INDICANURIA AND THE PSYCHOSIS OF A PELLAGRIN

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PELLAGRA with marked mental symptoms in a boy of 10, was cured by nicotinamide (Hersov, 1955). The boy's diet prior to development of the pellagra did not however appear to have been deficient in nicotinic acid derivatives. The following studies were initiated in search for a metabolic peculiarity which might explain this.

URINARY NICOTINAMIDE METABOLITES

The subjects and procedure. Clinical details concerning the boy, M.H., have been reported by Hersov (1955). Symptoms possibly pellagrous had been evident between February and July, 1952 and again from April, 1953 until his admission to the Maudsley Hospital on 9 May, 1953. Nicotinamide at 100 mg./day was administered from 16 May, 1953 until discontinued for the present investigations on 9 June, 1953. Eleven days later, M.H. and a boy P.R. of similar age (Table I) were placed on the same reproducible mixed diet which was estimated to contain 10 mg. nicotinamide/day. They were not confined to bed. The whole urine for a period of three days, was collected in Winchesters containing 100 ml. glacial acetic acid and toluene.

During a second experimental period, immediately following the first, the boys were kept on the same diet to which was added 100 mg./day of nicotinamide. This dose of nicotinamide was based on Goldsmith's (1942) study of nicotinamide metabolism in adult pellagrins, when 300 mg./day was administered. The total urine during 3 days was collected as before.

Nicotinic acid and nicotinamide were determined according to Friedemann and Frazier (1950) after a 10-fold concentration of a sample, *in vacuo*. Of the original urine 1 ml. was diluted to 20 ml. and treated with activated charcoal and *N*-methylnicotinamide determined according to Huff and Perlzweig (1947).

Results. The findings with both subjects are quoted in Table I, together with some data from other workers. Those with M.H. are not unusual, nor do the differences between M.H. and P.R. appear unusual when considered in the light of investigations with other subjects. The metabolites determined necessarily represent only a small proportion of the subjects' total nicotinamide intake.

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TABLE I

Nicotinic Acid Metabolites

Subject	Nicotinamide Administered (mg.)	Excreted: Nicotinic Acid and Nicotinamide (mg./72 hours)	Excreted: *N*-Methyl Nicotinamide (mg./72 hours)	Recovered (Percentage of amount administered)
Section A				
M.H.	0	0·61	8·8	—
M.H.	3×100	0·46	16·3	2·5
P.R.	0	1·15	16·5	—
P.R.	3×100	1·66	21·0	1·7
Section B				
J, H and M: C ..	0	0·87	10·8	—
D	0	1·68	42·8	—
E ..	0	1·01	8·5	—
F ..	0	0·94	13·1	—
E and C: 1 ..	0	—	7·6	—
2 ..	0	—	6·7	—
3 ..	0	—	4·0	—

Section A: present investigations. *Section B:* J, H and M: Johnson, Hamilton and Mitchell (1945); E and C: Ellinger and Coulson (1944); in these investigations adults were studied and the excretion quoted is that for 24 hours.

IDENTIFICATION AND DETERMINATION OF A CHROMOGEN IN URINE FROM M.H.

During the preceding analyses, chromogens in the urine specimens were found to interfere with some of the determinations. Thus in estimating *N*-methylnicotinamide an extraneous green colour developed in acid acetone solutions, while acid aqueous solutions became pink.

Urinary pigments in pellagrins. Bodansky (1952) and Duncan (1947) survey observations of the excretion of both indole chromogens and porphyrin pigments in the urine of pellagrins. There has been some confusion between the two categories of pigment. Indicanuria without quantitative determination was reported by some earlier workers, as also was a precursor of urorosein. Beckh, Ellinger and Spies (1937) derived a red pigment from the urine of pellagrins which they considered to be coproporphyrin and regarded as of diagnostic value; its excretion was reported to be reduced by nicotinamide together with other signs of pellagra. Watson (1939) and Rimington, Holiday and Jope (1946) have however given evidence suggesting this and a pigment observed in sprue to be indirubin, an isomeride of indigo.

Characteristics of the pigment from M.H. The pigment was most simply formed by heating at 100° for a few minutes acidified specimens of the urine, for example after adding 1/10 vol. of conc. HCl. It was then reddish blue and could easily be extracted with chloroform or *n*-butanol. When extracted with chloroform and examined with a direct-vision spectroscope, its major band was clearly of somewhat longer wave-length than the D line, being about 6,000 Å. No absorption was seen around 5,500 Å, the position of the band of urorosein and porphyrins. A weaker band appeared at 5,300 Å. Tests for urorosein and porphyrins were negative. The main pigment was concluded to be indigo blue, derived from indican in M.H.'s urine.

