Congenital Tryptophanuria with Dwarfism

(“H” Disease-like Clinical Features without Indicanuria and Generalized Aminoaciduria):—A Probably New Inborn Error of Tryptophan Metabolism

By

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Recently new inborn errors of amino acid metabolism have been found with the development of analytical technique of amino acid metabolism.¹⁾ “H disease” which was first described by Baron *et al.*²⁾ in 1956, is supposed to be associated with an abnormality of tryptophan metabolism. The disease is characterized by pellagra-like skin rash, mental retardation, and neurological changes resembling cerebellar ataxia. Laboratory studies of H disease have revealed an excessive excretion of indican and indoleacetic acid in addition to aminoaciduria.

Recently we experienced a case which was clinically similar to H disease but definitely different from it in laboratory findings.

The present studies revealed a probably new inborn error of tryptophan metabolism, to which we may as well give the name: “Congenital Tryptophanuria with Dwarfism”.

CASE REPORT

M.K., a girl, born on December 1, 1952, was referred to our Hospital at the age of 9 years because of retardation of mental and physical development. The parents were consanguineous (first cousins) and the pedigree of the patient indicated a complicated consanguinity as was shown in Fig. 1. In the relatives of the patient there were two members who had developmental retardation and died in infancy. The parents appeared to be healthy except for showing a tendency to hyperpigmentation of the exposed area of the skin.

The patient had two siblings who were living and well. The patient was normally born at term and weighed 3,180 g. During the first two months of life,

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Fig. 1. Pedigree of the patient.

she seemed to show a normal development. But, thereafter, the parents noticed that a developmental retardation of the child was gradually increasing; she could sit alone at seven months of age and walked alone at 26 months. Throughout her childhood, she showed a very slow development in both physical and mental aspects, without affection of major illness. Photosensitivity of the child was noticed first at the age of six months, when she went to seaside and developed erythema and vesicle on the face and teleangiectasia on the conjunctivae. The skin surface exposed to sunlight became gradually harsh and dry, and resulted in hyperpigmentation like pellagra. Such a photosensitivity had a tendency to be aggravated in summer and to be improved in winter every year. The patient was so mentally backward that she could not learn letters or figures, despite having attended primary school since the age of 7 years.

Physical examination, at the age of 9 years in September of 1962, revealed a dwarfish girl with a dull countenance. The size of the patient was that of five-year-old child; her weight was 12.3 kg, and height 107 cm (Fig. 2). She seemed to be normally proportionated. The exposed surfaces of the skin, including the face, neck, hands, and legs, were dry, harsh and hyperpigmented (Fig. 3). There were teleangiectasia and hyperemia on the bullar conjunctivae. No abnormal findings were found in the chest or abdomen. Superficial reflexes were intact. The patellar reflex was weak but no pathological reflex was elicited. Nuchal rigidity or Kernig's sign was absent. No sensory abnormalities were detected. Speech was slow and high-pitched. The gait was unsteady with a wide base. An intention tremor of the hands and disturbance in co-ordination were found. There was no malformation throughout the body. Intelligence was shown to be correspond to that of three-or four-year-old child, indicating 30 of I.Q.

Fig. 2. Size of the patient
Right: Patient
Left: Control child of the same age as the patient.

Fig. 3. Hyperpigmentation on the hands of the patient.

Laboratory examination. Routine urinalysis was within normal limits. Ferric chloride tests were negative on several occasions. No porphyrin in urine was detected. Stools were free of ova or parasites and negative for enteric pathogens. Examination of the blood disclosed a hemoglobin of 13.4 g/dl, R.B.C.

$5.19 \times 10^4/\text{mm}^3$ and W.B.C. $5,650/\text{mm}^3$, with a differential count of 0% basophils, 5% eosinophils, 33% lymphocytes, 2% monocytes and 60% neutrophils (no nuclear shift to the left was present). Serum chloride was 106.5 mEq/L; calcium, 9.5 mg/dl; potassium 4.7 mEq/L; sodium, 142 mEq/L; phosphorus, 5.56 mg/dl; total protein, 7.4 g/dl; and total cholesterol, 200 mg/dl.

