OBSERVATIONS ON THE USE OF NICOTINIC ACID IN THE TREATMENT OF PELLAGRA AND ALLIED CONDITIONS

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IN September 1937 Elvehjem *et al.* discovered that a single dose of 30 mg. of Eastman Kodak Company nicotinic acid improved the appetite and stopped the diarrhœa in a dog suffering from black tongue; since this date many people have treated human pellagrins with nicotinic acid. Results from this form of treatment have been so successful that nicotinic acid is now established as a specific cure for pellagra.

A large amount of research has been carried out in the United States where pellagra is very common. Smith *et al.* (1937) reported a cure with 60 mg. of nicotinic acid daily for twelve days. The appetite improved after 24 hours and mental improvement was noted after 48 hours. The skin was improved after 3 days.

Spies *et al.* (1938) reported an immediate increase in appetite and cessation of nausea and diarrhœa. Twenty-four hours after administration of nicotinic acid, the tongue became less sore and salivation diminished. He recommended a full well-balanced diet in addition to nicotinic acid.

Spies and Aring (1938) drew attention to beri-beri symptoms in pellagra cases. They found that many pellagrins in the U. S. A. suffered from alcoholic neuritis.

In India cases of pellagra are frequently met with. Rau and Raman (1936) reported 8 cases in Vizagapatam. They carried out blood analysis and found that the blood showed a fairly constant reduction in the albumin fraction.

In March 1939, Napier drew attention to the importance of this disease in India in a detailed description of it, and Sen Gupta, Napier and others (1939) recorded five cases treated in Calcutta. Bajaj (1939) treated one of six cases in the Punjab with nicotinic acid and found it to be 'very helpful in improving the local condition of the mouth and the skin'.

A Hindu agriculturist was treated successfully in Midnapore in July 1939 with six injections of nicotinic acid, and further interest in this form of treatment was aroused by two more cases in the Presidency General Hospital. At the same time it was observed that several other patients, particularly Anglo-Indians, showed some of the symptoms of pellagra though not clinically suffering from that disease. Many of this latter group showed improvement under nicotinic-acid treatment.

Altogether 20 cases were treated with nicotinic acid and for study purposes these were divided into three groups.

(1) Cases of true pellagra.
(2) Cases of nicotinic-acid deficiency.
(3) Miscellaneous cases.

Cases of true pellagra

Only three cases were allotted to this group. The distinction, however, between this group of cases and those classified under nicotinic-acid deficiency was mainly one of degree. Patients with marked skin lesions, gastro-intestinal and nervous symptoms were classified as true pellagra cases. Less definite cases were classed as cases of nicotinic-acid deficiency. All three were men between the ages of 30 and 50 years. One was a Hindu agriculturalist and the other two were unemployed Anglo-Indians.

Rice was the main article of diet in each case though the Hindu was in the habit of eating fish fairly frequently, and the Anglo-Indians ate meat when they could afford it.

The duration of symptoms varied from 7 months to 12 years. The most severe was case 1 : he complained of indigestion, itchiness, and 'insects flying out of his ears' and 'worms crawling in the skin'. His condition became worse each winter but he had managed to do his work till a year ago when fever and diarrhœa left him very thin, and he had to give up his employment as a boiler-maker. He had previously been treated in hospital for gastritis.

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On admission he was found to be 'slightly mental' and his general appearance suggested it (*see* photo). He was very thin and covered with a pigmented coarse skin which was most marked on the front of his chest, on the face and on the outer aspects of his arms and legs. He had fever and diarrhœa and his knee jerks were markedly exaggerated. He had a very moist tongue with red edges and a pronounced tremor.

He received six daily intramuscular injections of 2 c.cm. nicotinic acid. His appetite improved, he became more alert and his skin began to peel off. After six days' interval he received 2 c.cm. (50 mg.) intravenously followed by daily intravenous injections of 3 c.cm. (75 mg.) of nicotinic acid. This caused his skin to go pink

Pellagra.

