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# Tryptophan Metabolism in a Patient with Phenylketonuria and Scleroderma:

## A Proposed Explanation of the Indole Defect in Phenylketonuria

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ABSTRACT

**Phenylketonuria and severe focal scleroderma were observed in a white male child. This is the first instance in which the association of these two rare disorders has been reported. Studies carried out on this patient provide a possible explanation for the abnormalities of indole metabolism in phenylketonuria. On an unrestricted diet, when serum phenylalanine levels were elevated, excessive urinary excretion of indolic tryptophan metabolites was seen 18-24 hours after oral tryptophan loading, and tryptophan was demonstrable in the stool. This was not observed when the serum phenylalanine was within normal limits on a low phenylalanine diet. Impaired intestinal tryptophan absorption secondary to elevated serum phenylalanine, by providing tryptophan substrate for bacterial degradation to indolic compounds which are absorbed and excreted in the urine, may partially explain the abnormalities of indole metabolism in phenylketonuria.**

SOMMAIRE

**On a observé, chez un enfant blanc du sexe masculin, une sclérodermie localisée grave et de la phénylcétonurie. C'est la première fois qu'on rapporte l'association de ces deux pathologies rares. L'étude effectuée sur le malade fournit une explication possible des anomalies du métabolisme de l'indole dans la phénylcétonurie. Avec un régime sans restriction, quand les concentrations sériques de phénylalanine étaient élevées, on observait dans un délai de 18 à 24 heures après administration buccale de trytophan, une excrétion urinaire excessive des métabolites du tryptophan indolique, et on retrouvait le tryptophan dans les selles. Ceci n'existait pas quand la concentration sérique de phénylalanine était dans les limites normales avec un régime pauvre en phénylalanine. Un trouble de l'absorption intestinale du tryptophan, secondaire à une augmentation de la concentration de phénylaline, en apportant un substrat de tryptophan pour la dégradation bactérienne en composée indoliques, qui sont absorbés et éliminés par l'urine, peut constituer une explication, au moins partielle, des anomalies constatées dans le métabolisme de l'indole, au cours de la phénylcétonurie.**

CUTANEOUS abnormalities associated with phenylketonuria include eczema, scaliness, hyperhydrosis, dermatographia, oiliness and increased sensitivity to sunlight.[1, 2] This communication records the first reported occurrence of a rare skin disorder, focal scleroderma, in a phenylketonuric patient. The results of studies performed on this patient provide a possible explanation for some of the abnormalities in tryptophan metabolism described in phenylketonuria.

### CASE REPORT

This white male child was first seen at the University of Minnesota Hospitals in September 1960, at the age of 19 months, because of a progressive induration of the skin. He was the product of an uncomplicated term pregnancy, weighing 8 lb. 10 oz. at birth; there were no paranatal complications. He was bottle-fed with a cows' milk formula. During the first six months of life he had several episodes of pneumonia and frequent ear infections. Umbilical and inguinal hernias were repaired at six weeks of age. At about six months an induration of the skin of the abdomen was first noted; over the next year this gradually progressed to involve the skin of the buttocks and legs. Initially, the lesions were pink, firm and pruritic, but over a period of several months became pale and indurated. The skin was bound down to the underlying subcutaneous tissue, and as scar tissue developed an irregular surface was seen, especially over the buttocks and abdomen. Several weeks before the first University Hospital visit, these skin changes were noted on the face, where they assumed a peculiar circumferential distribution around the eyes.

The past history was remarkable in that the mother had noted slowness in the child's motor and mental development. He sat alone at 8 months, stood alone

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at 18 months, and by 19 months would walk only with support. The mother had also noticed a very strong, unpleasant odour to his urine. There was one healthy 8-year-old male sibling; otherwise the family history was non-contributory. They were of Anglo-Saxon origin and Caucasian race.