The fasting blood sugar was 86 mg/dl and both the adrenalin test and the glucose tolerance test showed normal findings. The liver function tests were within normal limits except for a slight increase of transaminase: T.T.T., was 1.2 units; Z.S.T., 0.6; C.C.F., negative; B.S.P., 6.9% (after 30 minutes); alkaline phosphatase, 3.5 B.L. units; GOT, 52 units; and GPT, 57 units. Histological findings of the biopsied liver showed no evidence of abnormality (cf. Fig. 4).

Fig. 4. Histological findings of the liver biopsied from the patient. Hematoxylin-eosin stain.

Electrophoretic pattern of the serum protein indicated an evidence of hypergamma-globulinemia, consisting of 41% albumin, 11% α -globulin, 12% β -globulin and 36% γ -globulin. Free amino N in plasma was 3.8 mg/dl and urinary excretion of free amino N per day was 55 mg. Wassermann's reaction was negative. Thorn's test showed a decrease of 66% in eosinophils (within normal limits). Urinary excretion of 17-KS and 17-OHCS was 3.3 mg/day and 1.2 mg/day, respectively. The I^{131} uptake test showed 36% in 24 hours (within normal limits). X-ray examinations of the chest, skull, spine and extremities exhibited no abnormal findings. X-ray films of the wrist revealed a normal development of ossification centers. EKG revealed no abnormality. EEG showed a monotonous pattern with lack of arousal response against stimulus, but no localized abnormality was found. Ophthalmological examinations were noncontributory. Chromosomal analysis disclosed no abnormality in number or configuration.

The clinical and laboratory findings of the patient as were mentioned above, led us to a view that the present patient might belong to congenital metabolic disorders. Among the known congenital metabolic disorders, the present case was thought to be clinically most similar to H disease which was characterized by a pellagra-like skin rash, mental retardation, and neurological changes resembling cerebellar ataxia. Biochemical features in H disease have been demonstrated to be a renal aminoaciduria and an excessive excretion of indican and of indoleacetic acid.²⁾ Therefore, the following analyses were carried out.

Twenty-four-urine specimens were collected and were subjected to investigation of amino acids and indole derivatives. Amino acid analysis by paperchromatography was performed principally according to Ghadimi *et al.*'s method.³⁾ Urine specimen was passed through a column of Dowex 50-W-X8 (H⁺ form) and then amino acids adsorbed in the column were eluted with 2N NH₄OH. The eluate was gently evaporated to dryness over a water bath. It was reconstituted by an addition of 0.5 ml of water. An aliquot of 0.02 ml was spotted on a filter paper of Toyoroshi No. 50. Paperchromatography was carried out in two dimensions, using 80% phenol for the first direction and water-saturated n-butanol with addition of glacial acetic acid (water: n-butanol: glacial acetic acid=5: 4: 1 in volume) for the second direction. The spots of amino acids were stained by spraying with a 0.2% solution of ninhydrin in acetone. Paperchromatography of indole derivatives was performed according to Jepson's method.⁴⁾ 0.005 ml of the filtered urine was spotted on a filter paper of Toyoroshi No. 50. Paperchromatography was carried out in two dimensions, using isopropanol-ammonia (isopropanol: water: ammonia=20: 2: 1 in volume) for the first direction and butanol-acetic acid (n-butanol: water: glacial acetic acid=12: 5: 3 in volume) for the second direction. The spots of indole derivatives were stained by dipping the dried paper through Ehrlich's reagent⁵⁾ (p-dimethylaminobenzaldehyde in hydrochloric acid-acetone).

Quantitative determination of indoleacetic acid was made by Weissbach's method.⁶⁾ Qualitative determination of indican was made by Obermyer's method.

Paperchromatogram of amino acids revealed an excessive excretion of tryptophan as compared with excretion of the other amino acids (Fig. 5). The spot of tryptophan was identified by Ehrlich's reagent (Fig. 6). This increase in tryptophan excretion was confirmed by the paperchromatographic assay of different urine specimens from the patient. Paperchromatogram of indole derivatives also indicated an excessive excretion of tryptophan and a slight excess of indoleacetic acid but no other indole derivatives were detected (Fig. 7). Urinary excretion of indoleacetic acid was 5.5 or 4.3 mg per day, indicating the value of a slightly higher level from the normal. Obermeyer's test gave negative results on repeated examinations. These results were not in agreement with those in H

Fig. 5. Paperchromatogram of urinary amino acids of the patient.