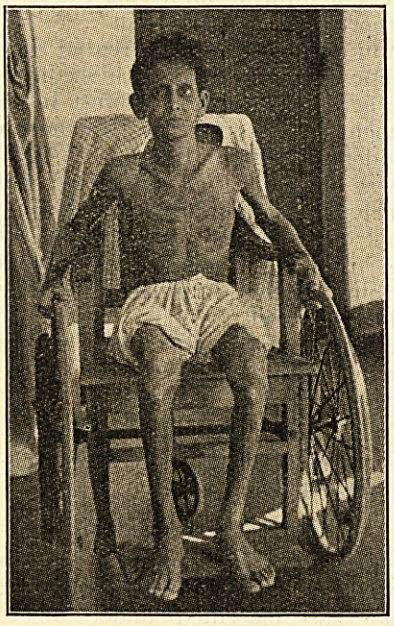

Fig. 1. *Case* 1.—A photograph taken about 10 days after admission. The distribution of the skin lesions can be seen. A certain amount of leucoderma is present on the hands.

in the less affected areas and hastened the peeling process. He complained of a burning sensation all over his body. His bowels moved less frequently, his weight began to increase, and he had no more fever. He now received three tablets (150 mg.) three times a day for a month, when the dose was reduced to two tablets thrice daily. He received a total dose of 16,975 mg. of nicotinic acid.

His condition on discharge was very good. He gained 13 lbs. 4 oz. in weight, his appetite was good and his tongue was no longer sore. His skin was practically normal, but when the coarse skin peeled off it left paler skin underneath. His mental state showed a marked improvement and he felt well enough to regain his employment as a boiler-maker.

The two other cases of pellagra were less severe. The Hindu (case 3) improved greatly after 6 intravenous injections of 50 mg. each. The most striking change was in his demeanour. He was a morose silent man on admission but after treatment he became brighter and more inclined to talk. His skin began to peel off but he left before complete cure was obtained.

The third patient in this group (case 2) suffered principally from diarrhœa and emaciation. His skin was not so coarse and pigmented as that of the other two. He had a very sore tongue and achlorhydria.

He was treated for more than 2 months as a case of chronic bacillary dysentery, but showed no improvement until nicotinic acid was administered. This had an almost immediate effect on

Pellagra.

Fig. 2.—The same case after treatment with nicotinic acid. Note the increase in weight and appearance of the face. The coarse scaly skin has fallen off and lighter coloured skin is left behind.

the diarrhœa which stopped after five days. He received a total of 2,800 mg. of nicotinic acid.

Nicotinic-acid deficiency.—Twelve cases were considered to be suffering from deficiency of nicotinic acid. Seven of these were children and the other five adults. Four were females and eight males. They all belonged to the poorer classes and lived mainly on rice and dâl. Four of them complained of a sore tongue and one boy of 13 (case 9) had a swollen tongue with ulceration round the edges and on the surrounding mucous membrane of the mouth. He improved rapidly under nicotinic-acid treatment.

Gastro-intestinal symptoms were present in seven cases and consisted mainly of slight diarrhœa. In two cases, however, diarrhœa was severe and at times was accompanied by vomiting.

All except one case showed some change in the condition of the skin. In some there was a dryness and scaliness with a certain amount of itching. In others the skin was thickened, pigmented and coarse, the distribution of the pigmentation being symmetrical and usually on the forehead, outer aspects of the arms and legs, and on the chest and neck. Almost invariably the patients attributed these changes to the cold weather and asserted that in the summer their skins became perfectly normal until the next winter.

Symptoms of nervous involvement were often present. In seven cases the knee jerks were exaggerated, in two cases diminished, and in two cases absent. One patient had previously suffered from 'beri-beri' and one Chinese boy had had beri-beri symptoms. He left hospital before completing his treatment. One African negro (case 13) suffered from peripheral neuritis due to alcoholic excess, and had no knee or ankle jerks. A marked tremor of the tongue was noticed in two cases only. The majority of cases were rather dull and apathetic, especially the children.

Nicotinic-acid deficiency.

Fig. 3. *Case* 4.—The photograph shows the slight pigmentation and rough skin which is often present in cases of nicotinic-acid deficiency.