On examination at 19 months the patient was placid and uncommunicative. The vital signs were normal; the height was 34 in. and the weight 33 lb. (both 97th percentile). Motor and mental retardation of moderate severity was present. The hair was blond. The most striking finding was extensive induration of the skin. This was most marked on the abdomen, buttocks and thighs, but also involved the thorax, neck and pectoral regions, and the periorbital skin of the face. The fingers and toes were not involved. The skin lesions appeared to be in several stages of development. Early lesions were pink, firm and slightly raised; older lesions were pale, occasionally pigmented, brown and very firm. In some areas scarring had caused an irregular suface (Fig. 1).

The hemoglobin value was 13.9 g. %, and the sedimentation rate 27 mm./hr. (Westergren). The urine ferric chloride test was strongly positive; the serum phenylalanine level was 27.7 mg. % (method of Udenfriend and Cooper[3]). Radiographic studies of the esophagus, stomach, small bowel and heart were all normal. An electrocardiogram was normal. Skin biopsies from the thigh and abdomen revealed thickening of the dermis, a decreased number of dermal appendages and hyalinized collagen bundles in the subepidermal region, changes indicative of the diagnosis of scleroderma.

A psychological evaluation revealed that in the area of motor skills the child functioned at an 11-month level; the mental alertness, responsiveness and language development were at the 9-month level.

A diagnosis of severe focal scleroderma with phenylketonuria was made and the patient was started on a low phenylalanine diet,* containing 15 mg./kg. of phenylalanine per day, plus a daily vitamin supplement.† On this diet the serum phenylalanine level fell to within normal values, the hair became darker and the patient was less irritable. No changes in the skin condition occurred which could be attributed to the diet. Over the course of the next two years the oldest lesions showed a decrease in induration and the skin became slightly more pliable. His mental development remained severely retarded. At 3 years he spoke six words and functioned at an 18-month level.

In January 1962, at 3 years of age, he was placed on an unrestricted diet consisting of a regular diet at home and the standard ward diet in the hospital. This dietary change caused no detectable differences in behaviour or intelligence. Serum phenylalanine levels ranged from 1 to 3.5 mg. % on the low phenylalanine diet and from 25 to 32 mg. % on the unrestricted diet.

At subsequent clinic visits the degree of mental retardation has appeared unchanged. The skin induration has become less; areas of scalp alopecia have developed at sites of previous sclerodermatous involvement.

*Lofenalac (Mead Johnson).
†Poly-vi-sol (Mead Johnson), 0.6 ml./day.

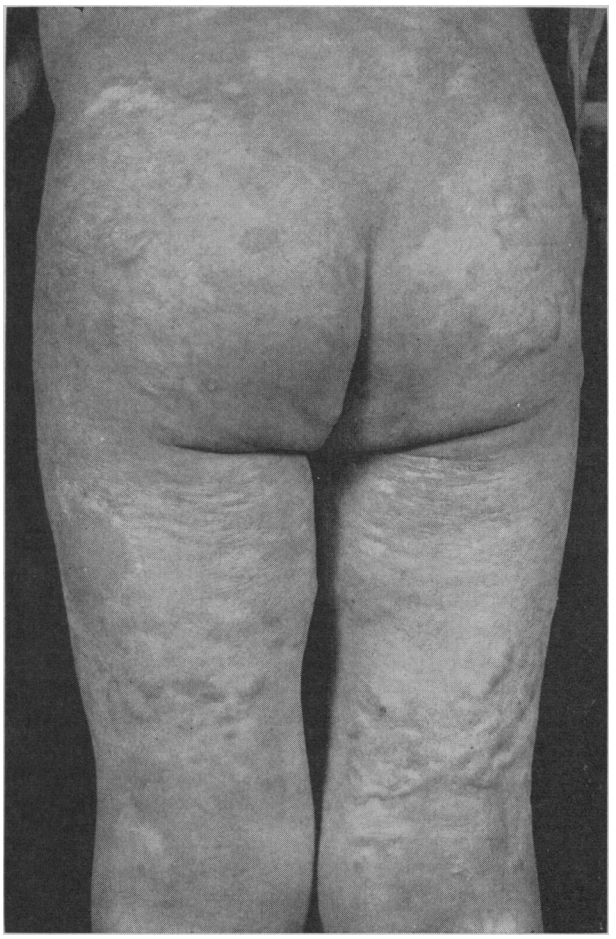

Fig. 1.—The irregular scarred surface of both buttocks and thighs is noted. The skin was tough and unpliable; areas of brownish pigmentation alternate with paler areas.