Key: 1. Tryptophan, 2. Tyrosine, 3. ?, 4. Alanine, 5. Threonine, 6. Glutamine, 7. Histidine & Lysine, 8. Glycine & Serine, 9. Glutamic acid, 10. Aspartic acid, 11. Asparagine

Fig. 6. Paperchromatogram of urinary tryptophan of the patient. The paperchromatogram was sprayed with Ehrlich's reagent.

Left: Patient's urine

Right: Standard

Fig. 7. Paperchromatogram of urinary indole derivatives of the patient.
Key: 1. Urea. 2. Indoleacetic acid. 3. Tryptophan

disease. Further studies were, therefore, carried out in order to elucidate a derangement in tryptophan metabolism in the present case.

Tryptophan loading test

40 mg of L-tryptophan per kg of bodyweight was orally administered. 24-hour urines were collected before and following the test dose. Urinary analysis was made by the following procedures: Ichihara *et al.*'s method⁷⁾ for tryptophan, kynurenine and anthranilic acid; Glazer *et al.*'s method⁸⁾ for xanthurenic acid; Weissbach *et al.*'s method⁶⁾ for indoleacetic acid; Sato's method⁹⁾ for 5-hydroxyindoleacetic acid; and Huff's method¹⁰⁾ for N-methylnicotinamide. Plasma tryptophan levels were estimated by the method of Dickman and Crockett¹¹⁾ at intervals of 0, 1/2, 1, 2, 4, and 8 hours following the tryptophan loading. As controls, children without hepatic or renal lesion were subjected to the tryptophan loading test in the same way.

The results obtained were shown in Tables I and II. Urinary excretion of tryptophan was significantly increased in the present patient than in the controls. After the tryptophan loading, its excretion was remarkably increased in the patient while there was insignificant increase of the excretion in the controls. The patient showed a somewhat lower excretion of kynurenine and N-methylnicotinamide before and after the tryptophan loading as compared with that in the controls. Anthranilic acid and xanthurenic acid were not detected in

TABLE I. Urinary Excretion of Tryptophan Derivatives in the Patient and the Control Children, Without L-Tryptophan Loading

Urinary output of tryptophan derivatives	Patient	Control		
		No.	Range	Average
Tryptophan (mg/day)	65.5 32.8 58.6 81.5	6	12.0-37.6	22.6
Kynurenine (mg/day)	2.5 1.5 1.8 0.8	6	2.7- 5.7	4.2
Anthranilic acid (mg/day)	Not detectable	6	Not detectable	
Xanthurenic acid (mg/day)	Not detectable	6	Not detectable	
N-methylnicotinamide (mg/day)	1.20 0.98 1.60 2.80	6	2.9- 6.8	4.1
Indican (Obermeyer's test)	Negative	6	Negative	
Indoleacetic acid (mg/day)	5.50 4.30	6	1.2- 3.4	2.48
5-OH-indoleacetic acid (mg/day)	1.87	2	2.25 2.81	2.53

TABLE II. Urinary Excretion of Tryptophan Derivatives Before and After L-Tryptophan Loading (40 mg/kg)

	Patient		Controls	
	Before loading	After loading	Before loading	After loading
Tryptophan (mg/day)	58.6	113.2	A 14.2 B 20.4 C 21.5	16.4 19.8 25.5
Kynurenine (mg/day)	1.5	3.0	A 2.70 B 3.25 C 4.60	3.36 5.80 7.45
Anthranilic acid (mg/day)	N.D.*	N.D.	N.D.	N.D.
Xanthurenic acid (mg/day)	N.D.	N.D.	N.D.	N.D.
N-methylnicotinamide (mg/day)	2.80	4.95	A 2.85 B 3.15 C 5.20	10.00 9.20 14.20
Indoleacetic acid (mg/day)	5.50	8.30	A 1.20 B 2.35	0.95 2.25
5-OH-indoleacetic acid (mg/day)	1.87	2.50	A 2.25 B 2.81	2.00 2.50
Indican (Obermeyer's test)	Negative	Negative	Negative	Negative

* N.D.: Not detectable

the urines from the patient and controls even after the tryptophan loading, while 5-hydroxyindoleacetic acid excretion after the loading was much elevated in the patient than in the controls. Obermeyer's test gave negative results in all specimens tested. The fasting plasma levels of tryptophan were significantly higher in the patient as compared with those in the controls (cf. Table III). After the tryptophan loading, the levels were further increased and remained elevated for 4 hours in the patient while in the controls the levels were less increased and returned to the pre-loading level at 4 hours following the loading (cf. Fig. 8). These results suggested that there might be a disturbance in pathway of tryptophan to N-methylnicotinamide in the present case.

