Tryptophan Metabolism in Humans with Various Types of Anemias

By L. V. HANKES, R. R. BROWN, L. SCHIFFER AND M. SCHMAELER

STUDIES OF TRYPTOPHAN metabolism in man and animals with radioactively labeled compounds require a recognition of an inherent problem related to dosages employed if meaningful quantitative data are to be gathered and analyzed. Variations in amounts of tryptophan load used could account for the lack of a sound baseline for the evaluation of results obtained in different laboratories.

In the past number of years it has been shown that tryptophan metabolite levels vary greatly in some disease categories.1 The level of tryptophan given to a patient may greatly affect the per cent of tryptophan metabolized to carbon dioxide. The observation that loading doses may significantly affect the per cent of the C14O2 excreted by a patient suggested that the loading dose with labeled tryptophan may be a test for deranged tryptophan metabolism regardless of the urinary excretion patterns.2

In previous studies2 we found that in a given individual, the results obtained from a single tracer dose without carrier differ significantly from those when a carrier dose of tryptophan (1 or 2 Gm.) was given with the tracer dose. This procedure was chosen not as a quantitative measurement of metabolic pathways of physiologic levels of tryptophan, but rather with the thought that this method of approach might be helpful to the clinician in detecting aberrations in tryptophan metabolism in man. Price et al.3 in a review article emphasized that loading experiments could be useful in allowing the detection of abnormal metabolism, which might not be detected otherwise. It has been shown2 that the C14O2 production in man is a function of the loading dose given. With this fact in mind it was thought that the two gram loading dose combined with a tracer dose could be used to determine the severity of a disease.

Tryptophan pyrrolase enzyme is an iron porphyrin (apoenzyme) which can be reconstituted with either heme or hematin with the latter being more associative than the former. A chemical reduction of hematin-enzyme yields
the active heme-enzyme.\textsuperscript{4,5} Since there is such a close relationship between heme-hematin metabolism and tryptophan metabolism, the authors felt that a study of carbon-14 tryptophan metabolism in advanced cases of anemia should show any gross abnormalities in the metabolism of tryptophan in the disease and, in addition, provide information concerning the utility of the tryptophan tracer load test as a diagnostic tool.

For this study a group of patients on our metabolic wards, who had severe anemias, were chosen for the study. Following administration of tryptophan to patients, the per cent of the tracer dose excreted as CO\textsubscript{2} in the breath and the quantitative excretion of metabolites in the urine were determined as two important parameters of tryptophan metabolism.

**Materials and Methods**

The commercially available DL-tryptophan-2-C\textsubscript{14} used in the study was checked for purity by paper chromatography and autoradiography. Its specific activity was checked by combustion to CO\textsubscript{2} and analysis in Ballentine gas counting tubes.\textsuperscript{6}

The samples of patient expired air were collected with a system of a plastic hood connected by plastic tubing to a pair of large glass (15 cm. x 55 cm.) gas absorption towers. A continuous stream of air was pulled through the system at a rate which insured the trapping of the CO\textsubscript{2} in the 2N NaOH in the glass towers and at the same time kept the patient comfortable. The plastic hood made possible the study of patients who otherwise could not tolerate a tight conventional face mask. The sodium hydroxide samples containing the C\textsubscript{14}O\textsubscript{2} were analyzed for C\textsubscript{14} activity by acidification in a Van Slyke chamber, followed by transfer of the liberated gas into Ballentine gas counting tubes. The following equations were used to calculate the per cent of administered C\textsubscript{14} expired as C\textsubscript{14}O\textsubscript{2} per minute:

\[
\text{sc-C}\textsubscript{14}/\text{mMCO}_2 \times \text{body surface area (M\textsuperscript{2})} \times 4.8 = \frac{\text{sc-C}\textsubscript{14}/\text{minute}}{\text{sc-C}\textsubscript{14} \text{administered}} \times 100 = \% \text{ dose expired/minute}
\]

An average value of 4.8 was used for millimoles CO\textsubscript{2} per minute per square meter. This was calculated from published tables.\textsuperscript{7}

Urine samples were collected for a 24 hour period prior to the administration of the tryptophan and for three consecutive 24 hour periods afterwards. The urine samples were collected under toluene in dark glass bottles and refrigerated until the collections were completed. After measuring the total volumes collected, aliquots were stored frozen in plastic bottles until analyzed.