*Special Studies*

Special studies were carried out on this patient over a period of two years. Control data were obtained from 10 normal children.[4] Oral L-tryptophan was administered both on an unrestricted diet and on a low phenylalanine diet, using a dose of 100 mg./kg. body weight. Urine was collected on ice in four- or six-hour periods for the 24 hours preceding and following the load, and was frozen at -20° C. shortly after collection. Other 24-hour urine specimens were obtained without tryptophan administration while the patient was on each dietary regimen. Indole-3-acetic acid and indican (indoxyl sulfate) were determined by the methods of Weissbach *et al.*[5] and Meiklejohn and Cohen,[6] respectively.

Two-dimensional paper chromatography was done on urine for indoles and on stool specimens for indoles and amino acids according to the method of Smith,[7] and the chromatograms were stained with p-dimethylaminobenzaldehyde (Ehrlich's reagent) and ninhydrin. Volumes of 80 microlitres of urine and 60 microlitres of stool extract were spotted. Stool specimens (5-25 g.) were obtained after tryptophan loading and prepared as described previously.[4, 8]

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TABLE I.—URINARY INDOLIC TRYPTOPHAN METABOLITES*

| Metabolite | Normal children** | | Patient | | | |
|---|---|---|---|---|---|---|
| | | | Low phenylalanine diet | | Unrestricted diet | |
| | Before tryptophan loading | After tryptophan loading | Before tryptophan loading | After tryptophan loading | Before tryptophan loading | After tryptophan loading |
| Indole-3-acetic acid | 1.68 ± .25 | 4.09 ± 1.06 | 3.01 | 7.63 | 4.26 | 8.49 |
| Indican | 6.24 ± 3.02 | 6.61 ± 3.39 | 9.72 | 8.05 | 9.38 | 15.8 |

*Data are expressed as micromoles excreted per kilogram body weight for the 24-hour periods immediately before and after tryptophan loading.

**Data for the normal children are expressed as mean ± one standard deviation.[4]

## RESULTS

### *Quantitative determination of urinary indolic tryptophan metabolites*

These data are presented in Table I and are expressed as micromoles excreted per kilogram body weight in the 24-hour periods preceding and following tryptophan loading.

*Indole-3-acetic acid.*—Excretion before and after tryptophan loading was above normal values on both dietary regimens. The highest rate was obtained following oral loading while the patient was on an unrestricted diet. Sequential studies revealed a marked increase in excretion in the first six hours following tryptophan in both loads, such as is seen normally;[4] however, with the oral load on the unrestricted diet there was an additional rise 18-24 hours after loading. The magnitude of this late rise was about one-fifth that of the immediate post-load rise.

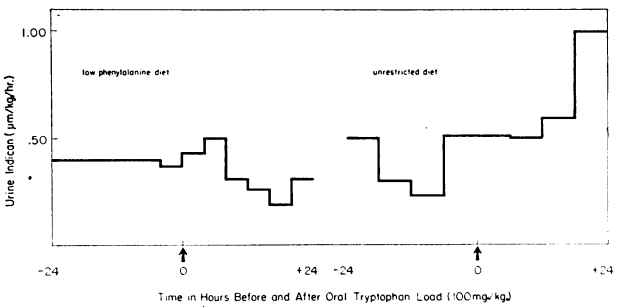


Fig. 2.—Urine excretion of indican following oral L-tryptophan loading. Note the late rise in excretion when the patient is on an unrestricted diet.