Fever was present in nearly all cases at some stage of their illness and nearly all cases had lost weight.

Laboratory investigations

The cerebro-spinal fluid was examined in five cases. Apart from a reduction in the number of cells present and in the protein in some cases, there was no constant abnormality.

On examination of the urine, porphyrin was found in four cases. Hypochlorhydria was an almost constant feature.

The blood was examined in some detail. In only two cases did the red cells reach the level of 4,000,000 per c.mm. The hæmoglobin remained in most cases between 50 per cent and 60 per cent with a colour index in the region of 0.8.

The Wassermann and van den Bergh tests were always negative.

The blood calcium was slightly reduced in several cases, but the serum albumin and globulin were unaltered.

Treatment

Nicotinic acid was given to all cases in varying dosage according to the severity of the case. A usual dose was 6 intravenous injections of 2 c.cm. (50 mg.) of nicotinic acid (Glaxo), followed by nicotinic-acid tablets (50 mg. each) two or three times daily.

In severe cases 4 c.cm. (100 mg.) was given daily intravenously for six to ten days, followed by three tablets (150 mg.) three times a day for 3 weeks.

As hypochromic anæmia was a feature of every case treatment was supplemented with ferrous sulphate gr. iii thrice daily, or 'polyhæmen' tablets six daily. Small doses of thyroid were given in some cases, and all received a mixed well-balanced diet.

As a result of this treatment practically all cases complained of burning and itching in the skin which quickly passed off. In most cases the appetite improved after one or two injections, and there was a marked improvement in their mental attitude. They became brighter and more lively. This was particularly noticeable with children who responded rapidly. Several children became very flushed and almost pink, but this wore off soon and did not appear to worry them. The pulse and temperature remained normal.

Four or five injections were required before any effect was noticed in diarrhœa cases, and the skin lesions were the last to disappear, though scaling commenced early on in treatment. The average gain in weight was 4 pounds during treatment.

Miscellaneous cases

Nicotinic acid was administered to five cases suffering from various conditions other than pellagra. One was a Jewess who ate a good mixed diet, including meat and fruit, as well as rice and dâl.

She suffered from scabies with secondary infection which gave rise to an extremely offensive odour due to the pus which oozed from the numerous sores on her fingers, hands and toes. She had suffered from this condition off and on for one year. She received 12 intravenous injections of nicotinic acid (600 mg.) and 4,700 mg. by mouth. The skin of her fingers peeled off