Each urine was analyzed for C\textsubscript{14} content. The pre-tryptophan and post-tryptophan (first 24 hours) urines were analyzed for fifteen components by chemical or microbiologic methods (see Fig. 1). The urinary components determined were kynurenic acid (8), xanthurenic acid (8), indoxyl sulfate (9), anthranilic acid glucuronide (10), o-aminohippuric acid (10), acetylkynurene (10), anthranilic acid (11), kynurenine (10), hydroxykynurene (12), N\textsuperscript{1}-methylnicotinamide (13), N\textsuperscript{1}-methyl-2-pyridone-5-carboxamide (14), 4-pyridoxic acid (15), creatinine (16), quinolinic acid (17), and nicotinic acid (18).

Patients were placed on a tryptophan controlled (0.7 to 1 Gm./day) diet for a period of five days prior to and during the study period. All drugs were avoided during the test period, and the patients were studied in the resting state. DL-Tryptophan-2-C\textsubscript{14} was given orally in a gelatin capsule one hour after breakfast. The doses were 12.29 to 30.75 mg. containing 96.46 to 108.76 $\mu$C of C\textsubscript{14} activity. Some patients were given a 2 Gm. loading dose of L-tryptophan simultaneously with the tracer dose. One patient was studied with a tracer dose, placed on pyridoxine for several weeks and the tracer study then repeated. The exhaled CO\textsubscript{2} was collected continuously for the first 4 hours.
Fig. 1.—Pathways of tryptophan metabolism in animal and man.

and then at multiple hour intervals for an additional 27 hour period. The dosage schedule as well as general patient information is shown in Table 1

Patient Material

All patients were aware of the experimental nature of the procedures and gave their informed consent. The patients were hospitalized for a variety of reasons and their selection for this study was random and was based on the severity of their anemia. By chance, 6 of the 7 patients had anemias characterized by abnormally low production of erythrocytes. The seventh patient had an excessive production of abnormal erythrocytes (P-4 sickle cell-Thalassemia). All patients were heavily iron-loaded.

Patient P-1 was a 22 year old white male with a 14 year history of microcytic hypop-
Table 1.—General Information on Patients

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<th>Sideroblastic Anemia</th>
<th>Aplastic Anemia</th>
<th>Sickle Cell Anemia</th>
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<th>Aplastic Anemia</th>
<th>Aplastic Anemia</th>
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*Six subjects were Caucasian and one Negro.
†Subject P-1 was studied four times and subject P-2 studied twice.
chronic anemia which was partially pyridoxine responsive. Bone marrow aspiration showed increased erythroid activity, with a maturation defect in the cytoplasm of early erythroid cells, and markedly increased iron deposits. There was marked hepatomegaly and splenomegaly. Upon administration of 100 mgm. pyridoxine 1.M., 3 times daily, the reticulocytes rose, followed shortly by the hemoglobin. The severe diabetes and neurologic symptoms did not change. The pyridoxine was changed from intramuscular to oral with another rise in hemoglobin to 10.5 Gm. per cent. Serum iron and TIBC were 250 γ per cent and did not change after pyridoxine therapy. He died of cardiac failure resulting from myocardia deposition of iron. The initial studies were performed prior to institution of pyridoxine treatment, when the Hgb was 4.8 Gm. per cent, and the second study was performed after the intramuscular pyridoxine, when the Hgb. was 8.7 Gm. per cent.

Patient P-2 was a 35 year old white male, known to have had a mild macrocytic anemia with increased iron stores since childhood. His Hgb. was 10.6 Gm. per cent and reticulocytes 3.8 per cent. There was anisocytosis, poikilocytosis, and macrocytosis of peripheral red blood cells. The bone marrow was markedly hyperplastic, with a great increase in the erythroid series, and marked iron deposits and sideroblasts. Serum iron was 216 to 247 γ per cent with a small UIBC. The anemia was not responsive to pyridoxine, folic acid, or vitamin B12. Studies were performed before pyridoxine treatment.

Patient P-3 was a 52 year old white male who had been anemic for 6 months and had required several transfusions during that time. At the time of the pyridoxine study his Hgb was 8.6 Gm. per cent and reticulocytes 0 per cent. The bone marrow showed hyperplasia of early erythroid precursors and maturation arrest at the proerythroblast stage. Serum iron and TIBC were 300 γ per cent. The patient lived for 3 years and required approximately 140 transfusions during that period. His bone marrow was aplastic at the time of death.