Determination of indican. Sharlit's (1932) method was applied, using 2 ml. of a 1/20 dilution of the urine with thymol, potassium persulphate and trichloro-

acetic acid, and measuring the colour with a Hilger Spekker absorptiometer using a filter with maximum absorption at 550 mμ. As a standard an 0·96 per cent. w/v solution of anhydrous cobalt sulphate was used. The indican equivalent of this, calculated from Sharlit's data and confirmed approximately by ourselves was 10 μg. (final vol. 3 ml.).

Persistent Indicanuria in M.H. in Comparison with Other Subjects

A comparison between the urinary indican of M.H. and of P.R., in Table II, emphasizes the high, persistent level seen in M.H. It is to be noted that these observations commenced eight weeks after his pellagra had been terminated with nicotinamide. The high levels were maintained over the total period of detailed observation of a further eight weeks, and were also observed again four months later. The indicanuria now observed is therefore very different from the transitory excretion of chromogen described by Beckh, Ellinger and Spies (1937) during actual pellagra, when many bodily functions are disturbed; it may, rather, be constitutional.

Table II

Urinary Indican in M.H. and P.R. Consuming a Similar, Standard Diet

Date	Subject: M.H. Age: 10 years 8 months Weight: 5 st. 5 lb. Indican (mg./24 hours)	Subject: P.R. Age: 9 years Weight: 4 st. 8 lb. Indican (mg./24 hours)
16 July	—	44
18 July	233	51
21 July	280*	—
24 July	210*	—
29 July	268	—
5 August	200*	—
6 August	288	—
7 August	310	—

* Incomplete collection of urine: estimate based on creatinine output.

Normal levels of indican excretion in children do not appear to have been recorded, in spite of the many earlier observations on indicanuria referred to below. Levels in adults were reported (Sharlit, 1932) to be between 40 and 160 mg./24 hours, with a mean value of 100 mg. or about a third the average level observed in M.H. It was therefore decided to determine typical levels in children and these are presented in Fig. 1. We are greatly indebted to Dr. W. W. Payne of the Hospital for Sick Children, Great Ormond Street, for co-operation in providing these specimens.

A significant increase in daily excretion with age is to be seen. Excretion in M.H. is exceptionally high in comparison with all the 30 subjects examined.

Other Observations

The indican excreted is believed to originate from indole, itself derived from tryptophane. While this latter conversion has been suggested as taking place in the tissues of the body, a more clearly demonstrated source is from intestinal micro-organisms. It was accordingly attempted to modify the microbial flora in M.H. by administering succinyl sulphathiazole, 7·5 g. orally per day

for 7 days. No consistent change in indole excretion was apparent. Values before treatment were as indicated in Table II, that immediately preceding the sulphathiazole being 230 mg./day; during it, 215, 280, 255, 210, and following it 360 mg./day were excreted. Faecal examination showed a considerable preponderance of *Strep. faecalis* over coliform organisms during the treatment. Wooldridge, Mast and Hoffman (1950) have had similar experience with adult subjects.

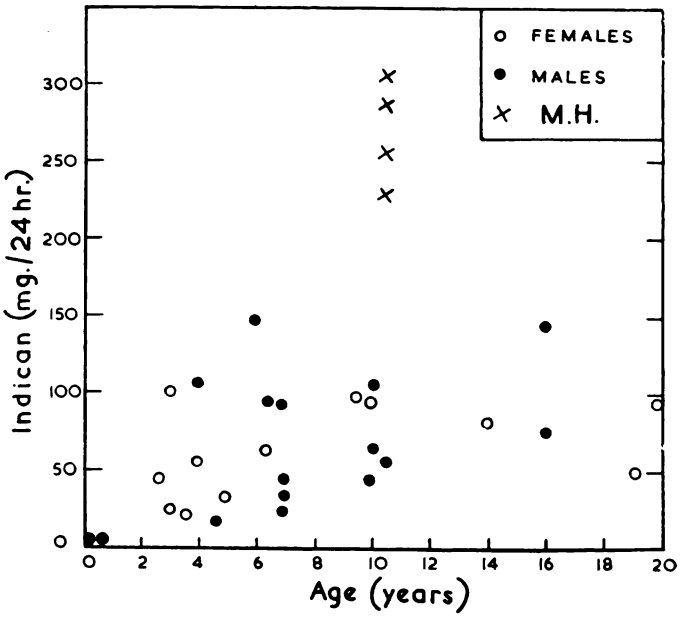

FIG. 1.—Urinary indican in male (●) and female (○) children and in M.H. (×).

