ . Case 2: haemoglobin 80 per cent., R.B.C. 3,600,000, colour index 1.2, diameter of red cells 8.00μ . Case 3: haemo-

globin 80 per cent., R.B.C. 3,700,000, colour index 1.1, diameter of red cells 8.00μ . In these three cases marked poikilocytosis, polychromasia and occasional normoblasts were seen. Megaloblasts were not seen. The first case had 1 per cent. reticulocytes prior to treatment and 8 per cent. a week after this had begun. The third case exhibited 20 per cent. reticulocytes a week after commencing dietetic treatment (marmite).

A slight degree of leucocytosis with a relative lymphocytosis was present in most cases. The white cell count averaged 13,200 and ranged from 8,400 to 23,000, a high count indicating infection.

The differential white cell count averaged:—polymorphonuclears 49 per cent., lymphocytes 41 per cent., mononuclears 7 per cent., eosinophils 3 per cent. No basophils were seen in any of the films. The Arneth index showed a shift to the left in the three cases in which it was estimated.

STOOL FAT CONTENT. Direct smears from the stools were made in every case. Undigested vegetable cells were present in a large number, so were fatty acid crystals and oil globules. Undigested meat fibres were not observed, but the diet contained only a very small amount of meat. Sixteen cases were examined for the fat content of the stool. They were unselected cases; death or early discharge prevented some patients from being examined. The results were expressed as percentages of the dried faeces and the figures were compared with those given by Cammidge. Seven of the sixteen cases fell within the normal range, the remaining nine cases gave abnormally high figures and are now given:—

	CAMMIDGE'S NORMAL. PER CENT.	AVERAGE OF 9 CASES. PER CENT.	RANGE OF 9 CASES. PER CENT.
Total fat	15 - 25	42.9	33.0 - 57.4
Unsoaped fat	10 - 15	30.25	25.2 - 39.1
Combined fatty acid (soaps)	10 - 15	18.62	12.0 - 24.0
Free fatty acids	9 - 13	12.25	0.5 - 30.0
Neutral fat	1 - 2	9.14	2.0 - 24.6

In these nine cases there was a high fat content, nearly twice the normal figure being obtained. This was explained mostly by the high unsoaped fats and to a less extent by the high neutral fat content. Even in the six cases with a normal total fat content five had abnormally high neutral fat figures. There had been a considerable splitting of fat, but not as much as normally occurs since the neutral fats formed roughly a quarter of the total fat content as opposed to the normal ratio of one-tenth. In coeliac disease the splitting is adequate, so that the higher proportion of neutral fats in infantile pellagra than in coeliac disease forms an important distinction between the two diseases.

These findings in infantile pellagra indicate that there are two sources of failure in fat digestion; firstly, a slight failure to split fat (owing to a failure probably of pancreatic secretion), secondly, an even more marked failure to absorb such fat as is split (probably due to atrophic changes in the intestinal mucosa as will be demonstrated later). In coeliac disease there exists only the second factor.

BLOOD SUGAR ESTIMATION. Three cases were examined for the blood sugar variations after an amount of glucose proportional to the weight of the child had been administered. The following figures were obtained and are expressed as milligrams of glucose present in 100 c.c. of blood:—

Fasting level 72 mgm.; 30 minutes 130 mgm.; 60 minutes 137 mgm.; 90 minutes 80 mgm.; 120 minutes 67 mgm.

There was thus a low fasting level and a corresponding flatter type of curve. The number of cases is too few to allow the findings to be regarded as conclusive, but in this connexion the lower blood sugar curves may be compared to those found in coeliac disease, when there is also a failure of fat absorption (Fairley and Ross⁷).

Course and prognosis

Of the twenty-six patients nine died in hospital, five were discharged by impatient parents in an improved condition and ten were discharged free from all clinical signs of disease, and if any of these relapsed they did not report again to the hospital. The average period of stay in hospital of those who survived was about four weeks, after which it usually proved impossible to detain them or to secure their re-attendance. Patients who were rapidly cured presented themselves in the first week or two of the recognized illness; only two of those who were cured had been ill for as long as a month. These early cases responded fairly quickly but not dramatically to the treatment described later. When they were admitted the oedema was usually well marked, the skin changes were only slight, and no definite neurological changes, apart from hypotonia, were detected. Anaemia and fatty stools might be present. Diarrhoea was often present but responded slowly to the treatment. Fever was moderate and disappeared in every case that was improving.