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Case number	Sex	Age, years	Nationality	Diet	Duration, years	Gastro-intestinal symptoms	Skin lesions	Nervous symptoms	Seasonal exacerbation	Blood counts
I	M.	30	A.-I.	Rice, dâl.	12	Sore tongue, salivation, vomiting, diarrhœa.	Face, chest, abdomen, shoulders, arms, thighs, legs, dorsum of feet.	Hallucinations, tremor of tongue, plus knee jerks, ankle clonus, diplopia.	Winter	R. B. C. 2,230,000, W. B. C. 8,000, Hb. 38%.
II	M.	44	A.-I.	Rice, dâl.	7/12	Sore tongue, salivation, diarrhœa.	Legs, knees, arms, forehead.	Dull, apathetic, absent knee jerks.	..	R. B. C. 3,390,000, Hb. 60%.
III	M.	50	H.	Rice, fish.	3	Sore tongue, diarrhœa.	Neck, forehead, arms, legs.	Headache, morose, dull, plus knee jerks.	Winter	..
IV	F.	9	A.-I.	Rice, dâl.	6	Salivation, vomiting, diarrhœa.	Legs, arms, forehead.	Tremor of tongue, plus knee jerks.	Winter	R. B. C. 3,640,000, W. B. C. 10,200, Hb. 60%.
V	F.	5	A.-I.	Rice, dâl.	2	Vomiting, diarrhœa.	Forehead, arms, legs, back.	Listless, plus knee jerks.	Winter	R. B. C. 3,280,000, W. B. C. 4,250, Hb. 55%.
VI	F.	29	A.-I., sister of No. I.	Rice, dâl.	3	Sore tongue, salivation.	Forearms, legs, thighs.	Headache, sleeplessness, plus knee jerks, ankle clonus.	Winter	R. B. C. 3,640,000, W. B. C. 6,750, Hb. 55%.
VII	M.	11	A.-I.	Rice, dâl, meat.	1	Salivation, vomiting.	Forehead, arms, legs, dorsum of feet.	Knee jerks diminished.	..	R. B. C. 3,240,000, W. B. C. 5,600, Hb. 55%.
VIII	M.	55	A.-I.	Rice, dâl, tapioca, sago.	12	Sore tongue, salivation, vomiting, diarrhœa.	Arms, legs, thighs, dorsum of feet.	Apathetic, knee jerks absent, cramps.	Winter	R. B. C. 3,200,000, W. B. C. 9,750, Hb. 60%.
IX	M.	13	A.-I.	Rice, dâl, bread.	3	Sore tongue, salivation, diarrhœa.	Arms, legs, ankles.	Dull, tremor of tongue, plus knee jerks, ankle clonus.	Winter	R. B. C. 3,540,000, W. B. C. 7,250, Hb. 60%.
X	M.	12	Chinese	Rice	$1\frac{2}{12}$	..	Dry skin, leg pigmented slightly.	Knee jerks absent.	..	R. B. C. 3,510,000, W. B. C. 4,500, Hb. 65%.
XI	F.	$1\frac{3}{4}$	A.-I.	Rice dâl, arrow-root.	$\frac{2}{12}$	Diarrhœa	Skin slightly dry.	Listless, apathetic, plus knee jerks.	..	R. B. C. 3,640,000, W. B. C. 12,780, Hb. 60%.
XII	M.	1	A.-I.	..	$\frac{2}{12}$	..	Arms, legs, face.	Irritable, restless, plus knee jerks, ankle clonus.	..	R. B. C. 3,260,000, W. B. C. 10,750, Hb. 55%.
XIII	M.	43	African negro.	Fish, rice, dâl, meat.	5	..	Legs, arms, chest.	Absent, knee jerks.	Winter	W. B. C. 11,500
XIV	M.	39	A.-I.	Rice, dâl.	5	Sore tongue, salivation, diarrhœa.	Dry skin, arms and legs scaly.	Sleeplessness, plus knee jerks.	..	R. B. C. 3,260,000, W. B. C. 7,250, Hb. 60%.
XV	M.	59	A.-I.	Rice, dâl.	1/12	Diarrhœa	Dry skin	Dull, apathetic, sleeplessness.	..	..