TABLE III. Fasting Plasma Tryptophan Levels in the Patient, Her Parents and Control Subjects

	Plasma tryptophan (mg/dl)
Patient	1.85
Father	1.38
Mother	1.25
Controls (10 cases)	
Average	1.33
Range	1.05-1.65

Fig. 8. Plasma tryptophan levels in the patient and in control subjects following the oral administration of L-tryptophan (40mg/kg).

Nicotinic acid loading test

40 mg of nicotinic acid per kg of bodyweight was orally administered and 24-hour urines were collected before and after the nicotinic acid loading. Urinary excretion of N-methylnicotinamide was estimated by Huff's method.¹⁰⁾ There was no significant difference in its excretion between the patient and the controls (cf. Table IV). This indicated that there was no disturbance in the conversion of nicotinic acid to N-methylnicotinamide in the present case.

TABLE IV. Urinary Excretion of N-methylnicotinamide After Nicotinic Acid Loading (40 mg/kg)

	N-methylnicotinamide excretion (mg/day)		Recovery rate (%)
	Before loading	After loading	
Patient	1.60	74.4	14.0
Controls { A	3.15	92.5	12.1
{ B	2.88	85.9	14.8

TABLE V. Urinary Excretion of Tryptophan and Kynurenine Before and After L-Tryptophan Loading (80 mg/kg)

	Patient		Controls	
	Before	After	Before	After
Tryptophan (mg/day)	81.5	205.0	D 37.6	70.0
			E 29.7	43.5
Kynurenine (mg/day)	1.8	4.5	D 4.08	10.8
			E 4.80	16.6

The results obtained by the tryptophan loading test and the nicotinic acid loading test suggested that a major defect in the present case might lie in the process of tryptophan to kynurenine. In order to confirm further this view, the second tryptophan loading test (80 mg/kg, that is twice dose of the first test) was performed. The results (cf. Table V) exhibited a more accentuated evidence; a more increased excretion of tryptophan and a less increased excretion of kynurenine, as compared with the results of the first test.

Family studies: The parents of the patient were investigated for tryptophan metabolism in the same way as the patient was done. The results obtained were shown in Table VI. The fasting plasma level of tryptophan was within normal limits in both parents (cf. Table III). The mother showed a significantly increased output of tryptophan and almost normal output of kynurenine while the father showed a normal amount of both tryptophan and kynurenine in urine. The tryptophan loading test revealed a significantly higher output of tryptophan in both parents.

TABLE VI. Urinary Excretion of Tryptophan and Kynurenine in the Parents of the Patient After L-Tryptophan Loading (2 g)

		Tryptophan (mg/day)	Kynurenine (mg/day)
Father	Before	54.5	6.5
	After	98.5	9.0
Mother	Before	70.5	4.0
	After	165.0	11.0
Control adults			
1	Before	49.6	3.7
	After	66.4	8.5
2	Before	60.5	6.0
	After	86.9	10.5
3	Before	38.5	7.5
	After	45.0	11.0

DISCUSSION

There is a similarity in symptomatology between the present case and the cases of H disease. But in detail a noticeable difference exists between them (cf. Table VII). Mental defect is severer in the present case (indicating I.Q. of 30) than in the cases of H disease (indicating I.Q. of 61–114). Dwarfism is prominent in the former but not reported in the latter. Gait disturbance like cerebellar ataxia is described to be temporary and reversible in the latter²⁾ but it is considerably constant in the former.

Laboratory studies of the present case have revealed a definite difference from H disease. The patients with H disease are reported to show a renal type of aminoaciduria and an excessive excretion of indican and indoleacetic acid.^{2,13)} There are reports that the patients with H disease excrete free amino acids,^{13,14)} in amounts of five to ten times normal, 200 to 400 mg of indican per day (100 mg or less in normal subjects)¹⁵⁾ and 50 to 200 mg of indoleacetic acid per day (10 mg or less in normal subjects).^{12,13)} The present patient indicates a slightly higher level of urinary amino acids with the amino acid pattern characterized by a striking increase in tryptophan alone. Excretion of indican and indoleacetic acid in our own patient is not elevated. It is also shown that the plasma tryptophan level in H disease is lower than the normal. On the contrary, our own patient shows a higher level of it.