Patients presenting themselves later than a month usually had severe signs. None of them was discharged cured; some were discharged improved after about another month's treatment; the remainder died. Only one of the fatal cases was presented for treatment after having been ill for less than a month. Fatal cases were often admitted moribund and died within a few days. Without the correct treatment the disease usually steadily advanced with occasional exacerbations to a fatal termination in the second or third month from inanition or earlier if bronchopneumonia occurred. Both Gillan and Williams recognized the fatal nature of the complaint.

Pathology

Six post-mortem examinations were performed, three by the writer and three by Dr. F. W. Vint, Government Pathologist, Medical Research Laboratory, Nairobi. The findings, apart from complications of bronchopneumonia, urinary infection and the degree of intestinal congestion, were very consistent. The examinations were made on an average about twelve hours after death and for this reason the appearances recorded in the intestines must be taken with reserve.

Macroscopic changes.—These were obvious in the skin, thymus, liver and intestines. Normal appearances or only those of superimposed toxæmia and infection were present in the lungs, kidneys, spleen, heart, reproductive organs, brain and spinal cord. Subcutaneous fat was almost absent. Internal organs were pale if anaemia was present.

The thymus gland showed marked atrophy in all cases so that it was usually impossible to demonstrate it even after the most painstaking dissection. The liver was usually moderately enlarged and showed extreme fatty degeneration. Its surface and cut section were bright yellow, occasionally interspersed with small red areas of congestion. Its consistency was extremely soft except in cases in which a fine fibrosis was beginning to replace degenerate cells. The intestines had somewhat transparent thin walls and the mucous membrane appeared unduly smooth. This change was most marked in the small intestine but was present in all parts of the intestinal tract. Slight congestion but no ulceration was seen in the mucous membrane of the small and large intestine of those cases which had diarrhoea or dysentery. The suprarenal glands were moderately enlarged in size and weight and two cases showed hæmorrhages in the cut section. The thyroid and pituitary glands appeared normal.

Microscopic appearances.—Most of the internal organs were studied in every case but unfortunately the central nervous system was never adequately examined nor was the skin. This is because the writer was investigating in East Africa cases of 'Gillan's oedema,' and only quite late in the investigation was his attention drawn to suggestions concerning its relationship to pellagra. Only then were neurological changes detected clinically and only then was the central nervous system examined microscopically. Only in the last two post-mortem examinations was the cervical cord, but no other part of the nervous system, sectioned and no abnormality was detected.

Toxic changes were evident in the tissues of many organs, cloudy swelling was usually marked in the kidney. Extreme fatty degeneration was present in the liver. In most cases the thymus had atrophied so much that it was impossible to identify the tissue, in a few cases in which it was recognized it showed great decrease of the lymphoid elements, but Hassal's corpuscles appeared normal. The suprarenal glands appeared normal in structure apart from the presence in two cases of hæmorrhages in the zona reticularis of the cortex. The intestines revealed slight atrophy of the villi and mucous membrane and signs of congestion and inflammation in cases in which diarrhoea had been present. The skin revealed irregular changes according to the variety of the rash. There were areas of hyperkeratosis tending to separate from the corium. The papillary processes were shorter, had a less regular outline, and in some cases were markedly flattened. The pigment was distributed in an unequal manner, areas of hyperkeratosis containing excess, other areas of thinned atrophic skin where exfoliation had occurred revealing small patchy collections of pigment.

The pathological picture is therefore consistent with that of pellagra in negroes as described by Denton⁵. The atrophy of the thymus and the extreme fatty changes in the liver are anomalous features. The pathological picture is not proof of pellagra, since the distinctive changes in the gastrointestinal tract and central nervous system were not detected, for they were not searched for. The skin changes are however extremely suggestive.

The investigators had no experience of the pathological changes in pellagra were unable to find adequate descriptions in the literature available to them of the pathology of pellagra in the negro, and did not believe until the investigation was nearly completed that pellagra was a possibility.