Patient P-4 was a 21 year old male of Indian-Portuguese descent who had a long standing severe anemia and hemosiderosis. He had received over 300 transfusions and had had a splenectomy. There was marked hepatomegaly. At the time of the pyridoxine study his Hgb. was 6.6 Gm. per cent with 0 per cent reticulocytes. The bone marrow showed increased cellularity with a marked increase in erythropoiesis. There was marked hemosiderosis, but no typical sideroblasts. Hemoglobin studies of the patient and his parents confirmed the diagnosis of sickle cell-Thalassemia. Serum iron was 204 γ per cent with TIBC of 244 γ per cent.

Patient P-5 was a 12 year old Negro female who was known to be anemic throughout her life. The bone marrow showed a marked decrease in erythroid precursor cells. She had received numerous transfusions before admission. At the time of study her Hgb. was 7.6 Gm. per cent with 0.5 per cent reticulocytes. Serum iron and TIBC was 524 γ per cent. The discharge diagnosis was congenital erythroid hypoplasia.

Patient P-6 was a 64 year old white female with an aregenerative anemia of 4 years duration. She had received multiple transfusions. At the time of study her Hgb. was 10.2 Gm. per cent with 0 per cent reticulocytes. The bone marrow was cellular with decreased erythropoiesis and a shift towards the mature elements. Serum iron was 250 γ per cent and TIBC was 290 γ per cent. Further diagnostic procedures did not elicit the cause of the anemia.

Patient P-7 was a 67 year old white male with a 3 year history of anemia. He had received 150 transfusions. At the time of study his Hgb. was 6.3 Gm. per cent and there were 0 per cent reticulocytes. His bone marrow was cellular, but erythropoiesis was all but absent. Myelopoiesis predominated. The serum iron was 144 γ per cent and TIBC 187 γ per cent. The discharge diagnosis was aregenerative anemia, possibly myelocytic leukemia.

## RESULTS

Figure 1 shows the pathways of tryptophan metabolism in animals. General information about the patients in this study is given in Table 1. All seven
Table 2.—Patient Urinary Metabolite Levels compared to Normal People

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<th>HKYN</th>
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<td>171</td>
<td>405</td>
<td>131</td>
<td>30</td>
<td>12</td>
<td>237</td>
<td>19</td>
<td>140.54</td>
<td>6.08</td>
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<td></td>
<td>X</td>
<td>Post-1</td>
<td>78</td>
<td>24</td>
<td>433</td>
<td>14</td>
<td>31</td>
<td>17</td>
<td>29</td>
<td>24</td>
<td>132</td>
<td>161</td>
<td>4.03</td>
<td>49</td>
<td>2197</td>
<td>1.43</td>
<td>0.62</td>
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The abbreviations used are K.A., kynurenic acid; XA, xanthurenic acid; ISA, isovaleryl sulfate (indican); AAG, anthranilic acid glucuronide; O-AHA, N-acetylhydroxamic acid; KYN, kynurenic acid; KYN, kynurenic acid; HKYN, hydroxykynurenine; QA, quinoline acid; NA, nicotinic acid; N-MN, N-methylNicotinamide; MPCA, N-methylpyridone-3-carboxamide; 4-PA, 4-pyridone acid; CR, creatinine; P, pyridine. Values are given as micromoles per 24 hours except creatinine which is given as grams per 24 hours.

The loading dose of L-tryptophan was given orally. Control values are the mean values ± standard deviations. Pre-1 and post-1 refer to the day before and day after tryptophan administration. The loading doses of L-tryptophan were given orally in a single dose at the beginning of the post-tryptophan collection period.

*Indicates values different from controls by more than 2 S.D. For statistical purposes the values following tracer doses were compared with pre-supplement control values.

**Control values are from those reported by J. M. Price, R. R. Brown and N. Yem., with the exception of QA, NA, and N-MN, which are from H. R. Brown and associates.**
patients studied were given the tryptophan orally. Five patients (P-3, P-4, P-5, P-6, and P-7) were given the tracer dose together with the 2 Gm. loading dose. Two patients (P-1 and P-2) were studied with a tracer dose, and subsequently with a 2 Gm. loading dose. One patient (P-1) was placed on pyridoxine therapy for several weeks before a second tracer and 2 Gm. loading dose study were repeated.