A further experiment sought to modify his condition and the indicanuria by administering *l*-tryptophane, of which 1·5 g. (with 1 g. *D*-tryptophane) was given orally on two successive days, in two equal doses, as a suspension in blackcurrant puree. Indican remained at its usual high level (288, 310 mg./day) and observation showed no marked mental or physical change.

M.H. has not been accessible to us for further studies. A search, in which we have been aided by Dr. Denis Leigh and Dr. W. Hardwick, has revealed an adult case whose indicanuria and clinical history are similar to those of M.H., the indican again being much higher than that of her contemporaries. No other comparably high urinary indican has been observed in over 200 specimens. The studies are being continued.

DISCUSSION

Fifty to sixty years ago, indicanuria was regarded by several writers as a sign of "intestinal stasis and autointoxication" to which many disorders of the central nervous system were ascribed (Bouchard, 1894; Herter and Kendall, 1909). These suggestions were based on the hypothessis that indole or associated materials acted as toxic agents. Townsend (1905) reported instances of high indicanuria in depressed states and also in some maniacal phases, the severity of the mental disturbance varying with the elevation in indican output. Although general correlation of this type did not survive more critical examina-

tion (Folin, 1904; Segal, 1924), the present findings indicate that the psychosis of pellagra may be associated with a persistent indicanuria. After initial and often vague sensory, motor and emotional disturbances, the mental disorder of pellagra ordinarily has the appearance of a depressive or manic-depressive illness (Justin-Besançon and Lwoff, 1942). Pellagra has a long association with mental hospitals (Medical Research Council, 1930; Reiter and Jacobsen, 1935; Justin-Besançon and Lwoff, 1942; Caldwell and Hardwick, 1944; Leigh, 1952) and as its mental symptoms may occur before other indications of the disorder they may not always be recognized as part of a deficiency disease. Pellagra was indeed regarded as a microbial disorder in the 1890s, as also was the auto-intoxication.

Moreover, recent observations suggest a basis for association between nicotinamide deficiency and indicanuria, for tryptophane can serve as precursor not only of indican but also of nicotinamide sufficient for half the daily requirement of this substance. Thus indicanuria may represent a diversion of tryptophane from a more essential metabolic route, making an individual more exacting in his requirements for dietary nicotinamide. It is possible that these metabolic conversions take place in the body rather than or as well as occurring in the intestinal contents. Another important route from tryptophane leads to serotonin.

Greater nutritional needs in pellagrins in mental hospitals were envisaged by Reiter and Jacobsen (1935). Requirements for a given dietary essential can differ in individuals by a factor of 5 or more (Williams, Eakin, Beerstecher and Shive, 1950) indicating individual metabolic pecularities of which indicanuria offers a relevant example. Granted that the "normal" requirement for a vitamin is the mean or mode of a distribution curve, the extreme requirements can be understood in a large population to differ considerably. Very many metabolic and other processes are involved between the assimilation of foods containing nicotinamide and tryptophane, and the functioning of the coenzymes derived from either of these substances. It is presumably variation in such processes in different individuals which leads to requirements for nicotinamide which are higher or lower than usual. We suggest that indicanuria represents one group of processes leading to high nicotinamide requirement and thus an especial proneness to pellagra.

This study does not indicate new therapeutic measures other than that sympathetic consideration be given to peculiar feeding habits, for these may not only be the cause of some nutritional disorders but may in other instances be in part protective, as is anorexia in thiamine-deficient rats.

Summary

1. A boy who developed pellagra with marked mental disturbance on an apparently normal diet, did not show unusual quantities of urinary nicotinic acid, nicotinamide or *N*-methylnicotinamide on an ordinary diet nor on one supplemented with additional nicotinamide.

2. He showed unusually high persistent indicanuria, excreting about 280 mg./day of indican.

3. A survey of indicanuria in children indicated the average excretion to increase with age, the value in the boy's contemporaries being less than 100 mg./day.

4. Whereas indicanuria has in the past been thought to be connected with mental disorder through the toxic action of indole or associated materials, it is now suggested that such connection can be due to a diversion of tryptophane metabolism from more essential routes.

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