Diet

It was impossible to gain from the mothers any adequate description of the diet of the child prior to the onset of the disease. This was not for want of prolonged questioning. It is unnecessary to give all the reasons for failure. Intelligent Kikuyu orderlies could detect no point in which the feeding of cases differed from that of other children in this tribe. This will now be given, with the proviso that any 'scheme' of this nature depends mostly on what food is in garden or store. The population is composed of peasants and they do not buy food. Great monotony may occur at certain seasons of the year when a glut of one foodstuff may prove the sole article of diet until the new harvest matures.

Kikuyu infants are always suckled; no other method of feeding is known. This is performed whenever the child cries. It is continued until the child is about one-and-a-half to two years of age, but ceases at once if the mother becomes pregnant. At the age of four, five or six months other articles of diet are added and pushed by anxious mothers into refractory babies. Gruel made from ground millet, with or without milk, is commonly given and soft chewed banana may be given by what could be accurately described as a mouth to mouth infection (it is expelled direct from the mouth of the mother to that of the infant). Later, at about seven or eight months potatoes are added, both the sweet African and the European varieties. Beans and whole maize grain are added during the second year. They are cooked in various ways and form with millet the staple articles of diet. Various leafy forms of native vegetables are taken cooked with the diet. None of the cereals are milled to remove the outer layers. Milk is not drunk except in small amounts by the children. Eggs are not taken. Fruit of any variety is exceptional. Practically all food is taken cooked, and cooked for long periods of time often with large addition of a coarse soda from the local source at Magadi. This is the cheapest form of salt. Meat is taken at rare intervals. Wheat and rice are luxuries for the few. This is the average diet of a Kikuyu child. Those who desire more information will find it fully discussed by Orr and Gilkes²³ who made a detailed investigation.

Maize is the staple cereal in all parts of the world where pellagra is common. The reason is not known. Orr and Gilkes criticized the Kikuyu dietary on the grounds that it did not contain enough animal protein, fat and calcium, and they believed that certain vitamin deficiencies might be present. Although vitamin B₂ was at first referred to as the heat stable factor in the B complex, more recent work has confirmed that it is rapidly reduced in an alkaline medium, Williams, Waterman and Gurin²⁸ and Chick

and Roscoe⁴. It is possible that the practice of cooking the food with Magadi soda may be one of the factors responsible for the appearance of pellagra.

Treatment

The treatment carried out in every case was the dietetic treatment of pellagra, as far as this was compatible with gastro-intestinal upset. Symptomatic treatment and that of the complications followed the usual lines. Pellagra appears to be a disease associated with, if not caused by, a deficiency of vitamin B₂ in a diet usually deficient in animal protein, of which staple cereal is maize. The slow adult form of the disease does not improve when small amounts of vitamin B₂, comparable with the amounts necessary to maintain health, are added. Larger amounts are necessary and even then the response is not dramatic and many patients die. The acute form of the disease in infants cannot be expected to respond to small changes, but only to specific changes, in the diet. Numerous observers have noted that the disease does not respond to a diet 'rich in vitamins' and have concluded that the disease is not due to deficiency. When details of these diets are given they are found to consist largely of the vitamins A and D (cod-liver oil) and vitamin C (fruit juices).

Marmite was given in doses of a teaspoon a day for every year of age. Eggs and in severe cases liver were given. Milk one pint a day was drunk. Maize was eliminated from the dietary and replaced by wheat and rice. Other changes which were thought to be good, but are not regarded as essential now that the nature of the illness is thought to be known, were the addition of cod-liver oil and oranges. Iron in large doses for the anaemia and also calcium lactate were given as a routine mixture. Anorexia and indulgence by the mothers proved the greatest obstacles in the treatment. It proved necessary in these cases to separate completely mother and child and to forbid suckling. These small points unless duly appreciated will completely undermine any attempt to change the child's diet. Under this treatment only one case, admitted within a month of the onset, died, the remainder of these early cases were cured. Other observers who have not tried this form of treatment report that the disease is almost invariably fatal.