*Indican.*—Normal values were observed except following oral tryptophan administration on an unrestricted diet. Excretion at this time exceeded two standard deviations above normal. A sequential study revealed that the highest values occurred 12-24 hours following this load (Fig. 2). This finding was not observed with the other load.

### PAPER CHROMATOGRAPHY

*Urine.*—Indole chromatography of the urine was usually normal while the patient was on a low phenylalanine diet, although on several occasions a slight amount of indole-lactic acid was detected. On an unrestricted diet indole-lactic acid was present in large amounts, and following oral loading, indole-3-acetic acid and indican were present in greater amounts late in the 24-hour period than was the case on the low phenylalanine diet (Fig. 3).

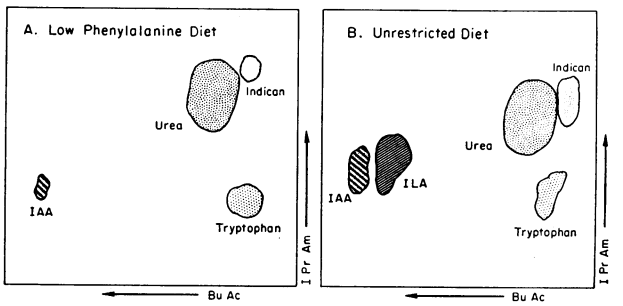


Fig. 3.—Urine indole chromatography (Ehrlich stain) 18-24 hours after oral tryptophan administration (100 mg./kg.). Excretion of indican, indole-lactic acid (ILA), and indole-3-acetic acid (IAA) is more pronounced when the patient is on an unrestricted diet. The solvents for the indole chromatography were isopropanol; ammonium hydroxide: water ( (I Pr Am) (200:10:20) ) and butanol: acetic acid: water ( (Bu-Ac) (120:30:50) ).

*Stool.*—Indole chromatograms of the stool extracts of control patients showed trace to slight amounts of tryptophan both before and after oral tryptophan loading when stained with Ehrlich's reagent. However, when these extracts were run for amino acids and stained with ninhydrin, tryptophan was not detectable.* In contrast to these findings the patient's stool extracts, obtained following oral loading while on an unrestricted diet, contained amounts of tryptophan which were readily detectable by amino acid chromatography using ninhydrin as a stain.

## DISCUSSION

Focal scleroderma is an uncommon skin disorder of unknown etiology in which induration and scarring of the skin and subcutaneous tissue occur. In contradistinction to diffuse or systemic scleroderma (acrosclerosis), a very rare condition in childhood, no involvement of the esophagus and viscera is seen in focal scleroderma. Although con-

*The Ehrlich reagent as used in our laboratory is about 10 times as sensitive an indicator of tryptophan as is ninhydrin.

siderable disability and disfigurement may result, the activity of this condition is usually self-limited, becoming quiescent after a period of about two to three years.[9, 10]

The occurrence of this relatively rare skin disorder in a patient with phenylketonuria may represent the chance association of two uncommon diseases; on the other hand it may reflect an as yet unrecognized metabolic disturbance which could underlie the variety of unexplained skin disorders in phenylketonuria.

Abnormalities in the indole metabolites of tryptophan have not been reported in focal scleroderma, whereas in phenylketonuria abnormalities involving indolic as well as other metabolic pathways or tryptophan have been described.[2, 11-16] These are manifested by excessive urinary excretion of indolic compounds and by decreased levels of plasma 5-hydroxytryptamine (serotonin) and urine 5-hydroxyindoleacetic acid. Most of these disturbances return to normal when serum phenylalanine is controlled by appropriate diet.

Inhibition of 5-hydroxytryptophan decarboxylation[13, 17] or of tryptophan hydroxylation[12, 18] by phenylalanine and its metabolites is a possible explanation for abnormalities in serotonin pathway metabolism seen in human and experimental phenylketonuria.[19-23]

On the other hand, studies by McKean, Schanberg and Giarman[24] in experimental phenylketonuria suggest that inhibition of transport of tryptophan metabolites rather than inhibition of hydroxylating or decarboxylating enzyme systems may account for these abnormalities.

