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Site of Conversion of Tryptophan into Nicotinic Acid in Man.*

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Although direct evidence is now available for the conversion of tryptophan into nicotinic acid in the mammalian organism and of the intermediate steps concerned[1,2,3] the site of such conversion is still a matter of dispute. It is possible that different animal species behave differently in this regard, since there seem to be species differences[4-10] in the ability of tryptophan to spare nicotinic acid and in the proportion of excreted nicotinic acid derivatives. Studies to determine the site of the conversion are confined to experimental animals and have given contradictory results.[11] Ellinger and Abdel-Kader[12] compared the oral and parenteral routes of administration in rats and observed a far greater rise in N^1 methyl nicotinamide output after oral administration. The magnitude of this response was markedly reduced by chemotherapeutic agents. This led them to conclude that the intestinal synthesis was of primary importance.

An opposite conclusion was reached by Schweigert and Pearson[13,14] who administered tryptophan both orally and intraperitoneally. The promptness of the response by the latter route, even though it was smaller in magnitude led them to believe that the conversion took place primarily in the tissues. This conclusion was somewhat modified in a later report by Junqueira and Schweigert[15] who studied the effect of succinyl sulfathiazole on the response to oral tryptophan with and without a pteroylglutamic acid supplement. In the presence of the sulfa drug when unsupplemented by pteroylglutamic acid, oral tryptophan had very little augmenting effect on N^1methyl nicotinamide excretion; but when pteroylglutamic acid was added the urinary excretion of the N^1methyl compound rose sharply.

In order to throw further light on this question we undertook to make comparisons of the effect of oral and intravenous tryptophan administration in infants.

Experimental. The subjects were 6 normal male infants, ranging in age from 3 to 24 months and in weight from 4.1 to 11.4 kg. They were maintained on standard formulae of evaporated milk and dextrimaltose through-

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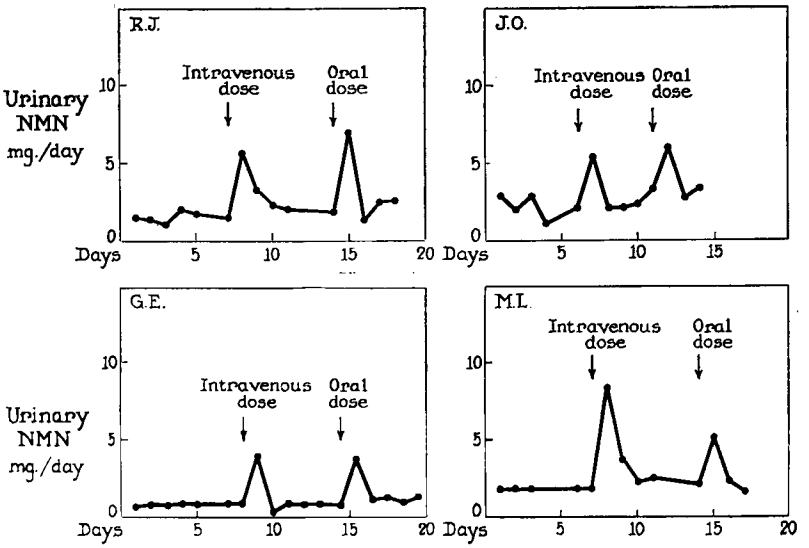

FIG. 1.
Effect of an intravenous and an oral dose of L-tryptophane on the urinary N¹methyl nicotinamide excretion.

out the period of study. After the urinary excretion of N¹methyl nicotinamide became fairly stable, the test dose of one gram L-tryptophan was administered either intravenously or orally.

The tryptophan solution for intravenous use was prepared in the following manner. One gram was dissolved in 30 cc of sterile distilled water containing 5 cc of 6 N hydrochloric acid, water was added to make a volume of 300 cc, and then the pH was adjusted with sodium hydroxide to neutrality. The solution was passed through a Seitz filter and then autoclaved for 10 minutes at 15 lb pressure. It was administered by slow drip, over a period of 3 to 6 hours. In 4 of the subjects the tryptophan was also administered orally, one week after the intravenous injection. The oral dose was divided in half and fed with the 10 A.M. and 2 P.M. bottles.