The quantitative excretion of urinary metabolites is shown in Table 2. Results in the table were considered abnormal if they were above or below normals by two standard deviations. Of the metabolites measured in urine, those showing the largest number of abnormal levels are kynurenic acid, acetyl kynurenine, anthranilic acid, kynurenine, N1-methylnicotinamide, N1-methyl-2-pyridone-5-carboxamide, and quinolinic acid. In almost all of the cases, the levels of these components were elevated, some very significantly.

Patient P-5 (congenital erythroid hypoplasia) excreted unusually high levels of kynurenic acid, acetylkynurenine and kynurenine, but only slightly elevated xanthurenic acid and hydroxykynurenine following tryptophan loading. This suggests a defect in the hydroxylation of kynurenine. This patient's urinary metabolite pattern is not similar to that of a simple vitamin B6 deficiency where urinary xanthurenic acid and hydroxykynurenine levels are high.

Patient P-1 initially showed only slightly elevated levels of several metabolites, particularly on the control days. While these abnormalities were small they appeared consistently in most fractions, in repeated studies, and they were essentially unchanged by large doses of pyridoxine. This patient had a very high urinary quinolinic acid and N1-methyl-2-pyridone-5-carboxamide levels which were depressed slightly in the load test, after the patient had been placed on pyridoxine (B6) for several weeks. A study of the effects of vitamin B6 levels on the metabolism of tryptophan in man has shown that as the level of vitamin B6 in a human was depleted, the urinary quinolinic acid levels significantly increased, and when the subjects were given vitamin B6, the urinary quinolinic acid levels returned to normal. This same type of response to pyridoxine was observed in patient P-1 and suggests that vitamin B6 may be required in the further metabolism of quinolinic acid or that vitamin B6 may be required by some pathway competing for precursors of quinolinic acid, such as the conversion of α-amino-β-carboxymuconic-ε-semialdehyde (precursor of quinolinic acid) into picolinic acid or the numerous intermediates in the pathway to CO2. It seems possible, also, that pyridoxine may function as a coenzyme for picolinic carboxylase although this has not been directly demonstrated. Arguing against this possibility is the data in Figure 2 which shows very similar C14O2 excretion curves for this patient before and after pyridoxine supplementation (curves P-1A versus P-1C). Patients P-4 (sickle cell-Thalassemia) and P-7 (aregenerative anemia) showed lower levels of urinary 4-pyridoxic acid and very high quinolinic acid levels. Patient P-7 also showed a high N1-methyl-2-pyridone-5-carboxamide level. The low creatinine excretion levels of P-4, P-6 and P-7 may be related to the small stature of these patients.
Table 3.—Excretion of $C^{14}$ by Patients After Oral Administration of DL-Tryptophan-2-$C^{14}$

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>SUBJECT</th>
<th>DL-LABELLED</th>
<th>L-UNLABELED</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>24</th>
<th>0-24</th>
<th>25-48</th>
<th>49-72</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>mg.</td>
<td>µc.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
<td>hr.</td>
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<tr>
<td>Microcytic Hypochromic</td>
<td>P-1A</td>
<td>17.54</td>
<td>96.45</td>
<td>0.1</td>
<td>0.57</td>
<td>2.13</td>
<td>2.63</td>
<td>4.04</td>
<td>27.47</td>
<td>1.11</td>
<td>0.25</td>
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<tr>
<td>Anemia</td>
<td>P-1C</td>
<td>18.78</td>
<td>103.28</td>
<td>0.25</td>
<td>0.8</td>
<td>1.95</td>
<td>2.74</td>
<td>3.94</td>
<td>29.95</td>
<td>1.41</td>
<td>0.66</td>
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<tr>
<td>Sidero-Achreatic Anemia</td>
<td>P-2A</td>
<td>18.16</td>
<td>99.87</td>
<td>—</td>
<td>0.04</td>
<td>0.28</td>
<td>1.81</td>
<td>2.42</td>
<td>3.43</td>
<td>28.96</td>
<td>1.36</td>
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<td>Aregenerative Anemia</td>
<td>P-3</td>
<td>12.29</td>
<td>106.08</td>
<td>2</td>
<td>0.12</td>
<td>2.44</td>
<td>9.36</td>
<td>11.83</td>
<td>15.38</td>
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<td>Sickle-cell Thalassemia</td>
<td>P-4</td>
<td>30.75</td>
<td>97.95</td>
<td>2</td>
<td>0.03</td>
<td>0.81</td>
<td>5.57</td>
<td>7.68</td>
<td>10.36</td>
<td>20.47</td>
<td>0.72</td>
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<td>Congenital Erythroid</td>
<td>P-5</td>
<td>19.32</td>
<td>106.27</td>
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<td>0.3</td>
<td>3.63</td>
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<td>Aregenerative Anemia</td>
<td>P-6</td>
<td>18.36</td>
<td>100.98</td>
<td>2</td>
<td>0.16</td>
<td>2.01</td>
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<tr>
<td>Anemia</td>
<td>P-7</td>
<td>19.77</td>
<td>108.76</td>
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<td>0.14</td>
<td>1.25</td>
<td>6.20</td>
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<td>12.90</td>
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Fig. 2.—Expiration of C\(^{14}\)O\(_2\) by patients after oral administration of tracer doses of DL-tryptophan-2-C\(^{14}\) and in one case pyridoxine therapy previous to the tracer dose.