The results of recent studies are inclined to the opinion that a primary lesion in H disease is a block of amino acid transport into cells, particularly those of the renal tubulus and jejunum.^{12,16)} The defect in amino acid transport in the renal tubulus may account for renal aminoaciduria and that in the jejunum may result in slow absorption of tryptophan. An excessive excretion of indican and indoleacetic acid may be ascribed to the disturbance in tryptophan absorption in

the gut,²⁸⁾ since indole, which is converted to indican in the liver, and indoleacetic acid are known to be formed from tryptophan by intestinal microorganisms.^{7,17,18)} On the other hand, in our own patient it seems likely that there is no disturbance in tryptophan absorption in the gut because plasma level of tryptophan elevates rapidly following the tryptophan loading. Accordingly, no excessive excretion of indican or indoleacetic acid would be expected in urine from our own patient. Indoleacetic acid is known to be in part formed in the liver or kidney.⁶⁾ It might be explained by the conversion of excess tryptophan to indoleacetic acid through the tissue enzymes, that the present patient showed a slight, but significant increase in indoleacetic acid excretion after the tryptophan loading.

It might be reasonable to presume that a major defect in the present case will lie in the conversion of tryptophan to kynurenine, basing upon the following evidence obtained by the present investigation: 1. Plasma tryptophan increased to a higher level and remained elevated for a longer period following the tryptophan loading as compared with that in the controls. 2. Urinary excretion of tryptophan was much increased but that of kynurenine was less increased following the tryptophan loading as compared with those in the controls.

The conversion of tryptophan to kynurenine is the first step in the tryptophan nicotinic acid pathway which is the major route of tryptophan degradation (cf. Fig. 9). The conversion of tryptophan to kynurenine is carried out by two enzymes: first, tryptophan is converted to formylkynurenine by the enzyme tryptophan pyrrolase^{19,20)} and then formylkynurenine is hydrolyzed to kynurenine and formic acid by the enzyme formylase.²¹⁾ Then kynurenine takes part in the three pathways as were shown in Fig. 9. It would be of interest that tryptophan pyrrolase is absent in the fetal tissue but develops after birth.²²⁾ If the present case is deficient in tryptophan pyrrolase, it could be considered that the condition is a carry-over of the fetal condition into postnatal life.

Less degradation of tryptophan to kynurenine may bring about an excessive excretion of tryptophan into the urine and may be driven to other routes of tryptophan degradation such as the pathways to indoleacetic acid or 5-hydroxyindoleacetic acid. Such a tendency could be recognized in our case after oral tryptophan loading.

The pellagra-like skin rash of the patient might be ascribed to niacin deficiency because "pellagra" which is due to dietary deficiency of niacin has similar skin lesion. In H disease, niacin deficiency may be brought about mainly by malabsorption of tryptophan in the intestine, while in case of the present patient the deficiency may be due to a block in tryptophan degradation to niacin pathway. Little is known about physiological significance of tryptophan derivatives such as kynurenine, kynurenic acid or anthranilic acid. Apart from nicotinic acid, there is also a possibility that the deficiency in the other tryptophan derivatives might play a role for development of the present disorder.