Several possible explanations for the excessive excretion of indolic compounds in phenylketonuria have been suggested. These include a tissue abnormality of indole metabolism and abnormal renal excretion of these metabolites.[16, 25]

Observations in this report indicate that a defect in transport of tryptophan in human phenylketonuria as a result of elevated serum levels of phenylalanine may be important in the genesis of the indole disturbances seen in this disorder. Further studies involving a number of phenylketonuric patients will be necessary to confirm this hypothesis.

There is a striking similarity between the indole abnormality in phenylketonuria and that of two other disorders in which abnormal tryptophan transport has been demonstrated, namely the blue diaper syndrome[8, 26] and Hartnup disease.[27] In the first of these, excessive urinary excretion of indican, indole-3-acetic acid, indole-lactic acid and other indolic compounds is seen. Impaired tryptophan absorption from the gastrointestinal tract, by providing substrate for bacterial degradation of tryptophan to indoles, is a probable explanation for the excessive indole excretion seen in the blue diaper syndrome. This is suggested by the finding of excess tryptophan in the stool and a rise in the excretion of indoles late in the 24-hour period following tryptophan loading. Indole-3-acetic acid is formed in liver from tryptophan;[5] this probably accounts for the immediate increased urinary excretion following either oral or intravenous tryptophan administration. Degradation of tryptophan by intestinal bacteria is another important source of indole-3-acetic and other indoles, and presumably accounts for the rise in excretion of these compounds 18 to 24 hours after oral tryptophan administration. Indican is formed in the liver from absorbed indole derived from the action of bacterial tryptophanase on tryptophan.

In Hartnup disease[27] excess urinary excretion of the same indolic compounds is seen following tryptophan loading. Here, also, excretion rate rises late in the 24-hour period following loading, and excessive tryptophan is demonstrable in the stool.

The absorption rate of D-tryptophan from the intestinal tract is much less than that of the L-isomer.[27, 28] When D-tryptophan is given to normal subjects, a marked increase in urinary excretion of indolic compounds is seen[11, 27, 29] and tryptophan is demonstrable in the stool. These observations in patients with the blue diaper syndrome, Hartnup disease, and normal subjects given D-tryptophan, suggest that impaired intestinal tryptophan absorption may be of paramount importance in the genesis of excessive urinary excretion of indole-3-acetic acid, indole-lactic acid and indican. The same explanation may be applicable for this aspect of the abnormal tryptophan metabolism in phenylketonuria. Support for this hypothesis is provided by the observation of tryptophan in the stool of our patient—a finding not seen in normal subjects[4, 27]—and the late rise in indole-3-acetic acid and indican excretion following oral tryptophan administration while on an unrestricted diet.

An explanation for the impaired tryptophan transport in phenylketonuria is suggested by the observation in our patient and in others[13, 16] that with reduction of serum phenylalanine levels the excretion of indican and indole-lactic acid decreases. In addition, in our patient, the late rise in urinary excretion of indican and indole-3-acetic acid, as well as the presence of tryptophan in the stool following oral loading, were seen only when the serum phenylalanine levels were elevated. Elevation of the serum phenylalanine may be of prime importance in inhibiting transport of tryptophan from the gastrointestinal tract. There is evidence that phenylalanine and tryptophan share at least one common step in their intestinal absorption,[30] and inhibition of L-tryptophan transport in the hamster intestine of L-phenylalanine has recently been demonstrated.[31] The observation that even on the low phenylalanine diet the excretion of indole-3-acetic acid was above normal values might be interpreted as evidence against the hypothesis presented here. A reasonable explanation for this finding is that the dietary

preparation used* contained 0.4% tryptophan which consisted of equal amounts of the D- and L-forms. The D-form by virtue of its impaired absorption could provide substrate for bacterial degradation to indolic metabolites.