Table 3 shows the dosages of labeled and unlabeled tryptophan given and the per cent of the dose excreted in CO\(_2\) and urine. When only the tracer dose was given, the patients expired only 3.43 to 4.04 per cent of the dose as C\(^{14}\)O\(_2\) compared to the 4.52 to 7.48 per cent levels observed in a previous study.\(^2\) Unfortunately, these patients were not given the combined tracer plus loading dose for comparative purposes. In those patients given the tracer plus loading dose this value increased to 10.36 to 18.2 per cent. However, this increased expiration of C\(^{14}\)O\(_2\) was considerably less than the 23 to 25 per cent observed in a previous study.\(^2\) Even though there were gross changes in the C\(^{14}\)O\(_2\) metabolism in those patients receiving the tryptophan load, the urinary carbon-14 levels were not appreciably changed from those receiving the tracer only, in this or the previous study.\(^2\)

As shown in Figure 2, the administration of vitamin B\(_6\) to patient P-1 increased the C\(^{14}\)O\(_2\) expiration very slightly, and shortened the period of time for appearance of C\(^{14}\)O\(_2\) in the breath after the administration of the oral dose.

Figure 3 shows the time lag of about 1.5 hours before the C\(^{14}\)O\(_2\) appeared in the breath. All three of the patients (P-3, P-4 and P-6) received the tracer dose with the 2 Gm. loading dose, and all three showed a depression of C\(^{14}\)O\(_2\) metabolism, which could have been a function of the severity of their disease.

**Discussion**

The practice of using a carbon-14 tracer plus loading dose of a compound in metabolic studies to determine the severity of a disease is relatively new, although the use of loading doses of varying sizes is not new in the field of tryptophan metab-
Fig. 3.—Expiration of C\textsuperscript{14}O\textsubscript{2} by patients after oral administration of tracer doses of DL-tryptophan-2-C\textsuperscript{14} with loads of L-tryptophan.

...
simply a function of the level of tryptophan pyrrolase enzymes, which have been shown in rats to be dependent on the blood hematin levels. After tryptophan loading, urinary levels of quinolinic acid, N1-methylnicotinamide and N1-methyl-2-pyridone-5-carboxamide were elevated in this patient, and although the pyridoxine administration lowered the urinary levels of quinolinic acid and the pyridone, they were not reduced to normal levels. The inability of the vitamin B6 therapy to return the urinary quinolinic acid levels to normal in this patient, as has been observed in normal adult, suggests that vitamin B6 deficiency alone is not the explanation for the elevated quinolinic acid levels and that an additional explanation must be sought. It may relate to the metal chelating ability of quinolinic acid formed in the liver. Since the C14-tryptophan was labeled in the side chain and since pyridoxine administration did not appreciably alter the production of C14O2, the data suggest that kynureninase activity was not appreciably changed and therefore suggests the possible role of vitamin B6 at a later step in the metabolism of hydroxynorcarboxylic acid, such as its conversion into a-amino-carboxylic acid-semialdehyde and the conversion of the semialdehyde into the numerous intermediates in the pathway to CO2. On the basis of the data presented here and in our previous works it may be postulated that vitamin B6 is involved in picolinate carboxylase activity. This would adequately explain the observation that quinolinic acid excretion is elevated in pyridoxine deficient subjects.

In general humans having a vitamin B6 deficiency show elevated urinary levels of hydroxvkynurenine, xanthurenic acid and kynurenic acid in that order. Yess et al. concluded that vitamin B6 dependent kynureninase activity was preferentially depressed over that of vitamin B6 dependent kynurenine transaminase allowing for the conversion of hydroxvkynurenine to xanthurenic acid and kynurenine to kynurenic acid. In patient P-5 the order of elevated components was kynurenine, hydroxy-kynurenine, kynurenic acid and xanthurenic acid. This order along with normal levels of quinolinic acid suggests that this patient was not suffering from a typical vitamin B6 deficiency. The relative amounts of hydroxylated and unhdroxylated metabolites of kynurenine suggests that kynurenine hydroxylase (TPNH and O2 dependent) was inhibited.