Discussion

Previous investigators in tropical Africa (Procter²⁵, Williams³⁵, Gillan¹⁰, Stones³⁴, Carman² and Sequeira²⁷) have concluded that the disease here described is not pellagra. They did this for two reasons; first, because the skin changes did not conform to the usual descriptions of pellagra, and secondly, because the unusual features of its incidence only in young children, its acute course, the absence of neurological signs, and the fatty stools could not be explained by pellagra. In addition, there must now be explained the presence of macrocytic anaemia, the fatty stools, and the atrophy of the thymus gland, which are the most obvious of the findings in this series but have not previously been recorded.

It is here contended that the skin changes are typical of pellagra—this point has been discussed already—and the gastro-intestinal symptoms, including fatty stools (Manson-Bahr¹⁸) are typical of pellagra, although in no former investigation of pellagra have fatty stools been so frequently observed. Manson-Bahr¹⁸ also reports pallor of the skin and loss of hair in pellagrous children. The neurological findings are typical of pellagra and are here recorded for the first time. They are absent in the majority of cases because of the rapidly fatal nature of the illness. The pathological picture is consistent with acute pellagra, except that the atrophy of the thymus has yet to be explained, and there is still missing pathological proof of neurological change. Other anomalous features may now be considered.

The incidence in young children and its absence or profound rarity in the adult population cannot be explained because the facts on which it could be explained are not known with precision. Too little is known about native diet. The acute course of the disease may be explained by its incidence in young children, and an analogy can be drawn to 'pellagra typhus,' an acute febrile form of the disease which occurred during the great war among Turkish prisoners. The acute nature of the disease explains the absence of definite neurological signs, apart from hypotonia, in two-thirds of the cases.

The fatty stools cannot be easily explained. They are not commonly reported in pellagra, but all of these patients were being fed on milk and cod-liver oil, and the steatorrhoea is possibly only secondary to the enteritis. This point had not presented itself to the writer during the period of investigation but was made by Stannus. Further investigation is needed in this matter, and the absence of steatorrhoea in Williams's cases suggest that the cause may be dietetic.

Oedema is a striking feature of these cases and is not often found in pellagra. In descriptions of pellagra in children it is usually described as a mild oedema in a few of the cases. It cannot be explained by any of the usual causes, there being no evidence of cardiac or renal disease, of nephrosis, or ankylostomiasis. The anaemia does not appear sufficiently severe to explain it. There is no evidence of beri-beri, a rare disease where rice is not eaten, and there is no evidence of heart failure or neuritis.

It is however by no means certain that it is the absence of vitamin B₁ which is responsible for the production of oedema in beri-beri since Rosedale²⁶ found that rats and pigeons need a factor other than B₁ in the absence of which oedema occurred. This has been confirmed by Williams, Waterman and Gurin²⁸ and Peters²⁴. Clinically the oedema of this condition may be regarded as comparable to the 'war oedema' produced experimentally by Kohman¹⁴ in rats. Both diseases are produced by a diet deficient in animal proteins. Bigland¹ has noted the fact that oedema is frequently a symptom of deficiency disease and Enright⁶ found that the only deficiency disease associated with the 'war oedema' cases was that of pellagra. Lastly, it is known that gastro-intestinal disease in infants is often complicated by oedema (Mavers¹⁹) and that diseases producing fatty stools, coeliac disease and sprue are often associated with this excess of fluids in the body tissues.

The anaemia when microcytic presents no difficulties and is only to be expected. Macrocytic anaemia may be explained along the lines of tropical macrocytic anaemia (Wills⁴⁰) due to a deficiency of the vitamin B complex and cured by marmite. Later work has thrown doubt upon the hypothesis that the extrinsic factor of pernicious anaemia is vitamin B₁₂, but the original clinical finding of Wills still stands. Macrocytic anaemia is also found in pellagra (Stannus³³). It is also well known that diseases associated with fatty stools are commonly associated with both microcytic and macrocytic anaemias.

The atrophy of the thymus gland may be correlated with the work of Williams and Crowell³⁷ who noted a similar change in polyneuritic chicken due to a deficiency of the vitamin B complex. The fatty and cellular degenerations of many organs (liver and intestinal mucosa) may be correlated with the findings of a variety of observers on vitamin B deficiency disease in animals, Funk and Douglas⁹, McCarrison²¹ and Findlay⁸. The increase in weight of the suprarenal glands and the presence of haemorrhages have been noted in the same diseased state by McCarrison²⁰ and Kellaway¹³ and Korenchevsky¹⁵.