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Cerebro-spinal fluid	Porphyrin	Fasting juice	Blood chemistry, per cent	Increase in weight, lb.	Concomitant disease	Treatment, nicotinic acid	RESULT
No increase in pressure, no cells, total protein 26 mgm., glucose 58 mgm.	—	Free acid 0.07, total acid 0.13.	C. 10.05 mg., P. 6.10 mg., Alb. 3.85 g., Glob. 3.39 g.	13¼	..	275 mg. IV, 600 mg. IM, 16,100 mg. oral, total 16,975 mg.	Cured.
No increase in pressure, no cells, total protein 15 mg. %, glucose 55 mg. %.	+	No acid	C. 9.33 mg.	10	..	1,600 mg. IV, 1,200 mg. oral, total 2,800 mg.	Cured.
..	..	..	..	..	..	300 mg. IV	Improved.
No increase in pressure, few R. B. C.	—	..	C. 8.96 mg., P. 4.76 mg., Alb. 3.9 g., Glob. 3.16 g.	4¼	Malaria (M. T.).	525 mg. IV	Cured.
No increase in pressure, no cells, total protein 24 mg. %, glucose 49 mg. %.	..	..	C. 8.85 mg., P. 4.9 mg.	4¾	Kala-azar	150 mg. IV	Cured.
No increase in pressure, no cells, total protein 17 mg. %, glucose 55 mg. %.	—	Trace of acid	..	..	..	500 mg. IV	Cured.
No increase in pressure, no cells.	+	Free acid 0.07, total acid 0.12.	C. 8.29 mg., P. 5.0 mg., Alb. 3.84 g., Glob. 3.0 g.	2	Malaria (M. T.).	300 mg. IV	Cured.
..	—	Free acid 0.01, total acid 0.03.	C. 9.26 mg., P. 6.07 mg., Alb. 4.06 g., Glob. 3.0 g.	11	Prostatic hypertrophy.	900 mg. IV	Improved.
No increase in pressure, R. B. C., W. B. C.: total protein 20 mg., glucose 50 mg.	+	Free acid 0.19, total acid 0.25.	Alb. 3.92 g., Glob. 3.16 g.	7½	..	600 mg. IV, 3,300 mg. oral, total 3,900 mg.	Cured.
..	—	Free acid 0.07, total acid 0.09.	C. 8.95 mg., P. 4.0 mg., Alb. 4.09 g., Glob. 3.00 g.	..	Beri-beri	300 mg. IV	Left before treatment completed.
..	—	..	Alb. 3.96 g., Glob. 2.87 g.	1	..	150 mg. IV, 1,650 mg. oral, total 1,800 mg.	Cured.
..	—	..	..	1	..	150 mg. IV, 250 mg. oral, total 400 mg.	Improved.
..	—	No acid	C. 8.35 mg., P. 6.18 mg., Alb. 4.3 g., Glob. 3.16 g.	..	..	350 mg. IV	Cured.
..	+	..	C. 10.26 mg., P. 5.7 mg., Alb. 4.3 g., Glob. 3.15 g.	7	..	300 mg. IV, 6,300 mg. oral, total 6,600 mg.	Improved.
..	..	..	..	2	..	300 mg. IV	Improved.

TABLE

Case number	Sex	Age, years	Nationality	Diet	Duration, years	Gastro-intestinal symptoms	Skin lesions	Nervous symptoms	Seasonal exacerbation	Blood counts
XVI	F.	25	Jewess	Rice, dâl.	1	Vomiting	Hands, feet.	Dull, apathetic, headache, sleeplessness, plus knee jerks, ankle clonus.	Winter	R. B. C. 3,280,000, W. B. C. 10,250, Hb. 55%.
XVII	M.	52	A.-I.	Meat, fruit, rice, eggs.	3/365	Diarrhœa	Dry skin	Dull, apathetic.	..	R. B. C. 4,020,000, W. B. C. 10,750, Hb. 70%.
XVIII	M.	2	H.	Rice, dâl.	1/12	..	Buttock, chest, limbs.	Irritable, reflexes normal.	..	R. B. C. 3,860,000, W. B. C. 8,750, Hb. 65%.
XIX	F.	26	A.-I.	Rice, dâl, fish.	$\frac{3}{12}$	..	Erythema and blisters all over.	Simple hysterical, reflexes normal.	..	R. B. C. 4,020,000, W. B. C. 7,750, Hb. 70%.
XX	F.	3	A.-I.	Rice, dâl.	$\frac{2}{12}$	..	Dry skin	Listless, reflexes normal.	..	R. B. C. 3,280,000, W. B. C. 14,250, Hb. 60%.

H. = Hindu.
A.-I. = Anglo-Indian.

like a glove and left a healthy skin underneath. The same process occurred with her toes but some of the sores on her hands required touching with iodine to keep them from reinfecting the whole skin.

The remaining cases were two children of which one was a Bengalee, one Anglo-Indian male of 52 years, and one female of 26 years. The Bengalee child had an ulcer on his buttock and scabies with secondary infection. It improved temporarily on receiving nicotinic acid but relapsed and was removed by its father as he was going on leave. The other child had a dry skin and was dull and apathetic. Her general condition improved with nicotinic acid, and she became brighter and more interested in her surroundings. The Anglo-Indian male suffered from a septic scrotum and scabies. He had no appetite and was very apathetic. His appetite improved with nicotinic acid and he became more alert. The adult female suffered from rheumatism. She showed no improvement under nicotinic-acid treatment.

Summary and conclusions

1. A description is given of 20 cases treated with nicotinic acid. The successful treatment of three cases of pellagra is described.