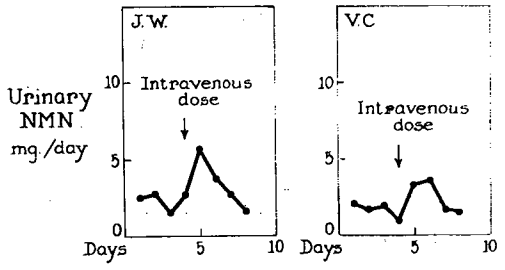

FIG. 2.
Effect of an intravenous dose of L-tryptophane on the urinary N¹methyl nicotinamide excretion.

The N¹methyl nicotinamide determinations were performed according to the method of Huff and Perlzweig[16] on 24 hour collections of urine. The urines were collected in amber bottles with enough glacial acetic acid to make a 2% solution.

Results. The data for the 6 subjects are expressed graphically in Figs. 1 and 2. The slow intravenous administration of one gram of L-tryptophan resulted in a marked increase of urinary N¹methyl nicotinamide on the day of the infusion in 5 of these 6 subjects. In the sixth subject (V.C., Fig. 2), there was a moderate increase both on the day of as well as the day following the tryptophan injection. This slighter response can perhaps be attributed to the much larger size of this particular infant who received the same dose as the smaller subjects. We do not have an explanation for the delay in excretion.

In those subjects who also received the tryptophan orally, the rise in N¹methyl nico-

[16] Huff, J. W., and Perlzweig, W. A., *J. Biol. Chem.*, 1947, **167**, 157.

tinamide excretion produced by this feeding was in the same range as that which resulted from the intravenous administration. Differences between the two routes of administration are within the limits of the usual daily variations that occur in the excretion of this substance. We have noted that the daily N^1 methyl nicotinamide excretion may fluctuate as much as 1.7 mg even when the infant is maintained on a constant diet.

Discussion. The rise of urinary N^1methyl nicotinamide excretion produced by the intravenous administration of L-tryptophan leads to the conclusion that the conversion of tryptophan to nicotinic acid in man takes place in the tissues rather than in the gastrointestinal tract as a result of bacterial action. This premise is strengthened both by the fact that the N^1methyl nicotinamide values are the same regardless of the route of administration, and by the fact that this increase takes place so promptly. For this conversion to occur as a result of tryptophan excretion into the gastrointestinal tract and subsequent action by bacteria there, one would anticipate a considerable time lag which actually did not occur.

The differences in the rates of administration are sufficient to explain the variance of our results from those of Schweigert *et al.*[13-15] One can postulate that our slow rate of injection raised the blood tryptophan level for a prolonged period of time thereby giving the tissues more time to produce the conversion. The method of a single large injection may provide such a large excess of tryptophan that it may be disposed of in other ways. This may also account for the results obtained by Ellinger and Abdel-Kader[12] who do not give any details regarding the technic of their parenteral tryptophan.

Of interest in this connection are the recent communications of Schweigert *et al.*[17] and of Singal, Sydenstricker and Littlejohn.[18] The former, working with chick embryos observed an increase in the nicotinic acid content of the tissues after an injection of tryptophan. The latter authors reported that the administration of L-tryptophan to rats caused an increase above normal of the nicotinamide concentration of the liver, a phenomenon observed in this organ alone.

Summary. The intravenous administration of one gram of L-tryptophan to infants on constant diets gave a prompt and large rise in the urinary N^1methyl nicotinamide which was equal in magnitude to that provoked by oral administration of the tryptophan. In view of these findings, the conversion of tryptophan to N^1methyl nicotinamide in man seems to be mediated by the body tissues rather than by bacterial synthesis in the gastrointestinal tract.

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Effect of Iodide on Thyroid Glands of Rats Kept at Low Temperature.

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A number of workers have noted that the thyroid glands of rats kept in the cold develop hyperplasia, thickened acinar epithelium, and loss of colloid characteristic of a hyperactive thyroid gland. It was of interest to determine whether the administration of iodide to rats kept under cold-room conditions would cause involution of the thyroid gland as it does in toxic goiter.

Four groups of male albino rats of the