All patients given the loading dose with the C14 tracer showed a lower C14O2 output than would normally be expected. In some cases this lowered C14O2 output coincided with elevated urinary kynurenine and quinolinic acid levels. The increased kynurenine levels would suggest that in these cases the pyrrolase enzyme activities were not too grossly depressed. However, the pyridoxine dependent enzymes converting the 3-hydroxyanthranilic acid metabolites into C14O2 may have been depressed, forcing large quantities of the a-amino-carboxylic acid-semialdehyde to convert spontaneously into quinolinic acid.

**SUMMARY**

Metabolic studies were performed in a number of patients to determine the effect of anemia on tryptophan metabolism. Patients were given a tracer dose of DL-tryptophan-2-C14 or the tracer dose plus a loading dose (2 Gm.) of L-tryptophan. In those patients given the loading dose, the C14O2 production over a 24 hour period was lower than that usually obtained in normals receiving the same dose. The loading dose did not have any significant effect on the total urinary radioactivity level. In some cases the post tryptophan loading urinary level of kynurenine, quinolinic acid, N1-methylnicotinamide and N1-methyl-2-pyridone-5-carboxamide were elevated. Vitamin B6 administration returned the kynurenine and N1-methylnicotinamide levels to normal but not the quinolinic acid or pyridone. The results obtained here indicate that in anemias the activity of the hematin dependent enzyme, tryptophan pyrrolase,
was depressed as well as the enzymes converting the amino acid into CO$_2$.
The data suggest that not only are the kynurenine catabolism enzymes vitamin
B$_6$ dependent but that vitamin B$_6$ is very important to the conversion of the
tryptophan metabolite 3-hydroxy-anthranilic acid into $\alpha$-amino-$\beta$-carboxymu-
conic-$\epsilon$-semialdehyde and the conversion of the semialdehyde into acetate and
CO$_2$. In addition vitamin B$_6$ may be involved in the further metabolism of
quinolinic acid into the pyridone.

**SUMMARIO IN INTERLINGUA**

Studios metabolic esseva effectuate in un numero de patientes con le objectivo de de-
terminar le effeeto de anemia super le metabolismo de tryptophano. Le patientes recipeva
un dose traciatori de DL-tryptophano-2-C$^{14}$ o iste dose traciatori plus un dose de cargation
(2 g) de L-tryptophano. In le patientes qui recipeva le dose de cargation, le production
de C$^{14}$O$_2$ per 24 horas esseva plus basse que illo usualmente obtenite in subjectos normal
recipiente le mesme tractamento experimental. Le dose de cargation non habeva un effeeto
significative super le total nivello urinari de radioactivitate. In plure cases le nivello
urinari, post cargation a tryptophano, de kynurenina, acido quinolinic, N$^\prime$-methyhuico-
tinamida, e N$^1$-methyl-2-pyridona-5-carboxamida esseva elevate. Le administration de vita-
min B$_6$ resultava in le renormalisation del nivello de kynurenina e de N$^1$-methylnoctina-
mida sed non in illo del nivello de acido quinolinic o de pyridona. Le resultatos obtenite
indica que in anemia le activitate del hematino-dependente enzyme pyrrolase tryptophanic
esseva deprimite si ben como le enzymes que converte le amino-acido in CO$_2$. Le datos
suggestiona que—a parte le facto que le enzymes del catabolismo de kynurenina depende
de vitamin B$_6$—il es equalmente ver que vitamina B$_6$ es importantissime pro le conversion
del metabolito tryptophanic acido 3-hydroxy-anthranilic ad in $\alpha$-amino-$\beta$-carboxymu-
con-$\epsilon$-semialdehyde e le conversion del semialdehyde ad in acetato e CO$_2$. In plus, il es possibile
que vitamina B$_6$ ha un parte in le metabolismo additional de acido quinolinic ad in
pyridona.

**ACKNOWLEDGMENT**
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Tryptophan Metabolism in Humans with Various Types of Anemias

L. V. HANKES, R. R. BROWN, L. SCHIFFER and M. SCHMAELER