2. It is suggested that, though pellagra is quite a common disease in Bengal, there are a much larger group of cases, especially amongst Anglo-Indians, showing such symptoms as sore tongue, anorexia, stomatitis, diarrhœa, and mental dullness, which respond well to treatment with nicotinic acid. These are classified as cases of nicotinic-acid deficiency for the purposes of this study.

3. It is suggested that certain skin conditions such as infected scabies show improvement with nicotinic-acid treatment which increases the blood supply of the affected area.

4. Treatment with nicotinic acid consisted generally in a course of six intravenous injections of 2 c.cm. followed by two tablets thrice daily. This treatment was combined with the administration of ferrous sulphate and a mixed well-balanced diet.

5. Hypochlorhydria and a hypochromic anæmia were invariable accompaniments. In some cases a reduction in the albumin content of the cerebro-spinal fluid was noted.

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Cerebro-spinal fluid	Porphyrin	Fasting juice	Blood chemistry, per cent	Increase in weight, lb.	Concomitant disease	Treatment, nicotinic acid	RESULT
..	Trace	..	C. 10.0 mg., P. 5.7 mg., Alb. 4.09 g., Glob. 3.0 g.	2	Dermatitis	600 mg. IV, 4,700 mg. oral, total 5,300 mg.	Cured.
..	—	Free acid 0.09, total acid 0.13.	Alb. 4.12 g., Glob. 3.0 g.	..	Ulcerated scrotum.	300 mg. IV	Cured.
..	—	..	..	1	Infected scabies.	3,000 mg. oral	Improved.
..	—	Trace of acid	C. 8.9 mg., P. 4.0 mg., Alb. 4.19 g., Glob. 3.0 g.	1	Rheumatism	300 mg. IV, 1,200 mg. oral, total 1,500 mg.	No improvement.
..	—	..	Alb. 3.96 g., Glob. 3.0 g.	..	Otitis media	150 mg. IV, 1,200 mg. oral, total 1,350 mg.	Improved.

C. = Calcium.
P. = Phosphorus.
IV = Intravenous.

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EXPERIENCE WITH DISEASES OF THE GALL-BLADDER

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FOR a long time it has been the general belief that diseases of the gall-bladder are of rare occurrence, are of a serious nature, occur only in elderly women, and are always associated with stones. The obsolete adage 'fair, fat, forty and fertile' is still committed to memory and quoted by medical students, and even by some medical men. However, by experience one finds that lesions of the gall-bladder are as common as, or perhaps more common than, lesions of the duodenum and the appendix, but, as the lesions of the two latter organs produce more acute symptoms for which the patient seeks the doctor's advice, they are noticed more by the surgeon and thought of primarily. In a good many cases symptoms due to gall-bladder disease are attributed not only to other abdominal viscera, such as the duodenum, appendix and kidney, but to extra-abdominal organs as well, especially the heart.

Ætiology and pathology of cholecystitis.—Pathological conditions of the gall-bladder that have any surgical significance are intramural, and the avenues of infection are mainly through the vascular and lymphatic systems, though rarely an ascending infection through the duodenum and the bile ducts is possible. Streptococci, staphylococci, *B. coli*, and *B. typhosus* have been found in cultures made from the bile in cholecystitis. Experimentally it has been found that when streptococci are injected into the bile, no change results. But when streptococci are injected intramurally into the gall-bladder a typical cholecystitis develops within a couple of months. In a good many cases the primary infection is in the gastro-intestinal canal, especially in the appendix or the gastro-duodenal area, and the gall-bladder is secondarily affected. The organ may also be affected from the liver by direct contact, in those cases where the liver cells are damaged by continued infection carried to it through the portal system.

The nervous system may also be responsible for the damage to the gall-bladder by the disturbance in the function of the vagus nerve. This may be due to the stimulus which reaches the vagus in its peripheral portion, its centre in the medulla, the mid-brain, and also the inter-brain. The irritation to the vagus may be caused by extrinsic poisons such as nicotine, intrinsic poisons such as a chronically inflamed appendix, or the vegetative impulses which are easily affected by psychological influences in people with a neurotic temperament. According