It is therefore maintained that this syndrome in infants reveals with slight modifications the main clinical signs of pellagra, and that the unusual features can all be related to experimental conditions produced in animals subjected to a vitamin B deficiency in a diet also poor in animal protein. The syndrome is therefore an infantile variety of pellagra.

Differential diagnosis from pink disease

It may appear presumptuous to introduce to the notice of those interested in pellagra who have seen pink disease and have pronounced that the two diseases have no affinities that most observers of infantile pellagra in East Africa have noted the striking resemblance of mild cases of infantile pellagra to pink disease. It was mentioned originally by Gillan¹⁰ and has been mentioned at numerous unreported clinical meetings at which the writer has been present. Manson-Bahr¹⁸ mentions that the two diseases may be confused and in his opinion the distribution of the rash is similar in both diseases. Some have suggested that pink disease may be a deficiency disease. There is little agreement concerning its pathology, many regarding the changes in the central nervous system as those due to intercurrent infection.

Pink disease, lacking its essential colour changes in a negro skin, would be a difficult diagnosis in a native child and the writer believes that the only cases of pink disease in native children in Kenya have been reported by him, are listed as such in the official statistics, but all subsequently developed signs of 'infantile pellagra.'

A mild case of 'infantile pellagra' presents a roughened desquamating skin, slight puffiness in all parts of the body, extreme petulance, photophobia, an irritable skin which is scratched, septic skin rashes, thinning of the hair and the nails, pronounced anorexia, cold clammy extremities, weakness of the limbs and marked hypotonia. Both diseases appear limited

to the same ages of from six months to five years. The diagnosis of 'infantile pellagra' is made when any of the major signs, massive oedema, the rash, or gastro-intestinal signs occur. Before this in the opinion of the writer the two conditions cannot be distinguished.

In the uncertain state of knowledge concerning either pink disease or infantile pellagra further discussion is undesirable. Infantile pellagra was considered to have nothing distinctive in its pathology until Vint demonstrated the atrophy of the thymus, it was not considered due to a dietetic deficiency until marmite in massive doses and liver were shown to cure the disease in the early stages.

In conclusion it should be stated that the differences between pink disease and infantile pellagra are more obvious than the similarities. Briefly, infantile pellagra appears to be a grave deficiency, pink disease a minor deficiency. Pink disease occurs in European children, infantile pellagra among poorly fed, usually maize-eating African children living under deplorable conditions of health and hygiene. Deficiency diseases are known to be modified by other constituents of the diet; this may explain the different and yet allied symptomatology of pink disease and infantile pellagra.

Summary

1. Previous observations in Africa have revealed a syndrome in young native children characterized by irritability, oedema, gastro-intestinal signs and complex skin changes.
2. A detailed investigation of the clinical, bio-chemical and pathological changes was made in twenty-six cases with six post-mortem examinations in Nairobi, Kenya Colony.
3. In addition to the signs previously noticed by other observers, microcytic and macrocytic forms of anaemia were demonstrated, fatty stools were analyzed and neurological signs of hypotonia or of a hypertonia, increased tendon reflexes and an 'extensor' response were demonstrated. The blood sugar curve was low. At post-mortem examination a remarkable atrophy of the thymus gland was demonstrated.
4. All the known clinical findings of pellagra were therefore present in this syndrome and the anomalous feature of oedema, anaemia and atrophy of the thymus can all be related to a deficiency of vitamin B₂ in a diet poor in animal protein, which deficiencies are more clearly related to pellagra than any other known disease.
5. Early cases were almost always cured by massive doses of marmite, liver, an increase of animal protein and the elimination of maize from the diet.
6. The points in which mild infantile pellagra may simulate pink disease are discussed. The attention of pathologists is invited to the post-

mortem appearances of infantile pellagra especially the atrophy of the thymus gland and of clinicians to the effect of massive doses of marmite and liver lest either of these might prove relevant in pink disease.

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