

This Week's Citation Classic®

Kappas A, Anderson K E, Conney A H & Alvares A P. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man.

Clin. Pharmacol. Ther. 20:643-53, 1976.

[The Rockefeller Univ., New York, NY and Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NJ]

This study demonstrated for the first time that changes in the macronutrient composition of the diet could alter the rates of metabolism and therefore presumably the pharmacological actions of the drugs that humans may receive for therapeutic purposes. The results strongly suggest that individuals with altered nutritional states may show substantial deviations from the normal in the rates at which they respond therapeutically to drugs metabolized by hepatic P-450-dependent monooxygenases as well as in their pattern of metabolism of endogenous steroid hormones. [The *SCI*® indicates that this paper has been cited in over 235 publications.]

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Our paper is one of the early reports originating from a series of studies we began in 1976¹ at The Rockefeller University Hospital, in which the influence of nutritional factors on the biotransformation of endogenous and exogenous chemicals was explored. These studies continue today,² made possible by the unique metabolic diet facilities developed earlier at this institution, which permit exacting control of specific food intake of patients and normal volunteers for long periods of time.

We had found that feeding a diet of charcoal-broiled meat to humans enhanced the metabolism of the analgesic phenacetin.³ In these experiments normal volunteers were fed a controlled diet during the study period, then given a therapeutic dose of phenacetin (900 mg). The levels of the drug in blood were markedly lower after the subjects were fed the charcoal-broiled diet, compared to the blood levels obtained when the same individuals were fed an identical diet cooked with aluminum foil placed between the meat and the burning charcoal.

When this study began, one of the normal volunteers had planned to go on the then-popular Atkin's diet, which permitted eating protein, but drastically

curtailed the intake of carbohydrate. Interestingly, after about two weeks on the Atkin's diet she was administered the 900 mg dose of phenacetin and her blood levels of the drug were extremely low compared to the other eight healthy individuals in the study group. These blood levels were further decreased by the end of the third week of the study when the volunteers were put back on the control diet.

The serendipitous finding in this young woman led us to conduct a major investigation on the metabolism of antipyrine and theophylline when dietary protein and carbohydrate contents were manipulated. The analgesic antipyrine and the bronchodilator theophylline were chosen because both drugs are rapidly absorbed when given orally, and both are substrates for the hepatic cytochrome P-450-dependent monooxygenases that metabolize steroid sex hormones as well as a great variety of structurally diverse drugs, carcinogens, and other environmental chemicals.

Six healthy volunteers were placed on a low carbohydrate/high protein diet (LC/HP) for the first two weeks of the test period. The same subjects were then placed on a high carbohydrate/low protein (HC/LP) diet for the second two-week study period. The fat content of the meals and the caloric intake per day during each of the test diets were unchanged. The metabolic clearance rates and the plasma half-lives of each drug were determined at the end of each test diet period. There was a significant increase in the metabolic clearance rates of both antipyrine and theophylline when the diet was changed from a customary home diet to an LC/HP diet. There was also a significant decrease in the metabolic clearance rates of the drugs when the change was made from an LC/HP diet to an HC/LP diet. Subsequent studies have shown that the biotransformation of natural steroid hormones can also be substantially influenced by such dietary manipulations.⁴

Nutritional-pharmacological interactions may occur, among other circumstances, in those individuals who undertake weight-reducing regimens of an unusual type, in malnourished subjects, in postoperative patients who receive glucose intravenously as a sole form of nourishment, in individuals with special dietary restrictions, such as vegetarians, and in large numbers of patients whose disease processes (for example, diabetes, cirrhosis of the liver, end-stage renal disease, obesity, and so on) require, or are associated with, significant nutritional restrictions. The potential clinical significance of such nutritional-pharmacological interactions is, we believe, considerable.

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2. Anderson K E, Conney A H & Kappas A. Nutrition as an environmental influence on chemical metabolism in man. (Kalow W, Goedde H W & Agarwal D P, eds.) *Progress in clinical and biological research. Volume 214. Ethnic differences in reactions to drugs and xenobiotics.* New York: Liss, 1986. p. 39-54.
3. Conney A H, Pantuck E J, Hsiao K-C, Garland W A, Anderson K E, Alvares A P & Kappas A. Enhanced phenacetin metabolism in human subjects fed charcoal-broiled beef. *Clin. Pharmacol. Ther.* 20:633-42, 1976. (Cited 80 times.)
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