first type, rats were pretreated with phenobarbitone for two days, and on the third day received phenobarbitone and emetine or 2,3-dehydroemetine. When liver microsomal fractions prepared 24hr. later under standard conditions were incubated *in vitro* with aminopyrine or neoprontosil, the drug-metabolizing enzyme activity in the phenobarbitone-stimulated rats was decreased by about 50% after co-administration of emetine or 2,3-dehydroemetine on the third day.

In the second type of injection schedule, animals were treated for 24hr. only, with phenobarbitone and emetine or 2,3-dehydroemetine alone or in combination. Both alkaloids blocked the stimulation of liver microsomal drug-metabolizing enzyme activity brought about by phenobarbitone.

The microsomes prepared from phenobarbitone-pretreated animals can *N*-demethylate *N*-methylated (−)-emetine *in vitro* at the rate of 50nmoles/mg. of microsomal protein/½hr. No such *N*-demethylating activity is seen in corresponding experiments with control microsomal preparations and *N*-methylemetine as substrate (Jondorf, Johnson & Drassner, 1969). This would explain why animals pretreated with phenobarbitone tolerate rather lower doses of *N*-methylemetine than control animals. Lethal concentrations of metabolically formed emetine may build up in rats with *N*-demethylating drug-metabolizing enzyme activity enhanced by phenobarbitone.

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The Metabolism of Caffeic Acid in Humans: the Dehydroxylating Action of Intestinal Bacteria

By JACQUELINE DAYMAN and J. B. JEPSON. (*Courtauld Institute of Biochemistry, The Middlesex Hospital Medical School, London W1P 5PR*)

Previous reports that caffeic acid (3,4-dihydroxycinnamic acid), administered orally to humans, gave rise to urinary *m*-hydroxyphenyl derivatives by a dehydroxylation process (Booth, Emerson, Jones & De Eds, 1957; Shaw, Gutenstein & Jepson, 1963) have been confirmed and extended. Oral caffeic acid rapidly causes the urinary appearance of *O*-methylated phenolic acids (including ferulic acid, isoferulic acid and vanillic acid and their conjugates), whereas the dehydroxylation process is delayed many hours after ingestion. The relationship between the methylation (a tissue reaction) and the dehydroxylation (due solely to the action of intestinal bacteria) has been established by suppressing the gut flora with neomycin, or by delaying caffeic acid absorption by administering it in specially-coated capsules, or both. In addition to the acid, each capsule contained quinine sulphate, which acted as a readily excreted fluorescent marker to indicate when the capsule released its contents. The capsule technique was also used to release *m*-hydroxybenzoic acid directly into the small intestine, to show that neomycin treatment really had prevented dehydroxylation and was not just interfering with the absorption of *m*-hydroxy acids that were still being formed.

The bacteria responsible for this dehydroxylation have not yet been investigated, but Perez-Silva, Rodriguez & Perez-Silva (1966) claimed that a strain of *Pseudomonas* in rat faeces is capable of performing the reaction.

All the feeding experiments were performed with the patient on a diet containing the minimum of plant and fruit foodstuffs, with rigorous exclusion of foods known to contain or give rise to caffeic acid and related phenolic acids.

The importance of considering the part played by the varied and largely unidentified species of intestinal bacteria in the metabolism of minor dietary components, including therapeutic agents, is emphasized.

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