TABLE VII. Comparative View of Clinical and Laboratory

Investigators	Case	Consanguinity of the parents	Clinical signs and symptoms [age when symptom was		
			Photosensi- tivity + Pellagra like rash	Gait distur- bance like cerebellar ataxia	Mental status
Baron <i>et al.</i> ²¹⁾	E.H.		(+)[9Y]	(+) Temporary [12Y]	Mental deterioration (temporary) I.Q. 74
	P.H.	Siblings (+)	(+)[3Y]	(+) Temporary [5Y]	Mental deterioration (temporary) I.Q. 61
	H.H.		(-)	(-)	I.Q. 101
	Jh.H.		(+)[8Y]	(+) Temporary [11Y]	I.Q. 93
Hickish, G.W. ²⁹⁾	T.S.	Not reported	(+)[4Y]	(-)	Mental confusion (temporary)
Hersov, L.A. ^{30,31)}	M.H.	(-)	(+)[10]	(+) Temporary	Mental deterioration (temporary) I.Q. 67
	J.	(-)	(+)[9Y]	(+) Temporary [18Y]	Anxiety state (temporary) I.Q. 114
	E.	(-)	(+)[8Y]	(+) Temporary [17Y]	Depersonalization (temporary) I.Q. 95
Herderson, W. ³²⁾	A.P.	(-)	(+)[5Y]	(+) Temporary [15Y]	Normal
Jonxis, J.H. ³³⁾	"D" Sister of "D"	(+)	(+)[3Y] (+)[3Y]	(+) Temporary (+) Temporary	Low Normal
	"C"	(+)	(+)[6Y]	(+) Temporary [5Y]	Below normal
Weyers, H. & Bickel, H. ³⁴⁾	G.B.	(-)	(+)[7Y]	(-)	Normal
Halvorsen, K. & Halvorsen, S. ³⁵⁾	N.A.	(-)	(+)[1Y]	(+) Temporary [11Y]	Mental confusion (temporary) I.Q. 82
	E.A.	(-)	(+)[5Y]	(-)	Occasional headache I.Q. 105-109
Tada, K. <i>et al.</i>	M.K. (Our own case)	(+)	(+)[6M]	(+) Constant [3Y]	I.Q. 30

Findings of Known Cases of "H" Disease and Our Own Case

first noticed]	Biochemical findings					
Dwarfism	Indicanuria	Indoleacetic aciduria	Aminoaciduria	Urinary trypto-phan	Urinary kynurenine	Plasma tryptophan
(-)	(+)	(+) 50-200 mg/day	(+) Generalized Amino N 530-1130 mg/day			
(-)	(+)	(+)	(+) Generalized			Low 1.00 mg/dl
(-)		(+)	(+)			Low
(-)		45 mg/day	Generalized			0.78 mg/dl
		(+)	(+)			Low
		45 mg/day				0.62 mg/dl
(-)						
(-)	(+) 196 mg/day	5.0 mg/day	(+) Generalized			
(-)	(+) 350 mg/day	1.70 mg/day	(+) Generalized 1290 mg/day	High 40 mg/day	Low 0.74 mg/day	
(-)	(+) 390 mg/day	0.95 mg/day	(+) Generalized 1099 mg/day	High 40 mg/day	Low 0.66 mg/day	
(-)	(+)		(+)			
(-)	(+)		(+)			
(-)	(+)		(+)			
(-)	(+)	(+) 31 mg/day	(+) Gneralized Amino N 194 mg/day			
(-)	(+)	(+)	(+) Generalized			
(-)	(+)	(+)	(+) Generalized			
(+)	(-)	(-) 4.3-5.5 mg/day	(+) Specific (Tryptophanuria) Amino N 55 mg/day	High 32.8-81.5 mg/day	Low 0.80-2.50 mg/day	High 1.85 mg/dl

Fig. 9. Metabolism of tryptophan.

The degradation of tryptophan to nicotinic acid is dependent on vitamin B₆.²³⁻²⁵⁾ Therefore, B₆ deficiency can cause a disturbance in tryptophan degradation. In case of B₆ deficiency, urinary excretion of kynurenine and of xanthurenic acid increases because kynureninase is B₆-dependent. The presence of B₆ deficiency in the present case could be excluded since neither kynurenine nor xanthurenic acid was elevated in urine.

Family studies of the patient revealed that both parents might have the same metabolic lesion to a lesser extent as that of the patient because they showed a somewhat increased excretion of tryptophan following its loading. These suggest that the present disorder may be transmitted as an autosomal recessive trait and that the affected individual would be homozygous for the condition and both his parents would be heterozygous carriers.

SUMMARY

A case which was suggested to be a new inborn error of tryptophan metabolism was described. The patient, a 9 year-old girl, was characterized by dwarfism, mental defect, photosensitivity and gait disturbance like cerebellar ataxia. These symptoms and signs were clinically similar to those in H disease but definitely different from it in laboratory findings. Laboratory studies revealed

that the patient excreted an excessive amounts of tryptophan without increase in indican or indoleacetic acid excretion. The tryptophan loading test exhibited that plasma level of tryptophan, following the loading, increased markedly and remained elevated longer accompanied with much increase in tryptophan and less increase in kynurenine in urine as compared with those in the controls. Basing upon the above-mentioned results, it was presumed that a biochemical lesion in the present disorder might lie in the conversion of tryptophan to kynurenine.

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