## SUMMARY

The associated occurrence of phenylketonuria and severe focal scleroderma in a child is documented. On an unrestricted diet excess tryptophan was demonstrable in the stool and a rise in urine indole-3-acetic acid and indican excretion was seen 18 to 24 hours after oral tryptophan loading. These findings were not seen when serum phenylalanine levels were normal.

These data suggest that impairment of tryptophan transport from the bowel, secondary to high concentrations of phenylalanine, may partially explain the indole defect in phenylketonuria.

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*Lofenalac (Mead Johnson).

## PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

### AN INCIDENT AT JASPER AVENUE, 5TH STREET WEST

The Provincial Health Act passed in 1910 has now been in force four years, and its practicability and efficiency have been tested, especially in the larger centres of population. On the whole, the Act has been found to work out satisfactorily from the public health standpoint. Certain defects and weaknesses, however, have from time to time been revealed by prosecutions instituted under its provisions where the chicanery of the law has been invoked to defeat the intention of the provincial board in making the Regulations and to the chagrin and discomfiture of health officials, failure to obtain a conviction has frequently resulted from legal technicalities and quibbles which to a layman seem frivolous, but which under skilful manipulation of clever and subtle young lawyers acting as counsel for the defendant, are made to appear of sufficient importance to justify the verdict "dismissed with costs", even when the evidence clearly indicates the guilt of the accused. The burden of proof rests with the prosecution as is usual, and infractions of the law respecting public health are perhaps from their very nature more difficult of proof than those of common law. It does appear that magistrates generally exhibit a reluctance to convict on matters of public health unless every jot and tittle of evidence has been produced respecting identity, dates, time, place, service of writ, etc. Curiously enough, the public in whose interests such prosecutions are instituted almost invariably regard such action, brought against the individual, as persecution rather than prosecution and exhibit an unholy levity when the delinquent succeeds in escaping a fine through some slight technicality of the law.

Some years ago I had occasion to prosecute an individual who persisted and insisted in living in a small tent as a dwelling on our main business street. Water and sewer mains had been in use for several years on this street, and the charge was that he had failed to put sanitary fixtures in his place of abode. I had to produce the city engineer with his blue prints to prove that the city had laid sewer and water pipes there. This having been established to the satisfaction of the court, I was then nonplussed by the magistrate asking me if I was sure there was water in the mains. Nothing daunted, I produced the occupants of neighbouring houses who testified that they obtained fluid from their taps commonly known as city water. Eventually the case was dismissed on the ground that a few boards having been built inside the tent as side walls, it was therefore no longer a tent but a dwelling with a canvas roof, not a tent as stated in the indictment. Learning, however, that there was a law regarding brick chimneys as against stove pipes, I instituted another action requiring the replacement of the stove pipe by a brick chimney. This got him and he removed his belongings in a few days and shortly afterwards his ramshackle structure from Jasper Avenue, 5th Street West. In passing, I may say he was a citizen possessed of more than the average share of worldly goods.

A prominent citizen was allowed by me as a concession to answer a charge of breaking quarantine for his wife, who, while her child was under quarantine, left her house to attend a fashionable public gathering where I had the misfortune to meet her and thus became aware of the liberty she had taken. In this case the family doctor, who was catering for fashionable practice, came to the rescue and testified that he had advised her for her health occasionally to take a walk round the block. This, the same magistrate thought justified him in dismissing the case, magnanimously refusing the accused his costs which he asked for. A few days earlier he had assessed a much less flagrant case of breaking quarantine for scarlet fever, $10 and costs. But this man had the honesty to plead guilty and was a comparatively obscure and unknown citizen.

Another action was brought against a prominent citizen, for failing to report a case of chicken-pox in his family. This case was contracted from a previous case in the same house for which quarantine had been imposed and removed the day before, after recovery. For this second case no physician had been called, but the mother of the child had stated to the health inspector that it was chicken-pox. . . In summing up the case, the magistrate stated that the health department appeared to have no case, because no actual medical authority had been produced as to a case of chicken-pox having existed in defendant's house.—T. H. Whitelaw, *Canad. Med. Ass. J.*, 6: 313, 1916.